SeHCAT (Tauroselcholic [^{75}Selenium] acid) for the investigation of bile acid diarrhoea: a systematic review and cost effectiveness analysis

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Marie Westwood and Edyta Ryczek planned and performed the systematic review and interpretation of evidence. Isaac Corro Ramos, Hannah Penton and Marscha Holleman planned and performed the cost-effectiveness analyses and interpreted results. Nigel Armstrong contributed to planning and interpretation of the systematic review and the cost-effectiveness analyses, acquisition of input data and conducted model peer review. Caro Noake devised and performed the literature searches and provided information support to the project. Jos Kleijnen and Maiwenn Al provided senior advice and support to the systematic review and cost-effectiveness analyses, respectively. All parties were involved in drafting and/or commenting on the report.

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ABSTRACT

Background

Bile acid diarrhoea (BAD) is a form of chronic diarrhoea in which the recycling of bile acids in the body is not functioning properly. SeHCAT (tauroselcholic [75 selenium] acid) is a radiopharmaceutical capsule that is indicated for use in the investigation of bile acid malabsorption (BAM). SeHCAT testing may be useful in diagnosing BAD and informing the treatment of adults with chronic, previously unexplained, diarrhoea.

Objectives

To assess the clinical- and cost-effectiveness of SeHCAT testing for the investigation of BAM in adults with chronic diarrhoea with an unknown cause, suspected or diagnosed diarrhoea-predominant irritable bowel syndrome, or functional diarrhoea (suspected primary BAD), and adults with chronic diarrhoea and a diagnosis of Crohn's disease, who have not undergone ileal resection (suspected secondary BAD).

Methods

Sixteen databases were searched to November 2020. Review methods followed published guidelines. Studies were assessed for quality using appropriate risk of Bias tools. Results were summarise using a narrative synthesis, structured by clinical application (diagnosis of primary or secondary BAD).

The cost effectiveness analysis combined a short-term (6-month) decision analytic model reflecting the diagnostic pathway and initial response to treatment and a lifetime Markov model consisting of three health states: diarrhoea, no diarrhoea and death, with transitions determined by probabilities of response to relevant treatments.

Results

Twenty-four studies (25 publications) were included in this review.

Most (21/24) studies were of the lowest level of evidence eligible for inclusion; observational studies which reported some outcome data for patients treated with bile acid sequestrants (BAS), where only those patients with a positive SeHCAT test were offered treatment with BAS.

The median rate of response to a trial of treatment with BAS, in patients with a diagnosis of primary BAD based on a 7-day SEHCAT retention value ≤15% (a threshold commonly used in UK clinical practice), was 68% (range 38% to 86%), eight studies. The estimated sensitivity of SeHCAT in predicting a positive response to treatment with colestyramine, using the ≤15% threshold was 100% (95% CI: 54.1 to 100%) and the corresponding specificity estimate was 91.2% (95% CI: 76.3 to 98.1%), one study.

The median proportion of treated patients who were intolerant of BAS, or discontinued treatment for unspecified reasons was 15% (range 4% to 27%), eight studies. There was insufficient information to determine whether levels of intolerance varied between colestyramine, colestipol and colesevelam.

For both populations, the SeHCAT 15% strategy showed the potential to be cost-effective by either dominating the other strategies or resulting in ICERs below the threshold range of £20,000-£30,000 per QALY gained.

Conclusions

There is a lack of evidence linking the use of SeHCAT testing to patient-relevant outcomes. The optimal SeHCAT decision threshold, to define presence of BAM and select patients for treatment with BAS, is uncertain. The extent to which patients with 'borderline' or 'equivocal' 7-day SeHCAT retention values (e.g. between 10% and 15%) could benefit from treatment with BAS is unclear, and the extent to which patients with 7-day retention values >15% may benefit from treatment with BAS is unknown. While the results of the economic evaluation conducted seem to suggest that SeHCAT could be cost-effective, there is great uncertainty surrounding these analyses, which should be based on more robust evidence.

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LIST OF ABBREVIATIONS

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

AiC	Academic in confidence
BAD	bile acid diarrhoea
BAM	bile acid malabsorption
BAS	bile acid sequestrants
BSG	British Society of Gastroenterology
CADTH	Canadian Agency for Drugs and Technologies in Health
CCT	controlled clinical trial
CDSR	Cochrane Database of Systematic Reviews
CEAC	cost effectiveness acceptability curve
CEAF	cost effectiveness acceptability frontier
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CRD	Centre for Reviews and Dissemination
CV	coefficient of variation
DAR	Diagnostic Assessment Report
DARE	Database of Abstracts of Reviews of Effects
DG	Diagnostic Guidance
DTA	diagnostic test accuracy
FD	functional diarrhoea
FN	false negative
FP	false positive
HES	Hospital Episode Statistics
HR	hazard ratio
HRQoL	health-related quality of life
HSROC	hierarchical summary receiver operating characteristic
HTA	health technology assessment
IBS-D	diarrhoea-predominant irritable bowel syndrome
ICER	incremental cost effectiveness ratio
INAHTA	International Network of Agencies for Health Technology Assessment
IQR	interquartile range
LILACS	Latin American and Caribbean Health Sciences Literature
LR+	positive likelihood ratio
LR-	negative likelihood ratio
LY	life year
NA	not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NIHR	National Institute for Health Research
NPV	negative predictive value
NR	not reported

ONS	Office for National Statistics
OR	odds ratio
PPV	positive predictive value
PSA	probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life year
RCT	randomised controlled trial
ROC	receiver operating characteristic
SCI	Science Citation Index
SD	standard deviation
SeHCAT	Tauroselcholic [^{75}Selenium] acid
SIGN	Scottish Intercollegiate Guidelines Network
SROC	summary receiver operating characteristic
TN	true negative
TP	true positive

GLOSSARY

Cost effectiveness analysis	An economic analysis that converts effects into health terms and describes the costs for additional health gain.
Decision modelling	A mathematical construct that allows the comparison of the relationship between costs and outcomes of alternative healthcare interventions.
False negative (FN)	Incorrect negative test result – number of diseased persons with a negative test result; in the context of this assessment, the number of responders to bile acid sequestrants with a negative test result.
False positive (FP)	Incorrect positive test result – number of non-diseased persons with a positive test result; in the context of this assessment, the number of non-responders to bile acid sequestrants with a positive test result.
Incremental cost effectiveness ratio (ICER)	The difference in the mean costs of two interventions in the population of interest divided by the difference in the mean outcomes in the population of interest.
Index test	The test whose performance is being evaluated.
Likelihood Ratio (LR)	Likelihood ratios describe how many times more likely it is that a person with the target condition will receive a particular test result than a person without the target condition.
Meta-analysis	Statistical techniques used to combine the results of two or more studies and obtain a combined estimate of effect.
Meta-regression	Statistical technique used to explore the relationship between study characteristics and study results.
Opportunity costs	The cost of forgone outcomes that could have been achieved through alternative investments.
Positive predictive value (PPV)	The probability that people with a positive test have the disease; in the context of this assessment, the probability that people with a positive test will respond positively to treatment with bile acid sequestrants.
Publication bias	Bias arising from the preferential publication of studies with statistically significant results.
Quality of life	An individual's emotional, social and physical well-being and their ability to perform the ordinary tasks of living.
Quality-adjusted life year (QALY)	A measure of health gain, used in economic evaluations, in which survival duration is weighted or adjusted by the patient's quality of life during the survival period.
Receiver Operating Characteristic (ROC) curve	A graph which illustrates the trade-offs between sensitivity and specificity which result from varying the diagnostic threshold.
Reference standard	The best currently available method for diagnosing the target condition. The index test is compared against this to allow calculation of estimates of accuracy.
Sensitivity	Proportion of people with the target disorder who have a positive test result; in the context of this assessment, the proportion of people who respond positively to treatment with bile acid sequestrants who have a positive test result.
Specificity	Proportion of people without the target disorder who have a negative test result;

	in the context of this assessment, the proportion of people who do not respond positively to treatment with bile acid sequestrants who have a negative test result.
State-transition model	A model in which individuals move (**transition**) between disease **states** as their condition changes over time. Time spent in each disease **state** for a single **model** cycle (and **transitions** between **states**) is associated with a cost and a health outcome.
True negative (TN)	Correct negative test result – number of non-diseased persons with a negative test result; in the context of this assessment, the number of non-responders to bile acid sequestrants with a negative test result.
True positive (TP)	Correct positive test result – number of diseased persons with a positive test result; in the context of this assessment, the number of responders to bile acid sequestrants with a positive test result.

EXECUTIVE SUMMARY

Background

Bile acid diarrhoea (BAD) is a form of chronic diarrhoea in which 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 bowel to aid digestion. Usually, bile acids are reabsorbed into the liver in the final section of the small bowel. If they are not reabsorbed or the body produces more bile acid than can be reabsorbed, excess amounts of bile travel from the small bowel to the colon, stimulates salt and water secretion and bowel movements and results in diarrhoea. The most common form of BAD is caused by overproduction of bile acid in people with no physical damage to the bile acid recycling system, however, BAD can also appear as a secondary condition following damage to the small bowel or another part of the bile acid recycling system.

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. 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. 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 BAD is usually made when 15% or less of SeHCAT remains in the body.

Current British Society of Gastroenterology (BSG) guidelines list BAD amongst the “common disorders” to be investigated as part of secondary clinical assessment and state that a positive diagnosis of BAD should be made using either SeHCAT testing or measurement of the serum bile acid precursor 7-alpha-hydroxy-4-cholesten-3-one, depending on local availability. Whereas NICE diagnostic guidance (DG7), published in 2012 states that there is insufficient evidence to determine whether SeHCAT is a cost effective option for diagnosing BAM in people with diarrhoea-predominant irritable bowel syndrome (IBS-D) or functional diarrhoea (FD) and people with Crohn's disease without ileal resection and recommends its use in research only. The availability and use of SeHCAT testing vary across the UK and, in some secondary care settings, bile acid sequestrant (BAS) treatment of BAD is started without a diagnostic test being performed (trial of treatment).

This update assessment has been undertaken in order to ensure that guidance is based on current evidence.

Objectives

This assessment aims to evaluate the clinical and cost effectiveness of [^{75}Se] tauroselcholic acid (SeHCAT) for investigating BAD 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 IBS-D (i.e. people with suspected primary BAD), and adults with chronic diarrhoea and a diagnosis of Crohn's disease, who have not undergone ileal resection (i.e. people with suspected secondary BAD).

Methods

Assessment of clinical effectiveness

Sixteen databases, including MEDLINE and EMBASE, research registers and conference proceedings were searched for relevant studies from inception to November 2020. Search results were deduplicated against the existing project library, from our previous assessment for DG7, and new records were independently screened for relevance by two reviewers. Full text inclusion assessment, data extraction, and quality assessment were conducted by one reviewer and checked by a second. The methodological quality of included predictive accuracy studies (studies assessing the accuracy of the SeHCAT test for predicting response to treatment with BAS) was assessed using QUADAS-2. The methodological quality of observational studies, which reported treatment outcome only for those participants with a positive SeHCAT result, was assessed using a topic-specific adaptation of a published checklist (as used in our previous assessment).

Meta-analysis was considered inappropriate, due to the small number of test accuracy studies with varying diagnostic thresholds and between study heterogeneity with respect to population (prior investigations), treatment regimen, definition of response, follow-up period, and SeHCAT administration); we therefore employed a narrative synthesis. The clinical effectiveness results section of this report is structured by clinical application (diagnosis of primary BAD and diagnosis of secondary BAD in people with Crohn's disease who have not undergone ileal resection).

Assessment of cost effectiveness

In the health economic analyses, the cost effectiveness of SeHCAT for the assessment of BAD was estimated in the two different populations described above (adults with suspected primary BAD and adults with suspected BAD who have Crohn's disease without ileal resection). For both populations the cost effectiveness of SeHCAT (test cut off 15%) compared to both trial of treatment with BAS and No SeHCAT was assessed. The cost effectiveness analysis combined a short-term diagnostic decision analytic model (with an assumed duration of six months) and a long-term (lifetime) Markov model.

In the SeHCAT branch of the short-term decision analytic model, patients who tested positive were assumed to receive treatment with BAS. Patients who did not respond followed the No SeHCAT branch. In the BAS trial of treatment strategy, all patients are treated with a BAS, and those not responding followed the no SeHCAT path. In the No SeHCAT strategy, patients could either receive a colonoscopy, or not. If they tested positive for IBD following the colonoscopy, they could receive treatment for IBD. If they tested negative for IBD or did not receive a colonoscopy, patients were assumed to be treated for IBS-D. In the Crohn's model, no colonoscopy was included, and patients were assumed to immediately receive the relevant treatments for their diarrhoea.

The long-term Markov model consists of three health states: diarrhoea, no diarrhoea and death. Patients who had a treatment response in the short-term model start in the “No diarrhoea” health state and are assumed to continue to receive the relevant treatment from the short-term model. Patients who did not respond to treatment in the short-term model start in the “Diarrhoea” health state. No link between diarrhoea and increased mortality was identified and, therefore, transitions to death are determined by background mortality. Transitions between the “Diarrhoea” and “No diarrhoea” health states were informed by clinical expert opinion since clinical data regarding the long-term effectiveness of BAS, IBD and IBS-D treatments were not identified, and diarrhoea treatment in Crohn's patients. The cycle length is six months, and the model estimates the lifetime costs and QALYs of patients in each population.

Where possible, input for the model was based on our SeHCAT systematic review, other published literature and UK databases. When such evidence was not available, expert opinion was used. The impact of uncertainty about the various input parameters on the outcomes was explored through probabilistic sensitivity analyses and scenario analyses. ICERs were estimated as additional cost per additional QALY.

Results

Assessment of clinical effectiveness

The evidence base relating to the use of SeHCAT testing in adults referred to a secondary care for the investigation of chronic diarrhoea with an unknown cause, suspected or diagnosed IBS-D (population one), and adults with chronic diarrhoea and a diagnosis of Crohn’s disease, who have not undergone ileal resection (population two) has not changed substantively since our previous assessment. This current assessment includes a total of 25 publications relating to 24 studies, as compared to the 24 publications relating to 21 studies included in our previous assessment; six of the previously included studies did not meet the inclusion criteria for this assessment and nine new studies were included. All of the new studies were of the lowest level of evidence eligible for

inclusion; these were observational studies which reported some outcome data for patients treated with BAS, where only those patients with a positive SeHCAT test were offered treatment with BAS.

Three studies, all of which were included in our previous assessment for DG7, provided limited data on the accuracy of the SeHCAT test for predicting response to treatment with BAS, in population one. Merrick et al. (1985) reported sufficient data to allow the calculation of the performance of SeHCAT for predicting treatment response at the seven-day-retention threshold ≤15%, commonly used in UK clinical practice. The estimated sensitivity of SeHCAT in predicting a positive response to treatment with colestyramine, using the ≤15% threshold was 100% (95% CI: 54.1 to 100%) and the corresponding specificity estimate was 91.2% (95% CI: 76.3 to 98.1%). These results would appear to indicate that the use of the SeHCAT, with a 15% threshold, could identify patients with IBS-D who may benefit from treatment with BAS. However, it should be noted that confidence intervals around the sensitivity estimate were wide and, although all 31 patients with a negative SeHCAT test result were classified as true negatives, this assessment was based on long term follow-up and none of these patients received a trial of treatment with colestyramine. The remaining two studies provided data for SeHCAT thresholds (5% and 8%).

Eight studies reported information about the rate of positive response to a trial of treatment with BAS in patients with a positive SeHCAT, based on the 15% threshold, for population one. The median proportion of SeHCAT test positive patients who received a trial of treatment with BAS was 86% (range 70% to 100%) and the median response rate was 68% (range 38% to 86%). The equivalent data from the predictive accuracy study by Merrick et al. (1985) indicated a treatment response rate of 67% in patients with seven-day SeHCAT retention values ≤15%; in this study, 9/12 (75%) patients with SeHCAT retention values of ≤15% threshold received a trial of treatment with colestyramine. The remaining 13 studies reported information about the rate of positive response to a trial of treatment with BAS, using various SeHCAT test thresholds, predominantly 10% and/or 5%.

The single study that reported information about response to treatment with BAS for population two provided only limited information about response rates in patients with a positive SeHCAT test result (seven-day retention <10%) who were treated with colestyramine or colestipol. Only 9/24 patients with a positive SeHCAT test result received a trial of treatment with BAS and the numbers receiving each drug were not reported; 8/9 (89%) patients treated with BAS responded positively.

Eight studies reported the proportion of treated patients who were intolerant of BAS, or discontinued treatment for unspecified reasons; rates of intolerance/discontinuation were generally

high, median 15% (range 4% to 27%). There was insufficient information to determine whether levels of intolerance varied between colestyramine, colestipol and colesevelam.

Assessment of cost effectiveness

For both populations, the SeHCAT 15% strategy has shown the potential of being considered a cost effective alternative by either dominating the other two strategies or by resulting in ICERs below the common thresholds of £20,000 or £30,000 per QALY gained. Dominance or cost effectiveness was led, in general, by response since the SeHCAT 15% was the strategy with the highest response rate in the majority of the scenarios explored, including the base-case analysis for both populations. In scenarios where the other two strategies were estimated to provide higher response rates than SeHCAT, the scenarios were probably based on unrealistic assumptions regarding response with No SeHCAT or BAS trial of treatment. Even in those scenarios where overall response in the BAS trial of treatment strategy was higher than in SeHCAT 15%, the ICERs for the comparison of BAS trial of treatment vs. SeHCAT 15% were well above the £20,000 or £30,000 per QALY gained thresholds. SeHCAT 15% was also the strategy in which more colonoscopies were avoided.

Conclusions

Despite the apparent significance of BAM in the adult IBS-D/FD population, and the expansion of provision of SeHCAT testing in the UK, there remains a surprising lack of evidence linking the use of SeHCAT testing to patient-relevant outcomes. The available evidence is largely limited to studies which describe the proportion of patients with a positive SeHCAT result who responded positively to treatment with BAS. The optimal SeHCAT decision threshold, to define presence of BAM and select patients for treatment with BAS, is uncertain. The extent to which patients with 'borderline' or 'equivocal' seven-day SeHCAT retention values (e.g. between 10% and 15%) could benefit from treatment with BAS remains unclear, and the extent to which patients with seven-day retention values >15% may benefit from treatment with BAS is unknown. It has been suggested that SeHCAT testing and the assignment of a diagnosis of BAM may improve adherence to treatment with BAS. However, despite some evidence indicating that these treatments are generally poorly tolerated, there is a lack of information about the relative rates of adherence for different BAS and about the acceptability, to patients, of SeHCAT testing. Finally, there is a paucity of evidence about the efficacy and safety of BAS for the treatment of patients who have been diagnosed with BAM.

While the results of the economic evaluation conducted for both populations seem to suggest that SeHCAT could be a cost effective strategy, there is great uncertainty surrounding these analyses, which should be based on more robust evidence. Therefore, the implications for service provision of

SeHCAT are still uncertain and the main reason for this uncertainty is the lack of good quality evidence.

PLAIN ENGLISH SUMMARY

Bile acids are produced in the liver, secreted into the biliary system, stored in the gallbladder and are released after eating. They are important for the digestion and absorption of fats and fat-soluble vitamins (A,D, E and K) in the small bowel. Usually over 95% of bile acids are absorbed before reaching the colon and are taken up by the liver and recycled. When larger amounts of bile acids enter the colon, they stimulate salt and water secretion and intestinal motility, which causes symptoms of chronic diarrhoea. This is called bile acid diarrhoea (BAD).

Symptoms of BAD may include explosive, smelly or watery diarrhoea, urgency to empty bowels, abdominal pain, distension or bloating and faecal incontinence.

A [^{75}Se] tauroselcholic acid (SeHCAT) test is a diagnostic procedure, which may help to tell whether diarrhoea is being caused by problems with bile acid recycling. 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 retained, and thus whether the patient has BAD.

The purpose of this project was to assess the clinical benefits, risks and cost effectiveness of SeHCAT testing, in people with chronic diarrhoea with an unknown cause. The assessment focussed on people with suspected or diagnosed irritable bowel syndrome or functional diarrhoea, and people with a diagnosis of Crohn's disease and no ileal resection, who have been referred to secondary care for investigation of possible BAD.

Despite the apparent significance of BAD in the adult population with chronic unexplained diarrhoea, and the expansion of provision of SeHCAT testing in the UK, there remains a surprising lack of evidence linking the use of SeHCAT testing to patient-perceived outcomes, such as relief of symptoms by treatment with bile acid sequestrants (BAS). There is also a lack of information regarding the preferences of patients for SeHCAT testing before trying treatment with BAS and regarding the relative tolerability of different BAS.

The results of the economic evaluation conducted for both populations seem to suggest that SeHCAT could be a cost effective strategy. However, there is great uncertainty surrounding these analyses, which should be based on more robust evidence. The implications for service provision of SeHCAT are still uncertain and the main reason for this uncertainty is the lack of good quality evidence.

1. OBJECTIVE

The overall objective of this project was to provide an update to National Institute for Health and Care Excellence (NICE) diagnostics guidance on [^{75}Se] tauroselcholic acid (SeHCAT) testing for the investigation of diarrhoea in adults with diarrhoea-predominant irritable bowel syndrome (IBS-D) or Crohn's disease without ileal resection (DG7), published in November 2012.[1] This update report summarises the current evidence on the clinical and cost effectiveness of [^{75}Se] tauroselcholic acid (SeHCAT) for investigating bile acid diarrhoea (BAD) 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, or functional diarrhoea (FD), suspected or IBS-D (i.e. people with suspected primary BAD). This up-date also considered SeHCAT for the investigation of possible secondary BAD in adults with chronic diarrhoea and a diagnosis of Crohn's disease, who have not undergone ileal resection.

In order to address the stated objective, the following research questions were 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 pathway for the investigation of chronic diarrhoea, in the specified populations?

2. BACKGROUND AND DEFINITION OF THE DECISION PROBLEM(S)

2.1 Population

The primary indication for this assessment is the investigation of possible BAD in adults presenting with FD, suspected or diagnosed IBS-D (i.e. people with suspected primary BAD).

Bile acid diarrhoea is a form of chronic diarrhoea in which 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 bowel to aid digestion. Usually, bile acids are reabsorbed into the liver in the final section of the small bowel. 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 BAD 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 BAD is caused by overproduction of bile acid in people with no physical damage to the bile acid recycling system. This primary form of BAD is often missed as a cause of chronic diarrhoea. Because of the similarity in symptoms between BAD and both IBS-D and FD, BAD may be misdiagnosed. The actual cause of diarrhoea in up to a 30% of people with suspected IBS-D or FD may be BAD.[2]

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 also considered SeHCAT for the investigation of possible secondary BAD in adults with chronic diarrhoea and a diagnosis of Crohn's disease, who have not undergone ileal resection.

2.2 Intervention technology

SeHCAT is a radiopharmaceutical capsule that is indicated for use in the investigation of 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 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 BAD 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 to be indicative of BAD, although values between 15% and 20% may sometimes be considered 'borderline' (clinical opinion of specialist committee members). SeHCAT results are also sometimes used to grade the severity of BAD:

- retention values from 10% to 15% indicate mild BAD
- retention values from 5% to 10% indicate moderate BAD
- retention values from 0% to 5% indicate severe BAD

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.[3]

There are no alternative technologies which are currently in routine use in the National Health Service (NHS), England.

2.3 Comparator

The comparators for this technology appraisal are:

- No SeHCAT testing and no treatment with BAS
- No SeHCAT testing and trial of treatment with BAS

2.4 Care pathway

2.4.1 Diagnostic assessment

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".[4] 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".[2] The BSG guidelines position SeHCAT testing as part of secondary clinical assessment, following initial assessment/investigations to exclude coeliac disease (coeliac serology and upper gastrointestinal 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).[2]

The BSG guidelines list BAD amongst the "common disorders" to be investigated as part of secondary clinical assessment and state that a positive diagnosis of BAD should be made using either SeHCAT testing or by measuring the serum bile acid precursor 7-alpha-hydroxy-4-cholesten-3-one, depending on local availability.[2] The BSG guidelines also state that "there is insufficient evidence to recommend use of an empirical trial of treatment for BAD rather than making a positive diagnosis".[2] Referral to secondary care is required for investigation and diagnosis of BAD.

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 defecation 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.[5] The guideline also states that further tests such as colonoscopy or imaging are not necessary to confirm an IBS diagnosis.[5] Investigation of BAD 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 BAD.[5]

Investigation of BAD 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), BAD is so common (more than 95% of cases)[6] 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.[3, 7, 8] Multiple interactions with different clinicians over many years often take place before BAD is investigated.[9]

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,[10] the trusts in which SeHCAT testing is available perform about 10,000 SeHCAT tests per year. The number of tests performed in different trusts varies widely, ranging from less than 50 tests per year to more than 500 tests per year.

2.4.2 Management/treatment

The symptoms of BAD are most often controlled with BAS medication. Bile acid sequestrants bind to bile acids in the small bowel and prevent them from irritating the colon and may also slow transit time. The treatment may be long-term.

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 BAD is currently off-label (NICE Evidence summary ESUOM22 "Bile acid malabsorption: colesevelam".[11] 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 or weight loss. Increases in dose, addition of anti-diarrhoea medication or changes in diet may also be needed to achieve adequate symptom control. Long-term use of colestyramine has been associated with reduced vitamin and folate levels.[12] However, one to two years of colestipol use has been reported to have no effect on vitamin A or folic acid and only a small effect on vitamin D levels.[12] Colesevelam was not associated with significant reductions in the absorption of vitamins A, D, E or K in studies of up to one year.[12] Guidelines made no recommendation about routine monitoring of fat soluble vitamins during long-term BAS therapy, whilst noting that that approved product labels recommend supplementation of vitamins A, D and K only if deficiency occurs.[12]

In current practice, in some UK secondary care settings, BAS treatment of BAD is started without a diagnostic test being performed (trial of treatment). The estimated time taken to ascertain the

effectiveness of trial of treatment was between 4 and 12 weeks (clinical opinion of specialist committee members).

3. ASSESSMENT OF CLINICAL EFFECTIVENESS

Systematic review methods followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care,[13] NICE Diagnostics Assessment Programme manual[14] and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[15] Data extraction tables for studies included in our previous Diagnostic Assessment Report (DAR),[16] conducted to support the development of DG7,[1] were used as a starting point for this report.

3.1 Systematic review methods

3.1.1 Search strategy

Search strategies utilised in the original report were updated in line with the NICE final scope.[17] Search strategies were 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.[13, 15, 18, 19]

Searches were undertaken to identify studies of SeHCAT in the diagnosis of bile acid diarrhoea (BAD). The search strategies combined relevant search terms comprising indexed keywords (e.g. Medical Subject Headings [MeSH] and EMTREE) and free text terms, strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Only studies conducted in humans were sought. Searches were not limited by language or publication status (unpublished or published). The original 2011 strategies were adapted to incorporate changes to the preferred terminology and search methods for each resource. Due to the time elapsed some resources were no longer available, but additional resources have been searched to maintain completeness.

Searches for studies on economic evaluations, costs and quality of life were also conducted (see Section 4.1 for further detail). To ensure no relevant studies were missed, these results of the clinical effectiveness searches were also screened for records relevant to the cost effectiveness evaluation and all cost effectiveness results, including guidelines searches, were screened for studies relevant to the clinical effectiveness section.

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

- MEDLINE (Ovid) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily: 1946- 2020/11/30
- EMBASE (Ovid): 1974-2020/11/25
- Cochrane Database of Systematic Reviews (CDSR) (Wiley): up to 2020/11/Iss11

- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): up to 2020/11/Iss11
- Database of Abstracts of Reviews of Effects (DARE) (CRD): up to 2015/03
- Health Technology Assessment Database (HTA) (CRD): up to 2018/03
- Science Citation Index (SCI) (Web of Science): up to 2020/11/27
- KSR Evidence (Internet) (https://ksrevidence.com/): up to 2020/12/01
- LILACS (Latin American and Caribbean Health Sciences Literature) (Internet) http://regional.bvsalud.org/php/index.php?lang=en: up to 2020/11/27
- NIHR Health Technology Assessment Programme (Internet): up to 2020/11/26
- PROSPERO (International Prospective Register of Systematic Reviews) (Internet) http://www.crd.york.ac.uk/prospero/: up to 2020/11/26

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

- NIH ClinicalTrials.gov (http://www.clinicaltrials.gov/): up to 2020/11/26
- WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/): up to 2020/12/02
- EU Clinical Trials Register (EUCTR) (https://www.clinicaltrialsregister.eu/ctr-search/): up to 2020/12/02

Conference abstracts and proceedings were identified in a three-stage approach, conducted as follows:

- The main Ovid Embase search strategy was employed to include conference abstracts and proceedings.
- A second set of tailored searches was conducted on:
    - Northern Light Life Sciences Conference Abstracts (Ovid): 2010-2020/12/ Wk46
    - Conference Proceedings Citation Index - Science (CPCI-S) (Web of Science): 1990-2020/11/30
- In addition, the 2020 UEG Week proceedings (not currently covered by Embase, Northern Light or CPCI-S) were searched manually.

Additional searches

An additional targeted search for trial of treatment in IBS/Crohn's using bile acid sequestrants was performed on the following databases:

- MEDLINE (Ovid) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily: 1946- 2021/02/17

- EMBASE (Ovid): 1974-2021/02/17

This additional search was conducted with the primary aim of identifying additional studies to inform the cost effectiveness modelling; search results were screened as part of the main clinical effectiveness searches.

All Identified references were downloaded in Endnote X20 software for further assessment and handling. These references were imported into the existing project library and deduplicated against the 2011 search results. All search results (both clinical effectiveness and economics) were screened for all areas of interest. Rigorous records were maintained as part of the searching process. Individual records within the Endnote reference library were tagged with search information, including the name of the searcher, date searched, database name and host, strategy name and iteration.

The main Embase search strategy for each set of searches was independently peer reviewed by a second Information Specialist, using the PRESS-EBC checklist.[20, 21] References in retrieved articles were checked for additional studies. Full search strategies are provided in Appendix 1.

3.1.2 Inclusion and exclusion criteria

Participants

Study populations eligible for inclusion were:

Adults (age ≥18 years) referred to a gastroenterology clinic for investigation and diagnosis of possible BAD, who had previously undergone primary clinical assessment/investigations (as recommended in the BSG guidelines[2]) 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, studies which did not fully report prior investigations, or where prior investigations do not match those specified above, have been included; full details of prior investigations (where reported) are provided in Appendix 2.

As detailed above, this assessment focused on two specific populations:

1. Adults presenting with chronic diarrhoea with unknown cause or FD, or suspected or diagnosed IBS-D (i.e. people with suspected primary BAD)

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

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 were:

- No SeHCAT testing and no treatment with BAS
- No SeHCAT testing and trial of treatment with BAS

Outcomes
Studies reporting any of the following outcomes were included:

- 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 the test (SeHCAT) result to predict clinical outcome (i.e. response to treatment)
- Predictive accuracy - sensitivity and specificity of the SeHCAT test for the prediction of treatment response
- 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 (HRQoL)

Study design
The following types of study were eligible for inclusion:

- Randomised controlled trials (RCTS), non-randomised controlled clinical trials (CCTs), or observational comparative studies where clinical or treatment planning outcomes are compared in patients who received SeHCAT testing vs. those who did not

- RCTs, CCTs, or observational comparative studies, where all patients receive SeHCAT testing and clinical outcomes were compared between treatment decisions based on different definitions of a positive SeHCAT result (different diagnostic thresholds)
- 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 BAS 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.])
- Predictive accuracy studies, which report sufficient data to support the calculation of the sensitivity and specificity of SeHCAT to predict response to treatment with BAS (i.e. studies which report the outcome of treatment with BAS 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 were eligible for inclusion.

No new studies, of the higher-level study designs described above, we identified. Therefore, studies which reported treatment outcome only for those participants with a positive SeHCAT result (i.e. sufficient data to calculate positive predictive value [PPV] only) were included.

Studies which were included in our previous Diagnostic Assessment Report (DAR),[16] conducted to support the development of DG7,[1] and which met the above inclusion criteria, were also included in this review.

Exclusion criteria
The following study/publication types were 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

3.1.3 Inclusion screening and data extraction

Two reviewers (MW and ER or GW) independently screened the titles and abstracts of all reports identified by searches and any discrepancies were discussed and resolved by consensus. Full copies of all studies deemed potentially relevant were obtained and the same two reviewers independently assessed these for inclusion; any disagreements were resolved by consensus. Details of studies excluded at the full paper screening stage are presented in Appendix 4.

Studies cited in materials provided by the manufacturer of the SeHCAT test (GE Healthcare Limited) were first checked against the project reference database, in Endnote X20; any studies not already identified by our searches were screened for inclusion following the process described above.

Where available/applicable, data were extracted on the following: study design/details, participant characteristics, 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 BAD (e.g. BAS used and dosing regimen, and any concomitant treatments such as diet or loperamide), any information about intolerance to or discontinuation of BAS, and the definition of response to treatment including duration of follow-up, outcomes (as defined in section 4.1). Data were extracted by one reviewer (MW and ER), using data extraction forms based on those used for the original systematic review[16] conducted to support the development of DG7.[1] A second reviewer (MW and ER) checked data extraction and any disagreements were resolved by consensus or discussion with a third reviewer (NA). Full data extraction tables are provided in Appendix 2.

3.1.4 Quality assessment

The methodological quality of included diagnostic accuracy studies was assessed using QUADAS-2.[22] The methodological quality of observational studies, which reported treatment outcome only for those participants with a positive SeHCAT result, was assessed using a topic-specific adaptation of the quality assessment checklist by Wedlake et al (2009),[23] as used in our previous Diagnostic Assessment Report (DAR),[16] conducted to support the development of DG7;[1] the use of this tool was carried forward to the current assessment in order to provide consistency. The results of the quality assessment are used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to inform recommendations for design of future studies. Quality assessment was undertaken by one reviewer and checked by a second reviewer (MW and ER), any disagreements were resolved by consensus or discussion with a third reviewer (NA).

The results of the quality assessments are summarised and presented in tables (Section 3.2.2) and, for QUADAS-2 assessments, are presented in full, by study, in Appendix 3.

3.1.5 Methods of analysis/synthesis

Meta-analysis was considered inappropriate, due to the small number of test accuracy studies with varying diagnostic thresholds and between study heterogeneity with respect to population (prior investigations), treatment regimen, definition of response, follow-up period, and SeHCAT administration); we therefore employed a narrative synthesis. The clinical effectiveness results section of this report is structured by clinical application (diagnosis of primary BAD and diagnosis of secondary BAD 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 is also provided, together with a description of how this may have affected the individual study results.

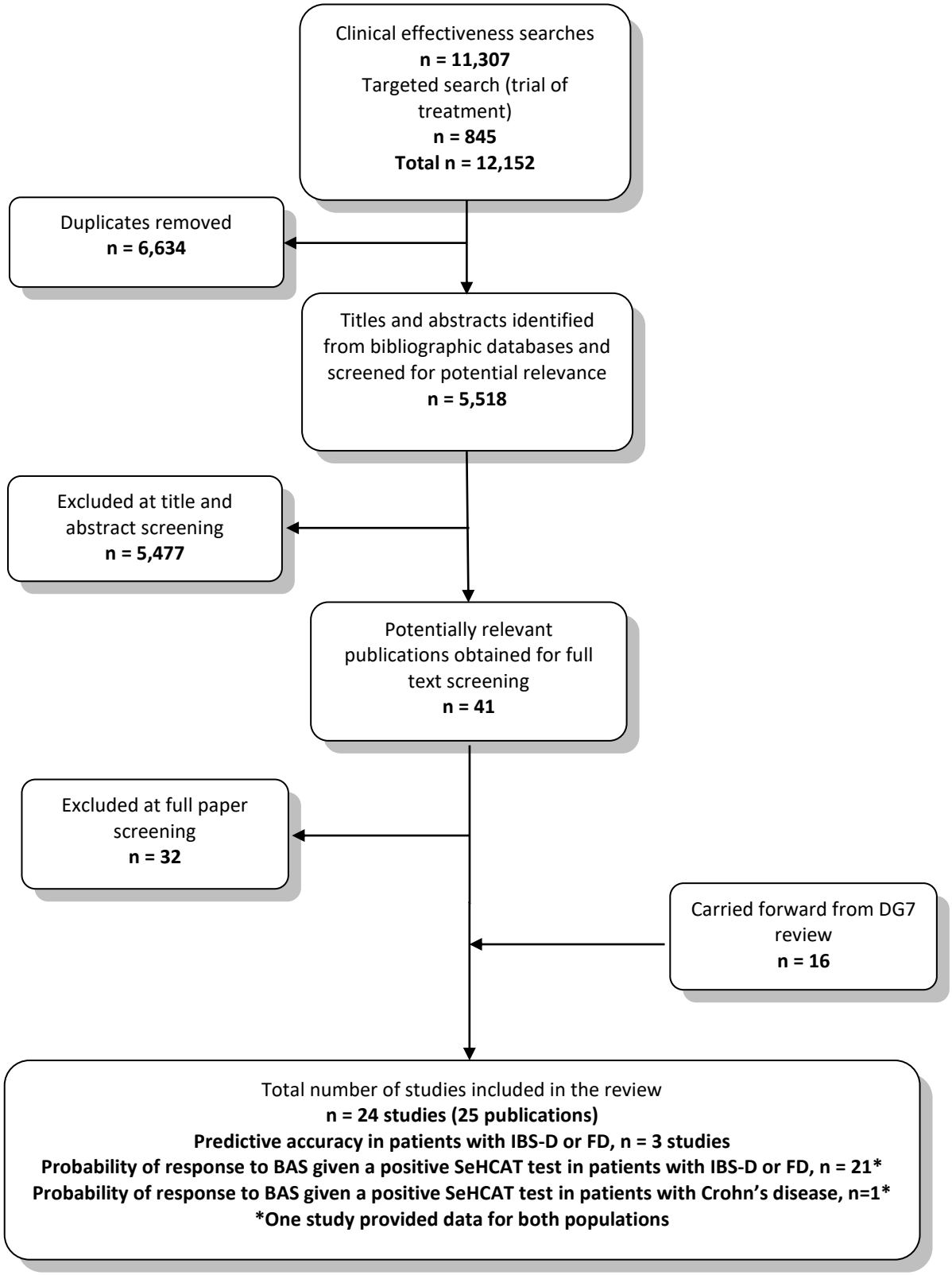
For predictive accuracy studies (studies which reported sufficient data to support the calculation of the sensitivity and specificity of SeHCAT to predict response to treatment with BAS), the absolute numbers of true positive, false negative, false positive and true negative test results of SeHCAT compared to the reference standard of treatment response, as well as sensitivity and specificity values, with 95% confidence intervals (CIs) are presented in Table 4. The results of individual studies were plotted in the receiver operating characteristic (ROC) plane, with the diagnostic threshold used for the SeHCAT test indicated (Figure 2).

The results of studies which reported treatment outcome only for those participants with a positive SeHCAT result (i.e. sufficient data to calculate PPV only) are presented in Table 5.

3.2 Results of the assessment of clinical effectiveness assessment

The literature searches of bibliographic databases conducted for this update identified 5,518 new references. After initial screening of titles and abstracts, 41 references were considered to be potentially relevant and ordered for full paper screening; of these nine publications were included in the review.[24-32] In addition 16 publications, taken from the assessment report conducted for DG7,[16] were carried forward and included in this review.[6, 33-47] All potentially relevant studies cited in documents supplied by the test manufacturer, GE Healthcare Limited, had already been identified by bibliographic database searches. Figure 1 shows the flow of studies through the review process. Appendix 4 provides details, with reasons for exclusion, of all publications excluded at the full paper screening stage. Six publications,[48-53] which were included in our previous systematic review,[16] did not meet the inclusion criteria for this systematic review and are listed in Appendix 4; in all cases this was because studies included participants with a variety of clinical presentations and did not report separate data for either of the two populations specified in the inclusion criteria for this assessment (section 3.1.2).

Figure 1: Flow of studies through the review process



3.2.1 Overview of included studies

Based on the update searches and inclusion screening described above and information taken from the assessment report conducted for DG7,[16] a total of 24 studies,[6, 24-34, 36-47] reported in 25 publications,[6, 24-47] were included in this review; the results section of this report cites studies using the primary publication only.

Fifteen of the included studies were published, in full, in peer-reviewed journals,[6, 29, 33, 34, 36-44, 46, 47] eight were published as conference abstracts only,[24-28, 30-32] and one was an unpublished dissertation.[45] It should be noted that all eight studies that were published as conference abstracts only were new studies, identified for this assessment, i.e. the majority of the new evidence identified (8/9 studies) was not published, in full, in peer-reviewed journals.

No RCTs, CCTs or observational comparative studies, which met the inclusion criteria for this review (see Section 3.1.2) were identified. Similarly, no multi-variable regression modelling, with response to treatment with BAS as the dependent variable and index test (SeHCAT) result (continuous or categorical) considered as one of the independent variables, were identified. Finally, no new predictive accuracy studies, (studies which reported sufficient data to support the calculation of the sensitivity and specificity of SeHCAT to predict response to treatment with BAS,) were identified. All of the nine new studies included in this review[24-32] were of the lowest level of evidence eligible for inclusion; these were observational studies which report some outcome data for patients treated with BAS, where only those patients with a positive SeHCAT test were offered treatment with BAS.

All 24 included studies provided some data about population one: Adults presenting with chronic diarrhoea with unknown cause, or FD, or suspected or diagnosed IBS-D (i.e. people with suspected primary BAD). Three of these studies,[39, 42, 43] all of which were previously included in the assessment report conducted for DG7,[16] provided limited predictive accuracy data for this population. The remaining 21 studies only reported information about the outcome of treatment with BAS for some or all of those participants who had a positive SeHCAT result.[6, 24-34, 36-38, 40-42, 45-47]

One study[6] also provided data on population two: Adults presenting with chronic diarrhoea and a diagnosis of Crohn's disease, who have not undergone ileal resection (i.e. people with suspected secondary BAD). This study only reported information about the outcome of treatment with BAS for people with Crohn's disease who had a positive SeHCAT result, and had previously included in the assessment report conducted for DG7.[16] No new studies, meeting the inclusion criteria for population two, were identified for this assessment report.

All 21 studies, for which information on geographic location was reported, were conducted in Europe; 10 were conducted in the UK,[6, 26-29, 39, 44, 45, 47] five in Italy,[24, 32, 38, 42, 43] three in Spain,[36, 37, 40] two in Denmark,[33, 46] and one each in Sweden[41] and France.[34]

Only three of the included studies provided any information about funding and only one UK study [39] reported receipt of any industry funding (SeHCAT test supplies provided by Amersham International); details of all reported funding sources are provided in Table 1.

Further details of the characteristics of study participants and the technical details of the conduct of the index test (SeHCAT) and reference standard (BAS treatment regimen) are provided in Appendix 2.

Table 1: Overview of included studies

Study ID	Study details	Objective	FD	IBS-D	Crohn's Disease	Study design and outcome extracted
Bellini 2020[24]	Prospective study of 70 consecutive patients with IBS-D or FD Conference abstract Single Centre, tertiary care gastroenterology Country: Italy Funded by: NR	To determine the prevalence of BAM among IBS-D and FD patients referred to a tertiary gastroenterological centre in Italy, to explore the possible correlation between BAM severity, symptom severity and quality of life, and to explore whether the response to colestyramine could be related to BAM severity.	✓	✓		Cohort Response to BAS given a positive test result.
Borghede 2011[$33]	Retrospective study in 298 patients Full paper Groups: Group 1: Crohn's disease, small bowel resection or radiation injury (n=87) Group 2: Diarrhoea unknown cause (n=114) Group 3: Diarrhoea other known cause (n=97) Single centre Country: Denmark Funded by: NR	To investigate the frequency of BAM and treatment responses to colestyramine with 75SeHCAT scanning among patients suffering from chronic watery diarrhoea.	✓			Cohort Response to BAS given a positive test result.

Study ID	Study details	Objective	FD	IBS-D	Crohn's Disease	Study design and outcome extracted
Farmer 2017[25]	Prospective study of 207 consecutive patients with IBS-D, according to the Rome III criteria (November 2014 to May 2016), or Rome IV criteria (May 2016 to November 2016). Conference abstract Single centre, secondary care Country: NR Funded by: NR	To compare rates of the BAM in Rome III and Rome IV defined patients with IBS-D.		✓		Cohort Response to BAS given a positive test result.
Fellous 1994[$34]	Prospective study in 129 patients (23 healthy volunteers and 106 patients with chronic diarrhoea). Full paper Patient groups: Group 1: Patients with diarrhoea and ileal involvement (n=33) Group 2: Patients with organic diarrhoea, without ileal involvement (n=20) Group 3: Patients with FD (n=53). Single centre Country: France Funded by: NR	To determine the performance and the clinical significance of a simplified version of 75 SeHCAT test which measures ileal absorption of bile salt.	✓			Cohort Response to BAS given a positive test result.

Study ID	Study details	Objective	FD	IBS-D	Crohn's Disease	Study design and outcome extracted
Fernandez-Banares 2001[$36] related publication[35]	Prospective study in 83 patients. Full paper Groups: Group 1: Patients with microscopic colitis (n=51). 40 were consecutive patients newly diagnosed between January 1996 and June 1998. 11 had already diagnosed but had persistent diarrhoea in spite of treatment with either mesalazine (500 mg three times a day; 9 patients) or mesalazine plus oral prednisone (1 mg/kg/day; 2 patients). Group 2: Patients with unexplained chronic FD. 32 consecutive patients were prospectively included between 1996 and 1999. All had unexplained watery diarrhoea. Single centre Country: Spain Funded by: Grant of the 'Fondo de Investigaciones Sanitarias', Ministry of Health, Spain.	To prospectively assess the frequency and severity of BAM in patients with collagenous colitis and lymphocytic colitis as well as in patients unexplained chronic FD. To evaluate if BAM might be related to the severity of histological changes in microscopic colitis. 3) To investigate the potential therapeutic benefit of colestyramine in microscopic colitis patients with or without BAM and in patients with previously unexplained chronic diarrhoea and BAM.	✓			Cohort Response to BAS given a positive test result.
Fernandez-Banares 2007[$37]	Prospective study in 62 consecutive patients with chronic watery diarrhoea of previously unexplained origin, fulfilling Rome II criteria of functional disease. Full paper	To assess prospectively the presence of gluten-sensitive enteropathy, BAM, and sugar malabsorption in consecutive patients with chronic watery	✓	✓		Cohort Response to BAS given a positive test result.

Study ID	Study details	Objective	FD	IBS-D	Crohn's Disease	Study design and outcome extracted
	Single centre Country: Spain Funded by: Grant of the 'Fundacio Banc de Sabadell (Barcelona, Spain)'	diarrhoea of obscure origin fulfilling Rome II criteria of functional disease. To evaluate the long-term response to specific therapy.				
Galatola 1992[$38]	Prospective study of 98 consecutive patients with IBS-D Full paper Multicentre, four secondary care gastroenterology departments Country: Italy Funded by: NR	To assess the prevalence of BAM and the efficacy of colestyramine therapy in improving symptoms associated with this condition in patients with IBS-D		✓		Cohort Response to BAS given a positive test result.
Holmes 2012[26]	Retrospective review of SeHCAT studies performed on 55 patients, for 44 of whom notes were available. Conference abstract Groups for 28 patients with BAM (positive SeHCAT test) and available notes: Type 1 BAM: terminal ileal disease/resection or bypass (n=10) Type 2 BAM: primary or idiopathic, characterised by lack of discernible change in ileal histology or obvious clinical history or pathology to account	Unclear	✓			Retrospective chart review Response to BAS given a positive test result.

Study ID	Study details	Objective	FD	IBS-D	Crohn's Disease	Study design and outcome extracted
	for the malabsorption (n=8) Type 3 BAM: all other causes, including gastric surgery, pancreatitis, cholecystectomy or associated with microscopic colitis, coeliac disease, diabetes and small bowel bacterial overgrowth (n=10) Single centre Country: UK Funded by: NR					
Kumar 2013[28]	Retrospective review of 88 consecutive patients referred for SeHCAT testing. Conference abstract Groups: Group 1: Ileal disease/resection (n=18) Group 2: Idiopathic (n= 57) Group 3: Secondary to other gastrointestinal disease (n=13) Single centre Country: UK Funded by: NR	To audit sequential patients referred for SeHCAT testing, in order to assess diagnostic value.	✓	✓		Retrospective review Response to BAS given a positive test result.
Kumar 2020[27]	Prospective study of 51 patients who had undergone SeHCAT testing for the investigation of chronic diarrhoea.	To investigate whether quality of life improves, with use of BAS, in patients diagnosed with	✓	✓		Cohort Response to BAS given a positive

Study ID	Study details	Objective	FD	IBS-D	Crohn's Disease	Study design and outcome extracted
	Conference abstract Groups: Group 1: IBS-D, SeHCAT negative and all diarrhoea investigations negative (n=18) Group 2: Idiopathic BAD, SeHCAT positive (n=20) Group 3: Post-cholecystectomy, SeHCAT positive (n=8) Group 4: Post-terminal ileal resection for Crohn's disease, SeHCAT positive (n=5) Number of centres: NR Country: UK Funded by: NR	BAD.				test result.
Lin 2016[29]	Retrospective review of all patients (n=515) referred for SeHCAT testing, between 2001 and 2012. Full paper* Groups for 58 patients with BAM (positive SeHCAT test), who were contactable at follow-up: Type 1 BAM: ileal disease including resections (n=11) Type 2 BAM: idiopathic (n=29) Type 3 BAM: other pathological causes (n=18)	To evaluate the natural history of BAD by examining individuals diagnosed with BAD and determining the use of and response to bile-acid sequestrants BAS.	✓	✓		Retrospective review Response to BAS given a positive test result.

Study ID	Study details	Objective	FD	IBS-D	Crohn's Disease	Study design and outcome extracted
	Single centre Country: UK Funded by: NR					
Merrick 1985[$39]	Prospective study in 106 patients and 63 controls. Full paper Groups: Group 1: Normal controls (n=63) Group 2: Previous small bowel resection (n=26) Group 3: Previous vagotomy or surgery for peptic ulcer (n=29) Group 4: Chronic diarrhoea of non-inflammatory origin (n=51), (43 IBS, 2 coeliac disease, 2 small bowel ischaemia, and 4 other miscellaneous conditions) Single centre Country: UK (Scotland) Funded by Amersham International (supplies of SeHCAT).	To assess the value of measuring absorption of SeHCAT as a test for the presence of BAM.		✓		Cohort Accuracy to predict BAM (defined as response to BAS) and response to BAS in SeHCAT +ve and SeHCAT –ve groups separately.
Notta 2011[$†40]	Prospective study of 37 patients with diarrhoea syndrome (within one month of diagnosis), referred for SeHCAT testing between May 2009 and February 2010.	To evaluate the utility of the quantification of abdominal retention of SeHCAT as a first-line diagnostic test in the early	✓			Cohort Response to BAS given a positive test result.

Study ID	Study details	Objective	FD	IBS-D	Crohn's Disease	Study design and outcome extracted
	Full paper Single centre Country: Spain Funded by: NR	pathophysiological diagnosis of patients with chronic diarrhoea.				
Notta 2014[†30]	Prospective study of 78 patients with chronic FD. Conference abstract Number of centres: NR Country: NR Funded by: NR	To evaluate the utility of SeHCAT testing to diagnose BAM and to assess the prevalence of BAM in patients with chronic FD.	✓			Cohort Response to BAS given a positive test result.
Notta 2017[†31]	Prospective study of 92 patients with chronic FD. Conference abstract Number of centres: NR Country: NR Funded by: NR	To evaluate the utility of SeHCAT testing to diagnose BAM and to assess the prevalence of BAM in patients with chronic FD.	✓			Cohort Response to BAS given a positive test result.
Rudberg 1996[$41]	Prospective study of 20 consecutive patients with chronic or recurrent diarrhoea of unknown cause Full paper Single centre Country: Sweden Funded by: NR	To investigate the usefulness of SeHCAT in patients suffering from FD and to document earlier radiological investigations performed in course of disease.	✓			Cohort Response to BAS given a positive test result.
Sciaretta 1986[$42]	Prospective study of 23 healthy volunteers and 66 patients with ileal dysfunction or diarrhoea	To evaluate the diagnostic accuracy, sensitivity, and	✓			Cohort Accuracy to

Study ID	Study details	Objective	FD	IBS-D	Crohn's Disease	Study design and outcome extracted
	Full paper Groups: Group A: Healthy volunteers with frequency of bowel movements between 2 per. Day and 3 per. week, no pathological changes in body weight and normal diet (n=23) Group B: Patients with resected or pathological distal ileum (n=36) Group C: Patients with intestinal pathology, but normal distal ileum (n=17) Group D: Patients with chronic or recurrent diarrhoea of unknown cause and >6 months duration (n=13) Single centre Country: Italy Funded by: NR	specificity of the 75SeHCAT test				predict BAM (defined as response to BAS) and response to BAS in SeHCAT +ve and SeHCAT -ve groups separately.
Sciaretta 1987[$43]	Prospective study of 23 healthy volunteers and 46 patients with chronic or recurrent diarrhoea (38 IBS-D and 8 post-cholecystectomy) Full paper Single centre Country: Italy Funded by: NR	To evaluate whether BAM, assessed by the SeHCAT test, had a pathogenetic role in functional chronic diarrhoea and to ascertain whether the small bowel transit time (SBTT) could be correlated with the 75SeHCAT test results.		✓		Cohort Accuracy to predict BAM (defined as response to BAS) and response to BAS in SeHCAT +ve and SeHCAT –ve

Study ID	Study details	Objective	FD	IBS-D	Crohn's Disease	Study design and outcome extracted
						groups separately.
Sinha 1998[$44]	Retrospective study of all patients referred to the department with chronic diarrhoea over a 2-year period, in whom BAM was considered and SeHCAT testing undertaken, based on a history suggestive of IBS-D (Manning criteria) and no other obvious cause of diarrhoea (n=17). Full paper Single centre Country: UK Funded by: NR	To identify patients with idiopathic BAM, to describe their clinical features, both qualitatively and quantitatively, and to assess their response to colestyramine treatment.		✓		Cohort Response to BAS given a positive test result.
Smith 2000[$6]	Retrospective study of 304 patients who had received a SeHCAT test for the investigation of chronic continuous or recurrent diarrhoea. Full paper Groups: Group 1: Crohn's disease with ileal resection, in clinical remission (n=37) Group 2: Crohn's disease, un-operated and in clinical remission (n=44) Group 3: vagotomy and pyloroplasty, with or	To investigate BAM and its response to treatment in patients seen in a district general hospital with chronic continuous or recurrent diarrhoea.		✓	✓	Cohort Response to BAS given a positive test result.

Study ID	Study details	Objective	FD	IBS-D	Crohn's Disease	Study design and outcome extracted
	without cholecystectomy (n=26) Group 4: IBS-D (n=197) Single centre, secondary care Country: UK Funded by: NR					
Tunney 2011[$45]	Retrospective study of 276 patients who underwent SeHCAT scanning for the investigation of chronic diarrhoea, between April 2005 and January 2011, of whom 136 had no known risk factors. Un-published dissertation Single centre Country: UK Funded by: NR	To assess the utility of the British Society of Gastroenterology guidelines for the investigation of chronic diarrhoea, focusing on whether or not SeHCAT should be prioritised in the investigation of chronic diarrhoea, rather than considered as a second-line option.	✓			Cohort Response to BAS given a positive test result.
Wildt 2003[$46]	Retrospective study of 135 patients who underwent SeHCAT scanning for the investigation of chronic diarrhoea of unknown cause, during a 5-year period (1997–2001). Groups, excluding 2 patients who were lost to follow-up (n=133): Group 1: Possible type 1 BAM, Crohn's disease with or without resection, ileocaecal resection, radiation enteropathy (n=13)	To evaluate the usefulness of SeHCAT testing by assessing the extent of BAM and describing the clinical characteristics in a group of patients with chronic diarrhoea. Clinical outcome after treatment with colestyramine was also evaluated.	✓			Cohort Response to BAS given a positive test result.

Study ID	Study details	Objective	FD	IBS-D	Crohn's Disease	Study design and outcome extracted
	Group 2: Possible type 2 BAM, idiopathic (n=56) Group 3: Possible type 3 BAM, other pathological causes including previous cholecystectomy (n=64) Full paper Single centre Country: Denmark Funded by: NR					
Williams 1991[$47]	Retrospective study in 181 patients referred for measurement of ^{75}SeHCAT retention because of unexplained diarrhoea between 1982 and 1989. Full paper Single centre Country: UK (Scotland) Funded by: NR	To determine the clinical characteristics of patients with idiopathic BAM and to identify their response to treatment.	✓			Cohort Response to BAS given a positive test result.
Zanoni 2018[32]	Retrospective review of 12 patients who underwent SeHCAT between November 2017 and April 2018 due to chronic diarrhoea without a known cause (n=3 patients) or IBS-D not responding to standard medications (n=9 patients). Conference abstract Single centre	To present preliminary experience with the use of SeHCAT test.	✓	✓		Cohort Response to BAS given a positive test result.

Study ID	Study details	Objective	FD	IBS-D	Crohn's Disease	Study design and outcome extracted
	Country: Italy Funded by: NR					

[$]Study taken from previous Diagnostic Assessment Report[16]

[*]Additional information provided by the study authors

[†]Possible overlapping study populations

BAM: bile acid malabsorption; BAS: bile acid sequestrants; FD: functional diarrhoea; IBS: irritable bowel syndrome; IBS-D: diarrhoea predominant irritable bowel syndrome; NR: not reported; SeHCAT: [^{75}Selenium] tauroselcholic acid

3.2.2 Study quality

The three studies,[39, 42, 43] all of which were previously included in the assessment report conducted for DG7,[16] which provided predictive accuracy data (information on the ability of the SeHCAT test to predict response to treatment with BAS) were assessed using the QUADAS-2 tool.

The included predictive accuracy studies were all published more than 30 years ago and were generally poorly reported; all three studies were rated as 'unclear' risk of bias with respect to patient selection and reference standard (no study provided details of whether the assessment of response to treatment was conducted blind to the results of SeHCAT testing), and two of the three studies[42, 43] were also rated as 'unclear' risk of bias with respect to flow and timing because the duration of follow-up, over which response to treatment was assessed was not reported. Merrick et al. (1985)[39] was rated 'high' risk of bias for the 'flow and timing' domain of QUADAS-2 because only patients with positive or equivocal SeHCAT test results received the reference standard (treatment with BAS); patients with a negative SeHCAT test result were managed with unspecified 'simple conservative treatment'. Sciaretta et al. (1986)[42] was rated 'high' risk of bias for the 'index test' domain of QUADAS-2 because the threshold used to define a positive SeHCAT test result was not pre-specified.

All three studies had at least one item of 'high' concern regarding applicability to this assessment. In some instances, the applicability issues identified are a consequence of the age of the studies. All three studies were rated as having 'high' or 'unclear' concerns regarding the applicability of the study population to that specified in the inclusion criteria for this review; all three studies included some participants with prior cholecystectomy and no study reported previous investigations equivalent to those specified in current BSG guidelines for the investigation of chronic diarrhoea.[2] All three studies were also rated as having 'high' concerns regarding the applicability of the index test; the age of the studies meant that no study used the current version of the SeHCAT test, manufactured by GE Healthcare Ltd., specified in the inclusion criteria for this assessment. Merrick et al. (1985)[39] was also rated as having 'high' concerns regarding the applicability of the reference standard, because the management of patients with a negative SeHCAT test was not considered likely to provide a reliable indication of whether or not these patients would have responded to treatment with BAS.

The results of the QUADAS-2 assessment are summarised in Table 2 and the full assessments are provided in Appendix 3.

Table 2: QUADAS-2 results for studies of the accuracy of SeHCAT for the assessment of treatment response

Study ID	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Study population	Index test	Reference standard
Merrick 1985[39]	?	☺	?	☹	?	☹	☹
Sciaretta 1986[42]	?	☹	?	?	☹	☹	☺
Sciaretta 1987[43]	?	☺	?	?	☹	☹	☺

☺Low Risk ☹High Risk ? Unclear Risk

The methodological quality of studies which reported treatment outcome only for those participants with a positive SeHCAT result (i.e. sufficient data to calculate PPV only) was assessed using a topic-specific adaptation of the quality assessment checklist by Wedlake et al. (2009)[23] as used in our previous diagnostic assessment report (DAR).[16] The results of this assessment are summarised in Table 3. These studies represent the lowest level of evidence specified in the inclusion criteria for this assessment (Section 3.1.2) and were generally of poor methodological quality. No study, in this group provided full outcomes data for patients with a negative SeHCAT test result. Ten[6, 26, 28, 29, 32, 33, 44-47] of the 21 studies[6, 24-34, 36-38, 40, 41, 44-47] of this type used a retrospective study design. Eleven studies provided no clear definition of chronic diarrhoea.[6, 24, 26-28, 30-33, 40, 45] Ten studies did not provide sufficient information about the SeHCAT test used to allow the testing procedure to be reproduced.[24-28, 30-32, 44, 46] Eight studies did not clearly describe how the decision to treat patients with BAS was made.[26, 28, 32-34, 41, 45, 47] Nine studies provided no or an incomplete description of the BAS treatment provided to patients with a positive SeHCAT test result.[26-28, 32-34, 40, 45, 47] Finally, six studies did not report an objective measure of response to treatment.[24, 26, 28, 29, 32, 45]

Table 3: Quality assessment results for observational studies reporting treatment outcome for patients with a positive SeHCAT test result

	Q1-prospective	Q2-diarrhoea	Q3-known cause	Q4-SeHCAT test	Q5-Cut-off	Q6-Reason treatment	Q7-Negative test	Q8-Treatment	Q9-Response
Bellini 2020[24]	P	N	N	N	Y	Y	N	Y	N
Borghede 2011[$33]	R	N	N (114) Y (184)	Y	Y	N	N	N	Y
Farmer 2017[25]	P	Y	N	N	Y	Y	N	N	Y
Fellous 1994[$34]	P	Y	N (36) Y (53)	Y	Y	N	Y-some	Y	Y
Fernandez-Banares 2001[$36]	P	Y	N	Y	Y	Y	N	Y	Y
Fernandez-Banares 2007[$37]	P	Y	N	Y	Y	Y	N	Y	Y
Galatola 1992[$38]	P	Y	N	Y	Y	Y	N	Y	Y
Holmes 2012[26]	R	N	N (8) Y (20)	N	Y	N	N	N	N
Kumar 2013[28]	R	N	N (57) Y (21)	N	Y	N	Y-some	N	N
Kumar 2020[27]	P	N	N (20) Y (31)	N	N	Y	N	N	Y
Lin 2016[29]	R	Y	N (29) Y (29)	Y	Y	Y	N	Y	N
Notta 2011[$40]	P	N	Unclear	Y	Y	Y	N	N	Y
Notta 2014[30]	P	N	N	N	Y	Y	N	Y	Y
Notta 2017[31]	P	N	N	N	Y	Y	N	Y	Y
Rudberg 1996[$41]	P	Y	N	Y	Y	N	N	Y	Y

	Q1-prospective	Q2-diarrhoea	Q3-known cause	Q4-SeHCAT test	Q5-Cut-off	Q6-Reason treatment	Q7-Negative test	Q8-Treatment	Q9-Response
Sinha 1998[$44]	R	Y	N	N	Y	Y	N	Y	Y
Smith 2000[$6]	R	N	N (241) Y (63)	Y	Y	Y	N	Y	Y
Tunney 2011[$45]	R	N	N (136) Y (140)	Y	Y	N	N	N	N
Wildt 2003[$46]	R	Y	N (56) Y (77)	N	Y	Y	N	Y	Y
Williams 1991[$47]	R	Y	N	Y	Y	N	N	N	Y
Zanoni 2018[32]	R	N	N (3) Y (9)	N	Y	N	Unclear	N	N

[$]Study taken from previous Diagnostic Assessment Report[16]

1: Does the study have a retrospective 'r' or prospective 'p' study design? (R/P/Unclear)
2: Has a clear definition of diarrhoea in the presenting population been given or a validated tool for assessing chronic diarrhoea been used? (Y/N)
3: Does the population include people with known causes of chronic diarrhoea? (Y/N/Unclear)
4: Has an adequate description of the SeHCAT test procedures been provided? (Y/N)
5: Are the cut-off values used for establishing severity of BAM clearly reported? (Y/N)
6: Are the reason for treating people clearly described (e.g. 'all with a positive test') (Y/N)
7: Are data provided for people with a negative SeHCAT test (>15%)? (Y-all/Y-some/N/Unclear)
8: Is the treatment clearly described, including dose and duration of treatment and follow-up? (Y/N)
9: Has an objective measure of response to treatment been provided? (Y/N)

3.2.3 Performance of the SeHCAT test for predicting response to treatment with BAS in patients with IBS-D or FD

All 24 included studies provided some data about population one: Adults presenting with chronic diarrhoea with unknown cause, suspected or diagnosed IBS-D or functional diarrhoea (i.e. people with suspected primary BAD).[6, 24-34, 36-47]

Three of these studies,[39, 42, 43] all of which were previously included in the assessment report conducted for DG7,[16] provided limited data on the accuracy of the SeHCAT test for predicting response to treatment with BAS, in this population. The results of these studies are summarised in Table 4. All three studies assessed the relationship between the SeHCAT test result and response to treatment with colestyramine.

Merrick et al. (1985)[39] reported sufficient data to allow the calculation of the performance of SeHCAT, for predicting treatment response, at two seven-day-retention thresholds (<8% and ≤15%). The estimated sensitivity of SeHCAT in predicting a positive response to treatment with colestyramine was 66.7% (95% CI: 22.3 to 95.7%), using the <8% threshold, and 100% (95% CI: 54.1 to 100%), using the ≤15% threshold. The corresponding specificity estimates were 97.1% (95% CI: 84.7 to 99.9%) and 91.2% (95% CI: 76.3 to 98.1%), respectively.[39] These results would appear to indicate that the use of the SeHCAT test with a threshold of seven-day retention ≤15% (commonly used in UK clinical practice) could identify patients with IBS-D who may benefit from treatment with BAS. However, it should be noted that, although all 31 patients with a negative SeHCAT test result were classified as true negatives, this assessment was based on long term follow-up: "None of the 31 patients with irritable bowel disease who retained more than 15% at seven days showed any evidence of small bowel disease, and none appeared during a follow up of at least 12, and in some up to 24 months. Simple conservative treatment resolved or eased most symptoms."[39] None of these 31 patients received treatment with colestyramine and it therefore remains uncertain whether any of these patients could have benefited from treatment with BAS. One patient with a SeHCAT test result <8% and two with an equivocal result (8% to 15%) did not receive treatment with colestyramine; these patients were excluded from the analysis.[39] The remaining nine patients were treated with colestyramine; five of these had a SeHCAT test result <8%, one of whom did not respond to treatment and four had an equivocal result (8% to 15%), two of whom responded to colestyramine and two did not.[39]

Sciaretta et al. (1986)[42] reported sufficient data to allow the calculation of the performance of SeHCAT, for predicting treatment response, at a threshold reported to be equivalent to a seven-day-retention threshold of <5%. The estimated the sensitivity of SeHCAT in predicting a positive response to treatment with colestyramine was 85.7% (95% CI: 42.1% to 99.6%) and the specificity as 100% (95% CI: 54.1 to 100%). However, only 13 patients were included in this analysis. A subsequent study by Sciaretta et al. (1987)[43] estimated the sensitivity of SeHCAT in predicting a positive response to colestyramine as 95.0% (95% CI: 75.1 to 99.9%) and the specificity as 96.2% (95% CI: 80.4 to 99.9%) using a seven-day retention threshold of <8% to define a positive SeHCAT test. It should be noted that there may have been overlap between the populations included in these two studies.

Figure 2 illustrates the variation in sensitivity and specificity with SeHCAT threshold, as reported in these three studies.[39, 42, 43]

The between study heterogeneity in these three studies was considerable. The principal diagnosis, method of SeHCAT administration, BAS treatment dose, definition of response to treatment and follow-up period was different between studies. Appendix 2 provides full details of study inclusion and exclusion criteria, participant characteristics, SeHCAT test methods, BAS treatment and definition of treatment response.

Table 4: Accuracy of the SeHCAT test for predicting response to treatment with BAS in patients with IBS-D or FD

Study ID	Number of participants	Index test (definition of a positive test result)	Reference standard	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	Tested/treated (n patients)
Merrick 1985[$39]	43 (IBS-D)	SeHCAT <8%	Response[a]	4	2	1	33[†]	0.667 (0.223, 0.957)	0.971 (0.847, 0.999)	3 patients not treated
	43 (IBS-D)	SeHCAT ≤15%	Response[a]	6	0	3	31[†]	1.000 (0.541, 1.000)	0.912 (0.763, 0.981)	3 patients not treated
Sciaretta 1986[$42]	13 patients (group d. only, IBS-D and 3 with previous cholecystectomy)	SeHCAT <5%[*]	Response[b]	6	1	0	6	0.857 (0.421, 0.996)	1.000 (0.541, 1.000)	All treated
Sciaretta 1987[$43]	46 patients (38 IBS-D and 8 post-cholecystectomy)	SeHCAT 8% cut-off	Response[c]	19	1	1	25	0.950 (0.751, 0.999)	0.962 (0.804, 0.999)	All treated

[$]Study taken from previous Diagnostic Assessment Report[16]

[†]These patients were not actually treated with colestyramine but were considered true negatives based on follow up: "None of the 31 patients with irritable bowel disease who retained more than 15% at seven days showed any evidence of small bowel disease, and none appeared during a follow up of at least 12, and in some up to 24 months. Simple conservative treatment resolved or eased most symptoms." Two equivocal patients responded to colestyramine.

[*]Positive test described as 'SeHCAT values below the norm.' The lower limit of normal was reported as 34% for data obtained from the exponential abdominal activity retention curve for healthy controls, on day three; this was described by the authors equivalent to a 7-day retention cut-off of 5%.

Definition of response:

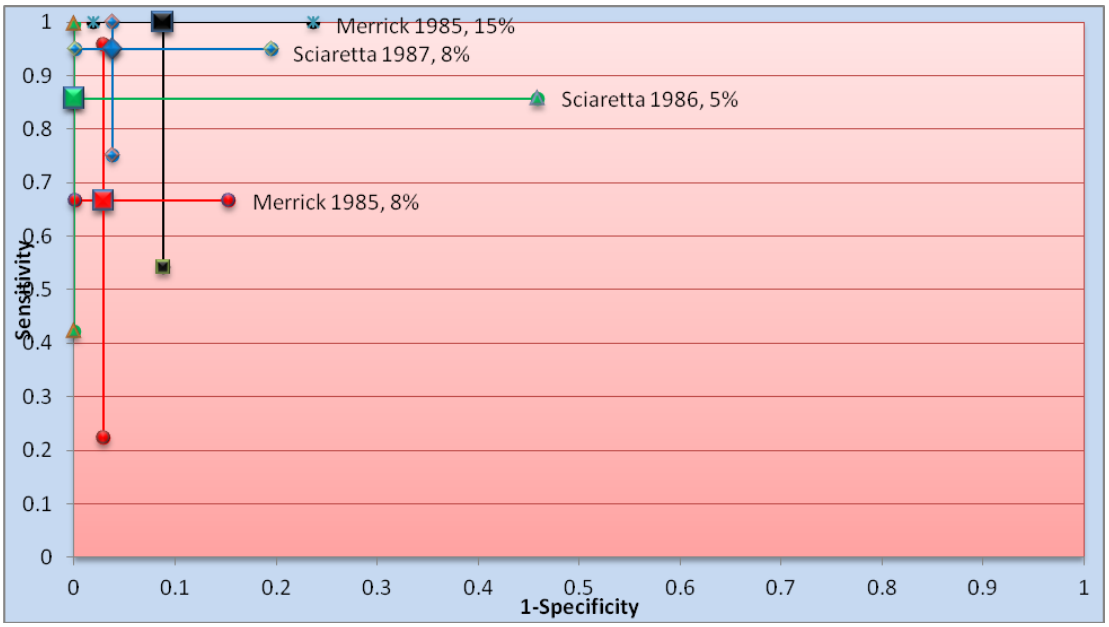
a. "asymptomatic" or "free of small bowel disease"

b. 'disappearance of diarrhoea' - no further details reported

c. response was considered positive when diarrhoea stopped with colestyramine administration and recurred without it.

IBS-D: diarrhoea predominant irritable bowel syndrome; SeHCAT: [^{75}Selenium] tauroselcholic acid; TP: true positive; FN: false negative; FP: false positive; TN: true negative

Figure 2: Accuracy of the SeHCAT test to predict a response to treatment with colestyramine at different thresholds, in patients with IBS-D*



*The centre dots represent the point estimates for sensitivity and specificity of SeHCAT in predicting response to treatment in the three studies at different cut offs (5%, 8% and 15%). The vertical and horizontal lines represent the 95% confidence intervals for sensitivity and specificity respectively.

The remaining 21 studies[6, 24-34, 36-38, 40-42, 45-47] only reported information about the outcome of treatment with BAS for some or all of those participants who had a positive SeHCAT result, i.e. sufficient information to estimate PPV, or other descriptive results.

As was the case for the predictive accuracy studies described above, between study heterogeneity in these studies was considerable. The principal diagnosis, threshold used to define a positive SeHCAT test, BAS treatment regimen, definition of response to treatment and follow-up period varied between studies. Appendix 2 provides full details of study inclusion and exclusion criteria, participant characteristics, SeHCAT test methods, BAS treatment and definition of treatment response, where these were reported.

Where information about the BAS treatment was provided, most (13/16) studies reported the use of colestyramine alone.[24, 30, 31, 33, 34, 36-38, 40, 41, 44, 46, 47] Four studies reported more than one option for BAS treatment, colestyramine or colesevelam,[27] colestyramine or colestipol,[6] and colestyramine or colesevelam or colestipol[29]; none of these studies reported either the numbers of patients treated with each drug, or the criteria used to select treatment. Eight studies reported the proportion of treated patients who were intolerant of BAS, or discontinued treatment for unspecified reasons;[24, 28-30, 33, 38, 44, 45] rates of intolerance/discontinuation were generally high, median 15% (range 4% to 27%). There was

insufficient information to determine whether levels of intolerance varied between colestyramine, colestipol and colesevelam. Only three studies reported the proportion of treated patients who were lost to follow-up, 14/56 (25%),[38] 8/32 (25%),[45] and 1/6 (17%).[26]

Study sizes were generally small; the median number of patients with a positive SeHCAT test (across all thresholds) who received treatment with BAS was 26 (range 6 to 57), and the proportion of patients who experienced a positive response to treatment varied widely within a given SeHCAT test threshold (see Table 5).

Most of the included studies evaluated one or more of three seven-day retention thresholds (5%, 10%, and 15%) for the SeHCAT test. Table 5 summarises the results for studies in this group.

Using a seven-day retention threshold of <5% to define a positive SeHCAT test, the proportion of test positive patients who responded positively to treatment with BAS was reported as 74%[33] and 100%,[47] by two studies; the proportion of SeHCAT test positive patients, in these studies, who received treatment with BAS was 95% and 100%, respectively. The equivalent data from the predictive accuracy study by Sciaretta et al. (1986)[42] indicated a treatment response rate of 100% in patients with seven-day retention values <5%; in this study, all patients with SeHCAT test results below the 5% threshold received treatment with colestyramine.

Eleven studies reported information about the rate of positive response to treatment with BAS, using a seven-day retention threshold of <10% or ≤10%.[6, 25, 30, 31, 33, 34, 36, 37, 40, 41, 47] The median proportion of SeHCAT test positive patients who received treatment with BAS was 100% (range 52% to 100%) and the median response rate was 85% (range 67% to 100%). It should be noted that three studies from the same group[30, 31, 40] may have had overlapping populations. All three of these studies[30, 31, 40] classified response to treatment as complete (normalisation of stool rhythm and consistency) or partial (decrease in stool frequency and/or improvement in stool consistency); the proportion of patients, in these studies, who achieved a complete response ranged from 50% to 76% and the proportion who achieved a partial response ranged from 15% to 50%.

Eight studies reported information about the rate of positive response to treatment with BAS, using a seven-day retention threshold of <15% or ≤15%.[26, 28, 33, 41, 44-47] The median proportion of SeHCAT test positive patients who received a treatment with BAS was 86% (range 70% to 100%) and the median response rate was 68% (range 38% to 86%). The

equivalent data from the predictive accuracy study by Merrick et al. (1985)[39] indicated a treatment response rate of 67% in patients with seven-day retention values ≤15%; in this study, 9/12 (75%) patients with SeHCAT test results below the 15% threshold received treatment with colestyramine.

The results of studies which used other thresholds to define a positive SeHCAT test are summarised in Table 5.

Four studies reported information about treatment response rates for multiple seven-day SeHCAT retention thresholds.[33, 41, 45, 47] Two studies reported information about treatment response rates for all of the three main thresholds (15%, 10% and 5%).[33, 47] In one study,[33] there was little variation in the rate of response to treatment (75%, 77% and 74%), across the three thresholds. By contrast, the second study[47] reported increasing response rates (69%, 81% and 100%) as the threshold for a positive SeHCAT test was lowered. Not all patients with a positive SeHCAT test received treatment with BAS and the reasons for treatment decisions were not reported. The results of both studies indicated that if a 5% or 10% threshold were applied some patients with a negative SeHCAT result (i.e. seven-day retention values between 5% and 15% or between 10% and 15%), who could be considered to be 'borderline' or 'equivocal' with respect to a diagnosis of BAM, and who may benefit from treatment with BAS, would be missed. The response rates for patients with seven-day SeHCAT retention values between 5% and 15%, were 14/18 (78%)[33] and 6/21 (29%)[47] and the response rates for patients with seven-day SeHCAT retention values between 10% and 15% were 2/4 (50%)[33] and 0/8 (0%)[47]; data sets were incomplete (i.e. not all patients received treatment with BAS) for all of these groups. An unpublished dissertation report provided information about treatment response rates for patients with a positive SeHCAT result, using two seven-day retention thresholds of 8% and 15%.[45] All patients with seven-day SeHCAT retention values below 8% received treatment with BAS and 32/36 (89%) of patients with seven-day SeHCAT retention values ≤15% received treatment with BAS; response rates were 10/20 (50%) and 12/32 (38%), respectively.[45] The results from this study also indicated that, if the lower threshold were applied, some patients with a 'borderline' or 'equivocal' test result (seven-day SeHCAT retention values between 8% and 15%), who may have benefited from treatment with BAS, would be missed; 12/16 (75%) of patients in this group received treatment with BAS and 2/12 (17%) responded positively.[45] It should be noted that no patients in any of these studies[33, 45, 47] who had seven-day SeHCAT retention values >15%, received treatment with BAS; estimates for the treatment response rate in

SeHCAT test negative patients do not, therefore, represent the complete spectrum of test negative patients. One further, very small (n=17), study[41] reported results for individual patients, which allowed the calculation of proportions treated and response rates for seven-day retention thresholds of 10% and 15%. In this study, all three patients with a seven-day retention value ≤10% received treatment with colestyramine and 2/3 (67%) responded positively, and 7/8 (88%) patients with a SeHCAT seven-day retention value ≤15% received treatment with colestyramine, 6/7 (86%) of whom responded positively.[41] As with the other studies that assessed multiple SeHCAT test thresholds, the results of this study also indicated that, if a 10% threshold were applied, some patients with a negative SeHCAT result, who may have benefited from treatment with BAS, would be missed; 4/8 (50%) patients, with a seven-day SeHCAT retention value >10%, who were treated with colestyramine responded positively to treatment, whilst 0/4 (0%) of patients, with a seven-day SeHCAT retention value >15%, who were treated with colestyramine responded positively to treatment.[41] It should be noted that data from Rudberg et al. (1996)[41] were incomplete; only 57% of patients who were SeHCAT test negative at the 10% threshold and 44% of patients who were SeHCAT test negative at the 15% threshold received treatment with colestyramine. In summary, few studies reported treatment response rates for multiple SeHCAT test thresholds and data were generally incomplete, hence, the extent to which patients with 'borderline' or 'equivocal' seven-day SeHCAT retention values could benefit from treatment with BAS remains unclear. The extent to which patients with seven-day retention values >15% may benefit from treatment with BAS is unknown.

Three studies reported further results for bowel symptoms, in addition to rates of response to treatment with BAS.[29, 36, 44] Fernandez-Benares et.al. (2001),[36] reported that in the 20 patients with FD and a seven-day SeHCAT retention value ≥10% who were treated with colestyramine, the median (IQR) number of daily bowel movements changed from five (four to eight) at baseline, to one (one to two) post-treatment. A change in stool consistency was also observed in all 20 treated patients; before treatment all 20 patients had liquid/semiliquid, and after treatment stools were formed/semi-formed in all 20 patients.[36] Urgency disappeared in 13 patients who had this symptom pre-treatment.[36] Lin et al. (2016)[29] reported that in 29 patents with type 2 BAM (seven-day SeHCAT retention values <10%) who were available for follow-up after treatment with BAS, the daily frequency of bowel movements was reduced from a median (range) of six (three to 16) at diagnosis to 3.5 (one to 16) at follow-up median time since diagnosis 82 months). Finally, Sinha et al. (1998)[44] reported a reduction in stool frequency across all nine patients with seven-day SeHCAT

retention values ≤15%, who were treated with colestyramine; the median stool frequency pre-treatment was 5/day versus 2/day post-treatment. One patient did not experience a reduction in stool frequency on treatment, although bowel motion consistency improved and the patient was reported to be happy with this outcome.[44]

Two studies also reported very limited results for changes in quality of life in patients with a positive SeHCAT test following treatment with BAS.[24, 27] Bellini et al. (2020)[24] reported that, after eight weeks of treatment with colestyramine, patients with mild BAM (seven-day SeHCAT retention values between 11% and 15%) showed a significant improvement on the pain domain of SF36 ($p<0.05$), and patients with severe BAM (seven-day SeHCAT retention values ≤5%) showed significant improvements on multiple domains of SF36 (emotional problems, energy/fatigue, emotional well-being, social functioning, pain, general health, health change) ($p<0.05$). Kumar et al. (2020)[27] reported that patients with idiopathic BAD (SeHCAT threshold not reported) showed significant improvements in the activity levels sub score ($p=0.00998$) of the EQ5DL questionnaire, following treatment with questran or colesevelam; the duration of follow-up was not reported.

Table 5: Treatment response rates in patients with IBS-D or FD and a positive SeHCAT test

Study ID	Participant details (n)	Positive SeHCAT test threshold	Reference standard	Number with positive/ negative test	Number (%) of patients with a positive test treated with BAS	Number (%) of patients with a negative test treated with BAS	Number (%) of patients with a positive SeHCAT test who responded to treatment with BAS (PPV)	Number of responders given a negative SeHCAT test	Number (%) discontinued / intolerant of BAS
Bellini 2020 [24]	All 70 patients with IBS-D and FD	≤5%	Response	12/58	NR/NR	NR	NR	NR	NR
		≤10%		15/55	NR/NR	NR	NR	NR	NR
		≤15%		31/39	22/31 (71%)	0/39 (0%)	NR	No patients treated	6/22 (27%)
Borghede 2011[$33]	Subgroup 114 patients with type II BAM	<5%	Response	41/73	39/41 (95%)	18/73 (25%)	29[a]/39 (74%)	14 [a]/18 (78%)	6/39 (15%)
		<10%		55/59	53/55 (96%)	4/59 (7%)	41[a]/53 (77%)	2 [a]/4 (50%)	7/53 (13%)
		≤15%		68/46	57/68 (84%)	0/46 (0%)	43[a]/57 (75%)	No patients treated	8/57 (14%)
Farmer 2107 [25]	All 207 patients with IBS-D 165 Rome III criteria 42 Rome IV	<10%	Response	48/159	48/48 (100%)	0/159 (0%)	36[b]/48 (75%)	No patients treated	NR

Study ID	Participant details (n)	Positive SeHCAT test threshold	Reference standard	Number with positive/ negative test	Number (%) of patients with a positive test treated with BAS	Number (%) of patients with a negative test treated with BAS	Number (%) of patients with a positive SeHCAT test who responded to treatment with BAS (PPV)	Number of responders given a negative SeHCAT test	Number (%) discontinued / intolerant of BAS
	criteria								
Fellous 1994[$34]	Subgroup 53 patients with FD	<10%	Response	20/33	NR	NR	8[c]/11 (73%)	2 [c]/5 (40%)	NR
Fernandez-Banares 2001[$36]	Subgroup 32 patients with FD	<11%	Response	24/8	20/24 (83%)	0/8 (0%)	20[d]/20 (100%)	No patients treated	3 SeHCAT positive patients not treated with BAS due to diarrhoea resolution (2 spontaneous and 1 with loperamide) 1 patient not accounted for

Study ID	Participant details (n)	Positive SeHCAT test threshold	Reference standard	Number with positive/ negative test	Number (%) of patients with a positive test treated with BAS	Number (%) of patients with a negative test treated with BAS	Number (%) of patients with a positive SeHCAT test who responded to treatment with BAS (PPV)	Number of responders given a negative SeHCAT test	Number (%) discontinued / intolerant of BAS
									8 patients discontinued BAS, without clinical relapse, during 6-month follow-up
Fernandez-Banares 2007[$37]	All 62 patients with FD or IBS-D	<11%	Response	37/25	37/37 (100%)	0/25 (0%)	28[□e]/37 (76%)	No patients treated	NR
Galatola 1992[$38]	All 98 patients with IBS-D	<11.7%	Response	56/42	56/56 (100%)	0/42 (0%)	39[f]/56 (70%)	No patients treated	14/56 (25%) lost to follow-up 2/56 (4%) intolerant of BAS

Study ID	Participant details (n)	Positive SeHCAT test threshold	Reference standard	Number with positive/ negative test	Number (%) of patients with a positive test treated with BAS	Number (%) of patients with a negative test treated with BAS	Number (%) of patients with a positive SeHCAT test who responded to treatment with BAS (PPV)	Number of responders given a negative SeHCAT test	Number (%) discontinued / intolerant of BAS
Holmes 2012[26]	Subgroup (post-test) 8 patients with type 2 BAM	<15%	Response	8/0	6/8 (75%)	NA	3[g]/6 (50%)	NA	1/6 (17%) lost to follow-up
Kumar 2013[28]	Subgroup 57 patients with unexplained symptoms	<15%	Response	24/33	23/24 (96%)	Unclear 13 patients with a final diagnosis of IBS-D 8 patients with a final diagnosis of inflammatory bowel disease 18 patients with a final diagnosis of FD	11[h]/23 (48%)	1/39 (3%)	6/23 (26%) intolerant of BAS

Study ID	Participant details (n)	Positive SeHCAT test threshold	Reference standard	Number with positive/ negative test	Number (%) of patients with a positive test treated with BAS	Number (%) of patients with a negative test treated with BAS	Number (%) of patients with a positive SeHCAT test who responded to treatment with BAS (PPV)	Number of responders given a negative SeHCAT test	Number (%) discontinued / intolerant of BAS
Kumar 2020[27]	Subgroup 20 patients with idiopathic BAD	NR	Response	20/0	20/20 (100%)	NA	9[i]/20 (45%)	NA	NR
Lin 2016[*29]	Subgroup (post-test) 29 patients with type 2 BAM, who were contactable at follow-up	<10%	Response	29/0	29/29 (100%)	NA	NR	NA	20/29 (69%) no longer taking BAS, at follow-up (March 2013) 5/29 (17%) receiving other treatments, at follow-up 15/29 (52%) receiving no treatment, at

Study ID	Participant details (n)	Positive SeHCAT test threshold	Reference standard	Number with positive/ negative test	Number (%) of patients with a positive test treated with BAS	Number (%) of patients with a negative test treated with BAS	Number (%) of patients with a positive SeHCAT test who responded to treatment with BAS (PPV)	Number of responders given a negative SeHCAT test	Number (%) discontinued / intolerant of BAS
									follow-up 3/29 (10%) intolerant of BAS
Notta 2011[$†40]	All 37 patients with chronic diarrhoea	≤10%	Response	16/21	16/16 (100%)	0/21 (0%)	8[j]/16 (50%) 8[k]/16 (50%)	No patients treated	NR
Notta 2014[†30]	All 78 patients with chronic FD	<10%	Response	34/44	34/34 (100%)	0/44 (0%)	25[j]/34 (74%) 5[k]/34 (15%)	No patients treated	3/34 (9%) discontinued BAS
Notta 2017[†31]	All 92 patients with chronic	<10%	Response	42/50	42/42 (100%)	0/50 (0%)	32[j]/42 (76%) 8[k]/42 (19%)	No patients treated	NR

Study ID	Participant details (n)	Positive SeHCAT test threshold	Reference standard	Number with positive/ negative test	Number (%) of patients with a positive test treated with BAS	Number (%) of patients with a negative test treated with BAS	Number (%) of patients with a positive SeHCAT test who responded to treatment with BAS (PPV)	Number of responders given a negative SeHCAT test	Number (%) discontinued / intolerant of BAS
	FD								
Rudberg 1996[$41]	All (excluding 3 patients with previous cholecystectomy or gastric resection) 17 patients with FD	≤10%	Response	3/14	3/3 (100%)	8/14 (57%)	2[l]/3 (67%)	4[l]/8 (50%)	NR
		≤15%		8/9	7/8 (88%)	4/9 (44%)	6[l]/7 (86%)	0[l]/4 (0%)	
Sinha 1998[$44]	All 17 patients with a history suggestive of IBS-D	<15%	Response	9/8	9/9 (100%)	0/8 (0%)	6[m]/9 (67%)	No patients treated	2/9 (22%) intolerant of BAS
Smith 2000[$6]	Subgroup	<10%	Response	65/132	34/65 (52%)	0/132 (0%)	28[n]/34 (82%)	No patients treated	NR

Study ID	Participant details (n)	Positive SeHCAT test threshold	Reference standard	Number with positive/ negative test	Number (%) of patients with a positive test treated with BAS	Number (%) of patients with a negative test treated with BAS	Number (%) of patients with a positive SeHCAT test who responded to treatment with BAS (PPV)	Number of responders given a negative SeHCAT test	Number (%) discontinued / intolerant of BAS
	197 patients with IBS-D								
Tunney 2011[$45]	Subgroup 86 patients with chronic diarrhoea and no known risk factors, who had no endoscopic or histologic abnormalities and negative coeliac	<8%	Response	20/66	20/20 (100%)	12/66	10[o]/20 (50%)	2[o]/12 (17%)	5/20 (25%) intolerant of BAS 3/20 (15%) lost to follow-up 1/20 (5%) refused treatment 1/20 (5%) diarrhoea resolved before treatment

Study ID	Participant details (n)	Positive SeHCAT test threshold	Reference standard	Number with positive/ negative test	Number (%) of patients with a positive test treated with BAS	Number (%) of patients with a negative test treated with BAS	Number (%) of patients with a positive SeHCAT test who responded to treatment with BAS (PPV)	Number of responders given a negative SeHCAT test	Number (%) discontinued / intolerant of BAS
	serology	≤15%		36/50	32/36 (89%)	0/50 (0%)	12°/32 (38%)	No patients treated	5/32 (16%) intolerant of BAS 8/32 (25%) lost to follow-up 1/32 (3%) refused treatment 1/32 (3%) diarrhoea resolved before treatment
Wildt 2003[$46]	Subgroup	<5%	Response	13/43	NR	NR	NR	NR	NR

Study ID	Participant details (n)	Positive SeHCAT test threshold	Reference standard	Number with positive/ negative test	Number (%) of patients with a positive test treated with BAS	Number (%) of patients with a negative test treated with BAS	Number (%) of patients with a positive SeHCAT test who responded to treatment with BAS (PPV)	Number of responders given a negative SeHCAT test	Number (%) discontinued / intolerant of BAS
	56 patients with possible type 2 BAM	<10%		21/35	NR	NR	NR	NR	
		<15%		24/32	17/24 (71%)	0/32 (0%)	14[φp]/17 (82%)	No patients treated	
Williams 1991[$47]	181 patients	<5%	Response[q]	23/158	23/23 (100%)	21/158 (13%)	23[r]/23 (100%)	6/21 (29%)	1/23with severe BAM (SeHCAT <5%) was intolerant to colestyramine and treated with aluminium hydroxide and 1/23 responded to aluminium hydroxide as
		<10%		39/142	36/39 (92%)	8/142 (6%)	29 [r]/36 (81%)	0/8 (0%)	
		<15%		60/121	42/60 (70%)	0/121 (0%)	29 [r]/42 (69%)	No patients treated	

Study ID	Participant details (n)	Positive SeHCAT test threshold	Reference standard	Number with positive/ negative test	Number (%) of patients with a positive test treated with BAS	Number (%) of patients with a negative test treated with BAS	Number (%) of patients with a positive SeHCAT test who responded to treatment with BAS (PPV)	Number of responders given a negative SeHCAT test	Number (%) discontinued / intolerant of BAS
									a first line treatment; 3/13 with moderate BAM (SeHCAT ≥5% to <10%) were treated with aluminium hydroxide (not clear whether this was first or second line treatment)
Zanoni 2018[32]	12 patients	<5%	Response	2/10	2/2 (100%)	6/10 (60%)	NR	NR	NR
		≤10%		6/6	6/6 (100%)	2/6 (33%)	NR	NR	
		≤15%		7/5	7/7 (100%)	1/5 (20%)	NR	NR	

Study ID	Participant details (n)	Positive SeHCAT test threshold	Reference standard	Number with positive/ negative test	Number (%) of patients with a positive test treated with BAS	Number (%) of patients with a negative test treated with BAS	Number (%) of patients with a positive SeHCAT test who responded to treatment with BAS (PPV)	Number of responders given a negative SeHCAT test	Number (%) discontinued / intolerant of BAS
		≤20%		8/4	8/8 (100%)	0/4 (0%)	6[$]/8 (75%)	No patients treated	

[$]Study taken from previous Diagnostic Assessment Report[16]

[□]Two further patients, with combined bile acid and sugar malabsorption, responded positively to combined treatment with BAS and a sugar-free diet

[*]Additional information provided by the study authors

[†]Possible overlapping study populations

[◊]The majority 11/14 (79%) patients with type 2 BAM, who responded to colestyramine, had severe BAM (7-day SeHCAT retention <5%).

Definition of response:

a. Response to treatment was defined as a lowered frequency of stools per day and/or a firmer consistency. A normal bowel habit was defined as 1-2 formed stools per day.

b. Response to treatment was defined as a 50% reduction in frequency of bowel movements.

c. Response was defined as treatment permitted the return to a normal transit (1 or 2 stools/day) with normal consistency or pasty-ish.

d. Response was defined as complete resolution of diarrhoea (passage of two or less formed or semi formed stools per day).

e. Response was defined as the relief of the diarrhoea (passage of 2 or fewer formed or semi formed stools per day), and absence of clinical relapse after 12-month follow-up. No response was defined as non-improvement in diarrhoea or diarrhoea relapse during follow-up.

f. Response was defined as patient-reported reduction in daily bowel frequency and subjective improvement in abdominal symptoms.

g. Response was defined as “improvement of symptoms”

h. Response defined as subjective global outcome “better”

i. Response defined as 50% improvement in stool frequency or fewer than 3 bowel movement per. day.

j. Complete response defined as normalization of stool rhythm and consistency.

k. Partial response defined as decrease of frequency and/or consistency.

l. Response defined as ‘complete relief’ - no details reported.

Study ID	Participant details (n)	Positive SeHCAT test threshold	Reference standard	Number with positive/ negative test	Number (%) of patients with a positive test treated with BAS	Number (%) of patients with a negative test treated with BAS	Number (%) of patients with a positive SeHCAT test who responded to treatment with BAS (PPV)	Number of responders given a negative SeHCAT test	Number (%) discontinued / intolerant of BAS

m. Response defined as reduction in stool frequency and improvement in stool consistency within 24 hours following the start of treatment; response maintained after withdrawal of loperamide

n. Response defined as qualitative, patient-reported response, based on reduced frequency of bowel movement (typically 2 to 3 times per. day), reduction in urgency, stools becoming more formed and solid, improved quality of life.

o. Response not defined.

p. Response defined as >25% reduction in bowel frequency, or file data reporting excellent or moderate response to treatment.

q. Including response to treatment with colestyramine or response to treatment with the bile acid chelator aluminium hydroxide.

r. A therapeutic response was defined as a reduction in stool frequency to ≤2 bowel actions/day with a concomitant increase in stool consistency occurring within 48 hours of beginning treatment.

s. 'Significant clinical benefit'

BAM: bile acid malabsorption; BAS: bile acid sequestrants; FD: functional diarrhoea; IBS-D: diarrhoea predominant irritable bowel syndrome; NA: not applicable; NR: not reported; SeHCAT: [^{75}Selenium] tauroselcholic acid; PPV: positive predictive value

3.2.4 Performance of the SeHCAT test for predicting response to treatment with BAS in patients with Crohn's disease, who have not undergone ileal resection

One study (results summarised in Table 6)[6] provided data on population two: Adults presenting with chronic diarrhoea and a diagnosis of Crohn's disease, who have not undergone ileal resection (i.e. people with suspected secondary BAD). This study only reported information about the outcome of treatment with BAS for people who had a positive SeHCAT result, and was included in our previous assessment report, conducted for DG7.[16] No new studies, meeting the inclusion criteria for population two, were identified for this assessment report. The single study that reported information about response to treatment with BAS in patients with Crohn's disease provided only very limited information about response rates in patients with a positive SeHCAT test result (seven-day retention <10%) who were treated with colestyramine or colestipol.[6] Fewer than half (9/24) of the patients with a positive SeHCAT test result received treatment with BAS and the reasons criteria used to decide whether or not to offer BAS were not reported. Most, 8/9 (89%), of the patients treated with BAS responded positively, [6] however, the numbers treated with each BAS (colestyramine or colestipol) were not reported.

Appendix 2 provides all reported details of the inclusion and exclusion criteria, participant characteristics, SeHCAT test methods, BAS treatment and definition of treatment response, for this study.

Table 6: Treatment response rates in patients with Crohn's disease, who have not undergone ileal resection, and a positive SeHCAT test

Study ID	Participant details (n)	Positive SeHCAT test threshold	Reference standard	Number with positive/ negative test	Number (%) of patients with a positive test treated with BAS	Number (%) of patients with a negative test treated with BAS	Number (%) of responders given a positive SeHCAT test	Number (%) of responders given a negative SeHCAT test	Number (%) discontinued/ intolerant of BAS
Smith 2000[$6]	Subgroup 44 patients with Crohn's disease and no prior surgery	<10%	Response	24/20	9/24 (38%)	0/20 (0%)	8[a]/9 (89%)	No patients treated	NR

[$]Study taken from previous Diagnostic Assessment Report[16]

a. Response defined as qualitative, patient-reported response, based on reduced frequency of bowel movement (typically 2 to 3 times per. day), reduction in urgency, stools becoming more formed and solid, improved quality of life.

3.2.5 Pooled estimates of treatment response rates for inclusion in cost effectiveness modelling

Meta-analysis was considered inappropriate, in this assessment, due to the small number of test accuracy studies with varying diagnostic thresholds and between study heterogeneity with respect to population (prior investigations), treatment regimen, definition of response, follow-up period, and SeHCAT administration). However, in order to provide input parameters for cost effectiveness modelling, some pooled estimates were calculated using the inverse variance method on the logit scale, for probability test positive at the 15% threshold and probability of response given test positive (see Tables 7 and 8).

Table 7: Proportion test positive at 15% threshold

Study ID	n	N	Proportion
Borghede , 2011[33]	68	114	0.60
Holmes, 2012[26]	8	8	0.99
Kumar, 2013[28]	24	57	0.42
Rudberg, 1996[41]	8	17	0.47
Sinha, 1998[44]	9	17	0.53
Tunney, 2011[45]	36	86	0.42
Wildt, 2003[46]	24	56	0.43
Williams, 1991[47]	60	181	0.33
Fixed effect, pooled estimate (95% CI)			0.416 (0.424,0.407)
Random effects, pooled estimate (95% CI)			0.454 (0.357, 0.555)

Table 8: Proportion respond to treatment given test positive at 15% threshold

Study ID	n	N	Proportion
Borghede , 2011[33]	43	57	0.75
Holmes, 2012[26]	3	6	0.50
Kumar, 2013[28]	11	23	0.48
Rudberg, 1996[41]	6	7	0.86
Sinha, 1998[44]	6	9	0.67
Tunney, 2011[45]	12	32	0.38
Wildt, 2003[46]	14	17	0.82
Williams, 1991[47]	29	42	0.69
Fixed effect, pooled estimate (95% CI)			0.642 (0.615, 0.668)
Random effects, pooled estimate (95% CI)			0.638 (0.495, 0.760)

4. ASSESSMENT OF COST EFFECTIVENESS

This chapter explores the cost effectiveness of including SeHCAT testing in the diagnostic pathway for investigation of diarrhoea due to BAM in adults with IBS-D or FD and in adults with Crohn's disease without ileal resection.

4.1 Identifying and reviewing published cost effectiveness studies

A series of literature searches were performed to identify published economic evaluations, cost data and utility studies for diagnostic techniques and procedures used in the investigation of patients with chronic diarrhoea that were not included within the scope of the clinical effectiveness searches. The searches aimed to identify studies that could be used to support the development of a health economic model, to estimate the model input parameters and to answer the research questions of the assessment, but not to perform a systematic review. Searches were therefore pragmatic in design, and date limits applied where appropriate.

Methodological study design filters were included in the search strategy where relevant. No restrictions on language or publication status were applied. Limits were applied to remove animal studies. The main Embase strategy for each search was independently peer reviewed by a second Information Specialist, using the CADTH Peer Review checklist[20, 21]Identified references were downloaded in Endnote X20 software for further assessment and handling. References in retrieved articles were checked for additional studies. In addition, the Endnote library created for the clinical effectiveness section (See section 3.1.1) was also screened to identify potentially relevant economic studies.

Full search strategies are reported in Appendix 1.

The following databases were searched for relevant studies with no date limits:

- MEDLINE (Ovid) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily: 1946-2020/12/21
- EMBASE (Ovid): 1974-2021/01/17
- NHS Economic Evaluation Database (NHS EED) (CRD): up to 2015/03*
- EconLit (EBSCO): up to 2020/12/22
- Science Citation Index (SCI) (Web of Science): 1988-2021/1/05
- RePEc (Research Papers in Economics) (Internet) http://repec.org/: up to 2021/02/23

*(Please note that since March 2015 NHS EED has been an archival resource only and the Wiley Health Economic Evaluation Database (HEED) searched as part of the original 2011 study is no longer available).

Supplementary searches on SeHCAT, BAD, IBS, Crohn's & chronic diarrhoea were undertaken on the following resources to identify guidelines and guidance (The search was conducted from 2011 to present):

- Guidelines International Network (G-I-N) (www.g-i-n.net): up to 2020/12/15
- NHS Evidence (www.evidence.nhs.uk): up to 2020/12/16
- ECRI Guidelines Trust (https://guidelines.ecri.org/): up to 2020/12/16
- NICE (www.nice.org.uk): up to 2020/12/15
- TRIP Database (https://www.tripdatabase.com/): up to 2020/12/10
- Health Technology Assessment Database (HTA) (CRD): up to 2018/03/31
- NIHR Health Technology Assessment (HTA)(Internet): up to 2020/12/16

Please note the National Guidelines Clearinghouse (NGC) resource included in the 2011 searches is no longer available.

As described by the NICE Methods Guide, the information process that supports the development of a model is "a process of assembling evidence and this reflects an iterative, emergent process of information gathering".[54] The following additional searches were requested by the health economists as part of this process:

Searches for Utility weights for BAD, IBS, Crohn's and chronic diarrhoea were conducted on the following resources:

- Cost-Effectiveness Analysis (CEA) Registry (Internet) (https://research.tufts-nemc.org/cear4/Home.aspx): up to 21/01/14
- ScHARRHUD (Internet) (https://www.scharrhud.org/): up to 2021/02/23

Additional searches were also requested for health-related quality of life and cost effectiveness for both Crohn's Disease and IBS on the following resources:

- NHS Economic Evaluation Database (NHS EED) (CRD): up to 2015/03
- MEDLINE (Ovid) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily: 1946-2020/12/15

4.2 Model structure and methodology

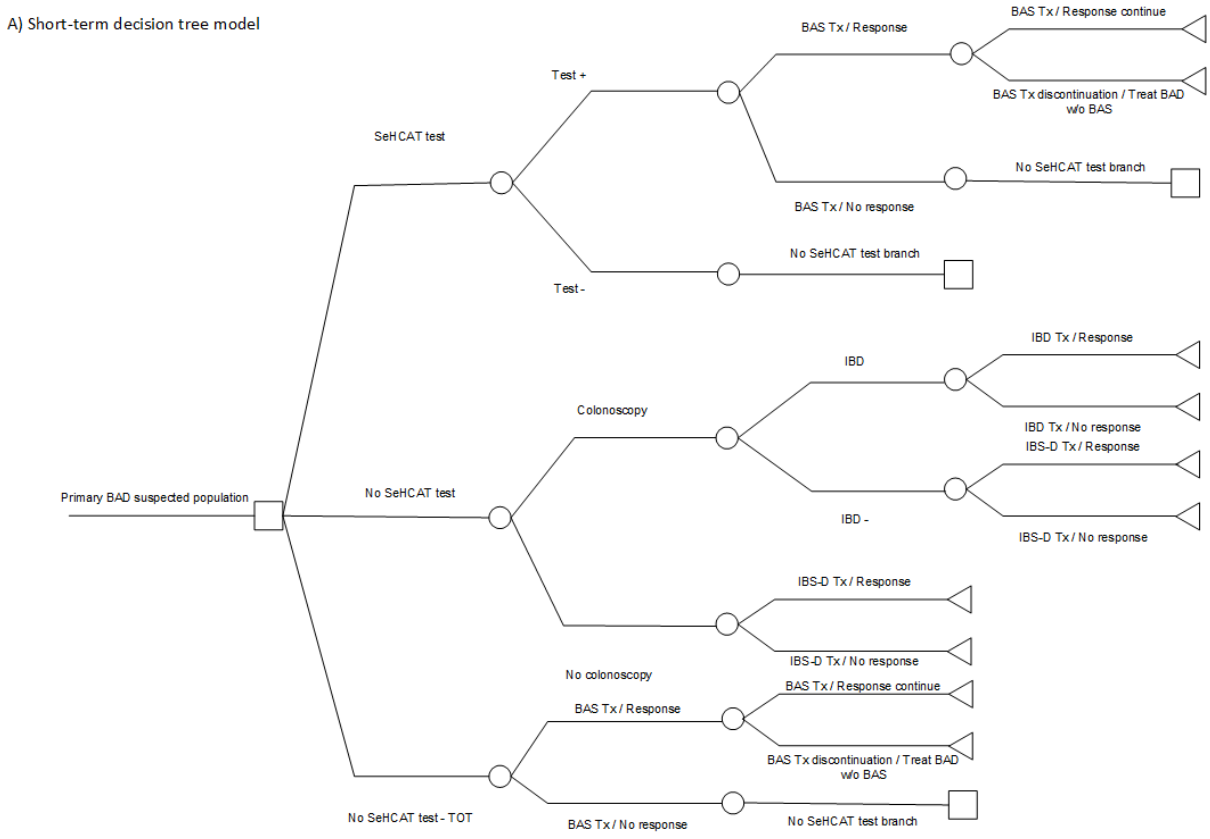
4.2.1 Model structure

The structure of the health economic model is in line with that developed for the previous assessment of SeHCAT.[16] Thus, the model consists of two parts:

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

An outline of the short-term model structure for the population of adults with suspected primary bile acid diarrhoea (population 1) is presented in Figure 3. The main difference with respect to the model developed for the previous assessment of SeHCAT,[16] is the potential inclusion of the colonoscopy investigation in the model, based on discussions during the scoping phase suggesting that SeHCAT could be used to avoid unnecessary colonoscopies. Thus, our base-case scenario for population 1 places colonoscopy after SeHCAT according to most clearly expressed clinical expert opinion and BSG guidelines where colonoscopy is required for investigation of cancer and not for ruling IBD out. As secondary scenario for population 1, we assumed that no colonoscopy would occur after SeHCAT since this would have already occurred in clinical pathway. Note that, in practice, colonoscopy can be excluded from the model by setting this probability equal to zero (i.e., at the colonoscopy branch all patients will follow the “No colonoscopy” path and, subsequently, will be treated as IBS-D patients).

Figure 3: Decision analytic model, population 1



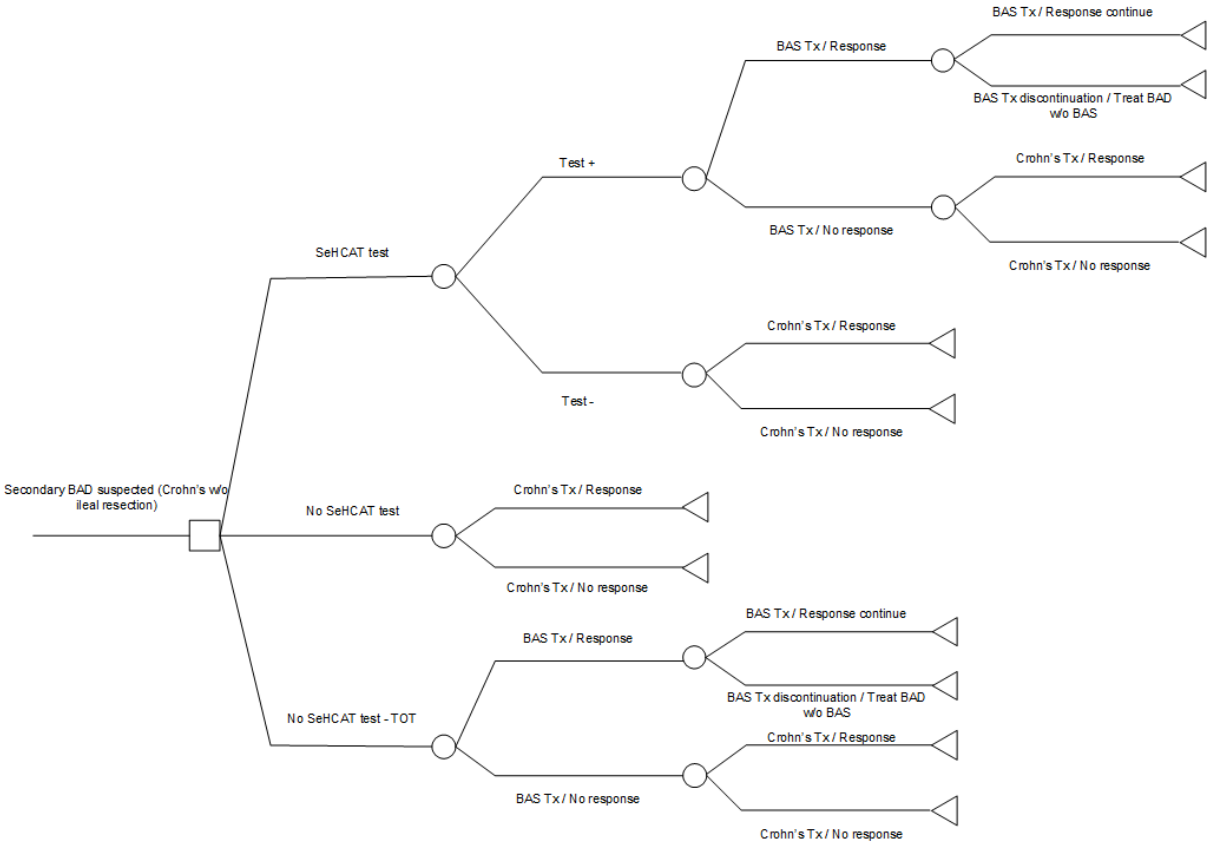
Abbreviations: BAD = bile accid diarhoea, BAD-1 = primary BAD, BAS = bile acid sequestrants, IBD = inflammatory bowel disease, IBS-D = irritable bowel syndrome diarrhoea, TOT = trial of treatment, Tx = treatment.

In the SeHCAT strategy, patients may have a positive or a negative test result. If the test is positive, i.e., the percentage of whole body retention 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. 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. If the result of the SeHCAT test is negative, a proportion of patients are investigated for IBD with a colonoscopy. If after the colonoscopy, patients are diagnosed as having IBD, then they are treated accordingly. Otherwise, patients are treated as having IBS-D. Patients testing SeHCAT negative and not undergoing colonoscopy are diagnosed as IBS-D and are treated accordingly. All endpoints of the SeHCAT negative branch, are thus determined depending on whether patients respond to treatment or not. The 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 strategy, all patients receive BAS at the beginning. If patients do not respond to BAS, 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 as in the SeHCAT positive branch of the model. Treatment discontinuation may vary between patients with a positive SeHCAT result and those not tested.

The short-term model for population 2 (adults with chronic diarrhoea and a diagnosis of Crohn's disease, who have not undergone ileal resection) is shown in Figure 4. The main difference with respect to the short-term model in Figure 4 is that Crohn's patients are not expected to undergo colonoscopy, since it is assumed that these patients would already have had colonoscopy to diagnose their Crohn's disease. Therefore, all endpoints of the decision analytic model are determined depending on whether patients respond to treatment (BAS or diarrhoea treatments for Crohn's patients) or not. This is the same structure assumed in the previous assessment of SeHCAT.[16]

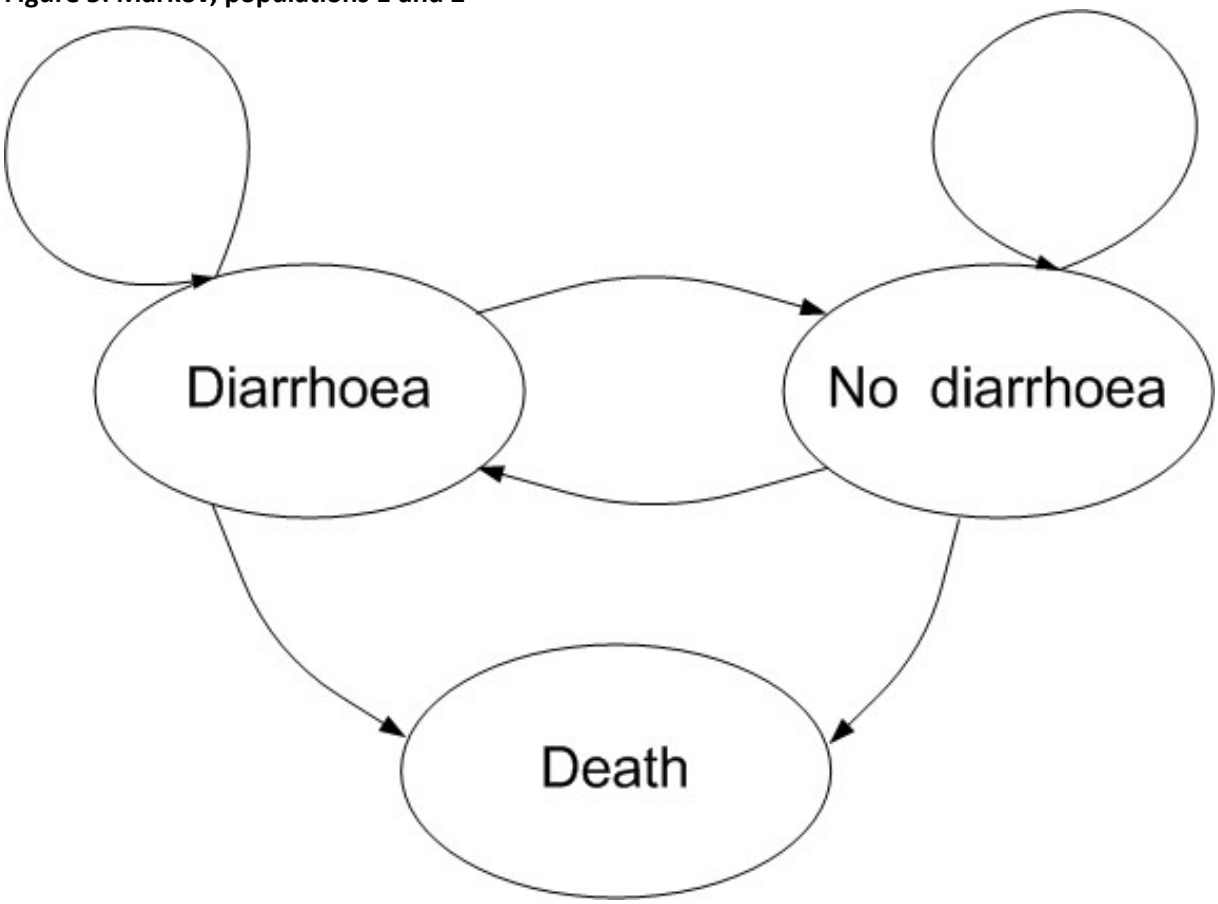
Figure 4: Decision analytic model, population 2



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

To assess the long-term costs and effects of the various strategies in both populations, patients are assumed to enter a simple three-state Markov model as shown in Figure 5.

Figure 5: Markov, populations 1 and 2



Patients who had a treatment response in the short-term model start in the "No diarrhoea" health state and patients who did not respond to treatment in the short-term model start in the "Diarrhoea" health state. Since 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.[55] Therefore, since there is no new evidence to suggest that this has changed, only background mortality was considered in the economic model. Transitions between the "Diarrhoea" and "No diarrhoea" health states were informed by clinical expert opinion since clinical data regarding the long-term effectiveness of BAS, IBD and IBS-D treatments were not identified. The cycle length is six months, as in the previous assessment of SeHCAT.[16] Long-term adverse events, such as constipation, and treatment discontinuation were not included in the Markov model due to lack of data. The Markov model is then parameterised according to treatment.

Population

The cost effectiveness of SeHCAT for the assessment of possible bile acid diarrhoea, was estimated in the two patient populations defined in Section 3.1.2:

1. 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). This condition is referred to as population 1.

2. Adults with chronic diarrhoea and a diagnosis of Crohn's disease, who have not undergone ileal resection. This condition is referred to as population 2.

Using the study by Summers et al. (2016),[3] we assumed that the average age in both populations was 50 years, and the ratio of male/female was 35/75.

Strategies

Various strategies could be defined for the SeHCAT treatment option based on the test cut-off points used to classify patients (see Section 3.2.3 for additional details). In the previous assessment of SeHCAT, cut-off points of 5%, 10% and 15% were used.[16] However, since it was not possible to obtain evidence to estimate all input parameters for these three SeHCAT cut-off points, many assumptions were made to populate the model for each SeHCAT cut-off value. Testing these assumptions resulted in an enormous number of scenarios, where almost every different cost effectiveness outcome was possible, without knowing the actual plausibility of such scenarios. However, in the clinical expert elicitation exercise to inform parameters for which data are lacking, all clinical experts consulted provided estimates for the 15% cut-off only. Therefore, for both populations we compared the SeHCAT strategy at a 15% cut-off point with (i) no SeHCAT testing and no treatment with bile acid sequestrants, and (ii) no SeHCAT testing and trial of treatment with BAS. Our systematic review revealed that most studies that reported data to inform the model used the 10% and 15% cut-off points. Those data included proportion test positive at the given cut-off as well as response to treatment given test positive. Therefore, clinical expert opinion was sought to inform treatment response given test negative as well as other parameters further downstream such as probability of colonoscopy.

Perspective, time horizon and discounting

All costs and effects were discounted by 3.5%. The models incorporated a lifetime (50 years) 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 were included.

4.2.2 Model parameters

This section describes the parameters used in the decision analytic and the Markov models and how their values were estimated. Where possible, input for the models were based on our systematic review (described in Section 3), other published literature and UK databases. When such evidence

was not available, expert opinion was used. We sent out a questionnaire to the specialist committee members of this assessment and their answers were used to inform the input parameters for which data were lacking. The full questionnaire can be found in Appendix 6. When experts were unable to provide estimates, modelling assumptions were made.

Diagnostic model suspected population 1

Probabilities

No SeHCAT strategy

As shown in Figure 4, five different probabilities (represented by the circles in the "No SeHCAT test" branch) need to be estimated when SeHCAT and BAS trial of treatment are not available.

Colonoscopy

When SeHCAT and BAS trial of treatment are not available, patients in population 1 may undergo colonoscopy to detect IBD. Clinical experts' responses to our questionnaire were used to estimate of the proportion of patients that currently undergo colonoscopy. Their responses are summarised in Table 9. Experts' answers were used to derived probabilities following the same approach as in the previous assessment of SeHCAT.[16] Thus, we assumed that the proportion of patients undergoing colonoscopy follows a triangular distribution with the point estimate given by the experts representing the mode of the distribution. In this case, we simulated three triangular distributions (one per expert response) to estimate the pooled mean and standard deviation of the probability of undergoing colonoscopy, which is further assumed to have a Beta distribution. We found a mean of 74% and a standard deviation of 1.42%. This probability was further parameterised as a Beta(706, 242) distribution. Note the low standard deviation might be due to the lack of uncertainty ranges provided in two of the answers in Table 9 (both equal to 100%). This might underestimate the uncertainty associated to this parameter, which will be further explored in scenario analyses. Additional details on the calculations of this and the other probabilities calculated following the same approach can be found in the file "*input parameter estimation.r*", which is part of the economic model.

Table 9: Probability of colonoscopy when SeHCAT and BAS are not available in population 1, per expert

Expert	Percentage of colonoscopy	Lowest	Highest
1*	20	20	30
2	100	NR	NR
3**	NR	NR	NR
4**	100	NR	NR

Abbreviations: BAS = bile acid sequestrants, NR = not reported, SeHCAT = Tauroselcholic [75Selenium] acid.
*This expert also mentioned 10% (range 1%-20%) CT colonography as alternative. This was included in the cost calculations as explained below.
**These experts indicated that colonoscopy would be used to detect microscopic colitis (MC) but not IBD. The role of MC is unclear and was not included in this assessment.

IBD prevalence and response to treatment

As explained above, our model was built under the assumption that colonoscopy is placed at the beginning of the No SeHCAT strategy to detect IBD patients. Experts indicated that the proportion of IBD patients at this point of the treatment pathway is expected to be small. This is in line with the findings in Patel et al. 2015,[56] where Table II reports that 11 patients were diagnosed as IBD from a total of 209 patients presented with IBS-D compatible symptoms. Thus, in our model, the probability of having IBD after colonoscopy was assumed to follow a Beta(11, 198) distribution.

Response to IBD treatment was also estimated from the answers to the questionnaire obtained from the experts, as presented in Table 10. The approach described above of simulating triangular distributions to derive the parameters of a Beta distribution was also followed in this case. We found a mean of 72% and a standard deviation of 5%, which was parameterised as a Beta(49, 19) distribution. The uncertainty associated to this parameter was not explored in scenario analyses. The main reason was that this is a small proportion of patients, as confirmed by the experts, and even though IBD medication is costly compared to IBS-D medication, the impact of this parameter on the model results is expected to be minor.

There is uncertainty regarding the initial response to IBD treatment and the and duration of this response. We assumed that response is achieved within six months since start of treatment, but this is variable as acknowledged by the clinical experts consulted. Regarding the duration of the treatment effect, experts indicated that the main difference with respect to IBS-D patients is that a lifetime effect should not be assumed, since relapses are expected after initial response.

Table 10: Probability of treating IBD patients successfully when SeHCAT is not available in population 1, per expert

Expert	Percentage of patients successfully treated	Lowest	Highest
1	70	50	90
2	75	70	80
3	70	60	80
4	NR	NR	NR

Abbreviations: IBD = inflammatory bowel disease, NR = not reported, SeHCAT = Tauroselcholic [75Selenium] acid.

IBS-D prevalence and response to treatment

The probability of undergoing colonoscopy (74%) and being diagnosed as IBD patient (5.3% of those undergoing colonoscopy) estimated above imply that the majority of patients (approximately 96% of all patients) would be treated as IBS-D patients. In line with the previous assessment of SeHCAT, it is assumed that IBS-D patients may receive a variety of drugs, diet advice and psychological treatment.[16] Due to the large array of treatment options and the various orders in which they are attempted, we did not find clear data from the literature regarding how many IBS-D patients will eventually, after trying various options, respond to treatment. Therefore, response to IBS-D treatment was estimated from the answers to the questionnaire obtained from the experts, as summarised in Table 11. Also in this case, we followed the approach described above of simulating triangular distributions to derive the parameters of a Beta distribution. We found a mean of 46% and a standard deviation of 8%, parameterised as a Beta(17, 20) distribution. The uncertainty associated to this parameter, was explored in scenario analyses.

There is also uncertainty regarding the initial response to IBS-D treatment and the and duration of this response. We also assumed that response is achieved within six months since start of treatment, but this is variable as acknowledged by the experts consulted. Unlike for IBD patients, we assumed a lifetime effect in the base-case, thus, in the Markov model there is no transition to the diarrhoea health state for patients initially responding to treatment. This assumption was based on responses from clinical experts who indicated that IBS-D is not a relapsing condition in general. In any case, scenarios where long-term relapses were allowed, were also explored in the scenario analysis section of this report.

Table 11: Probability of treating IBS-D patients successfully when SeHCAT is not available in population 1, per expert

Expert	Percentage of patients successfully treated	Lowest	Highest
1	60	30	70
2	30	20	50
3	50	25	75
4	NR	NR	NR

Abbreviations: IBS-D = diarrhoea predominant irritable bowel syndrome, NR = not reported, SeHCAT = Tauroselcholic [75Selenium] acid.

Finally, note that the answers given in Table 11 were obtained by assuming that patients had undergone a colonoscopy and IBD was ruled out. However, to complete the model, we also need to estimate the probability of responding to IBS-D treatment when patients do not undergo colonoscopy. Based on the answers in Table 9, we estimated that 26% of patients will not undergo colonoscopy. From these, we assumed that 5.3% of them are IBD patients (per Patel et al. (2015)),[56] and, therefore, they would not respond to IBS-D treatment. For the remaining patients, we assumed the same response probability as in Table 11 (46%). Thus, in total, the mean probability of responding to IBS-D treatment, without previous colonoscopy, was estimated as (100% - 5.3%)*46% = 44%. Assuming the same standard deviation of 8% in Table 11, this was parameterised according to a Beta(16, 20) distribution.

SeHCAT 15% strategy

As shown in Figure 3, 13 different probabilities need to be estimated when the SeHCAT test is available. Note that three of these correspond to probabilities associated to SeHCAT testing, i.e., the probability of testing positive, the probability of responding to BAS treatment (contingent on being SeHCAT positive) and the probability of discontinuation from BAS treatment. Additionally, patients testing negative for SeHCAT or not responding to BAS treatment after testing positive, are assumed to follow the same pathway as in the No SeHCAT strategy. Thus, for both model branches, the same five probabilities described above for No SeHCAT have to be estimated (i.e., 10 probabilities in total). SeHCAT related probabilities were estimated using the results from our clinical effectiveness review. The remaining probabilities were informed by clinical experts. Since our questionnaire did not include questions about patients not responding to BAS treatment after a positive SeHCAT result, we assumed for these patients the same estimates as those obtained for patients with a negative SeHCAT result. Thus, in practice, eight probabilities were estimated for the SeHCAT 15% strategy.

SeHCAT positive and response to BAS treatment

We estimated the probability of a positive SeHCAT test at the 15% threshold by performing a random effects meta-analysis on the data from the studies in Table 5 in Section 3.2.3. The pooled estimate (0.454) can be seen in Table 12. This probability was further parameterised as a Beta(2.10, 2.52) distribution.

Table 12: Probability of positive SeHCAT result in population 1, cut-off 15%

Study	N	Number SeHCAT positive	Probability SeHCAT positive
Borghede 2011[33]	114	68	0.60
Holmes, 2012[26]	8	7.9	0.99
Kumar, 2013[28]	57	24	0.42
Rudberg, 1996[41]	17	8	0.47
Sinha, 1998[44]	17	9	0.53
Tunney[45]	86	36	0.42
Wildt, 2003[46]	56	24	0.43
Williams, 1991[47]	181	60	0.33
		RE mean	0.454
		SE	0.21

Abbreviations: N = sample size study; RE = Random effects; SE = standard error, SeHCAT = Tauroselcholic [75Selenium] acid

Patients with a positive SeHCAT test result are assumed to be treated with a BAS. In our analyses, we assumed that this is either cholestyramine or colesevelam. In terms of response, however, it was not possible to distinguish between the type of BAS and estimated the response rate to BAS, in general, using the studies described in Section 3.2.3, conducting a random effects meta-analysis. The pooled estimate (0.638) can be seen in Table 13. This probability was parameterised as a Beta(1, 0.57) distribution.

Responses to our questionnaire also suggested that initial response to BAS treatment is achieved within six months since start of treatment and that a lifetime treatment effect duration might be assumed (thus, in the Markov model there is no transition to the Diarrhoea health state for patients initially responding to treatment). Scenarios with long-term relapses were explored in Section 4.3 of this report.

Table 13: Probability of a positive BAS response, given a positive test result, cut-off 15%

Study	N	Number positive response	Probability positive response
Borghede, 2011[33]	57	43	0.75
Holmes, 2012[26]	6	3	0.50
Kumar, 2013[28]	23	11	0.48
Rudberg, 1996[41]	7	6	0.86
Sinha, 1998[44]	9	6	0.67
Tunney, 2011[45]	32	12	0.38
Wildt, 2003[46]	17	14	0.82
Williams, 1991[47]	42	29	0.69
		RE mean	0.638
		SE	0.30

Abbreviations: N = sample size study, RE = Random effects, SE = standard error, SeHCAT = Tauroselcholic [75Selenium] acid.

Adherence to BAS treatment

It is known that adherence is usually not optimal when patients are treated with BAS. Four studies reported the proportion of treated patients who, after testing positive at a SeHCAT 15% cut-off value and started treatment with BAS, were intolerant of BAS, or discontinued treatment for unspecified reasons.[28, 33, 44, 45] The study by Borghede et al. (2011) reported 43 out of 57 patients responded to treatment.[33] It was also reported that 49 out of 57 patients used cholestyramine continuously, i.e., eight out of 57 patients were intolerant or discontinued. The study by Kumar et al. (2013), reported response to BAS in 11 out of 23 patients, and intolerance in six out 23.[28] In the study by Sinha et al. (1998), six out of nine patients responded to BAS treatment and two out of nine were intolerant.[44] Finally, the study by Tunney et al. (2011), reported response to BAS in 12 out of 32 patients and intolerance in five out of 32.[45] Therefore, in all these four studies, the response reported was based on a less than 100% compliance. Other four studies reported the proportion of patients intolerant of BAS but in those studies SeHCAT was used at cut-off values lower than 15%.[24, 29, 30, 38] The studies by Bellini et al. (2020) and Lin et al. (2016) reported that six out of 22 patients and three out of 29 patients, respectively, were intolerant to BAS but none of these studies reported response to BAS.[24, 29] In the study by Galatola et al. (1992), 39 out of 56 patients responded to BAS and two out of 56 were intolerant. Thus, the response reported was based on less than 100% compliance.[38] Likewise, the study by Notta at al. (2011) reported that many patients used cholestyramine on demand after achieving an initial response to counteract side effects.[40] Thus, this study also reported a response rate that is based on reduced compliance (25 out of 34 patients responded to BAS and three out of 34 were intolerant). Therefore, it seems reasonable to assume that in these studies the impact of reduced compliance on the response rate was implicitly included. Overall, rates of intolerance/discontinuation in these studies were high (median 15%, range 4% to 27%). However,

there was insufficient information to determine whether levels of intolerance differed between colestyramine and colesevelam.

Furthermore, based on the responses to our questionnaire, it seems that most patients present intolerance to cholestyramine and, when this occurs, patients are generally switched to colesevelam, in which compliance and response seem to be high. Also, based on the responses to our questionnaire, it was assumed in the base-case that 50% of patients started with cholestyramine and 50% with colesevelam. It was further assumed that a proportion of those patients starting with cholestyramine will switch to colesevelam. For simplicity, we assumed that these patients will effectively move to colesevelam at the beginning of the simulation. The impact of this assumption is expected to be minor since in practice, it could be assumed that these patients would switch to colesevelam at some point within the first 6 months (e.g., at month 3 in the model). Thus, this assumption would only affect BAS costs and utilities for half of the first model cycle. The proportion of patients treated with cholestyramine in the base-case was implemented as a Beta(7700, 7701) distribution.

The probability of switching from cholestyramine to colesevelam was then estimated based on the experts' responses to our questionnaire, as can be seen in Table 14. Again, we followed the approach described above of simulating triangular distributions to derive the parameters of a Beta distribution. We found a mean of 50% and a standard deviation of 2%, corresponding to a Beta(357, 356).

Table 14: Probability of switching from cholestyramine to colesevelam in population 1, per expert

Expert	Percentage of patients switching	Lowest	Highest
1	20	10	30
2	60	NR	NR
3	NR	NR	NR
4	NR	NR	NR

Abbreviations: NR = not reported.
Note: Expert 2 estimated a 5% colesevelam drop-out but this was not included in the model. Expert 3 indicated that *many patients* dislike cholestyramine, but *the majority* are okay with colesevelam. Expert 4 did not report any estimates but mentioned that suspected that *a lot of patients* would drop out from cholestyramine.

SeHCAT negative (or SeHCAT positive and no response to BAS treatment)

So far, we have described the modelled pathway assumed when patients respond to BAS after a SeHCAT positive result. When patients do not respond to BAS after a positive SeHCAT result, or when the SeHCAT results is negative, we assumed that patients follow the same pathway as in the No SeHCAT strategy. As explained above, this part of the model was informed by clinical experts only

and the probability estimates were assumed to be the same for patients who did not respond to BAS after a positive SeHCAT and for patients with a negative SeHCAT result.

Following the steps described above for the No SeHCAT strategy, we first estimated the probability of undergoing colonoscopy (contingent on a negative SeHCAT result, or a positive SeHCAT result and no response to BAS). Experts' answers can be seen in Table 15. These were used to simulate a triangular distribution to derive the parameters of a Beta distribution, as explained above. We found a mean of 49% and a standard deviation of 2%, corresponding to a Beta(338, 351) distribution. The uncertainty associated to this parameter, was explored in scenario analyses.

Table 15: Probability of colonoscopy after SeHCAT negative (or SeHCAT positive and no response to BAS) in population 1, per expert

Expert	Percentage of colonoscopy	Lowest	Highest
1	5	1	7.5
2	5	2	10
3	90	90	100
4	NR	NR	NR

Abbreviations: NR = not reported, SeHCAT = Tauroselcholic [75Selenium] acid.
Note: Expert 1 indicated that 10% (5%-15%) would receive a CT colonography as an alternative to colonoscopy. Expert 4 did not provide any estimates but mentioned that suspects *the majority* would still have a colonoscopy *to exclude MC*. To account for this answer in the model, we assumed the same answer as per expert 3.

The probability of having IBD after colonoscopy was also estimated based on the findings in Patel et al. (2015).[56] Thus, the probability of having IBD after colonoscopy, was assumed to follow a Beta(11, 198) distribution. Then, it was assumed that patients with a colonoscopy confirming IBD, would have the same response rate regardless the result of SeHCAT. Thus, IBD response is assumed to be the same as the one derived from Table 10, i.e., a mean of 72% and a standard deviation of 5%, modelled as a Beta(49, 19) distribution.

The majority of patients with a negative SeHCAT test receive IBS-D treatment. Since SeHCAT was negative for these patients, it might be assumed that most patients who have BAD are not included in the group receiving IBS-D treatment. Hence, it is expected that the response rate to IBS-D treatment in the SeHCAT negative sub-population to be higher than in the No SeHCAT strategy sub-population (see Table 11). As in the previous assessment of SeHCAT,[16] no data were available to confirm whether this assumption is correct and if so, how much higher the response rate should be. We used, therefore, the responses to our questionnaire to inform this probability. These can be seen in Table 16. After simulating triangular distributions, we found a mean of 56% and a standard

deviation of 5%, corresponding to a Beta(57, 45) distribution. The uncertainty associated to this parameter, was explored in scenario analyses.

Table 16: Probability of treating IBS-D patients successfully after SeHCAT negative in population 1, per expert

Expert	Percentage of patients successfully treated	Lowest	Highest
1	80	70	90
2	30	20	50
3	10	5	20
4	NR	NR	NR

Abbreviations: IBS-D = diarrhoea predominant irritable bowel syndrome, NR = not reported, SeHCAT = Tauroselcholic [75Selenium] acid
Note: Responses from expert 2 (same as in No SeHCAT) and 3 (lower than in No SeHCAT) did not match with the expectations of this probability being higher than in the No SeHCAT sub-population (it was estimated as 46% in the No SeHCAT group, and taking the average reported here would result in approximately 40%). Expert 3 answer was excluded from the calculation. Expert 2 answer was kept to account for some uncertainty but acknowledging that this is likely to be an underestimation.

Finally, the probability of responding to IBS-D treatment, without previous colonoscopy, was estimated as (100% - 5.3%)*56% = 53%. Assuming the same standard deviation of 5% as in Table 16, this was parameterised as a Beta(55, 49) distribution.

<u>No SeHCAT and BAS trial of treatment strategy</u>

As shown in Figure 3, seven different probabilities need to be estimated when BAS trial of treatment (without SeHCAT testing) is available. This strategy starts with the probability of responding to BAS treatment. In case of no response, patients are assumed to follow the same pathway as in the No SeHCAT strategy. Also, for this strategy, probabilities were informed by clinical experts.

Response to trial of BAS treatment

In the trial of treatment strategy, all patients are assumed to receive a BAS at the beginning of the modelled pathway. As in the SeHCAT 15% strategy, we assumed that this is either cholestyramine or colesevelam. The proportion of patients receiving each of the BAS options was estimated from the responses to our questionnaire. We found that 85% of patients started with cholestyramine and 15% with colesevelam. The proportion of patients treated with cholestyramine in the BAS trial of treatment strategy in the base-case was implemented as a Beta(48, 9) distribution. Note that this is different from the 50/50 distribution estimated for the SeHCAT strategy. While it is unclear why the BAS proportions might differ between strategies, the higher proportion of cholestyramine used in the trial of treatment strategy might be due to its lower costs. In any case, a range of different proportions was explored in scenario analyses.

In terms of response, it was not possible to distinguish between the type of BAS as in the SeHCAT 15% strategy. We estimated the response rate to BAS using the responses from our questionnaire, which are these are summarised in Table 17. Since, in the trial of treatment strategy all patients (including those without BAD) are treated with BAS, the overall response to BAS is expected to be lower than in the SeHCAT 15% strategy. After simulating triangular distributions, we found a mean of 30% and a standard deviation of 3%, corresponding to a Beta(60, 141) distribution. The uncertainty associated to this parameter, was explored in scenario analyses.

Table 17: Probability of response to trial of treatment with BAS in population 1, per expert

Expert	Percentage of response to BAS	Lowest	Highest
1	50	40	60
2	NR	NR	NR
3	10	5	15
4	NR	NR	NR
Abbreviations: bile acid sequestrants, NR = not reported.			

BAS adherence, initial response and duration of treatment effect are assumed to be the same as for the SeHCAT strategy described above. Thus, the probability of switching from cholestyramine to colesevelam was assumed to follow a Beta(357, 356) distribution (mean of 50% and a standard deviation of 2%).

When patients do not respond to BAS treatment, we assumed that patients follow the same pathway as in the No SeHCAT strategy. Thus, we first estimated the probability of undergoing colonoscopy, contingent on no response to BAS. Experts' answers can be seen in Table 18. These were used to simulate a triangular distribution to derive the parameters of a Beta distribution, as explained above. We found a mean of 90% and a standard deviation of 3%, corresponding to a Beta(89, 10) distribution. The uncertainty associated to this parameter, was explored in scenario analyses.

Table 18: Probability of colonoscopy after no response to trial of treatment with BAS in population 1, per expert

Expert	Percentage of colonoscopy	Lowest	Highest
1	80	70	90
2	NR	NR	NR
3	0	NR	NR
4	100	NR	NR
Abbreviations: bile acid sequestrants, NR = not reported. Note: Expert 2 indicated that this should not happen.			

The probability of having IBD after colonoscopy (contingent on no response to BAS) was assumed to follow a Beta(11, 198) distribution as estimated from Patel et al. (2015).[56] IBD response after colonoscopy was assumed to be the same as the one derived from Table 10, a mean of 72% and a standard deviation of 5%, corresponding to a Beta(49, 19) distribution.

We did not have any indication about the probability of IBS-D response after no response to BAS and colonoscopy, but we assumed that this is expected to lie somewhere in between the 46% of the No SeHCAT strategy and the 56% of the SeHCAT 15% strategy. We estimated the parameters of a Beta distribution for the base-case assuming a mean response of 50% (modelling choice) and a 5% standard deviation (as in the SeHCAT strategy, from Table 16), which resulted in a Beta(52, 52) distribution. The uncertainty associated to this parameter was explored in scenario analyses. Finally, the probability of responding to IBS-D treatment, without previous colonoscopy, was estimated as (100% - 5.3%)*50% = 47%. Assuming the same standard deviation of 5% as in Table 16, this corresponds to a Beta(49, 55) distribution.

Health-related quality of life

A literature search was performed in an attempt to identify updated sources of utility values for both responders (no diarrhoea) and non-responders (diarrhoea) in the model. Papers presenting utility values in IBS and IBS-D patients were retrieved from the records identified using a title and abstract screening. This resulted in six papers, of which three were systematic reviews. None of the empirical studies identified reported utility values for the health states required. None of the systematic reviews reported utilities measured using the EQ-5D. Given that the previous assessment of SeHCAT identified EQ-5D utility values for the required health states in IBS patients,[16] it was assumed to use the same utility values previously identified, as described below.

Spiegel et al. (2009) described EQ-5D utilities for patients with IBS who showed either “considerable relief” after three months of usual care or “no considerable relief”.[57] This study found no significant difference between the sub-types of IBS. The second paper with health state specific utilities by Mearin et al. (2004) presented utility scores for high and low severity symptoms.[58] These were aggregated across IBS sub-types for patients with high frequency symptoms (present >50% of the time), assuming that the utility gain associated with response to treatment was equivalent to an improvement in symptom severity from high to low.

The updated review also failed to identify any evidence on the impact of BAS treatment on utility. For BAS responders, two scenarios were considered: one where BAS responders have the same

utility gain as IBS-D treatment responders and one where the utility gain is lower, due to the generally cited unpleasantness of cholestyramine, which remains the most commonly selected first line treatment based on clinical expert opinion. As there are no data available to support this smaller increment, for the base-case it was assumed that cholestyramine responders have 75% of the utility increment observed in IBS-D treatment. Colesevelam responders were assumed to have the full utility increment as per IBS-D. A utility decrement due to colonoscopy was not included in the model since this was expected to have a negligible impact on the cost effectiveness results. The base-case utility values are summarised in Table 19.

Table 19: Base-case utility values for responders and non-responders, population 1

Non-responders/diarrhoea		
	Mean	SE
Mearin, 2004[58]	0.704	0.026
Spiegel, 2009 [57]	0.730	0.037
RE estimate	0.712	0.021
IBD/IBS-D/colesevelam responders/no diarrhoea		
	Mean	SE
Mearin, 2004[58]	0.775	0.014
Spiegel, 200 [57]	0.780	0.037
RE estimate	0.776	0.013
Cholestyramine responders/no diarrhoea		
	Mean	SE
Assumption	0.760	0.020
Abbreviations: BAS = bile acid sequestrants, IBD = inflammatory bowel disease, IBS-D = diarrhoea predominant irritable bowel syndrome, RE = random effects, SE = standard error		

Resource use and costs

Five different costs groups were distinguished in the model: a) the costs of a SeHCAT test, b) treatment of BAD with BAS, c) treatment of IBS-D, d) treatment of IBD and e) the cost of a colonoscopy.

The cost of the SeHCAT capsule was sourced from the manufacturer as £195. The tariff for administering this diagnostic test in the NHS was estimated at £282 (HRG Code RN14Z).[59] Thus, we arrived at a total cost of £477.

Patients with a positive SeHCAT test result were assumed to receive treatment with a BAS, either cholestyramine or colesevelam. The prices of the medications were derived from the BNF.[60] Exact details on medication use, dosage and fraction of patients receiving the treatment are presented in Appendix 7. We estimated the cost of BAS treatment taking the average of the dosage values reported by the experts. Thus, for cholestyramine we assumed a dosage of 5g per day resulting in a

cost of £0.35 per day, and for colesevelam we assumed a dosage of 2.5g per day resulting in a cost of £2.56 per day.

For the treatment of IBS-D, we distinguished three types of resource use: a) medication, b) diet therapy and c) psychological therapy. All of these were estimated based on expert opinion.

Patients treated for IBS-D may use a wide variety of medication. The experts consulted listed for example loperamide, codeine, and tricyclic antidepressants. We estimated the cost of medication for IBS-D taking the average of the dosage values and proportion of patients reported by the experts. Table 20 presents the (weighted) costs of medication per day. The prices of the medications were derived from the BNF.[60] Exact details on medication use, dosage and fraction of patients receiving the treatment are presented in Appendix 6, including the ranges suggested by the experts.

Table 20: Daily IBS-D medication costs

Drug	Percentage of patients (mean, lowest, highest)			Costs/day	Weighted average (mean, lowest , highest)		
Buscopan	0.15*	0.01	0.4	£0.11	£0.0161	£0.0011	£0.0429
Loperamide	0.57*	0.02	1	£0.05	£0.0300	£0.0011	£0.0527
Amitriptyline	0.24*	0.01	0.5	£0.04	£0.0102	£0.0004	£0.0212
Codeine	0.05	0.02	0.1	£0.12	£0.0059	£0.0024	£0.0118
				Total	**£0.06**	**£0.01**	**£0.13**

Abbreviations: IBS-D = diarrhoea predominant irritable bowel syndrome.
*Weighted average of experts' answers to the questionnaire
Note: alverine and mebeverine were excluded from the calculations, as experts did not provide full information needed to include them in the total costs.

Table 21 presents the responses of the experts to the question how many IBS-D patients would visit a dietician and how many visits would be involved. The cost of one visit to a dietician was estimated at £86.38 (NHS reference cost 2018/19, inflated to 2020).[60] Dietician costs for IBS-D were assumed for six months.

Table 21: Resource use and costs dietician IBS-D treatment, per expert

Percentage of patients	Number of visits (lowest, highest)		Costs per visit	Weighted cost per day (mean, lowest, highest)		
0.05	1	2	£86.38	£6.48	£4.32	£8.64
0.1	2	2	£86.38	£17.28	£17.28	£17.28
0.1	1	2	£86.38	£12.96	£8.64	£17.28
			Total	**£12.24**	**£10.08**	**£14.40**

Abbreviations: IBS-D = diarrhoea predominant irritable bowel syndrome.

Table 22 presents the response of the experts to the question how many patients would receive some form of psychological therapy and how many visits would be involved. The cost price of cognitive behavioural therapy was estimated at £174 per visit (NHS reference cost 2021/22),[59] for counselling £69.14 per visit and for hypnotherapy £101.41 per visit (previous report, inflated to 2020).[16] Psychological costs for IBS-D were also assumed for six months.

Table 22: Resource use and costs psychological treatment IBS-D patients, per expert

Type of therapy	% of patients (lowest, highest)		Number of visits (lowest, highest)		Costs per visit	Weighted cost per day (mean, lowest, highest)		
CBT	0.05	0.15	3	5	£171.00	£68.40	£25.65	£128.25
	0.01	0.05	2	2	£171.00	£10.26	£3.42	£17.10
	0.09	0.09	1	1	£171.00	£15.39	£15.39	£15.39
Hypnotherapy	0.01	0.05	2	2	£101.41	£6.08	£2.03	£10.14
	0.01	0.05	2	2	£101.41	£6.08	£2.03	£10.14
	0.01	0.01	1	1	£101.41	£1.01	£1.01	£1.01
Average CBT						**£31.35**	**£14.82**	**£53.58**
Average Hypnotherapy						**£4.39**	**£1.69**	**£7.10**
Total						**£35.74**	**£16.51**	**£60.68**

Abbreviations: CBT = cognitive behavioural therapy, IBS-D = diarrhoea predominant irritable bowel syndrome.

Patients treated for IBD may also use a wide variety of medication. The experts consulted listed for example 5ASA, azathioprine, and infliximab. We estimated the cost of medication for IBD taking the average of the dosage values and proportion of patients reported by the experts. Table 23 presents the (weighted) costs of medication per day. The prices of the medications were derived from the BNF.[60] Exact details on medication use, dosage and fraction of patients receiving the treatment are presented in Appendix 6, including the ranges suggested by the experts.

Table 23: Daily IBD medication costs

Drug	Percentage of patients (mean, lowest, highest)			Costs/ day	Weighted cost per day (mean, lowest, highest)		
asacol	0.8	0.7	0.9	£3.92	£3.14	£2.75	£3.53
octasa	0.8	0.7	0.9	£2.69	£2.15	£1.88	£2.42
pentasa	0.8	0.7	0.9	£2.46	£1.97	£1.72	£2.21
azathioprine*	0.5	0.4	0.6	£0.20	£0.10	£0.08	£0.12
infliximab**	0.2	0.1	0.3	£49.01	£9.80	£4.90	£14.70
adalimumab	0.2	0.1	0.3	£22.88	£4.58	£2.29	£6.86
				Total	**£21.73**	**£13.62**	**£29.85**

Abbreviations: IBD = inflammatory bowel disease.
*Dosage of 2.3mg/kg is weighted average of expert's answers, assumed 78kg. Per previous SeHCAT report.
**10mg/kg, assumed 78kg. Per previous SeHCAT report. Assumed maintenance dosing every 8 weeks.[61]
Note: vedolizumab, steroids, biologicals, and immunosuppressants are excluded, as experts did not give the full information.

Table 24 presents the responses of the experts to the question how many IBD patients would visit a dietician and how many visits would be involved. The cost of one visit to a dietician was estimated at £86.38 (NHS reference cost 2018/19, inflated to 2020).[60] Dietician costs for IBD were assumed for six months.

Table 24: Resource use and costs dietician IBD treatment, per expert

% of patients	Number of visits (lowest, highest)		Costs per visit	Weighted cost per day (mean, lowest, highest)		
0.1	1	4	£86.38	£21.59	£8.64	£34.55
0.8	4	4	£86.38	£276.41	£276.41	£276.41
			Total	**£149**	**£142.52**	**£155.48**
Abbreviations: IBD = inflammatory bowel disease.						

Table 25 presents the response of the experts to the question how many IBD patients would receive some form of psychological therapy and how many visits would be involved. The cost price of cognitive behavioural therapy was estimated at £174 per visit (NHS reference cost 2021/22),[59] for counselling £69.14 per visit and for hypnotherapy £101.41 per visit (previous report, inflated to 2020).[16] Psychological costs for IBD were also assumed for six months.

Table 25: Resource use and costs psychological treatment IBD patients, per expert

Type of therapy	% of patients (lowest, highest)		Number of visits* (lowest, highest)		Costs/visit	Weighted cost per day (mean, lowest, highest)		
CBT	1	1	3	5	£174.00	£696.00	£522.00	£870.00
	0.5	0.15	2	2	£174.00	£113.10	£174.00	£52.20
	0.1	0.1	1	1	£174.00	£17.40	£17.40	£17.40
Counselling	0.2	0.2	1	1	£69.14	£13.83	£13.83	£13.83
Average CBT						**£275.50**	**£237.80**	**£313.20**
Average counselling						**£13.83**	**£13.83**	**£13.83**
Total						**£289.33**	**£251.63**	**£327.03**
Abbreviations: CBT = cognitive behavioural therapy, IBD = inflammatory bowel disease. * Same number of visits as in IBS-D								

Cost of colonoscopy in the model was calculated as 90% colonoscopy plus 10% computed tomography colonoscopy (CTC), based on one expert answer to our questionnaire. For the cost of colonoscopy we used diagnostic colonoscopy £469 (HRG-code FE32Z). The cost of CTC was calculated as the average of the following elements: Single Photon Emission Computed Tomography with Computed Tomography (SPECT-CT) of One Area (£96, HRG-code RN04A), SPECT-CT of Two or Three Areas (£215, HRG-code RN05A), and SPECT-CT of more than Three areas (£311, HRG-code RN06A) for 18 years old and older. CTC cost was estimated to be £175.75.

All cost parameters included in the model, except the costs of a SeHCAT test, which are assumed to be fixed, were implemented as a triangular distribution with the limits calculated form the experts' responses and shown in the tables above. We acknowledge that this is not the most commonly used parameterisation and that it has certain limitations. First, we attempted to fit a Gamma distribution to the cost estimates derived from the experts' answers. However, this was not possible for all cost parameters since the method used to fit a Gamma distribution did not find a solution for all cost parameters. Given that it was not possible to implement all cost input parameters as Gamma distributions, we adopted a more pragmatic and simpler approach and cost input parameters were modelled as triangular distributions.

Markov model BAD-1 population

Patients enter the Markov model in the "No diarrhoea" or the "Diarrhoea" health state depending on whether they had an initial treatment response in the short-term decision analytic model or not. The Markov model is then parameterised according to treatment, thus, in practice, there are four different Markov models: two BAS models (one for cholestyramine and one for colesevelam), an IBD model and an IBS-D model. The cycle length used is six months, in line with the previous assessment of SeHCAT.[16]

In the previous assessment of SeHCAT, it was concluded that "*there are clear indications that patients may move from ND to D and vice versa. However, from the data available, these transition probabilities are impossible to quantify*".[16] A range of (a priori) equally plausible scenarios with various values was then defined with the purpose to show the impact of the transition probability assumptions on the model outcomes, without selecting one as a base-case. As explained above, testing the impact of these assumptions required a large number of scenario analyses, resulting in very different cost effectiveness outcomes, without knowing the actual plausibility of such scenarios. In this assessment, transitions between the "Diarrhoea" and "No diarrhoea" health states were thus informed by clinical expert opinion, since new clinical data regarding the long-term effectiveness of BAS, IBD and IBS-D treatments were not identified in our systematic review.

Clinical experts consulted for this assessment suggested that, in general, patients initially responding to BAS and to IBS-D treatments are expected to respond for their entire lifetime and that no relapses in the long-term should be expected. Therefore, for the base-case it was assumed that BAS and IBS-D responders start the Markov model in the "No Diarrhoea" health state and the only possible transition is to the "Death" health state (i.e., transition to "Diarrhoea" is not possible). To account

for the uncertainty regarding this base-case assumption, scenarios were conducted where relapses were allowed to occur over the time horizon.

Regarding IBD patients, experts indicated that unlike IBS-D patients, relapses are expected to occur after initial response to treatment. Therefore, transitions between “No Diarrhoea” and “Diarrhoea” were allowed in the IBD Markov model. In particular, it was assumed in the base-case that IBD responders experience on average one relapse every five years, as suggested by some clinical experts’ responses to our questionnaire. Since we assumed a time horizon of 50 years, a total 10 cycles (of six months) of relapse were considered (1 cycle = six months, 60 months = five years). Setting the transition probability from "No diarrhoea" to "Diarrhoea" equal to 0.0045, results in approximately five undiscounted life years in the "Diarrhoea" health state. Therefore, this was chosen for the base-case. Several scenarios were run to test the impact of this assumption on the cost effectiveness results.

In line with the previous assessment of SeHCAT,[16] we also assumed that no excess mortality is associated with BAD.[55] Age and gender specific mortality estimates were derived from the most recent England and Wales Interim Life Tables.[62] Using the study by Summers et al. (2016),[3] we assumed that the average age in population 1 was 50 years, and the ratio of male/female was 35/75. Although these age and gender estimates are for a wider population than that specified in our inclusion criteria, looking at the patient characteristics in Summers et al. (2016), we estimated that more than half of patients would fall into our population of interest. Since UK specific demographic data were not used in the previous assessment of SeHCAT, we considered Summers et al. (2016) to be the best option.

The Markov models for responders use the same resource use, costs and utility estimates as reported in previous sections for the short-term decision analytic model. Utilities were adjusted for ageing using the equation estimated by Ara and Brazier (2010).[63] For patients who did not respond to any treatment in the initial phase, i.e. the patients entering the Markov model in the "Diarrhoea" health state, we assumed that patients use loperamide to reduce the stool frequency.

Diagnostic model, population 2

The main difference with respect to the short-term model for population 1 is that Crohn's patients are assumed to already have had colonoscopy to diagnose Crohn's disease.

Probabilities

No SeHCAT strategy

As shown in Figure 4, only the probability of responding to diarrhoea treatment for Crohn's patients with suspected BAD (represented by the circle in the "No SeHCAT test" branch) has to be estimated when SeHCAT and BAS trial of treatment are not available. Diarrhoea treatments for Crohn's patients may vary between patients because the diarrhoea may occur as a symptom of relapse but also when patients are in remission. In the first case, treatment may be targeted at treating the relapse, since this is expected to decrease the diarrhoea. In the second case, diarrhoea-specific treatments such as loperamide, codeine, diet or nutritional therapies may be considered. Thus, due to the wide range of treatment options and the various orders in which they are attempted, it was not possible to find data from the literature regarding how Crohn's patients without ileal resection will eventually, after trying various options, respond to their treatment for the diarrhoea. Therefore, response to diarrhoea treatment was estimated from the answers to the questionnaire obtained from the experts. These are presented in Table 26. The approach described above of simulating triangular distributions to derive the parameters of a Beta distribution was also followed in this case. We found a mean of 40% and a standard deviation of 6% and it was implemented as a Beta(30, 45) distribution.

There is uncertainty regarding the initial response to diarrhoea treatment and the and duration of this response in Crohn's patients without ileal resection. Based on the experts' answers to our questionnaire, we assumed in the base-case that response is achieved within six months since start of treatment, even though this is also variable, as acknowledged by the clinical experts. Despite the uncertainty regarding the duration of the treatment effect, we assumed that relapses are expected as assumed for IBD patients in population 1. Scenarios to test this assumption, were explored in the scenario analysis section of this report.

Table 26: Probability of successfully treating diarrhoea, in population 2, when SeHCAT is not available, per expert

Expert	Percentage of patients successfully treated	Lowest	Highest
1	70	50	80
2	NR	NR	NR
3	10	5	25
4	NR	NR	NR

Abbreviations: NR = not reported, SeHCAT = Tauroselcholic [75Selenium] acid
Note: Expert 2 mentioned that if their underlying Crohn's is treated BAD may resolve. If Crohn's is active BAS achieves little often.

SeHCAT 15% strategy

As shown in Figure 4, five different probabilities need to be estimated when SeHCAT is available. Note that three of these correspond to the probabilities associated to SeHCAT testing, i.e., the probability of testing positive, the probability of responding to BAS treatment (contingent on being SeHCAT positive) and the probability of discontinuation from BAS treatment. Additionally, for patients testing negative for SeHCAT or not responding to BAS treatment after testing positive, the probability of responding to diarrhoea treatment for Crohn's patients with suspected BAD described above for No SeHCAT has to be estimated. SeHCAT related probabilities were estimated using the results from our clinical effectiveness review. The remaining probabilities were informed by clinical experts. Since our questionnaire did not include questions about patients not responding to BAS treatment after a positive SeHCAT result, we assumed for these patients, the same estimates as those obtained for patients with a negative SeHCAT result. Thus, in practice, four probabilities were estimated for the SeHCAT 15% strategy.

The probability of a positive test result in the Crohn's population was estimated from the study by Smith et al. (2000), as explained in Section 3.[6] This estimate can be seen in Table 27.

Table 27: Probability of positive SeHCAT result in population 2 (Crohn's disease and suspected BAD), cut-off 15%.

Study	N	Number SeHCAT positive	Probability SeHCAT positive
Smith 2000[6]	44	24	0.55
		Mean	0.55
		SE	0.08
Abbreviations: N = sample size study, SE = standard error, SeHCAT = Tauroselcholic [75Selenium] acid			

Patients with a positive SeHCAT test result are assumed to be treated with a BAS. Based on the responses to our questionnaire, we assumed in the base-case that 63% of patients started with cholestyramine and 37% with colesevelam. In terms of response, however, it was not possible to distinguish between the type of BAS and estimated the response rate to BAS, in general, based on Smith (2000).[6] This can be seen in Table 28. Note this is based on a small sample size and the relatively high response rate does not seem to be in line with experts' expectations, who in the answers to our questionnaire estimated this probability to be at most 70%. The uncertainty surrounding this input parameter was explored in scenario analyses.

Again, the answers provided by the experts seem to suggest that initial response to BAS treatment is achieved within 6 months since start of treatment. However, there is uncertainty regarding treatment effect duration. For consistency with the base-case in population 1 and in the absence of a better evidence source, we also assumed a lifetime effect as in this population (thus, in the Markov

model there is no transition to the Diarrhoea health state for patients initially responding to treatment), but this is unclear. Scenarios with long-term relapses were also explored in the scenario analysis section of this report.

Table 28: Probability of a positive BAS response in population 2 (Crohn's disease and suspected BAD), cut-off 15%

Study	N	Number positive response	Probability positive response
Smith 2000[6]	9	8	0.89
		Mean	0.89
		SE	0.11*
Abbreviations: BAS = bile acid sequestrants, N = sample size study, SE = standard error			

Regarding adherence to BAS treatment, the same approach described population 1 was also followed for this population. Thus, the impact of reduced compliance was assumed to be included in response and only switching from cholestyramine to colesevelam was permitted in the model. The probability of switching from cholestyramine to colesevelam was then estimated based on the experts' responses shown in Table 29. Again, we followed the approach described above of simulating triangular distributions to derive the parameters of a Beta distribution. We found a mean of 44% and a standard deviation of 3%, corresponding to a Beta(132, 169).

Table 29: Probability of cholestyramine drop-out in population 2, per expert

Expert	% of patients dropping-out	Lowest	Highest
1	15	10	30
2	70	NR	NR
3	2	2	5
4	NR	NR	NR
Abbreviations: NR = not reported			

When patients do not respond to BAS after a positive SeHCAT result, or when the SeHCAT results is negative, we assumed that patients follow the same pathway as in the No SeHCAT strategy. This part of the model was informed by clinical experts only. Since our questionnaire did not include questions about no response to BAS after a positive SeHCAT results, the same estimates as those obtained for patients with a negative SeHCAT result were assumed.

Patients with a negative SeHCAT test receive treatment for their chronic diarrhoea. Since SeHCAT was negative for these patients, it might be assumed that most patients who have BAD are not included in the group receiving chronic diarrhoea treatment. Hence, it is expected that the response rate to chronic diarrhoea treatment in the SeHCAT negative sub-population to be higher than in No

SeHCAT. In the previous assessment of SeHCAT,[16] no data were available to confirm this assumption. In fact, it was assumed the same increase as in the IBS-D population. In this assessment, we used the responses to our questionnaire to inform this probability. These can be seen in Table 30. After simulating triangular distributions, we found a mean of 42% and a standard deviation of 6%, corresponding to a Beta(26, 35) distribution. Note that this estimate is higher (as expected) but close to the same probability estimated for No SeHCAT (40%). In population 1, this difference was larger. The uncertainty associated to this parameter, will be further explored in scenario analyses.

Table 30: Probability of treating chronic diarrhoea Crohn's patients successfully after SeHCAT negative in population 2, per expert

Expert	% of patients successfully treated	Lowest	Highest
1	70	50	90
2	NR	NR	NR
3	10	5	25
4	NR	NR	NR
Abbreviations: NR = not reported, SeHCAT = Tauroselcholic [75Selenium] acid			

No SeHCAT and BAS trial of treatment strategy

As shown in Figure 4, three different probabilities need to be estimated when BAS trial of treatment (without SeHCAT testing) is available. This strategy starts with the probability of responding to BAS treatment. In case of no response, patients are assumed to follow the same pathway as in the No SeHCAT strategy. For this strategy, probabilities were informed by clinical experts.

In the trial of treatment strategy, all patients are assumed to receive a BAS at the beginning of the modelled pathway. We assumed that this is either cholestyramine or colesevelam. The proportion of patients receiving each of the BAS options was estimated from the responses to our questionnaire and they are summarised in Table 31. It was estimated that 58% of patients started with cholestyramine and 42% with colesevelam. Note that this is different from the 63/37 distribution assumed in the SeHCAT strategy. It is also unclear why the BAS proportions differed between strategies for this population. Furthermore, for population 1 it was argued that the higher proportion of cholestyramine used in the trial of treatment strategy might be due to its lower costs. In this population, this does not happen and it is unclear why. In any case, a range of different proportions was explored in scenario analyses.

Table 31: Probability of trial of treatment with cholestyramine in population 2, per expert

Expert	Percentage of patients treated with cholestyramine	Lowest	Highest
1	90	80	100
2	20	10	50
3	0	0	0
4	NR	NR	NR

Abbreviations: NR = not reported.
Note: Expert 2 also mentioned 10% for colesevelam. However, this was not included in the model.

In terms of response, we did not distinguish between the type of BAS. In the trial of treatment strategy all patients are treated with BAS, also those with no BAD, therefore, response to BAS is expected to be lower than in the SeHCAT 15% strategy. The probability of response to BAS trial of treatment was estimated from the answers to our questionnaire and they are summarised in Table 32. After simulating triangular distributions, we found a mean of 33% and a standard deviation of 3%, corresponding to a Beta(71,146). The uncertainty associated to this parameter, will be further explored in scenario analyses.

Table 32: Probability of response to trial of treatment with BAS in population 2, per expert

Expert	% of response to BAS	Lowest	Highest
1	50	40	60
2	NR	NR	NR
3	15	10	20
4	NR	NR	NR

Abbreviations: BAS = bile acid sequestrants, NR = not reported.

BAS adherence, initial response and duration of treatment effect are assumed to be the same as for the SeHCAT strategy. Thus, the probability of switching from cholestyramine to colesevelam was assumed to follow a Beta(132, 169) distribution. Also, for this population, we did not have any indication about what happens to patients after no response to BAS but, as we did for population 1, we assumed that this is expected to be somewhere between the 40% of the No SeHCAT strategy and the 42% of the SeHCAT 15 % strategy. Thus, the only choice possible was 41% (modelling choice) and then we estimated the parameters of a Beta distribution for the base-case assuming a 6% standard deviation as in the SeHCAT strategy, which resulted in a Beta(25, 36).The uncertainty associated to this parameter, was explored in scenario analyses.

Health-related quality of life

No studies were identified that specifically address the issue of diarrhoea in Crohn's patients. It was thus assumed that the utility decrement due to diarrhoea in this patient population is the same as

for population 1. In order to calculate QALYs, we utilised the utility estimate from Buxton et al. (2007), where EQ-5D utilities were estimated by mapping from the Inflammatory Bowel Disease Questionnaire (IBDQ) in a sample of 3,672 patients with moderate to severe active Crohn's disease.[64] A mean of 0.7 was found with a standard deviation of 0.25. It was assumed that this utility reflects the quality of life in the diarrhoea health state, and thus, the utility for the no diarrhoea health state would be 0.764. Again, in the base-case it was assumed that BAS (cholestyramine) responders would have a utility gain of 75% of diarrhoea decrement, to account for the tolerability issues associated with cholestyramine. This resulted in an estimated utility of 0.748 for cholestyramine responders. Colesevelam responders were assumed to have the full utility increment as per no diarrhoea. The base-case utility values are summarised in Table 33.

Table 33: Base-case utility values for responders and non-responders, population 2

Non-responders/diarrhoea		
	Mean	SE
Buxton, 2007[64]	0.70	0.004
Responders/no diarrhoea		
	Mean	SE
Assumption	0.764	0.004
BAS (cholestyramine) responders/no diarrhoea		
	Mean	SE
Assumption	0.748	0.004

Abbreviations: BAS = bile acid sequestrants, SE = standard error

Note: In population 1, the difference between diarrhoea and no diarrhoea is: 0.776-0.712 = 0.064. Thus, since diarrhoea here is 0.7, then no diarrhoea is 0.764. No diarrhoea in BAS is then 0.064*0.75 = 0.048, thus 0.748.

Resource use and costs

The costs considered for population 2 can be classified into three groups: a) the costs of a SeHCAT test, b) treatment with BAS and c) treatment of diarrhoea in Crohn's patients.

The cost of a SeHCAT test is the same as for population 1. The cost of the SeHCAT capsule was sourced from the manufacturer at £195 and the tariff for administering the test was estimated at £282; thus, we arrived at a total cost of £477.

Patients with a positive SeHCAT test result were assumed to receive treatment with a BAS, either cholestyramine or colesevelam. The prices of the medications were derived from the BNF.[60] Exact details on medication use, dosage and fraction of patients receiving the treatment are presented in Appendix 7. We estimated the cost of BAS treatment taking the average of the dosage values reported by the experts. We assumed the same dosages as in population 1, thus, for cholestyramine

we assumed a dosage of 5g per day resulting in a cost of £0.35 per day, and for colesevelam we assumed a dosage of 2.5g per day resulting in a cost of £2.56 per day.

Medical treatment of chronic diarrhoea in Crohn's patients without ileal resection was based on the previous SeHCAT report.[16] Table 34 shows the (weighted) costs of medication per day. The prices of the medications were derived from the BNF.[60] Exact details on medication use, dosage and fraction of patients receiving the treatment are presented in Appendix 6.

Table 34: Daily costs of diarrhoea medication in Crohn's patients*

Drug	Percentage of patients (mean, lowest, highest)			Costs/day	Weighted cost per day (mean, lowest, highest)		
Loperamide	0.6	0.25	1	£0.13	£0.08	£0.03	£0.13
Codeine	0.4	0	0.8	£0.12	£0.05	£0.00	£0.09
Corticosteroids	0.77	0.5	1	£1.38	£1.06	£0.69	£1.38
Adalimumab	0.1	0	0.3	£22.88	£2.29	£0.00	£6.86
Pentasa	0.6	0.4	0.7	£2.46	£1.48	£0.98	£1.72
Azathioprine	0.5	0.2	0.7	£0.17	£0.09	£0.03	£0.12
BAS	0.5	0.05	0.9	£1.46	£0.73	£0.07	£1.31
				Total	**£5.76**	**£1.81**	**£11.62**

Abbreviations: BAS = bile acid sequestrants
* Calculation details in Appendix X.

Markov model, population 2

The approach to derive transitions between the "Diarrhoea" and "No Diarrhoea" health states is the same as the one described for population 1 above. Patients enter the Markov model in the "No diarrhoea" or the "Diarrhoea" health state depending on whether they had an initial treatment response or not. The Markov model is then parameterised according to treatment. In practice, there are three different Markov models: two BAS models (one for cholestyramine and one for colesevelam) and one model for the treatment of chronic diarrhoea in Crohn's patients. The cycle length used is also six months.

Clinical experts consulted for this assessment suggested that, in general, patients initially responding to BAS are expected to respond for their entire lifetime and that no relapses in the long-term should be expected. Therefore, for the base-case it was assumed that BAS responders start the Markov model in the "No Diarrhoea" health state and the only possible transition is to the "Death" health state (i.e., transition to "Diarrhoea" is not possible). To account for the uncertainty regarding this assumption, scenarios were conducted where relapses are allowed to occur over the time horizon. For responders to diarrhoea treatment for Crohn's disease (without BAS), we followed the same approach as described for IBD patients in population 1, where a few relapses are expected to occur

during patients' lifetime. Therefore, transitions between “No Diarrhoea” and “Diarrhoea” are allowed in the Markov model. As in population 1, it was assumed in the base-case that responders to diarrhoea treatment (without BAS) experience on average one relapse every five years. Since we assumed a time horizon of 50 years, a total 10 cycles of relapse were considered (1 cycle = six months, 60 months = five years). Setting the transition probability from "No diarrhoea" to "Diarrhoea" equal to 0.00575, results in approximately five undiscounted life years in the "Diarrhoea" health state. Therefore, this was chosen for the base-case. Several scenarios were run to test the impact of this assumption on the cost effectiveness results

Regarding mortality, we followed the same approach as in the previous assessment of SeHCAT,[16] where no reports were found in the literature that chronic diarrhoea itself in Crohn’s patients would lead to excess mortality.[55] However, patients with Crohn’s disease have a shorter life expectancy compared to the general population. A meta-analysis by Canavan et al. (2007), showed a pooled estimate of the standardised mortality ratio (SMR) of 1.52 (CI: 1.32 to 1.74).[65] Thus, we have applied this SMR to the overall mortality in the UK population, for which we used again the most recent England and Wales Interim Life Tables.[62] Using the study by Summers et al. (2016),[3] we assumed that the average age in population 1 was 50 years, and the ratio of male/female was 35/75. We assumed the same age/gender distribution as in population 1 because the study does not separate between different subpopulations. Nevertheless, we still considered Summers et al. (2016) to be the best option also for the Crohn's population.

Also, for population 2, the Markov models for responders use the same resource use, costs and utility estimates as reported in previous sections for the short-term decision analytic model. Utilities were adjusted for ageing using the equation estimated by Ara and Brazier (2010).[63] For patients who did not respond to any treatment in the initial phase, i.e. the patients entering the Markov model in the "Diarrhoea" health state, we assumed that patients use loperamide to reduce the stool frequency.

4.2.3 Summary Input Parameters (TABLE ONLY)

Table 35: Model parameters, population 1

Category	Description	Mean value	Distribution	Distribution parameters
Branch probability	Probability of undergoing colonoscopy in No SeHCAT strategy	0.74	Beta	α = 706 β = 242
	Probability of having IBD after colonoscopy	0.053	Beta	α = 11 β = 198
	Probability of responding to IBD treatment (in IBD patients)	0.72	Beta	α = 49 β = 19
	Prob. of responding to IBS-D treatment	0.46	Beta	α = 17

Category	Description	Mean value	Distribution	Distribution parameters
	when no SeHCAT is available after colonoscopy			β = 20
	Prob. of responding to IBS-D treatment when no SeHCAT is available without colonoscopy	0.44	Beta	α = 16 β = 20
	Probability of having a positive SeHCAT test at cut-off value 15%	0.454	Beta	α = 2.10 β = 2.52
	Probability of responding to BAS given a positive SeHCAT test at cut-off value 15%	0.638	Beta	α = 1.00 β = 0.57
	Prob. of being treated with cholestyramine (as opposed to colesevelam) in SeHCAT 15% strategy	0.5	Beta	α = 7700 β = 7701
	Prob. of switching from cholestyramine to colesevelam	0.5	Beta	α = 357 β = 356
	Probability of undergoing colonoscopy after SeHCAT negative	0.49	Beta	α = 338 β = 351
	Prob. of responding to IBS-D treatment after SeHCAT negative and colonoscopy	0.56	Beta	α = 57 β = 45
	Prob. of responding to IBS-D treatment after SeHCAT negative without colonoscopy	0.53	Beta	α = 55 β = 49
	Prob. of being treated with cholestyramine (as opposed to colesevelam) in BAS TOT strategy	0.85	Beta	α = 48 β = 9
	Probability of responding to BAS trial of treatment	0.30	Beta	α = 60 β = 141
	Prob. of undergoing colonoscopy after no response to BAS trial of treatment	0.90	Beta	α = 89 β = 10
	Prob. of responding to IBS-D treatment after no response to BAS trial of treatment and colonoscopy	0.50	Beta	α = 52 β = 52
	Prob. of responding to IBS-D treatment after no response to BAS trial of treatment without colonoscopy	0.47	Beta	α = 49 β = 55
Transition probability	Transition probability from “Diarrhoea” to “No diarrhoea”	0	Fixed	NA
	Transition probability from “No diarrhoea” to “Diarrhoea” (IBS-D, BAS)	0	Fixed	NA
	Transition probability from “No diarrhoea” to “Diarrhoea” (IBD)	0.0045	Triangular	a = 0.0035 b = 0.0055 c = 0.0045
Cost	Cost per day of IBS-D medication	£0.06	Triangular	a = 0.01 b = 0.13 c = 0.06
	Diet costs per 6 months associated to IBS-D	£12.24	Triangular	a = 10.08 b = 14.40 c = 12.24
	Psychological costs per 6 months	£35.74	Triangular	a = 16.51

Category	Description	Mean value	Distribution	Distribution parameters
	associated to IBS-D			b = 60.68 c = 35.74
	Cost per day of IBD medication	£21.73	Triangular	a = 13.62 b = 29.85 c = 21.73
	Diet costs per 6 months associated to IBD	£149	Triangular	a = 142.52 b = 155.48 c = 149.00
	Psychological costs per 6 months associated to IBD	£289.33	Triangular	a = 251.63 b = 327.03 c = 289.33
	Cost per day of BAS medication (cholestyramine)	£0.35	Triangular	a = 0.14 b = 0.56 c = 0.35
	Cost per day of BAS medication (colesevelam)	£2.56	Triangular	a = 1.28 b = 3.84 c = 2.56
	Cost SeHCAT capsule	£195	Fixed	NA
	Cost for administering SeHCAT test	£282	Fixed	NA
	Maintenance and service costs of SeHCAT test	£0	Fixed	NA
	Cost of colonoscopy	£440	Triangular	a = 352 b = 528 c = 440
	Cost per day loperamide	£0.03	Triangular	a = 0.001 b = 0.053 c = 0.030
Utility	Utility associated to health state "Diarrhoea"	0.71	Beta	α = 317.95 β = 128.40
	Utility associated to health state "No diarrhoea" (IBS-D, IBD, colesevelam)	0.78	Beta	α = 781.54 β = 226.15
	Utility associated to health state "No diarrhoea" (cholestyramine)	0.76	Beta	α = 345.92 β = 109.38

Abbreviations: BAS = bile acid sequestrants, IBD = inflammatory bowel disease, IBS-D = diarrhoea predominant irritable bowel syndrome, NA = not applicable, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.

Table 36: Model parameters, population 2

Category	Description	Mean value	Distribution	Distribution parameters
Branch probability	Probability of responding to diarrhoea treatment for Crohn's patients when SeHCAT is not available	0.40	Beta	α = 30 β = 45
	Prob. of being treated with cholestyramine (as opposed to colesevelam) in SeHCAT 15% strategy	0.63	Beta	α = 43 β = 26
	Prob. of switching from cholestyramine to colesevelam	0.44	Beta	α = 132 β = 169

Category	Description	Mean value	Distribution	Distribution parameters
	Probability of having a positive SeHCAT test at cut-off value 15%	0.55	Beta	α = β =
	Prob. of responding to BAS given a positive SeHCAT test at cut-off value 15%	0.89	Beta	α = β =
	Prob. of responding to diarrhoea treatment for Crohn's patients after SeHCAT negative	0.42	Beta	α = 26 β = 35
	Prob. of being treated with cholestyramine (as opposed to colesevelam) in BAS TOT strategy	0.58	Beta	α = 27 β = 19
	Probability of responding to BAS TOT	0.33	Beta	α = 71 β = 146
	Prob. of responding to diarrhoea treatment for Crohn's after no response to BAS trial of treatment	0.50	Beta	α = 25 β = 36
Transition probability	Transition probability from “Diarrhoea” to “No diarrhoea”	0	Fixed	NA
	Transition probability from “No diarrhoea” to “Diarrhoea” (BAS)	0	Fixed	NA
	Transition probability from “No diarrhoea” to “Diarrhoea” (DT)	0.00575	Triangular	a = 0.00475 b = 0.00675 c = 0.00575
Cost	Cost per day of diarrhoea medication for Crohn’s patients	£5.76	Triangular	a = 1.81 b = 11.62 c = 5.76
	Cost per day of BAS medication (cholestyramine)	£0.35	Triangular	a = 0.14 b = 0.56 c = 0.35
	Cost per day of BAS medication (colesevelam)	£2.56	Triangular	a = 1.28 b = 3.84 c = 2.56
	Cost SeHCAT capsule	£195	Fixed	NA
	Cost for administering SeHCAT test	£282	Fixed	NA
	Maintenance and service costs of SeHCAT test	£0	Fixed	NA
Utility	Utility associated to health state “Diarrhoea”	0.70	Beta	α = 9,187 β = 3,937
	Utility associated to health state “No diarrhoea” (Crohn’s)	0.76	Beta	α = 8,609 β = 2,659
	Utility associated to health state “No diarrhoea”	0.75	Beta	α = 8,811 β = 2,969

Abbreviations: BAS = bile acid sequestrants, DT = diarrhoea treatment for Crohn's patients, NA = not applicable, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.

4.2.4 Overview of main model assumptions

Population 1 – Probabilities No SeHCAT strategy

- Colonoscopy takes place at the beginning of the No SeHCAT strategy to detect IBD patients.
- Response to IBD treatment is achieved within six months since start of treatment. No lifetime treatment effect was assumed, since relapses are expected after initial response.
- Response to IBS-D treatment is achieved within six months since start of treatment. We assumed a lifetime effect in the base-case, thus, in the Markov model there is no transition to the diarrhoea health state for patients initially responding to treatment.

Population 1 – Probabilities SeHCAT 15% strategy

- Patients testing negative for SeHCAT or not responding to BAS treatment after testing positive, are assumed to follow the same pathway as in the No SeHCAT strategy.
- Patients not responding to BAS treatment after a positive SeHCAT result or patients with a negative SeHCAT result were assumed to have the same estimates as those obtained for No SeHCAT strategy.
- Patients with a positive SeHCAT test result are assumed to be treated with a BAS (either cholestyramine or colesevelam). For treatment response, an overall response rate to BAS was estimated Initial response to BAS treatment is achieved within six months since start of treatment and a lifetime treatment effect duration is assumed.
- Patients with a colonoscopy confirming IBD, would have the same response rate regardless of the result of SeHCAT.
- The response rate to IBS-D treatment in the SeHCAT negative sub-population was assumed to be higher than in the No SeHCAT strategy sub-population.
- There is no BAS discontinuation but switching. BAS switching is allowed from cholestyramine to colesevelam only.
- Colesevelam seems to be well tolerated, thus, no drop out from colesevelam is modelled. Even though colesevelam drop-outs might occur in practice, this seems a reasonable assumption given that this is expected to happen in a small proportion of patients and the lack of information regarding how these patients will be treated afterwards.

- Drop-outs are assumed to occur in the first six months only. Therefore, long-term drop-out was not included in the model.

- Drop-out was assumed to have no effect on response rate. As explained above, it is assumed that the impact of reduced compliance on the response rate is implicitly included in the studies identified in our systematic review.

- Drop-out was assumed to have an effect on health-related quality of life and costs. Colesevelam is assumed to be associated with a higher utility than cholestyramine but it is also more costly.

Population 1 – Probabilities No SeHCAT and BAS trial of treatment strategy

- In case of no response to BAS trial of treatment, patients follow the same pathway as in the No SeHCAT strategy.

- All patients are assumed to receive a BAS at the beginning of the modelled pathway. 85% of patients started with cholestyramine and 15% with colesevelam.

- BAS adherence, initial response and duration of treatment effect are assumed to be the same as for the SeHCAT 15% strategy.

- When patients do not respond to BAS treatment, we assumed that patients follow the same pathway as in the No SeHCAT strategy.

- The probability of having IBD after colonoscopy and IBD response after colonoscopy were assumed to be the same as in the No SeHCAT strategy.

- The probability of IBS-D response after no response to BAS and colonoscopy were assumed to lie somewhere in between the 46% of the No SeHCAT strategy and the 56% of the SeHCAT 15% strategy. We assumed for the base-case a mean response of 50%.

Population 1 – Utility values

- It was assumed to use the same IBS utility values as identified in the previous report.

- For the base-case it was assumed that cholestyramine responders have 75% of the utility increment observed in IBS-D treatment. Colesevelam responders were assumed to have the full utility increment as per IBS-D.

- A utility decrement due to colonoscopy was not included in the model since this was expected to have a negligible impact on the cost effectiveness results.

Population 1 – Resource used and costs

- Resource use was based on expert opinion.

- IBS-D treatment costs (no SeHCAT and SeHCAT negative) consist of medication, diet and psychological therapy costs. Dietician and psychological therapy costs were assumed for six months.

- IBD treatment costs (no SeHCAT and SeHCAT negative) consist of medication, diet and psychological therapy costs. Dietician and psychological therapy costs were assumed for six months.

- BAM treatment (SeHCAT positive) consists of medication costs only.

- Cost of colonoscopy in the model was calculated as 90% colonoscopy plus 10% computed tomography colonoscopy (CTC), based on one expert answer to our questionnaire.

Population 2 – Probabilities No SeHCAT strategy

- Response to diarrhoea treatment in Crohn's patients is achieved within 6 months since start of treatment. Relapses are expected as assumed for IBD patients in population 1.

Population 2 – Probabilities SeHCAT 15% strategy

- For patients not responding to BAS treatment after a positive SeHCAT result, the same estimates as those obtained for patients with a negative SeHCAT result were assumed.

- Patients with a positive SeHCAT test result are treated with a BAS (63% started with cholestyramine and 37% with colesevelam). For treatment response, an overall response rate to BAS was estimated.

- Initial response to BAS treatment is achieved within 6 months since start of treatment and a lifetime treatment effect duration is assumed.

- When patients do not respond to BAS after a positive SeHCAT result, or when the SeHCAT results is negative, patients follow the same pathway as in the No SeHCAT strategy. The same estimates as those obtained for patients with a negative SeHCAT result were assumed.

- Patients with a negative SeHCAT test receive treatment for their chronic diarrhoea. Hence, it was assumed that the response rate to chronic diarrhoea treatment in the SeHCAT negative sub-population was higher than in No SeHCAT.

Population 2 – Probabilities No SeHCAT and BAS trial of treatment strategy

- In case of no response to BAS trial of treatment, patients are assumed to follow the same pathway as in the No SeHCAT strategy.
- All patients are assumed to receive a BAS (58% cholestyramine and 42% colesevelam).
- In terms of response, we did not distinguish between the type of BAS.
- BAS adherence, initial response and duration of treatment effect are assumed to be the same as for the SeHCAT strategy.

Population 2 – Utility values

- A mean of 0.7 was found for the quality of life in the diarrhoea health state. The utility for the no diarrhoea health state and BAS responders were calculated following the assumptions in population 1.

Population 2 – Resource use and costs

- Resource use was based on expert opinion.
- Medical treatment of Crohn's disease was assumed to be the same as in previous assessment of SeHCAT. Treatment costs were calculated by using updated unit costs.
- BAD treatment (SeHCAT positive) consists of medication costs only.

Markov model

- Cycle length: six months.
- Time horizon: 50 years (100 cycles).
- BAS and IBS-D responders start the Markov model in the "No Diarrhoea" health state and the only possible transition is to the "Death" health state (i.e., transition to "Diarrhoea" is not possible).
- 10 cycles (of six months) of relapse were considered (1 cycle = six months, 60 months = five years) for IBD responders.

- Average age in population 1 and 2 was 50 years, and the ratio of male/female was 35/75.
- Utilities were adjusted for ageing.
- For patients who did not respond to any treatment in the initial phase, i.e. the patients entering the Markov model in the "Diarrhoea" health state, we assumed that patients use loperamide to reduce the stool frequency.

4.3 Model analyses

Analyses were conducted as cost effectiveness analyses for both populations of interest. Costs and effects were discounted by 3.5%. Analyses incorporated a 50 year time horizon to estimate outcomes in terms of life years, lifetime QALYs and lifetime costs from the perspective of the NHS. Other outcomes included in the analyses were short-term costs, response to treatment and, in population 1, colonoscopies avoided. These three outcomes were calculated in the decision analytic model (thus, assumed to be in the first six months of the simulation). Parameter uncertainty was explored through probabilistic sensitivity analysis (PSA) and structural uncertainty through scenario analyses. Deterministic one-way or multi-way sensitivity analyses were not conducted. The main reason for this was the lack of published uncertainty data for most of the input parameters of the model. It was felt that any attempt to derive plausible and comparable uncertainty ranges for all input parameters (e.g., 95% confidence intervals) would be unfeasible and, thus, the results of the deterministic sensitivity analyses would be at risk of being misleading. Unlike the previous assessment of SeHCAT,[16] the value of information associated with the model uncertainty was not explored in this case because it was deemed unnecessary. Again, the main reason for this was the lack of data and because of that we believe that additional research is needed to reduce both parameter and structural uncertainty. Furthermore, it is no possible to assess whether the current model uncertainty has been properly captured since, for the majority of input parameters, uncertainty ranges were derived from clinical expert opinion (four experts at most, but in general one or two) and from modellers choices. Therefore, again, the results of any value of information analyses would be at risk of being misleading.

4.3.1 Secondary analysis

The base-case scenario was built under the assumption that colonoscopy was not part of the clinical pathway before patients enter the model. This analysis is, however, likely to deviate from current guidelines. As explained above, this was nevertheless chosen as the base-case analysis following scoping discussions. Given its importance, a scenario where colonoscopy is not included in the cost

effectiveness model (e.g., assumed to occur before SeHCAT testing or trial of treatment with BAS), was presented separately.

4.3.2 Sensitivity and scenario analysis

A series of scenario analyses were conducted in order to explore the most important areas of uncertainty in the model described above. A summary of the scenario analyses conducted is given below.

Scenario analysis 1: Alternative probability of undergoing colonoscopy in population 1

The number of colonoscopies avoided is one of the outcomes of interest for population 1. Thus, assumptions regarding the probability of undergoing colonoscopy are expected to be an important driver of the cost effectiveness results in this population. In the base-case analysis, it was assumed that the probability of undergoing colonoscopy (for all patients) in the No SeHCAT strategy was 74%. In the SeHCAT 15% strategy, colonoscopy was included in the model only after a SeHCAT negative result or after a positive result but no response to BAS treatment. For this subgroup of patients, the probability of undergoing colonoscopy was 49%. Likewise, in the BAS trial of treatment strategy, colonoscopy was included in the model only after no response to BAS treatment, and for this subgroup of patients, the probability of undergoing colonoscopy was 90%. Two additional scenarios were explored; one in which colonoscopy is not included in the model (note this is the secondary analysis for population 1 – results can be seen above) and one in which the probability of undergoing colonoscopy is 100%. The latter implies that 1) all patients in No SeHCAT, 2) patients with SeHCAT negative, or SeHCAT positive and no response to BAS treatment, and 3) patients not responding to BAS trial of treatment are assumed to undergone colonoscopy.

Scenario analysis 2: Alternative probability of response to IBS-D treatment in population 1

In the No SeHCAT strategy the probability of responding to IBS-D treatment (after colonoscopy ruled-out IBD) was estimated at 46%, based on clinical experts' answers to our questionnaire. For SeHCAT negative patients, it was assumed that most patients who have BAD are not included in the group receiving IBS-D treatment. Therefore, the response rate to IBS-D treatment in the SeHCAT negative sub-population was assumed to be higher than in the No SeHCAT strategy, and a mean response of 56% was estimated. In the absence of any evidence, for the BAS trial of treatment strategy, we assumed that the probability of IBS-D response was somewhere in between the other two strategies and a mean response of 50% was assumed. Additionally, within each strategy, it was assumed that the probability of IBS-D response was slightly lower in patients who did not underwent colonoscopy due to a larger proportion of IBD patients (who were consequently assumed not to respond to IBS-D treatment) included in this subgroup of patients. We explored several scenarios in

which we varied the percentage of response to IBS-D treatment for No SeHCAT, SeHCAT negative (or positive and no response to BAS) and BAS trial of treatment (no response to BAS) as shown in Table 37.

Table 37: Summary of IBS-D response-related scenarios, population 1

Percentage of response (after colo., after no colo.)	No SeHCAT	SeHCAT 15%	BAS TOT
Base-case	46%, 44%	56%, 53%	50%, 47%
IBS-D scenario 1	50%, 47%	56%, 53%	50%, 47%
IBS-D scenario 2	50%, 47%	56%, 53%	56%, 53%
IBS-D scenario 3	56%, 53%	56%, 53%	56%, 53%
IBS-D scenario 4	70%, 66%	56%, 53%	50%, 47%

Abbreviations: BAS = bile acid sequestrants, colo. = colonoscopy, IBS-D = diarrhoea predominant irritable bowel syndrome, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.
Note: Values assuming a higher response in No SeHCAT than in SeHCAT 15% or BAS TOT are likely to be implausible.

Scenario analysis 3: Alternative probability of SeHCAT positive result and response BAS treatment in population 1

The unconditional response to BAS treatment in the SeHCAT 15% strategy is obtained by multiplying the probability of testing positive by the probability of response to BAS given tested positive. In the base-case, these probabilities were estimated from our systematic literature review at 0.29, 0.454 and 0.638, respectively. We explored scenarios where in the SeHCAT 15% strategy the probability of testing positive and the probability of response to BAS were changed at the same time according to limits of their confidence intervals, in a form of worst-case and best-case scenarios. The probability of response to BAS trial of treatment was estimated at 30% from clinical experts' answers. We explored scenarios where this probability was decreased and increased by 10%. These scenarios are summarised in Table 38.

Table 38: Summary of SeHCAT positive and response to BAS scenarios, population 1

	SeHCAT 15% positive	Response to BAS | SeHCAT positive	Response to BAS TOT
Base-case	0.454	0.638	0.299
Scenario 1	0.357	0.495	0.299
Scenario 2	0.555	0.760	0.299
Scenario 3	0.454	0.638	0.2
Scenario 4	0.454	0.638	0.4

Abbreviations: BAS = bile acid sequestrants, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.

Scenario analysis 4: Alternative distribution of BAS treatment in population 1

Based on clinical experts' responses, in the base-case it was assumed that in the SeHCAT 15% strategy, 50% of patients started with cholestyramine and 50% with colesevelam. In the BAS trial of treatment strategy these were 85% and 15%, respectively. We explored scenarios where all patients were treated with cholestyramine, all patients were treated with colesevelam and where there was no difference in BAS distribution between the SeHCAT 15% and the BAS trial of treatment strategy (one scenario assumed a 50/50 proportion and the other one an 85/15). Note that, in terms of response, it was not possible to distinguish between the type of BAS. Therefore, these scenarios had an effect on costs and utilities only since these were different for cholestyramine and colesevelam.

Scenario analysis 5: Alternative health state utilities in population 1

We explored a scenario where it was assumed that patients who respond to cholestyramine (BAS) treatment receive 100% of the utility gain associated with not experiencing diarrhoea, instead of the 75% gain in utility assumed in the base-case to account for additional tolerability issues and side effects of this treatment. In an additional scenario, we assumed utility values from each individual literature source in Table 19 instead of the pooled values used in the base-case. In these scenarios the utility decrement associated to cholestyramine was still calculated based on an assumed 75% gain. Finally, a scenario where no age adjustment of the utility values was explored.

Scenario analysis 6: Alternative cost inputs in population 1

Because costs included in the model were estimated as combinations of several medications, resource use and assumptions, it was unfeasible to conduct scenario analyses on the costs components separately. Therefore, a pragmatic approach was taken in this case and all costs were varied by 20%.

Scenario analysis 7: Alternative transition probabilities in population 1

Transitions in the Markov model represent the probabilities of experiencing diarrhoea relapse or remission. In the base-case, it was assumed that only IBD patients experienced relapse after initial response to treatment. A probability of 0.45% per model cycle (six months) was assumed. BAS and IBS-D responders were assumed to remain in the no diarrhoea health state (or to die) for their entire time horizon. Likewise, non-responders (to any treatment) stayed in the diarrhoea health state where the only possible transition was to the death health state. We explored several scenarios where patients were allowed to experience relapse in all models. We increased the probability of relapse to assess how this would impact the results. In one scenario, the possibility to experience remission was also included in the analysis. The scenarios conducted are summarised in Table 39.

Table 39: Summary of transition probability scenarios, population 1

Transitions P[D-->ND], P[ND-->D]	BAS models	IBS-D model	IBD model
Base-case	0, 0	0, 0	0, 0.0045
Scenario 1	0, 0.0045	0, 0.0045	0, 0.0045
Scenario 2	0.0045, 0.0045	0.0045, 0.0045	0.0045, 0.0045
Scenario 3	0, 0.0045*2	0, 0.0045*2	0, 0.0045*2
Scenario 4	0, 0.0045*5	0, 0.0045*5	0, 0.0045*5

Abbreviations: BAS = bile acid sequestrants, IBD = inflammatory bowel disease, IBS-D = diarrhoea predominant irritable bowel syndrome.
Note: P[D-->ND] denotes the transition probability from the diarrhoea to the no diarrhoea health state, P[ND-->D] denotes the transition probability from the no diarrhoea to the diarrhoea health state.

Scenario analysis 8: Alternative mortality estimates in population 1

Following the advice of a clinical expert who suggested that BAD might be associated with an increased mortality compared to the general population, we run a scenario where excess mortality was included in the model. We used the SMR of 1.52 from Canavan et al. (2007) as in the Crohn's population analyses.[65]

Scenario analysis 9: Alternative probability of response to diarrhoea-specific treatment in population 2

In the base-case, the probability of responding to diarrhoea-specific treatment (without BAS) in the Crohn's population was 40% for the No SeHCAT strategy. For SeHCAT negative patients, a mean response of 42% was estimated and for the BAS trial of treatment strategy, we assumed a mean response of 41% (as the only possible value between the other two). The impact of assuming different response rates to diarrhoea-specific treatment on the cost effectiveness results was studied in the scenarios described in Table 40.

Table 40: Summary of response to diarrhoea treatment without BAS scenarios, population 2

Percentage of response to diarrhoea treatment without BAS	No SeHCAT	SeHCAT 15%	BAS TOT
Base-case	40%	42%	41%
Scenario 1	42%	42%	42%
Scenario 2	70%	42%	70%

Abbreviations: BAS = bile acid sequestrants, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.
Note: Values in scenario 2 for No SeHCAT and BAS TOT are likely to be implausible.

Scenario analysis 10: Alternative probability of SeHCAT positive result and response BAS treatment in population 2

The unconditional response to BAS treatment in the SeHCAT 15% strategy is obtained by multiplying the probability of testing positive by the probability of response to BAS given tested positive. In the base-case, these probabilities were estimated from our systematic literature review at 0.55, 0.89 and 0.49, respectively. We explored scenarios where in the SeHCAT 15% strategy the probability of testing positive and the probability of response to BAS were changed at the same time according to limits of their confidence intervals, in a form of worst-case and best-case scenarios. The probability of response to BAS trial of treatment was estimated at 0.33 from clinical experts' answers. We explored scenarios where this probability was decreased to 0.23 and increased to 0.5. These scenarios are summarised in Table 41.

Table 41: Summary of SeHCAT positive and response to BAS scenarios, population 2

	SeHCAT 15% positive	Response to BAS | SeHCAT positive	Response to BAS TOT
Base-case	0.55	0.89	0.33
Scenario 1	0.39	0.67	0.33
Scenario 2	0.71	1.00	0.33
Scenario 3	0.55	0.89	0.23
Scenario 5	0.55	0.89	0.50

Abbreviations: BAS = bile acid sequestrants, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.

Scenario analysis 11: Alternative distribution of BAS treatment in population 2

Based on clinical experts' responses, in the base-case it was assumed that in the SeHCAT 15% strategy, 63% of patients started with cholestyramine and 37% with colesevelam. In the BAS trial of treatment strategy these were 58% and 42%, respectively. We explored scenarios where all patients were treated with cholestyramine, all patients were treated with colesevelam and where there was no difference in BAS distribution between the SeHCAT 15% and the BAS trial of treatment strategy (one scenario assumed a 63/37 proportion and the other one an 58/42). Note that, in terms of response, it was not possible to distinguish between the type of BAS. Therefore, these scenarios had an effect on costs and utilities only since these were different for cholestyramine and colesevelam.

Scenario analysis 12: Alternative health state utilities in population 2

We explored the same scenarios as those defined for population 1. Thus, a scenario where patients who respond to cholestyramine (BAS) treatment receive 100% of the utility gain (instead of the 75% in the base-case) and a scenario where no age adjustment of the utility values was assumed.

Scenario analysis 13: Alternative cost inputs in population 2

As explained for population 1, a pragmatic approach was taken to define cost-related scenario analyses and all costs were varied by 20%.

Scenario analysis 14: Alternative transition probabilities in population 2

The same approach described for population 1 was followed for population 2. Thus, we explored several scenarios where patients were allowed to experience relapse in all models. We increased the probability of relapse to assess how this would impact the results. In one scenario, the possibility to experience remission was also included in the analysis. The scenarios conducted are summarised in Table 42.

Table 42: Summary of transition probability scenarios, population 2

Transitions P[D-->ND], P[ND-->D]	BAS models	D model
Base-case	0, 0	0, 0.00575
Scenario 1	0, 0.00575	0, 0.00575
Scenario 2	0.00575, 0.00575	0.00575, 0.00575
Scenario 3	0, 0.00575*2	0, 0.00575*2
Scenario 4	0, 0.00575*5	0, 0.00575*5

Abbreviations: BAS = bile acid sequestrants, D = diarrhoea-specific treatment (without BAS).
Note: P[D-->ND] denotes the transition probability from the diarrhoea to the no diarrhoea health state, P[ND-->D] denotes the transition probability from the no diarrhoea to the diarrhoea health state.

Scenario analysis 15: Alternative mortality estimates in population 2

In the base-case analysis, we used the SMR (1.52) estimated from Canavan et al. (2007).[65] In this scenario analysis, we explored the impact of mortality on the cost effectiveness results by using the limits of the confidence interval reported by Canavan et al. (2007) (1.32, 1.74).

4.4 Results of cost effectiveness analyses

In this section we summarised the cost effectiveness results of the three strategies per population. Long-term results are presented as ICERs estimated as costs per additional QALY gained in a full incremental analysis fashion. Short-term results (first six months) focused on the percentage of response to treatment and, for population 1, also the percentage of avoided colonoscopies. Given the uncertainties in the cost effectiveness evidence described above, many assumptions had to be made to make it possible to perform the cost effectiveness analyses. Assessing the impact of these assumptions on the cost effectiveness results, implied that a large number of scenarios had to be run. In this section, we focused on the scenarios that had the largest impact on the base-case ICERs. Full results are then presented in Appendix 7.

4.4.1 Results base-case analysis, population 1

The results of the base-case for population 1 are shown in Table 43. It can be seen that BAS trial of treatment was dominated by the SeHCAT 15% strategy (the latter provided more QALYs at lower costs). Therefore, the relevant comparison for the ICER calculation was SeHCAT 15% vs. No SeHCAT, where the ICER was £9,688; thus, below the commonly used threshold of £20,000/QALY. The SeHCAT 15% strategy was estimated to provide 0.23 additional QALYs at an incremental cost of £2,236 compared to No SeHCAT. The base-case analysis also revealed that, in the short-term, the SeHCAT 15% strategy is the one with more colonoscopies avoided per patient (65%) and with the highest response rate to any type of medication (68%) but that these come at the highest initial costs (£786), due to the costs of the SeHCAT test. The cost per colonoscopy avoided was the lowest for the SeHCAT 15 % strategy (£786/0.65 = £1,209) and the cost per response was the lowest for the BAS trial of treatment strategy (£507/0.65 = £780). Life years were 19.96 for all three strategies. Since no difference in mortality across strategies was assumed in the model, the same life years were expected to be estimated for the three strategies.

Table 43: Base-case cost effectiveness results, population 1

	Colo. avoided	Response	Initial costs	QALYs	Total Costs	Inc. QALYs	Inc. costs	ICER
No SeHCAT	26%	47%	£557	13.8242	£4,720			
BAS TOT	37%	65%	£507	14.0096	£7,449	Dominated by SeHCAT 15%		
SeHCAT 15%	65%	68%	£786	14.0550	£6,956	0.2308	£2,236	£9,688

Abbreviations: BAS = bile acid sequestrants, Colo. = colonoscopy, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, SeHCAT = Tauroselcholic [^{75}Selenium] acid, TOT = trial of treatment.

Note: Percentage of colonoscopies avoided per patient. Percentage of response to any medication (thus, IBS-D, IBD or BAS). Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

4.4.2 Results secondary analysis, population 1

As explained above, the secondary analysis was based on the assumption that patients had undergone colonoscopy before entering the model. Thus, in practice this scenario was run by removing all colonoscopy branches from Figure 3, i.e., by setting the probability of colonoscopy equal to 0.

The results of the secondary analysis for population 1 are summarised in Table 44. The SeHCAT 15% strategy was estimated to provide the highest QALYs at the highest costs, but, unlike the base-case, BAS trial of treatment was no longer dominated by the SeHCAT 15% strategy. We observed that both the ICER of BAS trial of treatment vs. No SeHCAT, and the ICER of SeHCAT 15% vs. BAS trial of

treatment, are close (but below) to the £20,000/QALY threshold. The secondary analysis also showed that, in the short-term, the SeHCAT 15% strategy was the one with the highest response rate to any type of medication (67%) but that these come at the highest initial costs (£553), due to the costs of the SeHCAT test. The cost per response was the highest for the SeHCAT 15% strategy (£553/0.67= £825). For the other two strategies, this cost was nearly the same: £134 for No SeHCAT and £135 for BAS trial of treatment. Life years (not shown in Table x) were also 19.96 for all strategies as in the base-case since no changes in mortality were assumed.

Table 44: Secondary analysis cost effectiveness results (no colonoscopy), population 1

	Colo. avoided	Response	Initial costs	QALYs	Total Costs	Inc. QALYs	Inc. Costs	ICER
No SeHCAT	NA	44%	£59	13.8026	£374			
BAS TOT	NA	63%	£85	13.9825	£3,767	0.1799	£3,393	£18,860
SeHCAT 15%	NA	67%	£553	14.0408	£4,922	0.0583	£1,115	£19,125

Abbreviations: BAS = bile acid sequestrants, Colo. = colonoscopy, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, SeHCAT = Tauroselcholic [^{75}Selenium] acid, TOT = trial of treatment.

Note: Percentage of colonoscopies avoided per patient. Percentage of response to any medication (thus, IBS-D, IBD or BAS). Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

4.4.3 Results probabilistic sensitivity analyses, population 1

The base-case PSA cost effectiveness results can be seen in Table 45. These aligned well with the deterministic results; BAS trial of treatment was dominated by the SeHCAT 15% strategy and the ICER of SeHCAT 15% vs. No SeHCAT was £9,661.

Table 45: PSA base-case cost effectiveness results, population 1

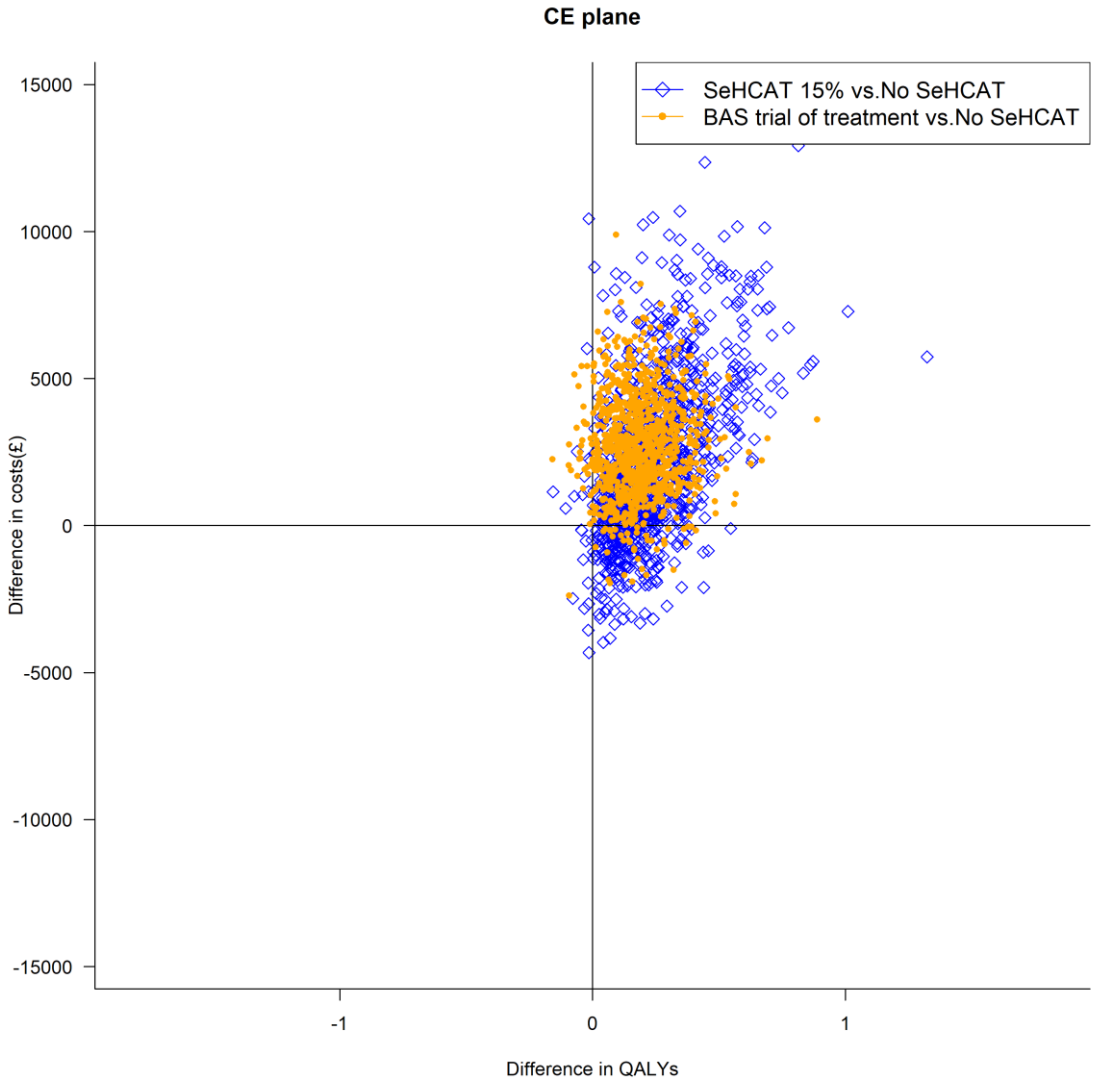
	Colo. Avoided	Response	Initial costs	QALYs	Total Costs	Inc. QALYs	Inc. costs	ICER
No SeHCAT	26%	46%	£560	13.8236	£4,687			
BAS TOT	37%	66%	£564	14.0151	£7,431	Dominated by SeHCAT 15%		
SeHCAT 15%	65%	68%	£826	14.0623	£6,993	0.2387	£2,306	£9,661

Abbreviations: BAS = bile acid sequestrants, Colo. = colonoscopy, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, SeHCAT = Tauroselcholic [^{75}Selenium] acid, TOT = trial of treatment.

Note: Percentage of colonoscopies avoided per patient. Percentage of response to any medication (thus, IBS-D, IBD or BAS). Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

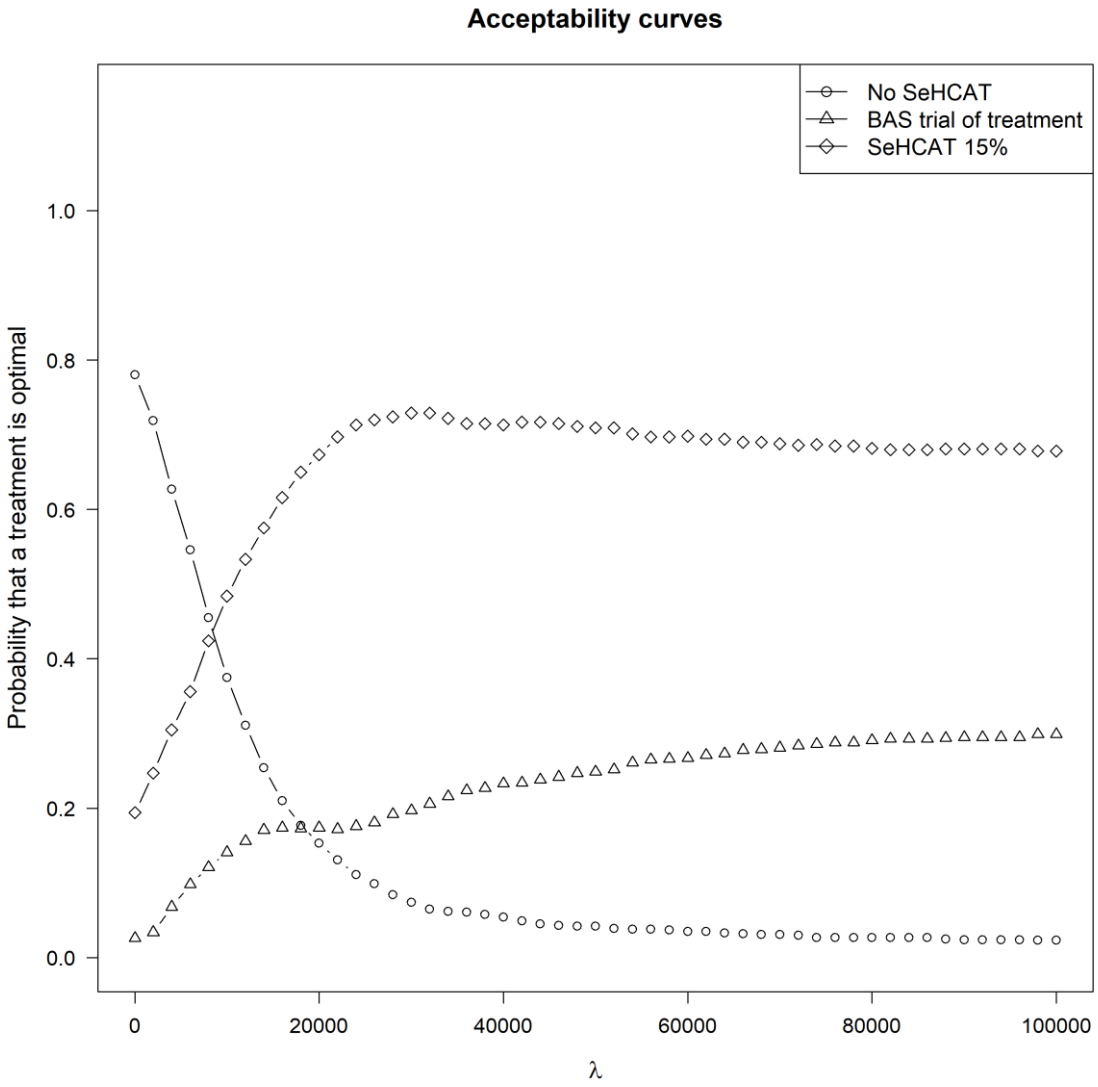
The CE-plane and CEAC resulting from the PSA are shown in Figures 6 and 7, respectively. Note the CE-plane shows the results of pairwise comparisons vs. No SeHCAT only. It can be seen that the vast majority of the simulations are in the eastern quadrants, in which both BAS trial of treatment and SeHCAT 15% are more effective than No SeHCAT. Most of the simulations are in the north eastern quadrant of the CE-plane, where BAS trial of treatment and SeHCAT 15% are also more costly than No SeHCAT. The CEACs show that at lower values of the threshold ICER, No SeHCAT is the strategy with the largest the probability of being cost effective given their lowest costs. However, this probability rapidly decreases as the threshold ICER increases, and SeHCAT 15% becomes the strategy most likely to be cost effective, with 67% probability of being cost effective at a threshold ICER of £20,000 per QALY gained, and 73% at a threshold ICER of £30,000 per QALY gained.

Figure 6: CE-plane from PSA base-case results, population 1



BAS = bile acid sequestrants, CE = cost effectiveness, PSA = probabilistic sensitivity analysis, QALY = quality-adjusted life year, SeHCAT = Tauroselcholic [^{75}Selenium] acid

Figure 7: CEACs from PSA base-case results, population 1



BAS = bile acid sequestrants, CEAC = cost effectiveness acceptability curves, PSA = probabilistic sensitivity analysis, SeHCAT = Tauroselcholic [^{75}Selenium] acid

A PSA was also run under the assumptions of the secondary analysis, where no colonoscopy was included in the model. The PSA results can be seen in Table 46. In this case, they are also in line with the results of the deterministic analysis. The SeHCAT 15% strategy was estimated to provide the highest QALYs at the highest costs, but no strategy was dominated. Both the ICER of BAS trial of treatment vs. No SeHCAT, and the ICER of SeHCAT 15% vs. BAS trial of treatment, were close to the £20,000/QALY threshold, but unlike the deterministic analysis, the ICER of SeHCAT 15% vs. BAS trial of treatment was now above this threshold.

Table 46: PSA secondary analysis cost effectiveness results (no colonoscopy), population 1

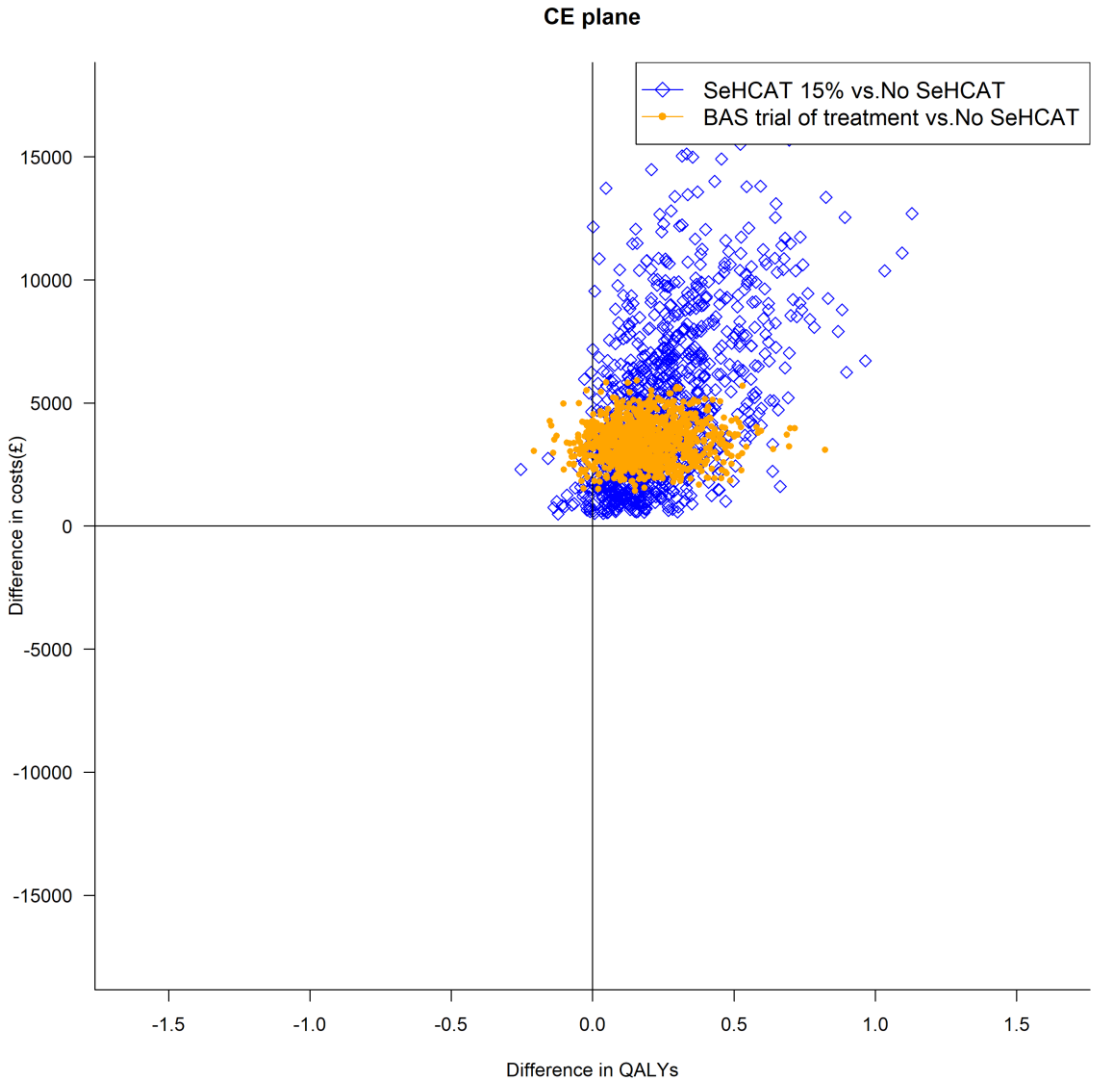
	Colo. Avoided	Response	Initial costs	QALYs	Total Costs	Inc. QALYs	Inc. Costs	ICER
No SeHCAT	NA	44%	£62	13.8021	£374			
BAS TOT	NA	63%	£143	13.9893	£3,806	0.1871	£3,432	£18,343
SeHCAT 15%	NA	67%	£596	14.0539	£5,168	0.0647	£1,361	£21,036

Abbreviations: BAS = bile acid sequestrants, Colo. = colonoscopy, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, SeHCAT = Tauroselcholic [^{75}Selenium] acid, TOT = trial of treatment.

Note: Percentage of colonoscopies avoided per patient. Percentage of response to any medication (thus, IBS-D, IBD or BAS). Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

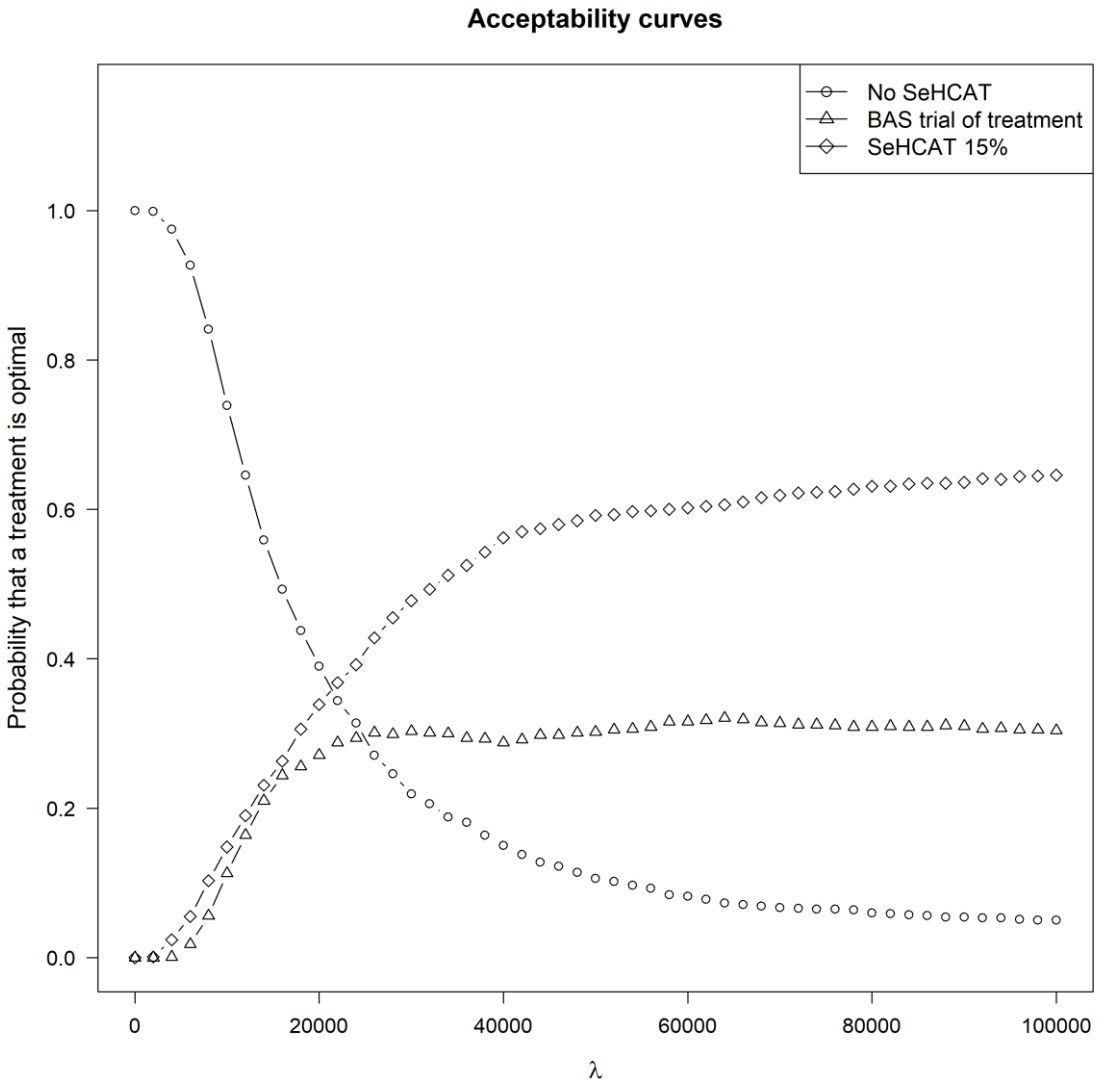
The CE-plane and CEAC resulting from the PSA in the secondary analysis are shown in Figures 8 and 9, respectively. The CE-plane shows again the results of pairwise comparisons vs. No SeHCAT only. It can be seen that the vast majority of the simulations are in the north eastern quadrant of the CE-plane, in which both BAS trial of treatment and SeHCAT 15% are more effective and more costly than No SeHCAT. The difference in uncertainty between the two comparisons is remarkable, especially on the costs side. However, this can be explained by the distribution of costs, which is notably wider in the SeHCAT strategy. The CEACs show that at lower values of the threshold ICER, No SeHCAT is the strategy with the largest the probability of being cost effective. This probability decreases as the threshold ICER increases, and approximately at a threshold ICER of £20,000 per QALY gained, SeHCAT 15% and No SeHCAT have nearly the same probability of being cost effective. At larger values of the threshold ICER, SeHCAT 15% is the strategy most likely to be considered cost effective. In particular, at a threshold ICER of £30,000 per QALY gained this probability is approximately 50%.

Figure 8: CE-plane from PSA secondary analysis results (no colonoscopy), population 1



BAS = bile acid sequestrants, CE = cost effectiveness, PSA = probabilistic sensitivity analysis, QALY = quality-adjusted life year, SeHCAT = Tauroselcholic [^{75}Selenium] acid

Figure 9: CEACs from PSA secondary analysis results (no colonoscopy), population 1



BAS = bile acid sequestrants, CEAC = cost effectiveness acceptability curves, PSA = probabilistic sensitivity analysis, SeHCAT = Tauroselcholic [^{75}Selenium] acid

4.4.4 Results scenario analyses, population 1

Scenario analysis 1: Alternative probability of undergoing colonoscopy in population 1

In the base-case analysis, the probability of undergoing colonoscopy (for all patients) in the No SeHCAT strategy was 74%. In the SeHCAT 15% strategy, this probability was 49%, but only for patients with a SeHCAT negative result, or with a positive result but no response to BAS treatment. In the BAS trial of treatment strategy, the probability of undergoing colonoscopy was 90% but only for patients not responding to BAS treatment. The impact of changing assumptions regarding colonoscopy on the cost effectiveness results was partially investigated in the secondary analysis described above in which patients undergone colonoscopy before entering the model. Additionally, the scenario where the probability of undergoing colonoscopy was 100% in all strategies was explored in this section. As can be seen in Table 47, short-term costs increased as expected given

that more patients underwent colonoscopy, but this resulted in a slightly higher response rate, mostly due to IBD patients more accurately identified with colonoscopy. The more responders, the higher the long-term QALYs and total costs. The SeHCAT 15% strategy was estimated to provide the highest QALYs at the highest costs, but without dominating any of the other two strategies. The ICER of BAS trial of treatment vs. No SeHCAT was £9,136, and the ICER of SeHCAT 15% vs. BAS trial of treatment was £21,140, thus, above the £20,000/QALY threshold. The analysis also revealed that, in the short-term, the BAS trial of treatment strategy was the one with more colonoscopies avoided per patient (30%) and positive SeHCAT 15% the one with the highest response rate to any type of medication (69%). The cost per colonoscopy avoided and the cost per response were the lowest for the BAS trial of treatment strategy (£1,847 and £839, respectively).

In summary, scenario analyses results showed that, by changing assumptions regarding the probability of undergoing colonoscopy, the cost effectiveness results also change. The base-case illustrates a situation where the SeHCAT 15% strategy dominates BAS trial of treatment and may be deemed cost effective compared to No SeHCAT. In the secondary analysis, there was no dominance and both ICERs were borderline cost effective. In the scenario with 100% probability of colonoscopy, BAS trial of treatment and may be deemed cost effective compared to No SeHCAT but the ICER of SeHCAT 15% vs. BAS trial of treatment was above the £20,000/QALY threshold. Note that the probability of colonoscopy is incorporated in the model through three different parameters (one per strategy). Other combinations were not explored because the number of scenarios would become unmanageable in practice. It is obvious but important nevertheless to emphasise that different combinations of these three parameters might result in different model outcomes. Therefore, it is important to determine in advance the plausibility of the assumptions made regarding these parameters to be able to focus on the scenarios that can be deemed as relevant in practice.

Table 47: Results of colonoscopy scenarios, population 1

	Colo. avoided	Response	Initial costs	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
Base-case (No SeHCAT = 74%, SeHCAT 15% = 49%, BAS TOT = 90%)								
No SeHCAT	26%	47%	£557	13.8242	£4,720			
BAS TOT	37%	65%	£507	14.0096	£7,449	Dominated by SeHCAT 15%		
SeHCAT 15%	65%	68%	£786	14.0550	£6,956	0.2308	£2,236	£9,688
Colonoscopy scenario 1 (secondary analysis, no colonoscopy)								
No SeHCAT	NA	44%	£59	13.8026	£374			
BAS TOT	NA	63%	£85	13.9825	£3,767	0.1799	£3,393	£18,860
SeHCAT 15%	NA	67%	£553	14.0408	£4,922	0.0583	£1,115	£19,125
Colonoscopy scenario 2 (No SeHCAT = 100%, SeHCAT 15% = 100%, BAS TOT = 100%)								
No SeHCAT	0%	47%	£727	13.832	£6,210			
BAS TOT	30%	66%	£554	14.013	£7,863	0.181	£1,653	£9,136
SeHCAT 15%	29%	69%	£1,028	14.070	£9,069	0.057	£1,206	£21,140

Abbreviations: BAS = bile acid sequestrants, Colo. = colonoscopy, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.

Note: Percentage of colonoscopies avoided per patient. Percentage of response to any medication (thus, IBS-D, IBD or BAS). Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

Scenario analysis 2: Alternative probability of response to IBS-D treatment in population 1

In the No SeHCAT strategy the probability of responding to IBS-D treatment (after colonoscopy ruled-out IBD) was 46%. For SeHCAT negative patients, a mean response of 56% was estimated and for the BAS trial of treatment strategy, we assumed a mean response of 50%. Within each strategy, it was assumed that the probability of IBS-D response was slightly lower in patients who did not undergo colonoscopy. These were estimated at 44%, 53% and 47% for the No SeHCAT, SeHCAT 15% and BAS trial of treatment strategies, respectively. The impact of assuming different response rates to IBS-D treatment on the cost effectiveness results can be seen in Table 48. Note that changes in IBS-D response rates do not affect the probability of colonoscopy nor the costs accrued during the first six months in the model (decision analytic model). Therefore, in Table 48, the percentage of colonoscopies avoided and the initial costs were not included since these were the same as in the base-case. As can be seen in Table 48, the more responders, the higher the long-term QALYs and total costs. The No SeHCAT strategy is dominated or not cost effective unless the response rate to IBS-D treatment is assumed to be larger than the overall response rate in the SeHCAT 15% or the BAS trial of treatment strategies. This can be seen in IBS-D scenario 4, where No SeHCAT became

dominant given that it is also the strategy with lowest costs. However, this scenario is based on a response rate to IBS-D treatment of 70%, which is likely to be unrealistic. The BAS trial of treatment strategy is more costly than the SeHCAT 15% strategy. Therefore, when the overall response to treatment is higher in the SeHCAT 15% strategy, BAS trial of treatment will be dominated. As shown in IBS-D scenarios 3 and 4, even if the overall response to treatment is higher in BAS trial of treatment, it does not imply that BAS trial of treatment will dominate or will be cost effective compared to SeHCAT 15%. In these two scenarios, the overall response rate was 1% higher for BAS trial of treatment, resulting in an ICER of £627,500. This scenario is already based on an equal response rate to IBS-D treatment for both strategies, which might be unrealistic. BAS trial of treatment might be deemed cost effective compared to the SeHCAT 15% strategy only when its overall response to treatment is much higher than in SeHCAT 15%, which again is likely to be unrealistic.

Table 48: Results of IBS-D response scenarios, population 1

	Response	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
Base-case						
No SeHCAT	47%	13.8242	£4,720			
BAS TOT	65%	14.0096	£7,449	Dominated by SeHCAT 15%		
SeHCAT 15%	68%	14.0550	£6,956	0.2308	£2,236	£9,688
IBS-D scenario 1 (response No SeHCAT increased = response BAS TOT)						
No SeHCAT	50%	13.8660	£4,728			
BAS TOT	65%	14.0096	£7,449	Dominated by SeHCAT 15%		
SeHCAT 15%	68%	14.0550	£6,956	0.189	£2,228	£11,788
IBS-D scenario 2 (response BAS TOT increased = response No SeHCAT, response No SEHCAT as in scenario 1)						
No SeHCAT	50%	13.8660	£4,728			
SeHCAT 15%	68%	14.0550	£6,956	0.1890	£2,228	£11,788
BAS TOT	69%	14.0558	£7,458	0.0008	£502	£627,500
IBS-D scenario 3 (equal response in the three strategies, equal to SeHCAT 15%)						
No SeHCAT	56%	13.9323	£4,741			
SeHCAT 15%	68%	14.0550	£6,956	0.1227	£2,215	£18,052
BAS TOT	69%	14.0558	£7,458	0.0008	£502	£627,500
IBS-D scenario 4 (No SeHCAT = 70%, SeHCAT and BAS TOT per base-case)						

	Response	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
BAS TOT	65%	14.0096	£7,449	Dominated by SeHCAT 15%		
SeHCAT 15%	68%	14.0550	£6,956	Dominated by No SeHCAT		
No SeHCAT	69%	14.0892	£4,771			

Abbreviations: BAS = bile acid sequestrants, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.
Note: Percentage of response to any medication (thus, IBS-D, IBD or BAS). Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

Scenario analysis 3: Alternative probability of SeHCAT positive result and response BAS treatment in population 1

First, we considered scenarios where in the SeHCAT 15% strategy the probability of testing positive and the probability of response to BAS were changed at the same time according to limits of their confidence intervals. Then, we explored scenarios where the probability of response to BAS trial of treatment was decreased and increased by 10%. In all scenarios, No SeHCAT was the strategy providing less QALYs but also the least costly. This was in general due to its overall low response rate (47%) compared to the other two strategies (at least 61% for BAS trial of treatment in the most pessimistic scenario) (see Table 49). Thus, dominance or cost effectiveness between SeHCAT 15% and BAS trial of treatment strategies was determined basically depending on overall response to treatment. When overall response was the highest in SeHCAT 15%, it always dominated or extendedly dominated BAS trial of treatment. In the two scenarios where BAS trial of treatment achieved the highest overall response (scenarios 1 and 4), the difference in QALYs with respect to SeHCAT 15% was small enough to result in ICERs equal to £272,969 and £919,167, respectively. These two scenarios are based on response rates to BAS treatment that are higher for the BAS trial of treatment strategy, which is likely to be unrealistic. In fact, in the base-case scenario, the response rate to BAS is nearly the same for the two strategies. This is in line with the assumption made in the previous assessment of SeHCAT,[16] where in the absence of evidence it was assumed that response to BAS in the trial of treatment strategy was equivalent to the percentage of BAS responders in the SeHCAT 15% strategy.

Table 49: Results of SeHCAT positive and response to BAS scenarios, population 1

	Colo. avoided	Response	Initial costs	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
Base-case (SeHCAT + = 0.454, BAS response | SeHCAT + = 0.638, BAS TOT response = 0.299)								
No SeHCAT	26%	47%	£557	13.8242	£4,720			
BAS TOT	37%	65%	£507	14.0096	£7,449	Dominated by SeHCAT 15%		
SeHCAT 15%	65%	68%	£786	14.0550	£6,956	0.2308	£2,236	£9,688
Scenario 1 (SeHCAT + = 0.357, BAS response | SeHCAT + = 0.495, BAS TOT response = 0.299)								
No SeHCAT	26%	47%	£557	13.8242	£4,720			
SeHCAT 15%	60%	63%	£819	14.0031	£5,702	0.1789	£982	£5,489
BAS TOT	37%	65%	£507	14.0096	£7,449	0.0064	£1,747	£272,969
BAS scenario 2 (SeHCAT + = 0.555, BAS response | SeHCAT + = 0.760, BAS TOT response = 0.299)								
No SeHCAT	26%	47%	£557	13.8242	£4,720			
BAS TOT	37%	65%	£507	14.0096	£7,449	Ext. dominated by SeHCAT 15%		
SeHCAT 15%	72%	74%	£748	14.1156	£8,423	0.2914	£3,703	£12,708
BAS scenario 3 (SeHCAT + = 0.454, BAS response | SeHCAT + = 0.638, BAS TOT response = 0.20)								
No SeHCAT	26%	47%	£557	13.8242	£4,720			
BAS TOT	28%	61%	£566	13.9644	£6,857	Ext. dominated by SeHCAT 15%		
SeHCAT 15%	65%	68%	£786	14.0550	£6,956	0.2307	£2,236	£9,692
BAS scenario 4 (SeHCAT + = 0.454, BAS response | SeHCAT + = 0.638, BAS TOT response = 0.40)								
No SeHCAT	26%	47%	£557	13.8242	£4,720			
SeHCAT 15%	65%	68%	£786	14.0550	£6,956	0.2307	£2,236	£9,692
BAS TOT	46%	70%	£446	14.0561	£8,059	0.0012	£1,103	£919,167

Abbreviations: BAS = bile acid sequestrants, Colo. = colonoscopy, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.

Note: Percentage of colonoscopies avoided per patient. Percentage of response to any medication (thus, IBS-D, IBD or BAS). Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

Scenario analysis 4: Alternative distribution of BAS treatment in population 1

In the base-case it was assumed that in the SeHCAT 15% strategy, 50% of patients started with cholestyramine and 50% with colesevelam, and in the BAS trial of treatment strategy these were 85% and 15%, respectively. We explored scenarios where all patients were treated with cholestyramine, all patients were treated with colesevelam and where there was no difference in BAS distribution between the SeHCAT 15% and the BAS trial of treatment strategy (one scenario

assumed a 50/50 proportion and the other one an 85/15). None of these scenarios differed significantly from the base-case; in all of them BAS trial of treatment was dominated by SeHCAT 15% and the ICER of SeHCAT15% vs. No SeHCAT ranged from £5,217 to £13,405. Full results are shown in Appendix 7.

Scenario analysis 5: Alternative health state utilities in population 1

In all utility scenarios run, BAS trial of treatment was dominated by SeHCAT 15% and the ICER of SeHCAT 15% compared to No SeHCAT ranged from £8,633 to £12,265. Assuming that patients responding to cholestyramine received the full utility benefit of not experiencing diarrhoea increased the incremental QALYs gained in the SeHCAT, No SeHCAT comparison resulting in a decrease in the ICER of approximately £800. Using different sources of utility values for IBS, selecting the values from either Mearin et al. (2004)[58] or Spiegel et al. (2009)[57] instead of the pooled values, impacted not only the health states utility values themselves, but the implied utility decrement for diarrhoea. Using the utilities from Mearin et al. (2004)[58] increased the effective decrement in utility due to diarrhoea (0.071 versus the base-case 0.064). This resulted in larger incremental QALYs and a drop of approximately £1,000 on the ICER. Using the utilities from Spiegel et al. (2009)[57] decreased the effective decrement in utility due to diarrhoea (0.05 versus the base-case 0.064), which increased the ICER by approximately £2,600 per QALY gained. Removing the age adjustment on utilities resulted in a small decrease in the ICER of approximately £600. Full results are shown in Appendix 7.

Scenario analysis 6: Alternative cost inputs in population 1

In all cost scenarios explored, the BAS trial of treatment strategy was dominated by the SeHCAT 15% strategy. In the comparison between SeHCAT 15% and No SeHCAT, the ICER ranged from £6,079 to £13,297. The cost elements that had the most influence on the ICER were the cost of BAS treatment, followed by the cost of IBD medication and the cost of SeHCAT. All other cost elements had a fairly small impact on the ICER, with an impact of less than £200. Full results are shown in Appendix 7.

Scenario analysis 7: Alternative transition probabilities in population 1

In all transition probability scenarios run, results were very similar to the base-case, with the BAS trial of treatment strategy being dominated by the SeHCAT 15% strategy, and all ICERs for comparison between SeHCAT 15% and No SeHCAT ranging from £8,658 to £9,688 (the base-case ICER). Thus, even multiplying by five the probability of relapse, results did not practically change, possibly because this increase in relapse was included in all strategies. In order to observe a larger impact, the difference in transition probabilities should be different per strategy, which is likely to be unrealistic. Full results are shown in Appendix 7.

Scenario analysis 8: Alternative mortality estimates in population 1

We run a scenario where excess mortality was included in the model using an SMR equal to 1.52 estimated from Canavan et al. (2007) as in the Crohn's analyses.[65] This scenario resulted in less QALYs and costs for all strategies as a consequence of a reduced life expectancy. However, the ICER was decreased by only £70. Full results are shown in Appendix 7.

4.4.5 Results base-case analysis, population 2

The results of the base-case for population 2 are shown in Table 50, where it can be seen that No SeHCAT was dominated by the BAS trial of treatment strategy. Therefore, the relevant comparison for the ICER calculation is SeHCAT 15% vs. BAS trial of treatment, where the ICER was £1,127. The SeHCAT 15% strategy was estimated to provide 0.1071 additional QALYs at an incremental cost of £185 compared to BAS trial of treatment. The base-case analysis also indicated that, in the short-term, the SeHCAT 15% strategy is the one with the highest response rate to any type of medication (71%) but that these come at the highest initial costs (£1,061), due to the inclusion of the SeHCAT test. The cost per response is the lowest for the BAS trial of treatment strategy (£756/0.6 = £1,260). Life years (not shown in Table 50) were 18.696 for all strategies. Since no difference in mortality across strategies was assumed in the model, the same life years were expected to be estimated for the three strategies.

Table 50: Base-case results, population 2

	Response	Initial costs	QALYs	Total Costs	Inc. QALYs	Inc. costs	ICER
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	60%	£756	12.9008	£13,946			
SeHCAT 15%	71%	£1,061	13.0079	£14,131	0.1071	£185	£1,727

Abbreviations: BAS = bile acid sequestrants, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, TOT = trial of treatment, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.
Note: Percentage of response to any medication. Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

4.4.6 Results probabilistic sensitivity analyses, population 2

The base-case PSA results for population 2 can be seen in Table 51. These aligned well with the deterministic results but now the SeHCAT 15% strategy is dominant due to the lowest total costs estimated for this strategy. In general, PSA costs are higher than the deterministic ones. This can be explained by the skewness of the triangular distributions chosen to parameterise the cost inputs of the model.

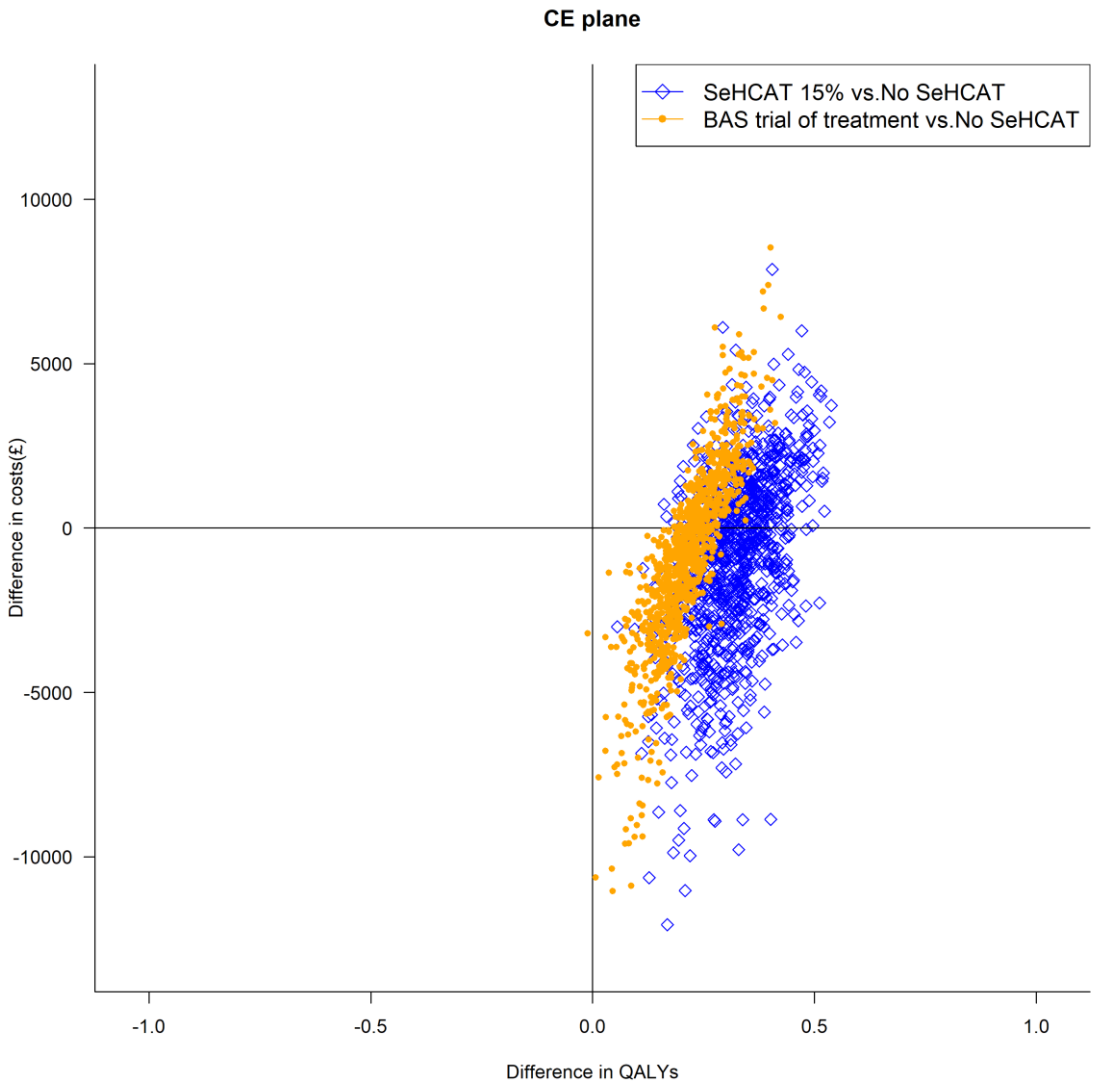
Table 51: PSA base-case results, population 2

	Response	Initial costs	QALYs	Total Costs	Inc. QALYs	Inc. costs	ICER
No SeHCAT	40%	£1,180	12.6857	£15,686	Dominated by BAS TOT		
BAS TOT	60%	£895	12.9006	£14,880	Dominated by SeHCAT 15%		
SeHCAT 15%	71%	£1,172	13.0084	£14,795			

Abbreviations: BAS = bile acid sequestrants, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, TOT = trial of treatment, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.
Note: Percentage of response to any medication. Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

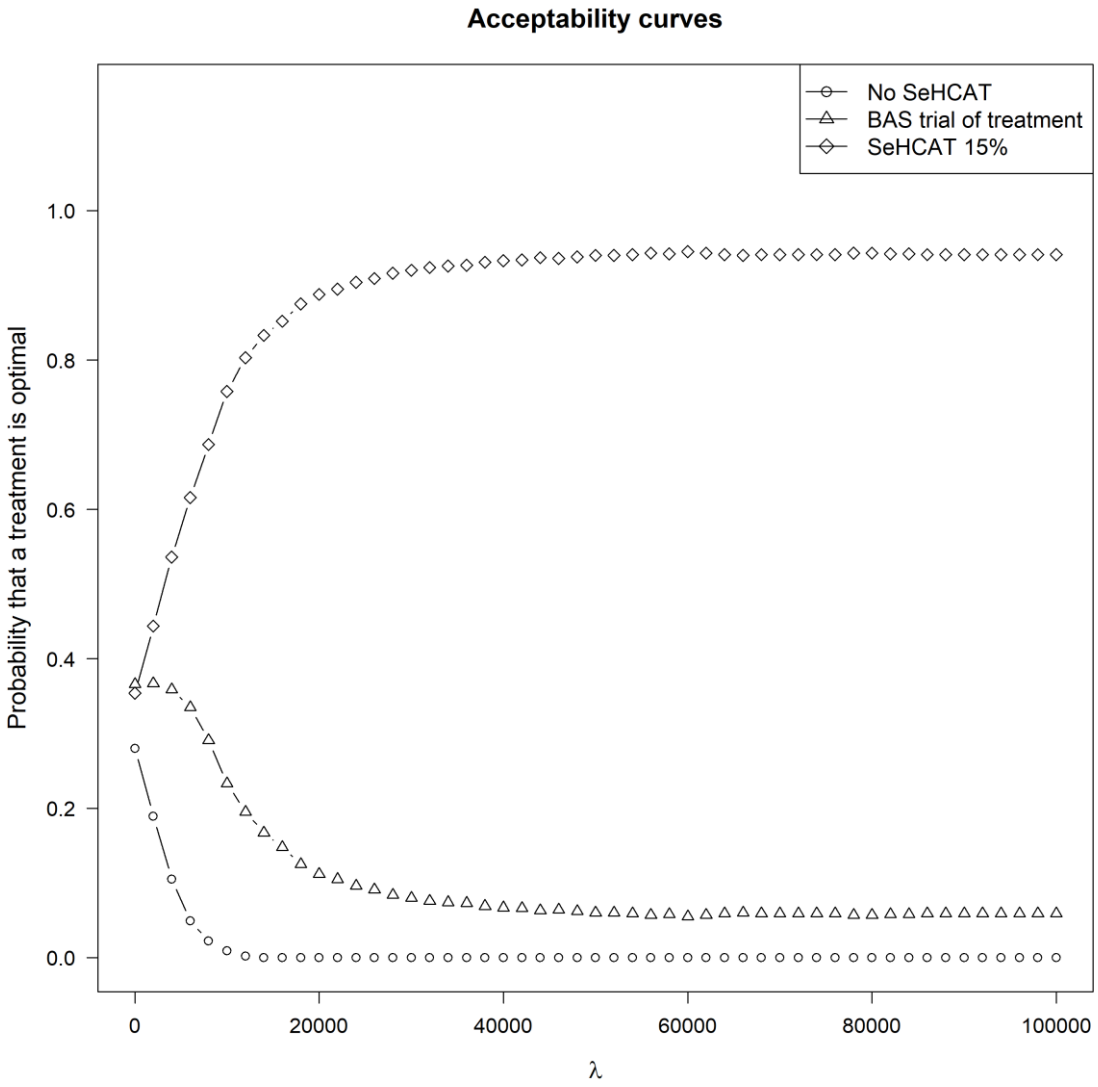
The CE-plane and CEAC resulting from the PSA are shown in Figures 10 and 11, respectively. Note the CE-plane shows the results of pairwise comparisons vs. No SeHCAT. It can be seen that all simulations (except one) are in the eastern quadrants, in which both BAS trial of treatment and SeHCAT 15% are more cost effective than No SeHCAT. Approximately half of the simulations are in the south eastern quadrant of the CE-plane, where BAS trial of treatment and SeHCAT 15% are dominant compared to No SeHCAT. The CEACs show that, for any positive value of the threshold ICER, SeHCAT 15% is the strategy with the largest the probability of being cost effective. In particular, at a threshold ICER of £20,000 per QALY gained the estimated probability of being cost effective is 89%, and 92% at a threshold ICER of £30,000 per QALY gained.

Figure 10: CE-plane from PSA base-case results, population 2



BAS = bile acid sequestrants, CE = cost effectiveness, PSA = probabilistic sensitivity analysis, QALY = quality-adjusted life year, SeHCAT = Tauroselcholic [^{75}Selenium] acid

Figure 11: CEACs from PSA base-case results, population 2



BAS = bile acid sequestrants, CEAC = cost effectiveness acceptability curves, PSA = probabilistic sensitivity analysis, SeHCAT = Tauroselcholic [^{75}Selenium] acid

4.4.7 Results scenario analyses, population 2

Scenario analysis 9: Alternative probability of response to diarrhoea-specific treatment in population 2

In the No SeHCAT strategy the probability of responding to diarrhoea-specific treatment was 40%. For SeHCAT negative patients, a mean response of 42% was estimated and for the BAS trial of treatment strategy, we assumed a mean response of 41% (as the only possible value between the other two). The impact of assuming different response rates to diarrhoea-specific treatment on the cost effectiveness results can be seen in Table 52. The more responders, the higher the long-term QALYs and total costs. The No SeHCAT strategy was dominated by either the SeHCAT 15% or the BAS trial of treatment strategies. The No SeHCAT strategy was also more costly than the other two

strategies because BAS treatments are less costly than the diarrhoea-specific treatment for patients responding to treatment in this population. Therefore, even when an unrealistically high response rate for No SeHCAT was assumed in scenario 2, No SeHCAT was still dominated due to its higher costs. Scenario 3 shows an interesting situation. The overall response to treatment is 9% higher in BAS trial of treatment (possibly unrealistic), but the ICER of £73,684. This high ICER is mostly caused by the difference in costs: in the BAS trial of treatment strategy there are more responders to diarrhoea-specific treatment than in SeHCAT 15% and this treatment is more costly than BAS. Also, because in SeHCAT 15% there are more non-responders, and medication for these patients is assumed to be loperamide only, the costs of non-responders are very low.

Table 52: Results of response to diarrhoea treatment without BAS scenarios, population 2

	Response	Initial costs	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
Base-case (No SeHCAT = 40%, SeHCAT 15% = 42%, BAS TOT = 41%)							
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	60%	£756	12.9008	£13,946			
SeHCAT 15%	71%	£1,061	13.0079	£14,131	0.1071	£185	£1,727
Diarrhoea treatment w/o BAS scenario 1 (No SeHCAT = 42%, SeHCAT 15% = 42%, BAS TOT = 42%)							
No SeHCAT	42%	£1,052	12.7059	£15,078	Dominated by BAS TOT		
BAS TOT	61%	£756	12.9075	£14,171	Dominated by SeHCAT 15%		
SeHCAT 15%	71%	£1,061	13.0079	£14,131			
Diarrhoea treatment w/o BAS scenario 2 (No SeHCAT = 70%, SeHCAT 15% = 42%, BAS TOT = 70%)							
No SeHCAT	70%	£1,052	12.9809	£24,295	Dominated by SeHCAT 15%		
SeHCAT 15%	71%	£1,061	13.0079	£14,131			
BAS TOT	80%	£756	13.0925	£20,373	0.0847	£6,241	£73,684

Abbreviations: BAS = bile acid sequestrants, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, TOT = trial of treatment, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.

Note: Percentage of response to any medication. Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

Scenario analysis 10: Alternative probability of SeHCAT positive result and response BAS treatment in population 2

As with population 1, we considered scenarios where in the SeHCAT 15% strategy the probability of testing positive and the probability of response to BAS were changed at the same time according to limits of their confidence intervals. Then, we explored scenarios where the probability of response to

BAS trial of treatment was decreased and increased. In all scenarios, No SeHCAT was always dominated by one of the other two strategies, which was dominating overall, as can be seen in Table 53. Thus, dominance between SeHCAT 15% and BAS trial of treatment strategies was determined basically depending on overall response to treatment, with the strategy with the highest response dominating the other one. The exception to this was observed in scenario 4 where the response rate for SeHCAT 15% was 71% and for BAS trial of treatment was 70%, but BAS trial of treatment was the dominant strategy. This was because in the base-case there are more patients treated with colesevelam in the BAS trial of treatment strategy, which are assumed to get the full utility associated to not having diarrhoea. Thus, in the long-term this resulted in more gain in QALYs compared to the SeHCAT 15% strategy where there are more patients treated with cholestyramine and, therefore, not getting the full utility of not having diarrhoea. Note, however, that as mentioned for population 1, this scenario is based on a response rates to BAS treatment that is higher for the BAS trial of treatment strategy, which is likely to be unrealistic.

Table 53: Results of SeHCAT positive and response to BAS scenarios, population 2

	Response	Initial costs	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
Base-case (SeHCAT + = 0.55, BAS response | SeHCAT + = 0.89, BAS TOT response = 0.339)							
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	60%	£756	12.9008	£13,946			
SeHCAT 15%	71%	£1,061	13.0079	£14,131	0.1071	£185	£1,727
Scenario 1 (SeHCAT + = 0.39, BAS response | SeHCAT + = 0.67, BAS TOT response = 0.33)							
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by BAS TOT		
SeHCAT 15%	58%	£1,282	12.8700	£14,893	Dominated by BAS TOT		
BAS TOT	60%	£756	12.9008	£13,946			
BAS scenario 2 (SeHCAT + = 0.71, BAS response | SeHCAT + = 1, BAS TOT response = 0.33)							
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	60%	£756	12.9008	£13,946	Dominated by SeHCAT 15%		
SeHCAT 15%	83%	£848	13.1411	£13,396			
BAS scenario 3 (SeHCAT + = 0.55, BAS response | SeHCAT + = 0.89, BAS TOT response = 0.23)							
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	55%	£852	12.8399	£14,190	Dominated by SeHCAT 15%		
SeHCAT 15%	71%	£1,061	13.0079	£14,131			
BAS scenario 4 (SeHCAT + = 0.55, BAS response | SeHCAT + = 0.89, BAS TOT response = 0.5)							

	Response	Initial costs	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by SeHCAT 15%		
SeHCAT 15%	71%	£1,061	13.0079	£14,131	Dominated by BAS TOT		
BAS TOT	70%	£586	13.0090	£13,511			

Abbreviations: BAS = bile acid sequestrants, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, TOT = trial of treatment, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.

Note: Percentage of response to any medication. Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

Scenario analysis 11: Alternative distribution of BAS treatment in population 2

In the base-case it was assumed that in the SeHCAT 15% strategy, 67% of patients started with cholestyramine and 37% with colesevelam, and in the BAS trial of treatment strategy these were 58% and 42%, respectively. As with population 1, we explored scenarios where all patients were treated with cholestyramine, all patients were treated with colesevelam and where there was no difference in BAS distribution between the SeHCAT 15% and the BAS trial of treatment strategy (one scenario assumed a 67/37 proportion and the other one an 58/42). When all patients were treated with cholestyramine, SeHCAT 15% was dominant. When all patients were treated with colesevelam, no strategy dominated but the relevant ICERs were both below the £20,000 threshold (BAS trial of treatment vs. No SeHCAT = £4,581, and SeHCAT 15% vs. BAS trial of treatment = £9,009). When the BAS distribution was mixed and equal in both strategies, No SeHCAT was dominated and the ICERs of SeHCAT 15% vs. BAS trial of treatment were £2,608 and £3,030. Full results are shown in Appendix 7.

Scenario analysis 12: Alternative health state utilities in population 2

In all utility scenarios tested, the No SeHCAT strategy was dominated by both BAS trial of treatment and SeHCAT 15%. When comparing SeHCAT 15% to BAS trial of treatment, the ICER was always below £3,000 per QALY gained, well within the threshold to be considered cost effective. Full results are shown in Appendix 7.

Scenario analysis 13: Alternative cost inputs in population 2

Increasing the cost of BAS treatment by 20% increased the costs of the BAS trial of treatment and SeHCAT 15% strategies, such that they no longer dominated the No SeHCAT strategy. However, the largest ICER obtained for the comparison SeHCAT 15% vs. BAS trial of treatment was £5,143, thus well below the commonly used threshold of £20,000 per QALY gained. Decreasing the cost of Crohn's anti-diarrhoea medication by 20% also prevented No SeHCAT from being dominated by

either alternative strategy but again the largest ICER, for the comparison SeHCAT 15% vs. BAS trial of treatment, was £5,647. Increasing the cost of Crohn's anti-diarrhoea medication by 20% however resulted in the highest costs being observed again for No SeHCAT and SeHCAT 15% was the dominant strategy in this scenario. SeHCAT 15% was also the dominant strategy in the scenario in which the cost of BAS treatment was decreased by 20%. ICERs were below £6000 per QALY gained in all scenarios. Full results are shown in Appendix 7.

Scenario analysis 14: Alternative transition probabilities in population 2

In all transition probability scenarios run, relapse was included in the BAS Markov models (in the base-case, relapse was only possible in the non-BAS model).

Including a probability of relapsing in the BAS strategies resulted in lower costs since the costs associated to the diarrhoea health state are very low (loperamide only). Thus, despite the loss in QALYs, SeHCAT 15% was dominant in all scenarios except the last one where the probability of relapse was the highest explored (five times higher than in the base-case). In this scenario, all strategies resulted in lower costs and QALYs than in the base-case but the ICER was nearly equal (£1,459). Full results are shown in Appendix 7.

Scenario analysis 15: Alternative mortality estimates in population 2

Replacing the SMR (1.52) from Canavan et al. (2007),[65] by the limits of its confidence interval (1.32, 1.74) had a minimal impact on the cost effectiveness. Using the SMR lower limit increased life years to 19.13 (18.70 in the base-case) and increased costs and QALYs for all strategies. Likewise, using the SMR upper limit increased life years to 18.25 and decreased costs and QALYs for all strategies. In both scenarios, No SeHCAT was still dominated and the ICER remained practically unchanged. Full results are shown in Appendix 7.

4.5 Validation

Validation of the health economic models was undertaken by one of the model developers. Validation was guided by the health economic model validation specific tools AdViSHE and TECH-VER.[66] A filled-in version of both tools can be found within the files included in the health economic model developed for this project.

5. DISCUSSION

5.1 Statement of principal findings

5.1.1 Clinical effectiveness

The evidence base relating to the use of SeHCAT testing in:

1. Adults presenting with chronic diarrhoea with unknown cause (FD), or suspected or diagnosed IBS-D (i.e., people with suspected primary BAD)

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

has not changed substantively since our previous systematic review,[16] which was conducted to support the development of DG7.[1] The search yield increased considerably in this update assessment; searches of bibliographic databases (from inception to November 2020) identified a total of 5,518 unique references, after deduplication against the Endnote library from our previous systematic review,[16] compared to the total of 4,240 unique references identified for the period from inception to April 2012 covered by the searches conducted for our previous systematic review.[16] However, despite the large number of records retrieved, only nine new studies were identified,[24-32] which met the inclusion criteria for this assessment. Most (8/9) of these studies were published as conference abstracts only.[24-28, 30-32] In addition, six publications,[49-53, 67] which were included in our previous systematic review,[16] did not meet the inclusion criteria for this assessment. This current assessment includes a total of 25 publications relating to 24 studies, as compared to the 24 publications relating to 21 studies included in our previous systematic review.[16]

No RCTs, CCTs or observational comparative studies, which met the inclusion criteria for this assessment (see Section 3.1.2) were identified. Similarly, no multi-variable regression modelling, with response to treatment with BAS as the dependent variable and index test (SeHCAT) result (continuous or categorical) considered as one of the independent variables, were identified. Finally, no new predictive accuracy studies, (studies which reported sufficient data to support the calculation of the sensitivity and specificity of SeHCAT to predict response to treatment with BAS,) were identified. All of the nine new studies included in this review[24-32] were of the lowest level of evidence eligible for inclusion; these were observational studies which reported some outcome data for patients treated with BAS, where only those patients with a positive SeHCAT test were offered treatment with BAS.

All 24[6, 24-34, 36-47] of the studies included in this assessment provided some data for population one and one study[6] also provided data on population two.

Three studies,[39, 42, 43] all of which were included in our previous assessment report, conducted for DG7,[16] provided limited data on the accuracy of the SeHCAT test for predicting response to treatment with BAS, for population 1. Merrick et al. (1985)[39] reported sufficient data to allow the calculation of the performance of SeHCAT, for predicting treatment response, at two seven-day-retention thresholds (<8% and ≤15%). The estimated sensitivity of SeHCAT in predicting a positive response to treatment with colestyramine, using the <15% threshold (commonly used in UK clinical practice),[3, 68] was 100% (95% CI: 54.1 to 100%) and the corresponding specificity estimate was 91.2% (95% CI: 76.3 to 98.1%).[39] These results would appear to indicate that the use of the SeHCAT, with a 15% threshold, could identify patients with IBS-D who may benefit from treatment with BAS. However, it should be noted that the confidence intervals around the sensitivity estimate were wide and, although all 31 patients with a negative SeHCAT test result were classified as true negatives, this assessment was based on long term follow-up: "None of the 31 patients with irritable bowel disease who retained more than 15% at seven days showed any evidence of small bowel disease, and none appeared during a follow up of at least 12, and in some up to 24 months. Simple conservative treatment resolved or eased most symptoms."[39] None of these 31 patients received treatment with colestyramine and it therefore remains uncertain whether any of these patients could have benefited from treatment with BAS. The remaining two studies[42, 43] provided data for seven-day SeHCAT retention thresholds of 5% and 8%.

Eight studies reported information about the rate of positive response to treatment with BAS, using a threshold of <15% or ≤15%, for population one.[26, 28, 33, 41, 44-47] The median proportion of SeHCAT test positive patients who received treatment with BAS was 86% (range 70% to 100%) and the median response rate was 68% (range 38% to 86%). The equivalent data from the predictive accuracy study by Merrick et al. (1985)[39] indicated a treatment response rate of 67% in patients with seven-day SeHCAT retention values ≤15%; in this study, 9/12 (75%) patients with SeHCAT retention values of ≤15% threshold received treatment with colestyramine. Eleven studies reported information about the rate of positive response to treatment with BAS, using a threshold of <10% or ≤10%.[6, 25, 30, 31, 33, 34, 36, 37, 40, 41, 47] The median proportion of SeHCAT test positive patients who received treatment with BAS was 100% (range 52% to 100%) and the median response rate was 85% (range 67% to 100%).

The single study that reported information about response to treatment with BAS for population two provided only limited information about response rates in patients with a positive SeHCAT test result (seven-day retention <10%) who were treated with colestyramine or colestipol.[6] Only 9/24

patients with a positive SeHCAT test result received treatment with BAS and the numbers receiving each drug were not reported; 8/9 (89%) patients treated with BAS responded positively.[6]

5.1.2 Cost effectiveness

We have assessed the cost effectiveness of SeHCAT in two populations described in the clinical effectiveness section. For both populations the cost effectiveness of SeHCAT compared to no SeHCAT and to trial of treatment with BAS was assessed. For the SeHCAT option, only the strategy based on the 15% cut-off point was included in the cost effectiveness analyses for both populations. The main reason for this was that in the clinical expert elicitation exercise to inform parameters for which data are lacking (the majority of parameters included in the model), all clinical experts consulted provided estimates for the 15% cut-off only.

For each population, two models were combined:

- a short-term decision analytic model reflecting the diagnostic pathway and initial response to treatment (assumed to be the first six months), and
- a long-term (Markov) model that estimates the lifetime costs and effects for patients receiving subsequent treatment. The Markov model is parameterised according to treatment, thus, in practice, there is one Markov model for each type of medication included in the analyses (i.e., BAS (cholestyramine and colesevelam), IBS-D, IBD and diarrhoea medication for Crohn's patients).

The main difference with respect to the model developed for the previous assessment of SeHCAT,[16] is that for population 1 our model places colonoscopy after SeHCAT according to most clearly expressed clinical expert opinion and BSG guidelines where colonoscopy is required for investigation of cancer and not for ruling IBD out. In practice, colonoscopy can be excluded from the model by setting this probability equal to zero. In the decision analytic model, the number of responders, the expected costs and the number of colonoscopies avoided (when applicable) were calculated for each comparator. In the Markov models, lifetime expected (quality adjusted) life years and expected costs per patient were calculated for each comparator.

Where possible, input parameters for the model were estimated based on our systematic review, other published literature and UK databases. When such evidence was not available, expert opinion was sought. The impact of parameter uncertainty was explored through probabilistic sensitivity analyses and scenario analyses. ICERs were estimated as additional cost per additional QALY. Other outcomes included in the analyses were short-term costs, response to treatment and, in population

1, colonoscopies avoided. These three outcomes were calculated in the decision analytic model (thus, assumed to be in the first six months of the simulation).

For both populations, the SeHCAT 15% strategy has shown the potential of being considered a cost-effective alternative by either dominating the other two strategies or by resulting in ICERs below the common thresholds of £20,000 or £30,000 per QALY gained. Dominance or cost effectiveness was led, in general, by response since the SeHCAT 15% was the strategy with the highest response rate in the majority of the scenarios explored, including the base-case for both populations. In scenarios where the other two strategies were estimated to provide higher response rates than SeHCAT, the scenarios were likely based on unrealistic assumptions regarding response No SeHCAT or BAS trial of treatment. Even in those scenarios where overall response in the BAS trial of treatment strategy was higher than in SeHCAT 15%, the ICERs for the comparison of BAS trial of treatment vs. SeHCAT 15% were well above the £20,000 or £30,000 per QALY gained thresholds. SeHCAT 15% was also the strategy in which more colonoscopies were avoided.

5.2 Strengths and limitations of assessment

5.2.1 Clinical effectiveness

Extensive literature searches were conducted in an attempt to maximise retrieval of relevant studies. These included electronic searches of a variety of bibliographic databases, as well as screening of clinical trials registers and conference abstracts to identify unpublished studies. Because of the known difficulties in identifying test accuracy studies using study design-related search terms,[69] no study design filters were used in order to maximise sensitivity at the expense of reduced specificity. Thus, large numbers of citations were identified and screened, however, the search yield (proportion of studies identified that met the inclusion criteria for this assessment) was very low.

The possibility of publication bias remains a potential problem for all systematic reviews. Considerations may differ for systematic reviews of test accuracy studies. It is relatively simple to define a positive result for studies of treatment, e.g. a significant difference between the treatment and control groups which favours treatment. This is not the case for test accuracy studies, which measure agreement between index test and reference standard. It would seem likely that studies finding greater agreement (high estimates of sensitivity and specificity) will be published more often. In addition, test accuracy data are often collected as part of routine clinical practice, or by retrospective review of records; test accuracy studies are not subject to the formal registration procedures applied to randomised controlled trials and are therefore more easily discarded when results appear unfavourable. It would seem likely that similar considerations would apply to the type

of observational study (studies in which only participants with a positive index test [SeHCAT] result receive the reference standard [treatment with BAS]) which comprises most of the evidence in this assessment. The extent to which publication bias occurs in studies of test accuracy remains unclear, however, simulation studies have indicated that the effect of publication bias on meta-analytic estimates of test accuracy is minimal.[70] Formal assessment of publication bias in systematic reviews of test accuracy studies remains problematic and reliability is limited.[70] We did not undertake a statistical assessment of publication bias in this review. However, our search strategy included a variety of routes to identify un-published studies and resulted in the inclusion of a number of conference abstracts.

Clear inclusion criteria were specified in the protocol for this review, , the review has been registered on PROSPERO (CRD42020223877) and the protocol is available from https://www.nice.org.uk/guidance/gid-dg10039/documents/final-protocol. The eligibility of studies for inclusion is therefore transparent. In addition, we have provided specific reasons for exclusion for all of the studies which were considered potentially relevant at initial citation screening and were subsequently excluded on assessment of the full publication (Appendix 4). The review process followed recommended methods to minimise the potential for error and/or bias;[13] studies were independently screened for inclusion by two reviewers and data extraction and quality assessment were undertaken by one reviewer and checked by a second (MW and ER). Any disagreements were resolved by consensus.

Three studies[39, 42, 43] included in the review were classified as predictive accuracy studies (studies which provided data on the sensitivity and specificity of the SeHCAT test for predicting response to treatment with BAS). The methodological quality of these studies was assessed using a modification of the QUADAS-2 tool,[71] which is recommended by the Cochrane Collaboration. [15] QUADAS-2 is structured into four key domains covering participant selection, index test, reference standard, and the flow of patients through the study (including timing of tests). Each domain is rated for risk of bias (low, high, or unclear); the participant selection, index test and reference standard domain are also, separately rated for concerns regarding the applicability of the study to the review question (low, high, or unclear). For continuity, the methodological quality of studies which reported treatment outcome only for those participants with a positive SeHCAT result (i.e. sufficient data to calculate PPV only) was assessed using a topic-specific adaptation of the quality assessment checklist by Wedlake et al. (2009),[23] as used in our previous Diagnostic Assessment Report (DAR).[16]

As was the case for our previous systematic review on this topic,[16] the main limitations for this assessment are the paucity of data (only nine new studies were identified for this update

assessment), the level of evidence (21/24 of the included studies were of the lowest level of evidence specified in the inclusion criteria) and the generally poor quality of the included studies (see Section 3.2.2). Studies which reported information about the rate of response to treatment with BAS, in participants who has a positive SeHCAT test, appeared not to be using the SeHCAT test result alone to determine treatment decisions, as not all participants with a positive SeHCAT test received BAS; other reasons for deciding whether or not to offer BAS were not reported. There were substantial differences between studies included in the review (studies were generally poorly reported and there was variation in the SeHCAT test methods and thresholds, BAS treatment regimens, and definition of response to treatment). The applicability of the included studies to the review question was unclear; previous investigations were generally poorly reported and not equivalent to those specified in current BSG guidelines for the investigation of chronic diarrhoea.[2] and the generally poor quality of the included studies (see Section 3.2.2).

5.2.2 Cost effectiveness

The main objective of this assessment was to update the previous assessment of SeHCAT conducted in 2012/2013.[16] As mentioned in the clinical effectiveness section, the evidence base relevant for this assessment has not changed substantively since the previous one. Therefore, current strengths and limitations are similar to those discussed in the previous report.

This report presents a full economic evaluation study in two populations of interest, 1) adult patients presenting with chronic diarrhoea with unknown cause (FD), or suspected or diagnosed IBS-D (i.e., people with suspected primary BAD); and 2) adults with chronic diarrhoea and a diagnosis of Crohn's disease, who have not undergone ileal resection (i.e., people with suspected secondary BAD). Short- and long-term consequences were assessed both in costs and effects of using SeHCAT at 15% cut-off threshold compared to No SeHCAT and trial of treatment with a BAS (cholestyramine or colesevelam). For both patient populations, a linked evidence approach was used to model cost and consequences, to combine outcomes of the SeHCAT test and the related changes in treatment decisions and final health outcomes. Our model and analyses distinguish between the initial diagnostic phase (treatment responder vs. non-responder, and colonoscopies avoided, at six months) and the long-term projection of treatment response into final health outcomes (lifetime costs and consequences, the latter expressed in QALYs).

There are several differences with respect to the analyses in the previous assessment of SeHCAT.[16] As mentioned in the previous section, for the SeHCAT option, only the strategy based on the 15% cut-off point was included in the cost effectiveness analyses due to the lack of data to inform other relevant SeHCAT strategies identified in the literature (e.g. 5% or 10%). While including just one

SeHCAT strategy could be seen as a limitation, it could be argued that it is indeed an advantage since including other SeHCAT strategies for which data are also lacking, would only increase the uncertainty around the plausibility of the cost effectiveness results.

Another important difference in this assessment is that the health economic model extends the model previously developed by placing colonoscopy after SeHCAT for the first population. This was assumed according to most clearly expressed clinical expert opinion and BSG guidelines where colonoscopy is required for investigation of cancer and not for ruling IBD out. In practice, colonoscopy can be excluded from the model by setting this probability equal to zero, and in that case the updated model can be seen as equivalent to the model in the previous assessment of SeHCAT.

The impact of using SeHCAT was included in the analyses in terms of BAS treatment response as reported in peer reviewed papers. We selected for this purpose only those papers that fulfilled our quality criteria as presented in Section 3. In all models developed we have used the best available evidence to inform input parameters that were relevant for the UK. Where evidence was not available through published studies or databases, we used the most likely and plausible values as reported by clinical experts. For this purpose, we sent out an updated questionnaire in which new questions were targeted to fill the evidence gaps from the previous models. The lack of evidence was handled by performing probabilistic sensitivity analyses and a wide range of scenario analyses. Unlike in the previous assessment of SeHCAT, this time it was preferred to have a base-case scenario for each population that was defined based on the assumptions that were deemed more plausible by the modelling team based on the available evidence and clinical experts' feedback.

In the updated assessment we were able to incorporate patients switching from treatment with cholestyramine to colesevelam using clinical experts' inputs. Unfortunately, it was not possible to translate it into changes in response rates, but at least changes in costs and quality of life due to treatment switching were included in the new analyses.

A strength of the HRQoL evidence is that EQ-5D utility values were identified for patients with IBS with and without diarrhoea. However, assumptions had to be made to estimate these utilities in patients with Crohn's and to estimate the utility of patients who respond to treatment with BAS in both populations, all of which represent important limitations in the HRQoL evidence.

Unit costs were retrieved from appropriate sources and were based on the latest costing year. Most of the information needed to calculate costs (e.g., medication use, dosage, proportion of patients requiring each type of medication, etc.) was based on experts' opinion. The costs estimated might be

considered uncertain, as questions were filled in by a maximum of four experts, but some questions were are answered by just one or two. For example, if for one medication different dosages were answered by different experts, the average of the experts' answers was used. It is uncertain whether these averages would approach the true value given the small sample size. When the full information of a certain medication was not available from the questionnaire, this medication was excluded from the model, for example vedolizumab for IBD patients. Since these costs are expected to be high, the current estimated IBD costs might be underestimated. Similar issues were encountered for infliximab or psychological treatment in the IBD population. Most notably, when clinical experts were asked about treatment of diarrhoea in Crohn's patients, their answers suggested that this was similar to treatment of BAD with BAS since cholestyramine and colesevelam were mentioned. However, assuming these as treatment of diarrhoea in Crohn's patients would result into no distinction between the No SeHCAT and the BAS trial of treatment strategies. Therefore, diarrhoea treatment for patients with Crohn's disease was assumed to be the same as in the previous SeHCAT report.[16]

One of the main limitations of this study is still that the studies used to estimate the probability of a positive SeHCAT test and the probability of BAS response, after positive SeHCAT test, were based on other populations than the ones defined in this evaluation. Most IBS-D studies included patients in whom various tests had been performed and where no organic cause of the diarrhoea was found. This is in contrast with the population defined in this assessment, which is patients with symptoms suggestive of functional disease in whom only basic blood tests have been performed. It is therefore likely that, in our population, the prevalence of BAD is lower than the prevalence observed in the published studies.

Another limitation that was already present in the previous assessment of SeHCAT concerns the modelling of non-responders. It is assumed in the model that non-responders would only use loperamide for some symptomatic relief. It might be likely that for example in the IBS-D population (i.e., patients in whom no diagnostic testing other than initial blood work has been performed) some non-responders will be referred for diagnostic testing to check for organic causes of the chronic diarrhoea.

The most important limitation is still the lack of data on various important parameters of the model. This is most notably the case for patients after testing negative for SeHCAT and for the BAS trial of treatment strategy. The necessity to rely on expert opinion was still high since the majority of parameters included in the model were informed by the answers provided to our questionnaire.

5.3 Uncertainties

5.3.1 Clinical effectiveness

Two systematic reviews, published since the publication of NICE diagnostic guidance DG7,[1] have provided estimates of the prevalence of BAM, as defined by a seven-day SeHCAT retention value <10%, in adults with IBS-D (defined by the Rome I, II, or III criteria),[72] or adults with IBS-D or FD with no organic explanation.[73] The pooled prevalence estimates from these two systematic reviews were 28.1% (95% CI: 22.6 to 34.0%), based on data from six studies (n=908),[72] and 30.8% (95% CI: 24.7 to 37.7%), based on data from 24 studies (total number of participants unclear).[73] These data support the idea that BAM may be a significant underlying pathology in a substantial proportion of patients with IBS-D or FD and, by extension, that 'under diagnosis' of BAM in this population could result in patients not receiving potentially beneficial treatment with BAS, or experiencing delays in treatment. A web-based survey of 227 UK Nuclear Medicine Departments, published in 2013 shortly after NICE diagnostic guidance DG7,[1] reported that 73/129 (57%) of responding centres were using SeHCAT, of whom 51/73 (70%) reported an increase workload over the preceding three years.[68] Although this study is approximately eight years old, and hence cannot be taken as a reliable representation of current service provision, it may be worth noting that responding centres reported a very wide range of annual patient workloads, median 30 studies per. year (range 1 to 300), indicating substantial geographic variation in service provision.[68] A subsequent prospective survey of 38 UK centres providing SeHCAT testing, published in 2016, reported that the total number of SeHCAT tests conducted by participating centres, over a six month period, was 1,070;[3] this study did not provide a breakdown of test numbers by centre.

Despite the apparent significance of BAM in the adult IBS-D/FD population, and the expansion of provision of SeHCAT testing in the UK, there remains a surprising lack of evidence linking the use of SeHCAT testing to patient-perceived outcomes. As described in sections 3.2.3 and 3.2.4 of this report, the available evidence is largely limited to studies which describe the proportion of patients with a positive SeHCAT result who respond positively to treatment with BAS. The thresholds used by these studies to define a positive SeHCAT test varied and, although some studies did evaluate multiple thresholds, data were sparse and the optimal SeHCAT decision threshold, to define presence of BAM and select patients for treatment with BAS, remains unclear. For example, two studies reported information about treatment response rates for three seven-day SeHCAT retention thresholds (5%, 10% and 15%).[33, 47] The results of both studies indicated that if a 5% or 10% threshold were applied some patients with a negative SeHCAT result that might be considered to be

'borderline' or 'equivocal' (i.e. seven-day retention values between 5% and 15% or between 10% and 15%), who may benefit from treatment with BAS, would be missed (see Section 3.2.3). Furthermore, there is apparent variation in UK practice, with respect to the threshold used to define a positive SeHCAT test result; the 2013 survey of UK practice found that 42/72 (58%) of centres providing SeHCAT tests reported using a seven-day retention value of >15% to define an 'unequivocally normal' test result, with 19% using a lower and 22% a higher threshold.[68] The 2016 survey of UK centres found that the majority 22/32 (69%) of reporting centres used a 'normal' threshold of ≥15%.[3] However, variation in practice remained, with 'normal' threshold values ranging from ≥10% to ≥20%; the key findings of this study included the statement that 'there was a high level of heterogeneity in practice, with no standardised protocol, and no consistently defined diagnostic threshold values of SeHCAT retention.[3] In summary, UK practice varies, with respect to the threshold used to define a 'normal' SeHCAT test result, and the extent to which patients with 'borderline' or 'equivocal' seven-day SeHCAT retention values (e.g. between 10% and 15%) could benefit from treatment with BAS remains unclear, and the extent to which patients with seven-day retention values >15% may benefit from treatment with BAS is unknown.

Given the uncertainty regarding the optimal SeHCAT decision threshold, to define presence of BAM and select patients for treatment with BAS, the potential for intra-individual variation in SeHCAT retention values (e.g. arising from variation in dietary intake before the test or concomitant medication use) may be an important consideration for the implementation of SeHCAT testing in clinical practice. The 2013 survey of UK practice found that 45/72 (62%) of centres providing SeHCAT tests reported issuing no specific instructions to patients regarding pre-test fasting and 31/72 (42%) gave no specific instructions regarding medication;[68] This information was not reported in the 2016 survey.[3]

'Trial of treatment' with BAS without testing, is sometimes advocated as an alternative approach to investigating BAM as a potential undiagnosed cause of symptoms in patients with IBS-D,[74, 75] and 'trial of treatment' is a comparator for the cost effectiveness modelling included in this assessment. However, it should be noted that a positive response to treatment with BAS cannot be considered to be 100% specific for a diagnosis of BAM, since these drugs can slow gut transit irrespective of any effect on bile acid metabolism. We identified a German language study, which reported the authors' experience (1991 to 2017) of using a 'trial of treatment' with colestyramine in patients with chronic diarrhoea in whom organic causes had been excluded.[75] This study did not meet the inclusion criteria for our systematic review, as only patients with a positive response to colestyramine were offered SeHCAT testing, and it did not provide data to inform cost effectiveness modelling, as the

total number of patients who received a 'trial of treatment' (and hence the proportion who responded) was not reported.[75] However, this study did report the proportion of people, 8/60 (13%), who responded positively to colestyramine and received a SeHCAT test, in whom that test was negative for BAM (seven-day retention ≥20%); this may be considered indicative of the proportion of patients with unexplained chronic diarrhoea who respond positively to BAS, in whom there is no evidence of BAM.[75] In support of SeHCAT testing, it has been suggested (scoping discussions for this assessment) that SeHCAT testing and the assignment of a diagnosis of BAM may improve adherence to treatment with BAS, which are generally considered to be poorly tolerated; where reported, rates of intolerance/discontinuation in the studies included in this assessment were generally high, median 15% (range 4% to 27%) and the 2016 survey of SeHCAT provision and practice in the UK found that 20/101 (20%) of patients who were prescribed BAS reported side effect including bloating, diarrhoea, constipation, nausea/vomiting, bloating, urticarial rash, pain and intolerance to tablets.[3] Where information about the BAS treatment was provided, most (16/20) studies included in this assessment reported the use of colestyramine alone.[24, 30, 31, 33, 34, 36-44, 46, 47] Three studies reported more than option for treatment with BAS, colestyramine or colesevelam,[27] colestyramine or colestipol,[6] and colestyramine or colesevelam or colestipol[29]; none of these studies reported either the numbers of patients treated with each drug, or the criteria used to select treatment. Similarly, the 2016 survey of UK practice did not provide a breakdown of side effects/intolerance by type of BAS received.[3] There was insufficient information to determine whether levels of intolerance varied between colestyramine, colestipol and colesevelam, and no study reported information about patient preferences. We did not identify any studies that reported information about patient preferences with respect to SeHCAT testing versus 'trial of treatment' without testing.

Finally, there is a lack of evidence about the efficacy and safety of BAS for the treatment of patients diagnosed with BAM; the clinical effectiveness searches conducted for this assessment identified only three treatment RCTs,[76-78] of which only one used a positive SeHCAT test (seven-day retention <10%) to define BAM and select patients for inclusion.[78] This latter was a very small (n=19) placebo-controlled RCT, evaluating two doses (250 mg and 1 g twice daily) of a colonic release formulation of colestyramine, which found no significant effect on the primary outcome (mean daily bowel movement at week two of treatment), but reported reductions in diarrhoea and improvements in stool consistency in the treated groups.[78] Although outside the scope of this assessment, it should be noted that our searches identified an ongoing systematic review on the effectiveness of non-pharmacological therapies in the management of BAD in adults.[79]

5.3.2 Cost effectiveness

The main uncertainties in the cost effectiveness analyses are still caused by a lack of essential data. The majority of the input parameters of the model were informed by clinical experts. In particular, after a SeHCAT negative result, the BAS trial of treatment and for the Crohn's population in general, evidence is especially limited. Therefore, a substantial number of assumptions had to be made to make it possible to perform the cost effectiveness analyses.

As in the previous assessment of SeHCAT,[16] the lack of evidence on the accuracy of SeHCAT based on a reference test implied that, in the diagnostic decision analytic models, the most common way of modelling test accuracy using sensitivity and specificity of the test was not feasible. Thus, it was not possible to indicate false positive and false negative probabilities of testing. The accuracy of SeHCAT testing was thus based on the test result in combination with response to BAS treatment. It might occur that patients responding to BAS may be true positive (patients with a true response) but may also be false positive patients with a placebo response.

Another unresolved uncertainty regarding the trial of treatment strategy relates to the placebo response that may be expected in the true IBS-D patients receiving BAS. It is well known that patients with IBS-D are likely to show high placebo responses to treatment.[80] Clinical experts pointed out that long-term inappropriate treatment with BAS could have implications for absorption of other drugs and vitamins. These long-term undesired consequences were not included in the modelled trial of treatment strategy. Clinical experts also indicated that a response to BAS is not helpful diagnostically since BAS are constipating drugs in any event, as known from when they were used for lowering cholesterol levels in people with no bowel problems. Therefore, using BAS as a diagnostic would be no better than using loperamide as a diagnostic test for any form of diarrhoea. Additionally, transitions between "diarrhoea" and "no diarrhoea" health stated might not be the same for BAS patients having a positive SeHCAT result and for patients responding to a BAS trial of treatment, since patients without a positive diagnosis may be less inclined to accept the side effects of BAS (cholestyramine).

The uncertainties in the Markov model are still also unresolved. The diarrhoea health state was valued by cost and utilities irrespective of the cause of the symptom. However, there is no evidence to confirm whether this is true or not. For the increase in utility when patients become responders, we made the same previous assumption that patients responding to BAS (cholestyramine) would only get 75% of the utility benefit of becoming responder. It is unknown to what extent this assumption of 75% is realistic. However, scenario analyses showed that the impact of this assumption on the model results is minor.

Transition probabilities in the Markov model remain uncertain as well. However, scenario analyses have shown that this also had little impact on the model results. This time it was also not possible to include a health state constipation or other adverse events in the long-term Markov model given the lack of data.

Finally, it is uncertain how the cost effectiveness results would change should other SeHCAT strategies be included in the analyses. The available clinical evidence regarding the cut-off values defining a positive SeHCAT test shows that the various cut-off values influence test-accuracy estimates expressed in BAS treatment response. The cost effectiveness analyses included in this report have shown that response to treatment is a key driver of the cost effectiveness results. The strategy with the highest response rate is likely to be the preferred one in terms of health benefits but it remains uncertain whether this will be translated into cost effectiveness.

6. CONCLUSIONS

6.1 Implications for service provision

Despite the apparent significance of BAM in the adult IBS-D/FD population, and the expansion of provision of SeHCAT testing in the UK, there remains a surprising lack of evidence linking the use of SeHCAT testing to patient-perceived outcomes. The available evidence is largely limited to studies which describe the proportion of patients with a positive SeHCAT result who respond positively to treatment with BAS. The optimal SeHCAT decision threshold, to define presence of BAM and select patients for treatment with BAS, is uncertain. The extent to which patients with 'borderline' or 'equivocal' seven-day SeHCAT retention values (e.g. between 10% and 15%) could benefit from treatment with BAS remains unclear, and the extent to which patients with seven-day retention values >15% may benefit from treatment with BAS is unknown. It has been suggested that SeHCAT testing and the assignment of a diagnosis of BAM may improve adherence to treatment with BAS. However, despite some evidence indicating that these treatments are generally poorly tolerated, there is a lack of information about the relative rates of adherence for different BAS and about the acceptability, to patients, of SeHCAT testing. Finally, there is a paucity of evidence about the efficacy and safety of BAS for the treatment of patients who have been diagnosed with BAM.

The evidence base has not advanced substantively since our previous assessment,[16] conducted to inform the development of NICE diagnostic guidance DG7.[1]

The results of the economic evaluation conducted for both populations seem to suggest that SeHCAT have the potential of being a cost effective strategy. However, there is great uncertainty surrounding these analyses, which should be based on more robust evidence. Therefore, the implications for service provision of SeHCAT are still uncertain and the main reason for this uncertainty is the lack of good quality evidence

6.2 Suggested research priorities

Given the deficiencies in the evidence base, outlined in Section 6.1, the optimum study design for maximum information gain would be a multi-arm RCT, in which participants meeting the inclusion criteria are randomised to receive colestyramine, colestipol, colesevelam, or placebo and all participants receive SeHCAT testing. Included participants should be adults (age ≥18 years) presenting with chronic diarrhoea with unknown cause, suspected or diagnosed IBS-D, or adults (age ≥18 years) presenting with chronic diarrhoea and a diagnosis of Crohn's disease, who have not undergone ileal resection. Participants should have undergone primary clinical assessment/investigations (as recommended in the BSG guidelines[2]) 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), prior to inclusion in the study. SeHCAT testing should be undertaken in all participants, irrespective of treatment group. A study of this type could potentially allow estimation of the comparative efficacy, safety and tolerability of colestyramine, colestipol, colesevelam and placebo in all participants (equivalent to the 'trial of treatment' option described in this assessment). In addition, stratified analyses based on different seven-day SeHCAT retention values, could be used to investigate variation in the comparative efficacy, safety and tolerability of colestyramine, colestipol, colesevelam and placebo with SeHCAT retention and hence to inform the optimal SeHCAT threshold to guide treatment decisions. A further option would be stratified randomisation to disclosure or non-disclosure of SeHCAT test results prior to treatment; this option could allow assessment of the effects of testing and diagnosis on adherence to treatment.

An alternative, pragmatic option would be a prospective cohort study in which all participants (inclusion criteria as described above) receive both treatment with a BAS and SeHCAT testing. Data from such a study could be analysed to determine the predictive accuracy (sensitivity and specificity) of one or more pre-defined SeHCAT thresholds for response to treatment with BAS. Alternatively, a receiver operating characteristic (ROC) analysis could be used to determine the clinically optimal SeHCAT threshold.

From the cost effectiveness perspective, it is important to emphasise that data on SeHCAT accuracy and response to BAS are not sufficient to conduct a full economic evaluation, since this would require data on all possible pathways including treatment of patients with a negative SeHCAT result and patients not responding to BAS. Since cost effectiveness studies usually adopt a lifetime time horizon, data on long-term effects are also required. Given the gaps in the HRQoL evidence already discussed, a priority in future research should be to provide diarrhoea specific utilities for patients with Crohn's disease in general as well as patients taking BAS, preferably using the EQ-5D. Since costs estimates were highly uncertain, priority should also be given to the research of costs of treatment of BAD, IBS-D, IBD and diarrhoea in Crohn's disease patients.

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APPENDIX 1: LITERATURE SEARCH STRATEGIES

The following search strategies were based on those reported in the 2011 review, strategies were amended in line with the agreed final scope and updated to include any new terminology for the condition and interventions and to compensate for any changes to search interfaces. Some resources such as HEED and the National Guidelines Clearing House are no longer available and additional resources such as Northern Lights conference proceedings and ECRI Guidelines Trust have been added to maintain the breadth of resources searched. To ensure completeness all searches in both the clinical and cost effectiveness sections were screened for all areas of interest. For full details of strategies used in the 2011 review, please see Appendix 1 of Riemsma et al. 2012.[16]

Clinical Effectiveness

Database	Dates covered	Hits
EMBASE	1974-2020/11/25	4797
MEDLINE + PreMedline	1946 to 2020/11/30	2282
CDSR + CDSR protocols	Up to 2020/11/Iss11	134
CENTRAL	Up to 2020/11/Iss11	404
DARE	up to 2015/03	13
HTA (CRD)	up to 2018/03	3
Science Citation Index (SCI)	1970-2020/11/27	1714
KSR Evidence	up to 2020/12/01	141
LILACS	up to 2020/11/27	246
NIHR HTA (Internet)	up to 2020/11/26	3
PROSPERO	up to 2020/11/26	77
ClinTrials.gov	up to 2020/11/26	388
WHO ICTRP	up to 2020/12/02	301
EUCTR	up to 2020/12/02	70
Northern Lights	2010-2020/12/wk46	341
CPCI-S	1990-2020/11/30	390
UEG Week 2020	2020	3
Total		**11307**

Embase (Ovid): 1974-2020/11/25
Searched 26.11.20

(SeHCAT OR BAS) + BAD (No A)

1 tauroselcholic acid/ (233)
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. (1596)
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. (860)
6 or/1-5 (2179)
7 bile acid sequestrant/ (1459)
8 ((bile adj3 (acid or salt) adj3 sequest$) or BAS).ti,ab,ot,hw,rn. (19061)
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. (2940)
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. (11381)
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. (1406)
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. (10894)
13 or/7-12 (41822)
14 6 or 13 (43803)
15 (BAM or I-BAM or IBAM or PBAM or BSM or BAD).ti,ab,ot,hw. (60921)
16 bile acid diarrh?ea$.ti,ab,ot,hw. (227)
17 chronic diarrhea/ or bile acid/ or bile salt/ (36292)
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. (16726)
19 (malabsorb$ or mal-absorb$ or malabsorp$ or mal-absorp$).ti,ab,ot,hw. (24005)
20 ((bile or biliary) adj3 (acid$ or salt$)).ti,ab,ot,hw. (50197)
21 or/15-20 (148024)
22 14 and 21 (5860)
23 animal/ (1492379)
24 animal experiment/ (2624468)
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. (6912383)
26 or/23-25 (6912383)
27 exp human/ (21744415)
28 human experiment/ (528150)
29 or/27-28 (21746205)
30 26 not (26 and 29) (5288236)
31 22 not 30 (4797)

MEDLINE(Ovid) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily: 1946-2020/11/30
Searched 1.12.20

1 (tauroselcholic or selenohomocholyltaurine or 75018-71-2).ti,ab,ot,hw,rn. (10)
2 (SeHCAT or Se-HCAT or 75SeHCAT or Se-75 or 75-SeHCAT or SE75).ti,ab,ot,hw,rn. (375)
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 or 75Se-homotaurocholate).ti,ab,ot,hw,rn. (373)
4 (selenium adj3 "75").ti,ab,ot,hw. (185)
5 or/1-4 (788)
6 ((bile adj3 (acid or salt) adj3 sequest$) or BAS).ti,ab,ot,hw,rn. (5844)
7 Colestipol/ or (Colestipol or cholestabyl or cholestipol or colestid or diethylenetriamine-epichlorohydrin-copolymer or diethylenetriamine-polymer-with-1-chloro-2,3-epoxypropane or epichlorohydrin-copolymer-with-diethylenetriamine or flavored-colestid or lestid or u-26,597a or u-26597-a or u-26597a or u-26,597a or 25085-17-0 or 37296-80-3 or 50925-79-6).ti,ab,ot,hw,rn. (551)
8 Cholestyramine Resin/ or (colestyramine$ 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. (3644)
9 Colesevelam Hydrochloride/ 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. (302)
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 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).ti,ab,ot,hw,rn. (6299)
11 or/6-10 (15925)
12 5 or 11 (16640)
13 (BAM or I-BAM or IBAM or PBAM or BSM or BAD).ti,ab,ot,hw. (40139)
14 bile acid diarrh?ea$.ti,ab,ot,hw. (111)
15 diarrhea/ (48230)
16 ((chronic or explosive or smelly or watery or recur$ or persist$ or protracted or continual$ or continuous$ or sustain$ or constant$ or relentless$ or unrelent$ or functional or aggressive) adj2 (diarrh?e$ or diarrea$)).ti,ab,ot,hw. (10235)
17 "Bile Acids and Salts"/ (22496)
18 (malabsorb$ or mal-absorb$ or malabsorp$ or mal-absorp$).ti,ab,ot,hw. (17246)
19 ((bile or biliary) adj3 (acid$ or salt$)).ti,ab,ot,hw. (40041)
20 or/13-19 (147664)
21 12 and 20 (2978)
22 animals/ not (animals/ and humans/) (4727656)
23 21 not 22 (2282)

Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): up to 2020/11/Iss11
Cochrane Database of Systematic Reviews (CDSR) (Wiley): up to 2020/11/Iss11
Searched 26.11.20

#1 (tauroselcholic or selenohomocholyltaurine or "75018-71-2") 5
#2 SeHCAT or "Se-HCAT" or 75SeHCAT or "Se-75" or "75-SeHCAT" or SE75 3000
#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 or "75Se-homotaurocholate" 6
#4 selenium near "75" 33
#5 #1 OR #2 OR #3 OR #4 3033
#6 ((bile near (acid or salt) near sequest*) or BAS) 4488
#7 MeSH descriptor: [Colestipol] explode all trees 90
#8 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" 177
#9 MeSH descriptor: [Cholestyramine Resin] explode all trees 275
#10 (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 "resincolestiramina" or resincolestiramina or "vasosan-p-granulat" or "vasosan-s-granulat" or "11041-12-6" or "58391-37-0") 556
#11 MeSH descriptor: [Colesevelam Hydrochloride] explode all trees 107
#12 (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") 177
#13 MeSH descriptor: [Aluminum Hydroxide] explode all trees 579
#14 (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 "1330-44-5" or "80206-84-4" or brasivil or rocgel or alugel or hydrated alumina or basalgel or dialume or nephrox) 7070
#15 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 11461
#16 #5 or #15 12601
#17 (bile acid near (diarrhoe* or diarrhe* or diarrea*)):ti,ab,kw 39
#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) near (diarrhoe* or diarrhe* or diarrea*):ti,ab,kw 1364
#19 (malabsorb* or "mal-absorb*" or malabsorp* or "mal-absorp*"):ti,ab,kw 1045
#20 (BAM or "I-BAM" or IBAM or PBAM or BSM or BAD):ti,ab,kw 2863
#21 ((bile or biliary) near (acid* or salt*)):ti,ab,kw 2196
#22 MeSH descriptor: [Bile Acids and Salts] explode all trees 1193
#23 MeSH descriptor: [Diarrhea] this term only 3119
#24 #17 or #18 or #19 or #20 or #21 or #22 or #23 10503

#25 #16 and #24 539

CDSR retrieved 131 records
CDSR Protocols retrieved 3 records
CENTRAL retrieved 404 records

Database of Abstracts of Reviews of Effects (DARE) (CRD): up to 2015/03
Health Technology Assessment (HTA) database (CRD): up to 2018/03
http://www.crd.york.ac.uk/CRDWeb/
Searched 26.11.20

1 (tauroselcholic or selenohomocholyltaurine or 75018-71-2) 3
2 (SeHCAT or Se-HCAT or 75SeHCAT or Se-75 or 75-SeHCAT or SE75) 3
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 opr 75Se-homotaurocholate) 0
4 (selenium near "75") 5
5 #1 OR #2 OR #3 OR #4 5
6 (((bile near (acid or salt) near sequest*) or BAS)) 30
7 MeSH DESCRIPTOR Colestipol EXPLODE ALL TREES 3
8 ((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)) 21
9 MeSH DESCRIPTOR Cholestyramine Resin EXPLODE ALL TREES 6
10 ((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 resincolestiramina or resincolestiramina or vasosan-p-granulat or vasosan-s-granulat or 11041-12-6 or 58391-37-0)) 37
11 MeSH DESCRIPTOR Colesevelam Hydrochloride EXPLODE ALL TREES 1
12 (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) 4
13 MeSH DESCRIPTOR Aluminum Hydroxide EXPLODE ALL TREES 4
14 ((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 1330-44-5 or 80206-84-4 or brasivil or rocgel or alugel or hydrated alumina or basalgel or dialume or nephrox)) 10
15 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 86
16 ((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) near (diarrhoe* or diarrhe* or diarrea*)) 50
17 ((malabsorb* or mal-absorb* or malabsorp* or mal-absorp*)) 44

18	((bile acid near (diarrhoe* or diarrhe* or diarrea*)))	0
19	((BAM or I-BAM or IBAM or PBAM or BSM or BAD))	76
20	((bile or biliary) near (acid* or salt*))	38
21	MeSH DESCRIPTOR Diarrhea EXPLODE ALL TREES	228
22	MeSH DESCRIPTOR Bile Acids and Salts EXPLODE ALL TREES	49
23	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	442
24	#1 OR #15	88
25	#23 AND #24	17
26	**(#25) IN DARE**	**13**
27	**(#25) IN HTA**	**3**

Science Citation Index (SCI) (Web of Science): 1970-2020/11/27
Searched 27.11.20

#21 1,714 #19 not #20
#20 3,873,007 TS=(cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamster or feline or ovine or canine or bovine or sheep or mice)
#19 2,659 #18 AND #12
#18 326,297 #17 OR #16 OR #15 OR #14 OR #13
#17 46,505 TS= ((bile or biliary) SAME (acid* or salt*))
#16 9,898 TS= (malabsorb* or mal-absorb* or malabsorp* or mal-absorp*)
#15 5,873 TS= ((chronic or explosive or smelly or watery or recur* or persist* or protracted or continual* or continuous* or sustain* or constant* or relentless* or unrelent* or functional or aggressive) SAME (diarrh?e* or diarrea*))
#14 308 TS=bile acid diarrh?ea*
#13 265,782 TS= (BAM or I-BAM or IBAM or PBAM or BSM or BAD)
#12 43,961 #11 OR #5
#11 41,620 #10 OR #9 OR #8 OR #7 OR #6
#10 31,554 TS= (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 hydroxyide 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)
#9 459 TS= (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)
#8 2,051 TS= (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)
#7 528 TS= (Colestipol or cholestabyl or cholestipol or colestid or diethylenetriamine-epichlorohydrin-copolymer 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)

#6 9,187 TS=((bile SAME (acid or salt) SAME sequest*) or BAS)
#5 2,542 #4 OR #3 OR #2 OR #1
#4 1,942 TS= (selenium SAME "75")
#3 85 TS= (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)
#2 964 TS= (SeHCAT or Se-HCAT or 75SeHCAT or Se-75 or 75-SeHCAT or SE75)
#1 9 TS=(tauroselcholic or selenohomocholyltaurine or 75018-71-2)

KSR Evidence (Internet) (https://ksrevidence.com/): up to 2020/12/01
Searched 1.12.20

1 SeHCAT OR "Se-HCAT" OR 75SeHCAT OR "Se-75" OR "75-SeHCAT" OR SE75 in All text 6 results
2 tauroselcholic OR selenohomocholyltaurine OR "selenium homocholic acid taurine" OR "tauroselenocholic acid" OR "75Se-homotaurocholate" in All text 2 results
3 ("bile acid sequest*" or "bile salt sequest*") in All text 14 results
4 Colestipol OR cholestabyl OR colestid in All text 4 results
5 colestyramine or Questra* or Cholybar or Olestyr in All text 3 results
6 Colesevelam or cholestagel or welchol or lodalis in All text 9 results
7 "aluminum hydroxide" or Ageldrate in All text 2 results
8 BAM or "I-BAM" or IBAM or PBAM or BSM in All text 16 results
9 (bile or biliary) AND (acid* or salt*) in All text 116 results
10 #9 or #8 or #7 or #6 or #5 or #4 or #1 or #2 or #3 in All text 141 results

Literature in the Health Sciences in Latin America and the Caribbean (LILACS) (Internet) (http://lilacs.bvsalud.org/en/): up to 2020/11/27
Searched: 27.11.20

(SeHCAT OR "Se-HCAT") OR (tauroselcholic OR selenohomocholyltaurine OR "selenium homocholic acid taurine" OR "tauroselenocholic acid" OR "bile acid sequest*") OR (Colestipol OR cholestabyl OR cholestipol OR colestid OR flavored-colestid OR lestid) 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 (Colesevelam OR cholestagel) 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 luagel 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 brasivil OR rocgel OR alugel OR "hydrated alumina" OR basalgel OR dialume OR nephrox) OR (BAM OR I-BAM OR IBAM OR PBAM OR BSM) OR (((bile OR

biliary) AND (acid* OR salt*) AND (diarrhoe* OR diarrhe* OR diarrea* OR malabsorb* OR mal-absorb* OR malabsorp* OR mal-absorp*)))

246 results (filtered to LILACS)

NIHR Health Technology Assessment (HTA) (Internet): up to 2020/11/26
https://www.nihr.ac.uk/
Searched 26.11.20

Browsed by relevant terms found 3 records

PROSPERO (International Prospective Register of Systematic Reviews) (CRD): up to 2020/11/26
https://www.crd.york.ac.uk/PROSPERO/
Searched 26.11.20

#1 SeHCAT OR Se-HCAT OR 75SeHCAT OR Se-75 OR 75-SeHCAT OR SE75 3
#2 tauroselcholic OR selenohomocholyltaurine OR selenium homocholic acid taurine OR tauroselenocholic acid OR 75Se-homotaurocholate 1
#3 bile acid sequest* 25
#4 MeSH DESCRIPTOR Colestipol EXPLODE ALL TREES 0
#5 Colestipol OR cholestabyl OR cholestipol OR colestid 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 10
#6 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 resincolestiramina or resincolestiramina or vasosan-p-granulat or vasosan-s-granulat or 11041-12-6 or 58391-37-0 13
#7 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 6
#8 MeSH DESCRIPTOR Aluminum Hydroxide EXPLODE ALL TREES 0
#9 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 1330-44-5 or 80206-84-4 or brasivil or rocgel or alugel or hydrated alumina or basalgel or dialume or nephrox 22
#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 59
#11 BAM or I-BAM or IBAM or PBAM or BSM 18
#12 ((bile or biliary) near (acid* or salt*) near (diarrhoe* or diarrhe* or diarrea* or malabsorb* or mal-absorb* or malabsorp* or mal-absorp*)) 5
#13 #10 OR #11 OR #12 77

Clinical Trials resources

Clinicaltrials.gov (Internet): up to 2020/11/26
http://clinicaltrials.gov/ct2/search/advanced
Searched 26.11.20

Expert search option

(SeHCAT OR Se-HCAT OR 75SeHCAT OR Se-75 OR 75-SeHCAT OR SE75) OR (tauroselcholic OR selenohomocholyltaurine OR selenium homocholic acid taurine OR tauroselenocholic acid OR 75Se-homotaurocholate) OR (Colestipol OR cholestabyl OR cholestipol OR colestid 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) 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 questran) 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) 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 hycolal OR hydracoll OR hydrated alumina OR hydrolum OR hydronal OR hydroxal OR lactalumina OR neutroxide)

ClinicalTrials.Gov retrieved 388 records

WHO International Clinical Trials Registry Platform (ICTRP) (Internet): up to 2020/12/02
http://www.who.int/ictrp/en/
Searched 2.12.20

Basic search option – search terms box

Search terms	**Results**
SeHCAT OR Se-HCAT OR 75SeHCAT OR Se-75 OR 75-SeHCAT OR SE75	2
tauroselcholic OR selenohomocholyltaurine OR selenium homocholic acid taurine OR tauroselenocholic acid OR 75Se-homotaurocholate	0
(Colestipol OR cholestabyl OR cholestipol OR colestid 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)	7/9

(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 questran)	39/64
(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)	66/76
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 hycolal OR hydracoll OR hydrated alumina OR hydrolum OR hydronal OR hydroxal OR lactalumina OR neutroxide	189/268
TOTAL	**303**
Total without duplicates	**301**

EU Clinical Trials Registry (EUCTR) (Internet) : up to 2020/12/02
https://www.clinicaltrialsregister.eu/ctr-search/
Searched 2.12.20

Advanced search option – search terms box

Search terms	**Results**
SeHCAT OR Se-HCAT OR 75SeHCAT OR Se-75 OR 75-SeHCAT OR SE75	11
tauroselcholic OR selenohomocholyltaurine OR selenium homocholic acid taurine OR tauroselenocholic acid OR 75Se-homotaurocholate	1
(Colestipol OR cholestabyl OR cholestipol OR colestid 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)	2
(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 questran)	58
(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	10

182815-44-7)	
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 hycolal OR hydracoll OR hydrated alumina OR hydrolum OR hydronal OR hydroxal OR lactalumina OR neutroxide	1
TOTAL	**83**
Total without duplicates	**70**

Conference Searches

Northern Light Life Sciences Conference Abstracts (Ovid): 2010-2020/12/ Wk46
Searched 1.12.20

SeHCAT OR (BAS + BAD)

1 (tauroselcholic or selenohomocholyltaurine or 75018-71-2).af. (1)
2 (SeHCAT or Se-HCAT or 75SeHCAT or Se-75 or 75-SeHCAT or SE75).af. (84)
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 or 75Se-homotaurocholate).af. (0)
4 (selenium adj3 "75").af. (0)
5 or/1-4 (84)
6 ((bile adj3 (acid or salt) adj3 sequest$) or BAS).af. (1813)
7 Colestipol/ or (Colestipol or cholestabyl or cholestipol or colestid or diethylenetriamine-epichlorohydrin-copolymer or diethylenetriamine-polymer-with-1-chloro-2,3-epoxypropane or epichlorohydrin-copolymer-with-diethylenetriamine or flavored-colestid or lestid or u-26,597a or u-26597-a or u-26597a or u-26,597a or 25085-17-0 or 37296-80-3 or 50925-79-6).af. (30)
8 Cholestyramine Resin/ or (colestyramine$ 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).af. (83)
9 Colesevelam Hydrochloride/ 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).af. (117)
10 or/6-9 (2000)
11 diarrhea/ (28402)
12 "Bile Acids and Salts"/ (0)
13 ((bile or biliary) adj3 (acid* or salt*)).af. (2490)
14 (malabsorb$ or mal-absorb$ or malabsorp$ or mal-absorp$).af. (922)
15 ((chronic or explosive or smelly or watery or recur$ or persist$ or protracted or continual$ or continuous$ or sustain$ or constant$ or relentless$ or unrelent$ or functional or aggressive) adj3 (diarrh?e$ or diarrea$)).af. (746)
16 bile acid diarrh?ea$.af. (53)
17 (BAM or I-BAM or IBAM or PBAM or BSM or BAD).ti,ab. (3287)
18 or/11-17 (34584)

19 10 and 18 (277)
20 5 or 19 (341)

Conference Proceedings Citation Index- Science (CPCI-S) (Web of Science): 1990-2020/11/30 Searched 1.12.20

Indexes=CPCI-S Timespan=All years

 # 18 390 #5 or #17
17 137 #10 and #16
16 63,296 #11 or #12 or #13 or #14 or #15
15 4,517 TS= ((bile or biliary) SAME (acid* or salt*))
14 761 TS= (malabsorb* or mal-absorb* or malabsorp* or mal-absorp*)
13 52 TS=bile acid diarrh?ea*
12 284 TS= ((chronic or explosive or smelly or watery or recur* or persist* or protracted or continual* or continuous* or sustain* or constant* or relentless* or unrelent* or functional or aggressive) SAME (diarrh?e* or diarrea*))
11 57,908 TS= (BAM or I-BAM or IBAM or PBAM or BSM or BAD)
10 1,306 #6 or #7 or #8 or #9
9 67 TS= (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)
8 143 TS= (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)
7 48 TS= (Colestipol or cholestabyl or cholestipol or colestid or diethylenetriamine-epichlorohydrin-copolymer 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)
6 1,088 TS=((bile SAME (acid or salt) SAME sequest*) or BAS)
5 257 #1 or #2 or #3 or #4
4 151 TS= (selenium SAME "75")
3 6 TS= (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)
2 148 TS= (SeHCAT or Se-HCAT or 75SeHCAT or Se-75 or 75-SeHCAT or SE75)
1 0 TS=(tauroselcholic or selenohomocholyltaurine or 75018-71-2)

Named conferences previously individually searched in 2011 review:

Conference	**On Embase**	**On Northern Lights**	**Web search**
British Society of Gastroenterology (BSG) Annual Meetings	2013-2018	Annual Meeting 2013-2019 No 2012 meeting found	2020 postponed until Feb 2021

Advances in Clinical Oesophageal Investigation Conference (ASCONA ESSENTIALS 2011) Online Learning in Gastroenterology (OLGa http://olga.uegf.org/portal/documents-explore.html#solr0	NA	NA	NA
8th Summer School of Gastroenterology (ASNEMGE-SS-PRAGUE2011) Online Learning in Gastroenterology (OLGa):http://olga.uegf.org/portal/documents-explore.html#solr0	NA	NA	NA
GASTRO2009 Online Learning in Gastroenterology (OLGa):http://olga.uegf.org/portal/documents-explore.html#solr0	NA	NA	NA
United European Gastroenterology Week Online Learning in Gastroenterology (OLGa):http://olga.uegf.org/portal/documents-explore.html#solr0* *Link no longer working.		United European Gastroenterology Week 2012-2019	2020 Online (see below)

United European Gastroenterology Week 2020 (https://ueg.eu/library)
Searched: 4.2.21

Limited to 2020

Keyword	**Results**
“SeHCAT”	3
"Se-HCAT"	0/3 (duplicate)
"75SeHCAT"	0/1
"75-SeHCAT"	0/1
TOTAL	**3**

Targeted search: Trial of treatment

Database	**Dates covered**	**Hits**
EMBASE	1974-2021/02/17	707
MEDLINE + PreMedline	1946-2021/02/17	138
Total		**845**

Embase (Ovid): 1974-2021/02/17
Searched: 18.2.21

IBS/Crohns + BAS

1 irritable colon/ (27190)
2 (Irritable bowel syndrome$ or IBS or IBS-D).ti,ab,ot,hw. (25851)
3 ((spastic or irritable or spasm or unstable) adj2 colon).ti,ab,ot,hw. (27358)
4 ((Colitis or colitides) adj2 (spastic or mucous or mucomembraneous or mucomembranous)).ti,ab,ot,hw. (33)
5 colonospasm.ti,ab,ot,hw. (0)
6 or/1-5 (33265)
7 ((cleron or Crohn$) adj3 disease).ti,ab,ot,hw. (103028)
8 exp Crohn disease/ (94904)
9 ((regional or regionalis or granulomatous) adj3 (enteritis or enterocolitis)).ti,ab,ot,hw. (686)
10 morbus crohn.ti,ab,ot,hw. (1247)
11 Ileocolitis.ti,ab,ot,hw. (626)
12 (ileitis adj3 (terminal or regional)).ti,ab,ot,hw. (601)
13 colitis granulomatous.ti,ab,ot,hw. (8)
14 or/7-13 (103673)
15 6 or 14 (134788)
16 bile acid sequestrant/ (1478)
17 ((bile adj3 (acid or salt) adj3 sequest$) or BAS).ti,ab,ot,hw,rn. (19064)
18 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. (2965)
19 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. (11483)
20 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. (1427)
21 or/16-20 (31271)
22 15 and 21 (707)

MEDLINE(Ovid) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily: 1946-2021/02/17
Searched 18.2.21
1 Irritable bowel syndrome/ (7599)
2 (Irritable bowel syndrome$ or IBS or IBS-D).ti,ab,ot,hw. (16494)
3 ((spastic or irritable or spasm or unstable) adj2 colon).ti,ab,ot,hw. (583)
4 ((Colitis or colitides) adj2 (spastic or mucous or mucomembraneous or mucomembranous)).ti,ab,ot,hw. (48)
5 colonospasm.ti,ab,ot,hw. (0)
6 or/1-5 (16927)
7 ((cleron or Crohn$) adj3 disease).ti,ab,ot,hw. (56412)
8 Crohn Disease/ (39573)

9 ((regional or regionalis or granulomatous) adj3 (enteritis or enterocolitis)).ti,ab,ot,hw. (1214)
10 morbus crohn.ti,ab,ot,hw. (869)
11 Ileocolitis.ti,ab,ot,hw. (430)
12 (ileitis adj3 (terminal or regional)).ti,ab,ot,hw. (757)
13 colitis granulomatous.ti,ab,ot,hw. (7)
14 or/7-13 (56906)
15 6 or 14 (73191)
16 ((bile adj3 (acid or salt) adj3 sequest$) or BAS).ti,ab,ot,hw,rn. (6014)
17 Colestipol/ or (Colestipol or cholestabyl or cholestipol or colestid or diethylenetriamine-epichlorohydrin-copolymer or diethylenetriamine-polymer-with-1-chloro-2,3-epoxypropane or epichlorohydrin-copolymer-with-diethylenetriamine or flavored-colestid or lestid or u-26,597a or u-26597-a or u-26597a or u-26,597a or 25085-17-0 or 37296-80-3 or 50925-79-6).ti,ab,ot,hw,rn. (550)
18 Cholestyramine Resin/ or (colestyramine$ 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. (3666)
19 Colesevelam Hydrochloride/ 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. (307)
20 or/16-19 (9845)
21 15 and 20 (138)

Guidelines

Database	Dates covered	Hits
TRIP	2011- 2020/12/10	1022
GIN	2011- 2020/12/15	11
HTA	up to 2018/03/31	117
NICE	up to 2020/12/15	13
NIHR HTA	up to 2020/12/16	42
ECRI	up to 2020/12/16	31
NHS Evidence	up to 2020/12/16	355
Total		**1591**

TRIP database (Internet): 2011-2020/12/10
http://www.tripdatabase.com/
Searched: 10.12.20

The search was conducted from 2011-C to provide a year's overlap with the original searches.

Terms searched (Guidelines only, 2011-C)	Hits
BAM or I-BAM or IBAM or PBAM or "Bile acid malabsorption"	Aus & NZ=3 Canada= 3 UK= 2 USA=8

	Other=4 **Total=20**
SeHCAT or Se-HCAT or 75SeHCAT or Se-75 or 75-SeHCAT or SE75	Canada=2 UK=1 USA=2 Other=1 **Total=6**
"chronic diarrhea" or "chronic diarrhoea" or "functional diarrhea" or "functional diarrhoea"	Aus & NZ=3 Canada=4 UK=15 USA=22 Other=15 **Results=59**
“Irritable bowel syndrome” or “Irritable bowel syndromes” or IBS or IBS-D or “spastic colon”	Aus & NZ=36 Canada=65 UK=140 USA=315 Other=142 **Results=697**
“Crohns disease” or “Crohn disease” or “Crohn’s disease”	Aus & NZ=6 Canada=17 UK=76 USA=108 Other=33 **Results=240**
Total	**1022**

GIN: International Guidelines Library (Internet): 2011-2020/12/15
http://www.g-i-n.net
Searched: 15.12.20

Terms searched	**Hits**
SeHCAT	0
Se-HCAT	0
75SeHCAT	0

Bile acid*	0
Bile salt*	0
BAM	0
BAD	0/1 (not relevant)
Irritable bowel syndrome*	3
IBS*	0
spastic colon	0
Crohn*	3
diarrhea*	5
diarrhoea*	0/2 (dupes)
Total (after to deduplication)	**11**

Health Technology Assessment Database (HTA) (CRD): up to 2018/03/31
https://www.crd.york.ac.uk/CRDWeb/HomePage.asp
Searched 16.12.20

1	MeSH DESCRIPTOR Irritable Bowel Syndrome EXPLODE ALL TREES	103
2	(((Irritable bowel syndrome* or IBS or IBS-D or spastic colon)))	189
3	((BAM or I-BAM or IBAM or PBAM))	1
4	(((Bile near acid*) OR (Biliary near acid*) OR (Bile near salt*) OR (Biliary near salt*)))	38
5	MeSH DESCRIPTOR Crohn Disease EXPLODE ALL TREES	220
6	(((Crohn* near disease)))	356
7	((((chronic near diarrhoea*) or (chronic near diarrhea*))))	22
8	MeSH DESCRIPTOR Diarrhea EXPLODE ALL TREES	228
9	((SeHCAT or Se-HCAT or 75SeHCAT or Se-75 or 75-SeHCAT or SE75))	3
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	792
11	**(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9) IN HTA**	**117**

National Institute for Health and Clinical Excellence (NICE) Guidance (Internet): up to 2020/12/15
http://guidance.nice.org.uk/
Searched 15.12.20

Limited to published guidelines only

Terms searched	**Hits**
SeHCAT	**1**
Bile acid	0/1
Bile salt	0
diarrhoea	2/3 (duplicate)
diarrhea	0

Irritable bowel syndrome	2/4 (dupes)
IBS	0/1
Crohn	8/9
Crohn's	0/5
Total (prior to deduplication)	**13/24**

NIHR Health Technology Assessment (HTA) (Internet): up to 2020/12/16
https://www.nihr.ac.uk/
Searched 16.12.20

Terms searched	**Hits**
SeHCAT	3
Bile acid	1/4 (dupe)
Bile salt	0/1
diarrhoea	18/20
diarrhea	0/1
Irritable bowel syndrome	11/13
IBS	2/13
Crohn	3
Crohn's	4
Total (prior to deduplication)	**42/62**

ECRI (Internet): up to 2020/12/16
https://www.ecri.org/
Searched: 16.12.20

Terms searched	**Hits**
BAM OR "I BAM" OR IBAM OR PBAM OR "Bile acid malabsorption" OR "Bile acid diarrhoea"	**0**
SeHCAT OR "Se HCAT" OR 75SeHCAT OR "Se 75" OR "75 SeHCAT" OR SE75	0
"chronic diarrhea" OR "chronic diarrhoea" OR "functional diarrhea" OR "functional diarrhoea"	3
"Irritable bowel syndrome" OR "Irritable bowel syndromes" OR IBS OR "IBS D" OR "spastic colon"	27/28 (dupe)
"Crohns disease" OR "Crohn disease" OR "Crohn's disease"	1

Total	**31/32**

NHS Evidence (Internet) https://www.evidence.nhs.uk/ :up to 2020/12/16
Searched 16.12.20

Limited to Guidance and HTAs

Terms searched	**Hits**
BAM OR "I BAM" OR IBAM OR PBAM OR "Bile acid malabsorption" OR "Bile acid diarrhoea"	**33**
SeHCAT OR "Se HCAT" OR 75SeHCAT OR "Se 75" OR "75 SeHCAT" OR SE75	4/13 (dupes)
"chronic diarrhea" OR "chronic diarrhoea" OR "functional diarrhea" OR "functional diarrhoea"	68/77
"Irritable bowel syndrome" OR "Irritable bowel syndromes" OR IBS OR "IBS D" OR "spastic colon"	181/220
“Crohns disease” OR “Crohn disease” OR “Crohn’s disease”	69/87
Total	**355/430**

Cost effectiveness searches

Database	**Dates covered**	**Hits**
EMBASE	1974-2021/01/17	908
MEDLINE + PreMedline	1946-2020/01/07	571
Science Citation Index (SCI)	1988-2021/01/05	1036
NHS EED	up to 2015/03	92
EconLit	up to 2020/12/22	87
IDEAS (RePEc)	up to 2021/02/23	94
CEA registry	2012-2021/01/14	270
ScHARRhud	up to 2021/02/23	6
Total	**3064**	

Embase (Ovid): 1974-2021/01/07
Searched 8.1.21

(SeHCAT or BAD) + (Costs or HRQoL)

1 tauroselcholic acid/ (236)
2 (tauroselcholic or selenohomocholyltaurine or 75018-71-2).ti,ab,ot,hw,rn,tn. (401)
3 (SeHCAT or Se-HCAT or 75SeHCAT or Se-75 or 75-SeHCAT or SE75).ti,ab,ot,hw,tn. (1604)
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. (865)
6 or/1-5 (2192)
7 (BAM or I-BAM or IBAM or PBAM or BSM).ti,ab,ot,hw. (5123)
8 bile acid diarrh?ea$.ti,ab,ot,hw. (234)
9 chronic diarrhea/ (6082)
10 ((chronic or explosive or smelly or watery or recur$ 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. (16950)
11 bile acid/ or bile salt/ (30709)
12 ((bile or biliary) adj3 (acid$ or salt$)).ti,ab,ot,hw. (50633)
13 or/11-12 (50633)
14 (malabsorb$ or mal-absorb$ or malabsorp$ or mal-absorp$ or diarrh?e$ or diarrea$ or f?eces).ti,ab,ot,hw. (456414)
15 13 and 14 (6257)
16 7 or 8 or 9 or 10 or 15 (27573)
17 6 or 16 (29353)
18 health-economics/ (33339)
19 exp economic-evaluation/ (314387)
20 exp health-care-cost/ (298733)
21 exp pharmacoeconomics/ (206492)
22 or/18-21 (663912)
23 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (1123509)
24 (expenditure$ not energy).ti,ab. (42225)
25 (value adj2 money).ti,ab. (2528)
26 budget$.ti,ab. (40216)
27 or/23-26 (1161371)
28 22 or 27 (1493189)
29 letter.pt. (1161283)
30 editorial.pt. (682769)
31 note.pt. (835840)
32 or/29-31 (2679892)
33 28 not 32 (1371483)
34 (metabolic adj cost).ti,ab. (1586)
35 ((energy or oxygen) adj cost).ti,ab. (4490)
36 ((energy or oxygen) adj expenditure).ti,ab. (32838)
37 or/34-36 (37782)
38 33 not 37 (1363739)
39 exp animal/ (26642890)

40 exp animal-experiment/ (2658841)
41 nonhuman/ (6445151)
42 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (5871157)
43 or/39-42 (28677854)
44 exp human/ (21887724)
45 exp human-experiment/ (531547)
46 44 or 45 (21889585)
47 43 not (43 and 46) (6789265)
48 38 not 47 (1240250)
49 17 and 48 (805)
50 quality adjusted life year/ or quality of life index/ (30846)
51 Short Form 12/ or Short Form 20/ or Short Form 36/ or Short Form 8/ (37865)
52 "International Classification of Functioning, Disability and Health"/ or "ferrans and powers quality of life index"/ or "gastrointestinal quality of life index"/ (3639)
53 (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot. (43041)
54 (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot. (2536)
55 (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (9907)
56 (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (1590)
57 (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (466)
58 (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (995)
59 "health related quality of life".ti,ab,ot. (66854)
60 (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (20857)
61 "assessment of quality of life".ti,ab,ot. (3015)
62 (euroqol or euro qol or eq5d$ or eq 5d$).ti,ab,ot. (22328)
63 (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (35847)
64 (hye or hyes).ti,ab,ot. (140)
65 health$ year$ equivalent$.ti,ab,ot. (41)
66 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (3255)
67 (quality time or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or index of well being).ti,ab,ot,hw. (1248)
68 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (5242)
69 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,ot. (26726)
70 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,ot. (12758)
71 15d.ti,ab,ot. (2629)
72 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,ot. (652)
73 (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,ot. (20906)
74 (utilities or disutili$).ti,ab,ot. (12817)
75 or/50-74 (201789)

76 animal/ or animal experiment/ (4123202)
77 (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).ti,ab,ot,hw. (6931026)
78 or/76-77 (6931026)
79 exp human/ or human experiment/ (21889542)
80 78 not (78 and 79) (5299870)
81 75 not 80 (198713)
82 letter.pt. (1161283)
83 editorial.pt. (682769)
84 note.pt. (835840)
85 or/82-84 (2679892)
86 81 not 85 (193533)
87 17 and 86 (117)
88 49 or 87 (908)

HRQoL free-text terms based on:
Figure 4: Common free-text terms for electronic database searching for HSUVs in Papaioannou D, Brazier JE, Paisley S. NICE DSU Technical Support Document 9: the identification, review and synthesis of health state utility values from the literature (Internet), 2011 [accessed: 18.8.11] Available from: http://www.nicedsu.org.uk

Economics terms based on Costs filter:
Centre for Reviews and Dissemination. Search strategies: NHS EED EMBASE using OvidSP (economics filter) [Internet]. York: Centre for Reviews and Dissemination; 2014 [accessed 2.6.14]. Available from:
http://www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedembase

MEDLINE(Ovid) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily: 1946-2021/01/07
Searched 8.1.21

1 (tauroselcholic or selenohomocholyltaurine or 75018-71-2).ti,ab,ot,hw,rn. (11)
2 (SeHCAT or Se-HCAT or 75SeHCAT or Se-75 or 75-SeHCAT or SE75).ti,ab,ot,hw,rn. (379)
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 or 75Se-homotaurocholate).ti,ab,ot,hw,rn. (375)
4 (selenium adj3 "75").ti,ab,ot,hw. (185)
5 or/1-4 (794)
6 (BAM or I-BAM or IBAM or PBAM or BSM).ti,ab,ot,hw. (4250)
7 bile acid diarrh?ea$.ti,ab,ot,hw. (114)
8 ((chronic or explosive or smelly or watery or recur$ or persist$ or protracted or continual$ or continuous$ or sustain$ or constant$ or relentless$ or unrelent$ or functional or aggressive) adj2 (diarrh?e$ or diarrea$)).ti,ab,ot,hw. (10304)
9 "Bile Acids and Salts"/ (22567)
10 ((bile or biliary) adj3 (acid$ or salt$)).ti,ab,ot,hw. (40304)
11 9 or 10 (40304)
12 (malabsorb$ or mal-absorb$ or malabsorp$ or mal-absorp$ or diarrh?e$ or diarrea$ or f?eces).ti,ab,ot,hw. (239246)
13 11 and 12 (4702)
14 6 or 7 or 8 or 13 (18913)

15 5 or 14 (19523)
16 economics/ (27278)
17 exp "costs and cost analysis"/ (241445)
18 economics, dental/ (1915)
19 exp "economics, hospital"/ (24882)
20 economics, medical/ (9116)
21 economics, nursing/ (4002)
22 economics, pharmaceutical/ (2965)
23 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (834449)
24 (expenditure$ not energy).ti,ab. (31015)
25 (value adj1 money).ti,ab. (36)
26 budget$.ti,ab. (30332)
27 or/16-26 (988351)
28 ((energy or oxygen) adj cost).ti,ab. (4195)
29 (metabolic adj cost).ti,ab. (1467)
30 ((energy or oxygen) adj expenditure).ti,ab. (25724)
31 or/28-30 (30394)
32 27 not 31 (981379)
33 letter.pt. (1116589)
34 editorial.pt. (553178)
35 historical article.pt. (361613)
36 or/33-35 (2011424)
37 32 not 36 (944275)
38 15 and 37 (460)
39 quality-adjusted life years/ or quality of life/ (212806)
40 (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot. (26438)
41 (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot. (2228)
42 (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (6146)
43 (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (869)
44 (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (411)
45 (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (624)
46 "health related quality of life".ti,ab,ot. (45881)
47 (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (13582)
48 "assessment of quality of life".ti,ab,ot. (1885)
49 (euroqol or euro qol or eq5d$ or eq 5d$).ti,ab,ot. (11979)
50 (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (21793)
51 (hye or hyes).ti,ab,ot. (73)
52 health$ year$ equivalent$.ti,ab,ot. (40)
53 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (1593)
54 (quality time or qwb or quality of well being or "quality of wellbeing" or "index of wellbeing" or "index of well being").ti,ab,ot,hw. (928)

55 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (4351)
56 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,ot. (15549)
57 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,ot. (8299)
58 15d.ti,ab,ot. (1754)
59 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,ot. (427)
60 (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,ot. (12970)
61 (utilities or disutili$).ti,ab,ot. (7771)
62 or/39-61 (271557)
63 animals/ not (animals/ and humans/) (4741294)
64 62 not 63 (269197)
65 letter.pt. (1116589)
66 editorial.pt. (553178)
67 historical article.pt. (361613)
68 or/65-67 (2011424)
69 64 not 68 (259509)
70 15 and 69 (130)
71 38 or 70 (571)

HRQoL free-text terms based on:
Figure 4: Common free-text terms for electronic database searching for HSUVs in Papaioannou D, Brazier JE, Paisley S. NICE DSU Technical Support Document 9: the identification, review and synthesis of health state utility values from the literature (Internet), 2011 [accessed: 18.8.11] Available from: http://www.nicedsu.org.uk

Economics terms based on Costs filter:
Centre for Reviews and Dissemination. Search strategies: NHS EED MEDLINE using OvidSP (economics filter) [Internet]. York: Centre for Reviews and Dissemination; 2014 [accessed 2.6.14]. Available from:
http://www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedmedline

Science Citation Index Expanded (SCI-EXPANDED): 1988-2021/01/05
Searched 5.1.21

Indexes=SCI-EXPANDED Timespan=All years

 # 48 1,036 #47 OR #23
47 522 #46 AND #12
46 946,570 #45 OR #44 OR #43 OR #42 OR #41 OR #40 OR #39 OR #38 OR #37 OR #36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24
45 291,280 TS=(utilities or disutili*)
44 161,090 TS=(utilit* SAME ("quality of life" or valu* or scor* or measur* or health or life or estimat* or elicit* or disease*))
43 27,032 TS=(HSUV* or health state* value* or health state* preference* or HSPV*)
42 2,073 TS=15d

41 41,585 TS=(timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble* or "willingness to pay")
40 15,178 TS=(QALY* or DALY* or HALY* or YHL or HYES or YPLL or YHLL or qald* or qale* or qtime* or AQoL*)
39 35,560 TS=(Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost")
38 444,159 TS=(quality time or qwb or quality of well being or "quality of wellbeing" or "index of wellbeing" or "index of well being")
37 1,915 TS=(hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3)
36 8,182 TS=(health* year* equivalent)
35 82 TS=(hye or hyes)
34 20,238 TS=(hql or hrql or hqol or "h qol" or hrqol or "hr qol")
33 12,058 TS=(euroqol or euro qol or eq5d* or "eq 5d*")
32 1,445 TS=("assessment of quality of life")
31 29,569 TS=(Quality adjusted life or Quality-adjusted-life)
30 47,359 TS=("health related quality of life")
29 37,605 TS=(sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight)
28 22,310 TS=(sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty)
27 1,757 TS=(sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D)
26 27,957 TS=(sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve)
25 59,806 TS=(sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six)
24 32,632 TS=(sf36 or sf 36 Or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six)
23 576 #22 AND #12
22 1,458,042 #17 NOT #21
21 214,593 #20 OR #19 OR #18
20 42,199 TS=((energy or oxygen) SAME expenditure)
19 14,878 TS=(metabolic SAME cost)
18 168,956 TS=((energy or oxygen) SAME cost)
17 1,637,264 #16 OR #15 OR #14 OR #13
16 85,538 TS=(budget*)
15 1,818 TS=(value NEAR/1 money)
14 30,032 TS=(expenditure* not energy)
13 1,557,509 TS=(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*)
12 15,074 #11 OR #5
11 12,835 #10 OR #7 OR #6
10 1,180 #9 AND #8
9 32,130 TS= (malabsorb* or mal-absorb* or malabsorp* or mal-absorp* or diarrh?e* or diarrea*)
8 46,799 TS= ((bile or biliary) SAME (acid* or salt*))
7 5,833 TS= ((chronic or explosive or smelly or watery or recur* or persist* or protracted or continual* or continuous* or sustain* or constant* or relentless* or unrelent* or functional or aggressive) SAME (diarrh?e* or diarrea*))

6 6,045 TS= (BAM or I-BAM or IBAM or PBAM)
5 2,434 #4 OR #3 OR #2 OR #1
4 1,858 TS= (selenium SAME "75")
3 79 TS= (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)
2 926 TS= (SeHCAT or Se-HCAT or 75SeHCAT or Se-75 or 75-SeHCAT or SE75)
1 5 TS= (tauroselcholic or selenohomocholyltaurine or 75018-71-2)

HRQoL free-text terms based on:
Figure 4: Common free-text terms for electronic database searching for HSUVs in Papaioannou D, Brazier JE, Paisley S. NICE DSU Technical Support Document 9: the identification, review and synthesis of health state utility values from the literature (Internet), 2011 [accessed: 18.8.11] Available from: http://www.nicedsu.org.uk

Economics terms based on Costs filter:
Centre for Reviews and Dissemination. Search strategies: NHS EED MEDLINE using OvidSP (economics filter) [Internet]. York: Centre for Reviews and Dissemination; 2014 [accessed 2.6.14]. Available from:
http://www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedmedline

NHS Economic Evaluation Database (NHS EED) (CRD): up to 2015/03
http://www.crd.york.ac.uk/CRDWeb/
Searched 22.12.20

1 ((tauroselcholic or selenohomocholyltaurine or 75018-71-2)) 3
2 ((SeHCAT or Se-HCAT or 75SeHCAT or Se-75 or 75-SeHCAT or SE75)) 3
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 or 75Se-homotaurocholate)) 0
4 ((selenium near "75")) 5
5 #1 OR #2 OR #3 OR #4 5
6 MeSH DESCRIPTOR Diarrhea EXPLODE ALL TREES 228
7 MeSH DESCRIPTOR Bile Acids and Salts EXPLODE ALL TREES 49
8 (((BAM or I-BAM or IBAM or PBAM or BSM or BAD))) 76
9 (((bile or biliary) near (acid* or salt*))) 38
10 (((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) near (diarrhoe* or diarrhe* or diarrea*))) 50
11 #6 OR #7 OR #8 OR #9 OR #10 404
12 #5 OR #11 406
13 (#12) IN NHSEED 92

EconLit (EBSCO): up to 2020/12/22
Searched 22.12.20

Search modes - Boolean/Phrase

S10 (S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9) (87)

S9 (bile N4 acid*) or (biliary N4 acid*) or (bile N4 salt*) (1)
S8 (bile N4 acid*) or (biliary N4 acid*) or (bile N4 salt*) (0)
S7 (BAM or I-BAM or IBAM or PBAM) (57)
S6 (diarrhoe* or diarrhe* or diarrea*) N4 (chronic or explosive or smelly or watery or recur* or persist* or protracted or continual* or continuous* or sustain* or constant* or relentless* or unrelent* or functional or aggressive) (5)
S5 (selenium N4 "75") (0)
S4 (selenium N4 "75") (0)
S3 (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) (0)
S2 (SeHCAT or Se-HCAT or 75SeHCAT or Se-75 or 75-SeHCAT or SE75) (0)
S1 TX (tauroselcholic or selenohomocholyltaurine or 75018-71-2) (0)

IDEAS: RePEc (Research Papers in Economics) (Internet) (https://ideas.repec.org/): up to 2021/02/23
Searched: 23.2.21

2010-2021

Search terms in Title	Hits
'SeHCAT | "Se-HCAT" | 75SeHCAT | "75-SeHCAT"'	0
"bile acid diarrhea"	0
"bile acid diarrhea"	0
"chronic diarrhea"	6
"chronic diarrhoea"	0
"Irritable bowel syndrome" | IBS	48
crohn | crohns	40
Total	**94**

Cost-Effectiveness Analysis Registry (CEA Registry) (http://healtheconomicsdev.tuftsmedicalcenter.org/cear2/search/search.aspx): 1976-2021/01/14
Searched: 14.1.21

Results were limited to 2012-C to follow on from the original search run on 6th Feb 2012

Terms searched	Ratios 2012-C	Utility Weights 2012-C	Total
#1 Bile acid	1	0	1
#2 chronic diarrhea	0	1	1
#3 chronic diarrhoea	0	0	0
#4 IBS	34	28	62

#5 Irritable bowel syndrome	1	5	5
#6 Crohn	100 (of 270 results, will only display first 100)	100 (of 230)	200
Total	**136**	**134**	**270**

ScHARRHUD (Internet) (https://www.scharrhud.org/): up to 2021/02/23
Searched 23.2.21

Terms searched	**Total**
(Bile acid* or bile salt* or chronic) AND (diarrhea or diarrhoea or malabsorption)	0
(IBS or Irritable bowel syndrome)	4
Crohn*	2
Total	6

Additional search for IBS/Crohns + Economic evaluations/Costs/HRQoL

Please note these searches are based on Search B: IBS + Cost/QoL and Search E: Crohn's + Cost/QoL from the 2011 review, these were combined for efficiency.

Database	**Dates covered**	**Hits**
MEDLINE + PreMedline	1946-2020/12/15	1869
NHS EED	up to 2015/03	95
Total		**1964**

MEDLINE(Ovid) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily: 1946-2020/12/15
Searched 17.12.20

IBS/Cohn's + Cost/QoL

1 Irritable bowel syndrome/ (7531)
2 (Irritable bowel syndrome$ or IBS or IBS-D).ti,ab,ot,hw. (16275)
3 ((spastic or irritable or spasm or unstable) adj2 colon).ti,ab,ot,hw. (580)
4 ((Colitis or colitides) adj2 (spastic or mucous or mucomembraneous or mucomembranous)).ti,ab,ot,hw. (46)
5 colonospasm.ti,ab,ot,hw. (0)
6 or/1-5 (16708)
7 ((cleron or Crohn*) adj3 disease).ti,ab,ot,hw. (55778)
8 Crohn Disease/ (39374)

9 ((regional or regionalis or granulomatous) adj3 (enteritis or enterocolitis)).ti,ab,ot,hw. (1211)
10 morbus crohn.ti,ab,ot,hw. (863)
11 Ileocolitis.ti,ab,ot,hw. (428)
12 (ileitis adj3 (terminal or regional)).ti,ab,ot,hw. (751)
13 colitis granulomatous.ti,ab,ot,hw. (7)
14 or/7-13 (56265)
15 6 or 14 (72337)
16 economics/ (27278)
17 exp "costs and cost analysis"/ (241055)
18 economics, dental/ (1915)
19 exp "economics, hospital"/ (24854)
20 economics, medical/ (9115)
21 economics, nursing/ (4002)
22 economics, pharmaceutical/ (2962)
23 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (830091)
24 (expenditure$ not energy).ti,ab. (30889)
25 (value adj1 money).ti,ab. (36)
26 budget$.ti,ab. (30225)
27 or/16-26 (983786)
28 ((energy or oxygen) adj cost).ti,ab. (4187)
29 (metabolic adj cost).ti,ab. (1463)
30 ((energy or oxygen) adj expenditure).ti,ab. (25656)
31 or/28-30 (30314)
32 27 not 31 (976823)
33 letter.pt. (1114970)
34 editorial.pt. (551460)
35 historical article.pt. (361434)
36 or/33-35 (2007937)
37 32 not 36 (939757)
38 (sf36 or sf 36 or short form 36 or shortform 36).ti,ab. (26334)
39 (sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (2)
40 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (2216)
41 (euroqol or euro qol or eq5d or eq 5d).ti,ab. (11866)
42 (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab. (21684)
43 (hye or hyes).ti,ab. (72)
44 health$ year$ equivalent$.ti,ab. (40)
45 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab. (1578)
46 (quality of well being or quality of wellbeing or qwb).ti,ab. (484)
47 (Disability adjusted life year$ or Disability-adjusted life year$ or health adjusted life year$ or health-adjusted life year$ or years of healthy life or healthy years equivalent or years of potential life lost or years of health life lost or quality adjusted life year$).ti,ab. (17231)
48 (QALY$ or HRQOL or HRQL or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL).ti,ab. (35444)
49 (FDDQL or GSRS-self or GSRS or GSRS-IBS or IBS-36 or IBS-QOL or IBS-SSS or IBS-D or WPAI:IBS* or IBSQoL).ti,ot. (95)
50 (GIQLI or DHSI or PDAI or HBI or "Harvey Bradshaw Index" or WPAI:CD* or "UC-CD Health Status" or SPACE-Q or PCDAI or CDEIS or CDAI or CLIQ or SES-CD).ti,ot. (135)
51 ((Irritable Bowel Syndrome or Crohn$) adj Quality Of Life).ti,ab,ot,hw. (55)

52 (Quality of Life Questionnaire for Functional Digestive Disorders or Gastrointestinal Symptom Rating Scale).ti,ab,ot,hw. (443)
53 (Gastrointestinal Quality of Life index or Digestive Health Status Instrument).ti,ab,ot,hw. (442)
54 or/38-53 (74796)
55 37 or 54 (992674)
56 animals/ not (animals/ and humans/) (4734778)
57 55 not 56 (932744)
58 15 and 57 (2793)
59 limit 58 to yr="2010 -Current" (1869)

NHS Economic Evaluation Database (NHS EED) (CRD): up to 2015/03
Searched: 22.12.20

1 MeSH DESCRIPTOR Irritable Bowel Syndrome EXPLODE ALL TREES 103
2 ((Irritable bowel syndrome* or IBS or IBS-D)) 189
3 (((spastic or irritable or spasm or unstable) NEAR colon))0
4 (((Colitis or colitides) NEAR (spastic or mucous or mucomembraneous or mucomembranous))) 0
5 ((colonospasm)) 0
6 #1 OR #2 OR #3 OR #4 OR #5 189
7 MeSH DESCRIPTOR Crohn Disease EXPLODE ALL TREES 220
8 (((cleron or Crohn*) NEAR disease)) 356
9 (morbus crohn) 0
10 (((regional or regionalis or granulomatous) NEAR (enteritis or enterocolitis))) 0
11 ((Ileocolitis)) 1
12 ((ileitis NEAR (terminal or regional))) 0
13 ((colitis granulomatous)) 0
14 #8 OR #9 OR #10 OR #11 OR #12 OR #13 356
15 #6 OR #14 537
16 (#15) IN NHSEED 95

APPENDIX 2: DATA EXTRACTION TABLES

Table 54: Inclusion criteria and participant details for all included studies

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Previous diagnostic investigations	Participant characteristics
Bellini 2020[24]	Total patients (n=70) IBS-D (n=30) FD (n=40)	Consecutive IBS-D and FD patients referred to a tertiary gastroenterology centre	None reported	NR	Mean (s.d.) age: 52 (17) years 42 females, 28 males
Borghede 2011[$33]	Total patients (n=298) Group 1: Crohn's disease, small bowel resection or radiation injury (n=87) Group 2: Diarrhoea unknown cause (n=114) Group 3: Diarrhoea other known cause (n=97)	All patients who received a 75SeHCAT scan during a five-year period (2004–2009).	None reported	NR	Median (range) age: 42 (16 to 82) years 198 females, 100 males
Farmer 2017[25]	Total patients (n=207) IBS-D (Rome III)	Consecutive patients, with IBS-D, from a	Serological/histological features of celiac disease or a	NR	IBS-D (Rome III): Mean (range) age: 37 (18 to 68) years

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Previous diagnostic investigations	Participant characteristics
	(n=165) IBS-D (Rome IV) (n=42)	secondary care centre. IBS-D was defined according to the Rome III criteria (November 2014 to May 2016) or the Rome IV criteria (May 2016 to November 2016).	prior history of cholecystectomy or small bowel resection.		112 females, 53 males IBS-D (Rome IV): Mean (range) age: 32 (20 to 71) years 39 females, 3 males
Fellous 1994[$34]	Total patients (n=106) Healthy volunteers (n=23) Group 1: Diarrhoea with ileal involvement (n=33) Group 2: Organic diarrhoea without ileal involvement (n=20) Group 3: FD (n=53)	Patients with chronic diarrhoea referred to the hospital between 1990 and 1992 for a SeHCAT test to explore the cause of diarrhoea. Diarrhoea was defined as at least three soft stools or liquid diarrhoea/day for more than 6 months. Normal hepatic balance.	Insufficient clinical/ biological information (n=63).	All patients were without clinical or biological abnormalities, and all had normal colonoscopy with biopsy and ileostomy. When the clinical context and the examinations listed above did not allow the functional character of the diarrhea to be confirmed, other investigations were carried out (duodenal biopsies ileal biopsies hail transit hormonal assays schilling test D-xylose test respiratory teats).	Group 1: Mean (s.d.) age: 46 (16) years, range 11 to 75 years 16 females, 17 males Group 2: Mean (s.d.) age: 55 (16) years, range 24 to 74 years 15 females, 5 males Group 3: Mean (s.d.) age: 47(14) years, range 23 to 77 years 30 females, 23 males

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Previous diagnostic investigations	Participant characteristics
Fernandez-Banares 2001[$36]	Total patients (n=83) Group 1: Microscopic colitis (n=51) Group 2: Diarrhoea, unknown cause (n=32)	Consecutive patients, recruited between 1996 and 1999, with: Group 1: Microscopic colitis: Clinical criteria included chronic or recurrent watery diarrhoea of at least one month duration and grossly normal full colonoscopy. Group 2: Diarrhoea, unknown cause: Patients with previously unexplained chronic and recurrent watery diarrhoea of at least 3 months duration and fulfilled the Rome II criteria for	None reported	All patients underwent the same diagnostic work-up or chronic diarrhoea: bacterial cultures and faecal examination for ova and parasites; routine blood biochemistry and haematology (C-reactive protein, serum Ta and TSH, IgA anti-gliadin and anti-endomysium antibody); small bowel follow through; colonoscopy with multiple biopsies. Additional investigations performed in some patients: Biopsies of the second and/or third part of the duodenum; lactose hydrogen breath test; anorectal manometry retrograde ileoscopy with biopsy of the terminal ileum.	Group 1: Mean (s.d.) age: 60.7 (2.2) years 41 females, 10 males Group 2: Mean (s.d.) age 52.7 (2.1) years 21 females, 11 males

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Previous diagnostic investigations	Participant characteristics
		functional diarrhoea. No detectable digestive or extra-digestive cause was found.			
Fernandez-Banares 2007[37]	Total patients (n=62) Chronic watery diarrhoea and fulfilling the Rome II criteria for FD or IBS-D.	Consecutive adult (>18 years) patients with non-bloody chronic watery diarrhoea, defined as more than 3 loose or liquid bowel movements a day for at least 4 weeks and a stool weight >200 g/day. Participants were required to fulfil the Rome II criteria for either FD or IBS-D.	Previous cholecystectomy or vagotomy	Normal physical examination and blood analysis, including routine blood biochemistry and haematological counts, C reactive protein, serum T4-TSH, and serum IgA-antiendomysial and IgA-human anti-tissue transglutaminase antibodies. Negative faecal bacterial cultures and exam for ova and parasites. Normal full colonoscopy with multiple biopsies.	Mean (s.d.) age: 52.2 (2) years 47 females, 15 males 32 IBS-D 30 FD
Galatola 1992[$38]	Total patients (n=98) IBS-D	Patients referred for a gastroenterological	Previous major abdominal surgical	Negative results for routine biochemical, haematological, endoscopic, radiological, and	Mean (range) age: 43 (14 to 76) years

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Previous diagnostic investigations	Participant characteristics
		consultation, by their GP, because of abdominal pain or distress, who gave a history of increased bowel frequency (>3 per day) lasting for at least 3 months.	procedures (except cholecystectomy), liver disease, or an identified organic cause of symptoms.	histological examinations implemented according to the clinical indications in order to search for an organic cause of their symptoms.	53 females, 45 males
Holmes 2012[26]	Total patients (n=55) Patients for whom notes were available (n=44) SeHCAT positive patients, with notes available (n=28) Type 1 BAM (n=10) Type 2 BAM (n=8) Type 3 BAM (n=10)	Patients who had undergone SeHCAT testing, between 1st January 2005 and 31st December 2010.	None reported	NR	Age range: 19 to 77 years 36 females, 19 males
Kumar 2013[28]	Total patients (n=88) Group 1: Ileal disease/resection (n=18) Group 2: Idiopathic (n= 57)	Consecutive patients referred for SeHCAT testing over a one-year period.	None reported	NR	None reported

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Previous diagnostic investigations	Participant characteristics
	Group 3: Secondary to other gastrointestinal disease (n=13)				
Kumar 2020[27]	Total patients (n=51) Group 1: IBS-D, SeHCAT negative and all diarrhoea investigations negative Group 2: Idiopathic BAD, SeHCAT positive Group 3: Post-cholecystectomy, SeHCAT positive Group 4: Post-terminal ileal resection for Crohn's disease, SeHCAT positive	Patients who had undergone a SeHCAT test for the investigation of chronic diarrhoea.	None reported	NR	None reported
Lin 2016[29]	Total patients (n=515) SeHCAT positive patients,	Patients who had undergone a SeHCAT test for the investigation of	None reported	Previous colonic investigation (colonoscopy/barium enema/colon capsule) 434/515 (84%)	Median (range) age: 48 (17 to 86) years 353 females, 162 males

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Previous diagnostic investigations	Participant characteristics
	commenced on BAS following diagnisis, who were contactable at follow-up: Type 1 BAM (n=11) Type 2 BAM (n=29) Type 3 BAM (n=18)	chronic diarrhoea, between 2001 and 2012.		Oesophagogastroduodenoscopy 305/515 (59%) Small bowel investigations 233/515 (45%) Coeliac serology 433/515 (84%)	Rome III criteria for IBS 167/515 (33%)
Merrick 1985[$39]	Patients (n=106), normal controls (n=63) Group 1: Normal controls (n=63) Group 2: Previous small bowel resection (n=26) Group 3: Previous vagotomy or surgery for peptic ulcer (n=29) Group 4: Chronic diarrhoea of non-inflammatory origin (n=51), (43 IBS, 2 coeliac disease, 2	Normal controls: People who did not have gastrointestinal symptoms. Patients: NR	None reported	Diagnoses were based on a combination of clinical history, haematological findings, biochemistry, and, when appropriate, barium follow through, barium enema, and biopsy of the colon or small bowel. A hydrogen breath test was performed in patients who had undergone vagotomy. All diagnoses were verified by follow-up of at least one year.	Group 1: Mean (range) age: 52 (24 to 72) years 56 females, 7 males Group 2: Mean (range) age: 48 (17 to 74) years 16 females, 10 males Group 3: Mean (range) age: 54 (28 to 72) years 10 females, 19 males Group 4: No details reported

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Previous diagnostic investigations	Participant characteristics
	small bowel ischaemia, and 4 other miscellaneous conditions)				
Notta 2011[$40]	Total patients (n=37)	Patients with chronic diarrhoea of more than one month duration and no previous treatment.	Patients who were age under 18 years, pregnant or breast-feeding.	NR	Age range: 20 to 80 years 26 females, 11 males
Notta 2014[30]	Total patients (n=78)	Patients with chronic FD.	None reported	NR	Age range: 20 to 87 years 56 females, 22 males
Notta 2017[31]	Total patients (n=92)	Patients with chronic FD.	None reported	NR	Age range: 20 to 87 years 60 females, 32 males
Rudberg 1996[$41]	Total patients (n=20) Patients who had not undergone cholecystectomy or gastric resection (n=17)	Patients with chronic or recurrent diarrhoea of unknown cause. Lactose restricted diet, loperamide, or anticholinergic agents had not relieved their symptoms.	Patients with periods of constipation, dominating abdominal pain or fragmented mucous stools.	Clinical, endoscopic and radiological examinations were performed, as well as laboratory tests to exclude IBD, lactose intolerance, coeliac disease, abuse of laxative or other forms of diarrhoea.	Mean (range) age: 50 (27 to 82) years 13 females, 4 males
Sciaretta	Total participants	None reported	None reported	Group D: No evidence of organic	Group D:

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Previous diagnostic investigations	Participant characteristics
1986[$42]	(n=89) Group A: Healthy (n=23) Group B: Patients with resected or pathological distal ileum (n=36) Group C: Patients with intestinal pathology, but normal distal ileum (n=17) Group D: Patients with chronic or recurrent diarrhoea of unknown cause (n=13)			pathology of the digestive tract, intestinal parasites, food allergies, or endocrine or metabolic diseases.	Mean (range) age: 51 (28 to 70) years 10 females, 3 males
Sciaretta 1987[$43]	Total participants (n=69), 23 healthy volunteers and 46 patients with IBS-D (n=38) or prior cholecystectomy (n=8)	Patients suffering from chronic or recurrent diarrhoea, which was thought to be functional.	None reported	Chemical and microbiological faecal analyses were normal. Radiographic examinations of the large and small bowel, carried out using two contrast media, were negative. Diabetes and other endocrine disorders,	Patients: Mean (range) age: 41 (17 to 73) years 26 females, 20 males

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Previous diagnostic investigations	Participant characteristics
				and food allergies were excluded.	
Sinha 1998[$44]	Total patients (n=17), patients with a positive SeHCAT test (n=9)	Patients with chronic diarrhoea referred to the department and selected to undergo the SeHCAT, based on a history suggestive of IBS-D (Manning criteria) and no other obvious cause of diarrhoea, who had a positive SeHCAT test result.	None reported	Possible secondary causes of BAM were excluded by performing the following investigations in all patients: routine blood tests; random glucose; haematinic screen; stool microscopy and culture; small bowel enema to exclude structural ileal disease; gastroscopy and duodenal biopsy to exclude coeliac disease; para amino benzoic acid (PABA) test to exclude pancreatic insufficiency; hydrogen and ^{14}C-glycocholate breath tests to exclude bacterial overgrowth; barium enema and colonoscopy (six out of nine patients) to exclude large bowel disease.	Patients with a positive SeHCAT test: Mean (range) age: 50.2 (43 to 57) years 3 females, 6 males
Smith 2000[$6]	Total patients (n=304)	Patients with chronic continuous or recurrent	None reported	NR	None reported

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Previous diagnostic investigations	Participant characteristics
	Group 1: Crohn's disease with ileal resection (n=37) Group 2: Crohn's disease, unoperated and in clinical remission (n=44) Group 3: Vagotomy and pyloroplasty, with/without cholecystectomy (n=26) Group 4: IBS-D (n=197)	diarrhoea.			
Tunney 2011[$45]	Total patients (n=276) with chronic diarrhoea, of whom 136 had no known risk factors.	Patients who underwent SeHCAT scanning, for the investigation of chronic diarrhoea, between April 2005 and January 2011.	Patients referred from and managed by other hospital trust and patients seen on a private basis. Patients who did not have a SeHCAT scan at 7 days or who had technically void results. Patients	Over 80% of the patients with no known risk factors or diarrhoea post-cholecystectomy had had documented coeliac screening, and 80% of the patients with no known risk factors for chronic diarrhoea had some form of bowel endoscopy.	All patients: Mean (range) age: 46 (16 to 90 years) 189 females, 87 males

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Previous diagnostic investigations	Participant characteristics
			taking a trial of BAS during investigation. Patients with no information in their electronic records.		
Wildt 2003[$46]	Total patients (n=135) Groups, excluding 2 patients who were lost to follow-up (n=133): Group 1: Possible type 1 BAM, Crohn's disease with or without resection, ileocaecal resection, radiation enteropathy (n=13) Group 2: Possible type 2 BAM, idiopathic (n=56) Group 3: Possible	Patients with chronic diarrhoea (defined by subjective reports of >3 weeks change in stool frequency and/or consistency) who were investigated for BAM using the SeHCAT test.	None reported	The SeHCAT test was generally carried out as a second-line investigation. First-line diagnostic evaluation, at minimum, included: sigmoidoscopy or colonoscopy with mucosal biopsies; faecal examination for parasites and bacteria; biochemistry (haemoglobin, white blood cell count, C reactive protein, electrolytes, renal parameters, liver function tests and thyroid stimulating hormone). First-line evaluation also frequently included tests for coeliac disease and lactose malabsorption, and stool volume and stool lipid concentration.	Age: NR 87 females, 48 males

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Previous diagnostic investigations	Participant characteristics
	type 3 BAM, other pathological causes including previous cholecystectomy (n=64)				
Williams 1991[$47]	Patients (n=181)	Patients referred for measurement of ^{75}SeHCAT retention because of unexplained diarrhoea between 1982 and 1989.	Patients with inflammatory bowel disease who had undergone previous radiotherapy to the abdomen, any form of bowel resection, or other abdominal surgery were excluded.	Stool culture, rigid sigmoidoscopy, barium enema, barium follow through, jejunal biopsy, and vitamin B-12 absorption studies were performed in all patients.	Patients with severe BAM (<5%) (n=23): Mean age (range): 45 years (17 to 77 years) 13 females, 10 males Patients with moderate BAM (≥5 to <10%), who were treated with BAS (n=13): Mean age (range): 44 years (25 to 64 years) 4 females, 9 males Patients with mild BAM (≥10 to <15%) (n=21[*]): Mean age (range): 30 years (13 to 72 years) 13 females, 18 males

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Previous diagnostic investigations	Participant characteristics
Zanoni 2018[32]	Total patients (n=12) with chronic diarrhoea without a known cause (n=3) or IBS-D not responding to standard medication (n=9)	Patients referred for SeHCAT with chronic diarrhoea without a known cause or IBS-D not responding to standard medication between November 2017 and April 2018.	NR	NR	Mean age (range): 45 years (22 to 64) 6 females, 6 males

[$]Study taken from previous Diagnostic Assessment Report[16]

*Number with mild BAM reported as 21 throughout the article, but proportion female:male in this category reported as 13:18

BAM: bile acid malabsorption; FD: functional diarrhoea; IBS: irritable bowel syndrome; IBS-D: diarrhoea predominant irritable bowel syndrome; IgA: immunoglobulin A; NR: not reported; SeHCAT: [^{75}Selenium] tauroselcholic acid; TSH: thyroid stimulating hormone

Table 55: Index test and reference standard details for all included studies

Study ID	SeHCAT (index test) details	Treatment and response (reference standard) details
Bellini 2020[24]	No details of the administration procedure were reported. 7-day retention ≤15% was considered to be indicative of BAM BAM was classified as: mild, 7-day retention >10% to ≤15%; moderate, 7-day retention >5% to ≤10%; severe, 7-day retention ≤5%	Treatment: colestyramine Dose: 2g/day, increasing by2g weekly until normal faecal consistency (Bristol Stool Chart [BSC] 3 to 5) and/or the maximum tolerated dose was reached. Duration of treatment: 8 weeks Follow-up: 8 weeks Response: patient reported "significant improvement" on the BSC, INS-SSS, SF-36 and a questionnaire on bowel habits.
Borghede 2011[$33]	Administrated after an overnight fast as an oral capsule (GE Healthcare, UK) containing 0.37 MBq. Basal activity was measured over the abdomen three hours after swallowing the capsule using a high-resolution collimator. The measurement was repeated after seven days and a fraction was calculated by dividing the 7-day activity by the basal activity. Retention <15% was considered abnormal. No further details.	Treatment: colestyramine Dose: NR Duration of treatment: NR Follow-up: NR

Study ID	SeHCAT (index test) details	Treatment and response (reference standard) details
	7-day retention; cut-off: 5%, 10% and 15%	Response: "positive effect on their bowel habits". Response to treatment was defined as a lowered frequency of stools per day and/or a firmer consistency. A normal bowel habit was defined as 1-2 formed stools per day.
Farmer 2017[25]	No details of the administration procedure were reported. 7-day retention <10% was considered to be indicative of BAM	Treatment: Unspecified BAS Dose: NR Duration of treatment: NR Follow-up: NR Response: 50% reduction in the frequency of bowel movements.
Fellous 1994[$34]	Patients fasted for 4 hours before ingesting the 10uCi (370Bq) ^{75}SeHCAT capsules (Amersham Int. Ltd) at mealtime. Radioactivity emitted by the body was measured according to the technique of Thaysen et al.[81], with an uncollimated gamma camera and placed 70cm from the patient lying down. Posterior and anterior detection was carried out successively for 5 minutes, with photoelectric peaks of ^{75}Se (220-300keV). Background was	Treatment: Colestyramine Dose: 8-12 g/ day Duration of treatment: minimum 15 days Follow-up: NR

Study ID	SeHCAT (index test) details	Treatment and response (reference standard) details
	measured in the absence of the patient using the same conditions and was subtracted from the radioactivity measure. Measures were made at 1 to 3 hours (J0) and 7 days (J7) after ingestion of the capsule. The percentage of retained ^{75}SeHCAT was calculated using the formula (radioactivity at J7/ radioactivity at J0)x100, for the geometric mean of the anterior and posterior measurements. The physical decay of ^{75}Se was negligible for the duration of the test. The half-life of ^{75}SeHCAT was 2.6 ±0.7 days for 96% of patients, and 62±17 days for the remaining 4% subjects. The dosimetry maximum test was 132 mrad for the gall bladder, 121 mrad for the terminal ilium and 11 mrad for the whole body. 7-day retention <10% was considered to be indicative of BAM	Response: Treatment permitted the return to a normal transit (1 or 2 stools/day) with normal consistency or 'pasty-ish'.
Fernandez-Banares 2001[$36]	After an overnight fast 10µCi of ^{75}Se homotaurocholate (Radiochemical Centre, Amersham) was administered orally. ^{75}Se activity was measured with a large-field-of view gamma camera equipped with a high-sensitivity collimator. The initial count rate (100% value) was measured 3hr (day 0) after administration of the isotope. Retention was then measured after 4 and 7 days. Abdominal retention <11% on day 7 was considered abnormal. Values lower than 5 % on day 7 were considered as severe	Treatment: Colestyramine (Resincolestiramina, 4g sachets, Rubio laboratories, Spain) Dose: Starting dose 4g/day. Patients visited weekly and the drug dose was increased or decreased according to clinical response ranging from 2 to 12 g/day.

Study ID	SeHCAT (index test) details	Treatment and response (reference standard) details
	BAM. 7-day retention <11% was considered to be indicative of BAM (<5% severe BAM)	Duration of treatment: unclear, patients were maintained with the same dose of colestyramine. Follow up: After achieving remission patients were followed up for every 3 months or sooner if diarrhoea reoccurred. Time to clinical response: Median (range) 5 (2 to 10) days Response: when complete resolution of diarrhoea was achieved (passage of two or less formed or semi formed stools per day).
Fernandez-Banares 2007[$37]	10 µCi of 75Se homotaurocholate (Radiochemical Centre, Amersham) were administered orally after overnight fast. 75 Se activities were measured with a large-field-of view gamma camera equipped with a high sensitivity collimator. The initial count rate (100% value) was measured 3 h (day 0) after administration of the isotope. 7-day retention <11% was considered to be indicative of BAM	Treatment: Colestyramine Dose: Variable dose the median dose required was 8g/day (IQR, 4-12). Duration of treatment: unclear Follow-up: 12 months

Study ID	SeHCAT (index test) details	Treatment and response (reference standard) details
		Time to clinical response: Median (range) 6 (2 to 11) days Response: The relief of the diarrhoea (passage of 2 or fewer formed or semi formed stools per day), and absence of clinical relapse after 12-month follow-up. No response was defined as non-improvement in diarrhoea or diarrhoea relapse during follow-up.
Galatola 1992[$38]	10 µCi of 75Se homotaurocholate (Amersham Ltd, Poole, UK) were administered orally in the fasting state together with a lunch meal at lunch time; 3h (t=0) and 171h (t=1) later abdominal scans were performed for 300s using a non-collimated γ- camera placed 70 cm from the couch surface, with a 35% window at 280 KeV. 7-day retention < 11.7% was considered to be indicative of BAM	Treatment: Colestyramine Dose: 2g before breakfast, increased in a stepwise manner every 5 days of therapy if no effect was reported by the patient in improving bowel frequency, up to a maximum of 4g three times daily. The mean (s.e.) 'optimal' dose was 4.8 (0.3) g/d, range 2 to 8 g/d. Duration of treatment: One month, if symptoms did not recur on trial of withdrawal, or ongoing.

Study ID	SeHCAT (index test) details	Treatment and response (reference standard) details
		Follow-up: Median (range) 12 (1 to 24) months. Response: Patient-reported reduction in bowel frequency and symptoms.
Holmes 2012[26]	No details of the administration procedure were reported. 7-day retention <15% was considered to be indicative of BAM	Treatment: Unspecified BAS Dose: NR Duration of treatment: NR Follow-up: NR Response: “Improvement in symptoms”
Kumar 2013[28]	No details of the administration procedure were reported. 7-day retention <15% was considered to be indicative of BAM	Treatment: Unspecified BAS Dose: NR Duration of treatment: NR Follow-up: NR Response: “Better”

Study ID	SeHCAT (index test) details	Treatment and response (reference standard) details
Kumar 2020[27]	No details of the administration procedure were reported. No details of the diagnostic threshold were reported.	Treatment: questran or colesevelam Dose: "titrated to symptomatic response" Duration of treatment: NR Follow-up: Unclear, patients were reviewed at 4-weekly intervals Response: 50% improvement in stool frequency or had fewer than three bowel movements/day
Lin 2016[29]	Patients were asked to ingest a single 370 kBq SeHCAT capsule (GE Healthcare, Little Chalfont, UK) with water, and a scan of the patient's abdomen was taken at 3 hours using a gamma camera to obtain baseline counts. Another scan was then obtained at 7-days to determine the percentage of SeHCAT retention. 7-day retention <10% was considered to be indicative of BAM	Treatment: colestyramine, colestipol or colesevelam Dose: NR Duration: NR Follow-up: Median 82 months (range 39 to 139 months) Response: NR
Merrick 1985[$39]	SeHCAT retention was measured using previously published methods.[82, 83]	Treatment: Colestyramine or 'simple conservative

Study ID	SeHCAT (index test) details	Treatment and response (reference standard) details
	A tracer dose of less than 100 µg SeHCAT was administered labelled with 40 kBq (1 µCi) selenium-75. 7-day retention of <8% was considered to be indicative of BAM and 7-day retention of 8% to 15% was classified as an equivocal result.	treatment' Dose: NR Duration of treatment: NR Follow up of at least 12, and in some up to 24 months. Response: "asymptomatic" or "free of small bowel disease".
Notta 2011[$40]	The examination consisted in the oral administration after 4 h of fasting of a capsule containing 0.01 mCi (0.37 MBq) ^{75}SeHCAT (provided by Amersham Radiochemical Centre, UK). The patient had to continue fasting for 3 h more after the test, after which the abdominal activity was recorded. This registry considered the initial activity or zero time (ACT_0). The registry of the abdominal activity was repeated at 4 and 7 days of administration (ACT_4 and ACT_7). All the measurements were performed with the patient in decubitus supine position with the detector centred on the abdominal region, maintaining a constant patient-collimator distance	Treatment: resin colestyramine Dose: NR Duration of treatment: NR Follow-up: clinical follow-up at 3 and 6 months (only data for 3 months reported). Response: Complete response: normalization of

Study ID	SeHCAT (index test) details	Treatment and response (reference standard) details
	(15 cm) and a 5-min acquisition was made. A dual headed gamma camera with low energy general purpose collimator (LEGP) was used. The following measurements were recorded: preacquisition background (B), anterior abdomen (AP), posterior abdomen (PA) and post-acquisition background (B). The percentage abdominal retention (AR) was calculated at 4 and 7 days. The formulas used to calculate retention were: Act_n = (((AP − B) + (PA − B)) / 2) Abd Ret4 : (Act_4 / Act_0) × 100 Abd Ret7 : (Act_7 / Act_0) × 100. 7-day retention ≤10% or 4-day retention ≤25% were considered to be indicative of BAM	stool rhythm and consistency. Partial response: decrease of frequency and/or consistency.
Notta 2014[30]	Abdominal retention was measured 7-days after oral administration of 0.01 mCi ^{75}SeHCAT. 7-day retention <10% was considered to be indicative of BAM	Treatment: resin colestyramine Dose: 3 to 12 g/d Duration of treatment: 3 months Follow-up: 3 months

Study ID	SeHCAT (index test) details	Treatment and response (reference standard) details
		Response: Complete or partial
Notta 2017[31]	Abdominal retention was measured 7-days after oral administration of 0.01 mCi ^{75}SeHCAT. 7-day retention <10% was considered to be indicative of BAM	Treatment: resin colestyramine Dose: 3 to 12 g/d Duration of treatment: 3 months Follow-up: 3 months Response: complete or partial
Rudberg 1996[$41]	One capsule of 370 kBq 75SeHCAT (Amersham International) was swallowed with water by the patient after an overnight fast. Three hours later the patient was placed supine 70cm beneath the face of the uncollimated gamma camera which was centred at mid-abdomen. Counts were acquired in a 20% window at 265 keV utilising the central peak of the 75Se energy distribution. The same registration was then performed with the patient in the prone position. Background counts were collected before and after each registration. A geometric mean value was then calculated. The same registration and calculations were performed after 7 days and corrected for the gamma decay.	Treatment: colestyramine. Dose: 2 to 4g, 3 times a day Treatment duration: 10 days to 6 months, depending on effectiveness Follow-up: at least 6 months. Response: 'complete relief' - no details reported.

Study ID	SeHCAT (index test) details	Treatment and response (reference standard) details
	7-day retention ≤15% was considered to be indicative of BAM	
Sciaretta 1986[$42]	370 kBq (10 µCi) of ^{75}SeHCAT, (provided by Amersham Radiochemical Centre, UK) in capsule form, containing <100 µg of active ingredient absorbed on inert carrier, was administered orally following the technique of Thaysen et al.[81] Patients fasted for at least 4 hours prior to administration. Whole body absorbed dose was ~0.2 µGy/kBq (1 mrad/µCi); the absorbed dose from the critical organ-gallbladder wall was 3.2 µGy/kBq (12 mrad/µCi). The ^{75}Se activity was measured with a small field of view uncollimated γ-camera (Pho-Gamma IV, Searle Consumer Products, Chicago, Ill.). To minimise the effects due to geometric variations, the crystal was kept 70cm away from the bed where the patient lay in a supine position, and the crystal was centred in the middle of the xiphoid umbilical line. For γ-counting, a 35% window centred at 260 keV was experimentally chosen, which allows energies from 214 to 305 keV to be detected with low background interference. Counting time was set at 5 min. In this condition, the initial count rate (time zero) was about $6x10^4$ cpm and the background count rate was always about $5x10^3$ cpm. Measurements were carried out 3h after the administration of the	Treatment: colestyramine Dose: 2 to 8 g/d Treatment duration: NR Follow-up: NR Response: 'disappearance of diarrhoea' - no further details reported.

Study ID	SeHCAT (index test) details	Treatment and response (reference standard) details
	isotope (1.5h in cases of severe diarrhoea) and at 1, 3, 5, and 7 days after the administration of the isotope; background activity was always subtracted. A standard source of ^{75}Se (~370 kBq) was also measured using the identical technique in order to monitor possible fluctuations in system stability. Correction for radioactive decay was not found to be necessary. Using the least-squares fit, a single exponential activity versus time curve was obtained from which the percentages of ^{75}SeHCAT retained in the abdomen on the third day were determined. The curve was obtained whenever at least 3 ^{75}SeHCAT retention values were different from zero. The percentage activities at days 3, 5 and 7 were also evaluated by direct measurements with the γ-camera. A positive test was described as 'SeHCAT values below the norm.' The lower limit of normal was reported as 34% for data obtained from the exponential abdominal activity retention curve for healthy controls on day three; this was described by the authors as equivalent to a 7-day retention cut-off of 5%.	
Sciaretta 1987[$43]	The ^{75}SeHCAT test was carried out in all patients using the method we described elsewhere and the control group consisted of the same 23	Treatment: colestyramine. Dose: 2 to 8g twice daily

Study ID	SeHCAT (index test) details	Treatment and response (reference standard) details
	subjects (see Sciaretta 1986[42]). Results are expressed as percentage retention values calculated by the exponential time activity curve on day 3. Measurements of abdominal radioactivity were taken by gamma camera counting on the day of administration of 370 KBq 75Se-homocholyltaurine (^{75}SeHCAT, Amersham Radiochemical Centre, England) (time zero) and on days 1-3-5 and 7. An abdominal retention of 34% or more on day 3 is considered normal by our method. The percentage abdominal retention on day 7, measured directly by gamma camera for both the control and the functional diarrhoea groups was considered. An abdominal retention of less than 8% (the lowest value in a normal subject) is considered pathologic. 7-day retention <8% was considered to be indicative of BAM	Treatment duration: minimum 10 days Follow-up: NR Response: response was considered positive when diarrhoea stopped with colestyramine administration, and recurred without it.
Sinha 1998[$44]	No details of the administration procedure were reported. 7-day retention <15% was considered to be indicative of BAM	Treatment: colestyramine. Dose: initial dose 1 to 2 sachets 3 times daily, 'titrated accordingly'. Adjunctive therapy with loperamide was used initially and was gradually withdrawn once a response was achieved. Treatment duration: NR

Study ID	SeHCAT (index test) details	Treatment and response (reference standard) details
		Follow-up: NR Response: reduction in stool frequency and improvement in stool consistency within 24 hours following the start of treatment; response maintained after withdrawal of loperamide.
Smith 2000[$6]	The SeHCAT retention test was carried out in a standard manner according to the manufacturers' instructions. Patients swallowed a single capsule containing 370kBq SeHCAT (Nycomed-Amersham, UK). After 3hrs for physiological equilibration, baseline counts were measured over the abdomen using an uncollimated gamma camera. Background-corrected counts were obtained in both antero-posterior and postero-anterior views, and the geometric mean of these counts recorded. The percentage of the baseline value retained on the 7th day was calculated. 7-day retention <10% was considered to be indicative of BAM	Treatment: Patients were initially given conventional therapy (prednisolone ± ASA drugs in Crohn's disease and anti-diarrhoeals in the others), if this failed patients were treated with BAS (colestyramine or colestipol). Dose: Treatment with either BAS was started at a low dose, one sachet (5g) daily, and gradually built up to a maximum of one sachet 3 times daily, titrating the dose against clinical response. Follow-up: NR

Study ID	SeHCAT (index test) details	Treatment and response (reference standard) details
		Response: qualitative, patient-reported response, based on reduced frequency of bowel movement (typically 2 to 3 times per. day), reduction in urgency, stools becoming more formed and solid, improved quality of life.
Tunney 2011[$45]	The amount of ^{75}Se being administered was always 370kBq, and patients were scanned at 3 hours and 7 days post-ingestion using an uncollimated gamma camera. 7-day retention <8% was considered to be abnormal, 7-day retention between 8% and 15% was considered to be equivocal, and 7-day retention >15% was considered to be normal.	Treatment: BAS (no details reported) Dose: NR Treatment duration: NR Follow-up: NR Response: NR
Wildt 2003[$46]	The SeHCAT test was performed as a measurement of the 7-day retention, modified from descriptions in Thaysen et al.[81] and Nyhlin et al.[82] No further details were reported. 7-day retention <5% was considered to be indicative of severe BAM, 7-day	Treatment: colestyramine Dose: 2 to 4 g/d; patients were recommended to increase or decrease dose according to response. The most common dose was 5 to 12 g/d. Duration of treatment: NR

Study ID	SeHCAT (index test) details	Treatment and response (reference standard) details
	retention 5% to <10% was considered to be indicative of moderate BAM, and 7-day retention 10% to <15% was considered to be indicative of mild BAM.	Follow-up: NR ("Several weeks after commencing treatment, the patients returned to the clinic reporting dose, response and perhaps further adjustment of dosage"). Response: >25% reduction in bowel frequency, or file data reporting excellent or moderate response to treatment.
Williams 1991[$47]	^{75}SeHCAT absorption was assessed following previously published methods,[84] by administering one capsule containing 40 kBq (1 µCi) ^{75}SeHCAT after an overnight fast. The 100% value for whole body retention was obtained at 30 minutes and the measurement was repeated at seven days using a shadow shield whole body counter. During the initial evaluation of ^{75}SeHCAT a lower limit of 15% retention at seven days was established on the basis of comparison with normal controls. 7-day retention <5% was considered to be indicative of severe BAM, 7-day retention ≥5% to <10% was considered to be indicative of moderate BAM,	Treatment: colestyramine or aluminium hydroxide. Dose: colestyramine was administered in divided doses in powder form (4 g sachets) during the day. The mean dose was 12 g. Four patients required doses greater than 12 g/day to control their symptoms. No information on the dosage of aluminium hydroxide. Follow-up: NR.

Study ID	SeHCAT (index test) details	Treatment and response (reference standard) details
	and 7-day retention ≥10% to <15% was considered to be indicative of mild BAM.	Response: A therapeutic response was defined as a reduction in stool frequency to ≤2 bowel actions/day with a concomitant increase in stool consistency occurring within 48 hours of beginning treatment.
Zanoni 2018[32]	No details of the administration procedure were reported. 7-day retention <5% was considered to be indicative of severe BAM, 7-day retention 5 to 10% was considered to be indicative of moderate BAM, and 7-day retention 10% to 15% was considered to be indicative of mild BAM.	Treatment: NR Dose: NR Follow-up: NR Response: NR
$ Study taken from previous Diagnostic Assessment Report[16] BAM: bile acid malabsorption; IQR: interquartile range; NR: not reported; SeHCAT: [^{75}Selenium] tauroselcholic acid		

APPENDIX 3: QUADAS-2 ASSESSMENTS

Study: Merrick 1985[39]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Prospective study but not clear if a consecutive or random sample of patients was enrolled. The study included four groups of patients:

1. Healthy controls
2. Small bowel resection
3. Diarrhoea after vagotomy
4. Chronic diarrhoea due to IBS, coeliac disease, small bowel ischaemia and 'other'

Data were extracted for the IBS subgroup of group four only.

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

The previous assessments/investigations undergone by patients in group four were not clear.

Do the included patients match the question?	**Concerns: Unclear**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS

A tracer dose of less than 100 µg SeHCAT was administered labelled with 40 kBq (1 µCi) selenium-75 (Amersham International). Seven days later the patients re-attended and a further whole-body count was obtained. Results were reported for pre-specified 7-day retention thresholds and the index test was conducted before the reference standard.

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS

Treatment: Simple conservative treatment (colestyramine) in test positive and 'equivocal' patients. Three patients (<10%) were not treated. Test negative patients were followed-up for 12 to 24 months and received 'simple conservative treatment', which was reported to have 'eased most or all symptoms'.

Is the reference standard likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS

Patients with SeHCAT 7-day retention >15% did not receive treatment with BAS; these patients were managed with 'simple conservative treatment'. Patients were followed up for 12 to 24 months.

Did all patients receive a reference standard?	Yes

Did patients receive the same reference standard?	No
Was response to treatment assessed over an adequate period?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: High**

Study: Sciaretta 1986[42]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

Prospective study but not clear if a consecutive or random sample of patients was enrolled. The study included four groups of patients:

a. Healthy controls
b. Patients with resected pathological distal ileum
c. Patients with intestinal pathology, but normal distal ileum
d. Patients with diarrhoea, but no evidence of intestinal pathology

Data were extracted for group d. only.

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Group d. included three patients with previous cholecystectomy. Patients in group d. had no evidence of organic pathology of the digestive tract, intestinal parasites, food allergies, or endocrine or metabolic diseases, however, details of specific previous assessments/investigations were not provided.

Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

370 kBq (10 µCi) of ^{75}SeHCAT, (provided by Amersham Radiochemical Centre) in capsule form, containing <100 µg of active ingredient absorbed on inert carrier, was administered orally. A positive test was described as 'SeHCAT values below the norm.' The lower limit of normal was reported as 34% for data obtained from the exponential abdominal activity retention curve for healthy controls on day three; this was described by the authors as equivalent to a 7-day retention cut-off of 5%. The index test was conducted before the reference standard.

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	**RISK: High**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD
A. RISK OF BIAS

All patients in group d. were treated with colestyramine.

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING
A. RISK OF BIAS

All patients in group d. received the index test and were treated with colestyramine. The follow-up period was not reported.

Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes

Was response to treatment assessed over an adequate period?	Unclear
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: Unclear**

Study: Sciaretta 1987[43]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

Not clear if the study was prospective or retrospective.
The study included healthy volunteers and patients with IBS or cholecystectomy. Data were only extracted for IBS/cholecystectomy patients.
There may be some overlap in populations in the two Sciaretta papers.

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Eight of the included patients had prior cholecystectomy. It was not clear that all assessments/investigations specified in current BSG guidelines[2] had been carried out: Chemical and microbiological faecal analyses were normal. Radiographic examinations of the large and small bowel, carried out using two contrast media, were negative. Diabetes and other endocrine disorders, and food allergies were excluded.

Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

370 kBq (10 µCi) of ^{75}SeHCAT, (provided by Amersham Radiochemical Centre) in capsule form, containing <100 µg of active ingredient absorbed on inert carrier, was administered orally. The threshold was pre-specified as a 7-day retention 8%. The index test was conducted before the reference standard.

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD
A. RISK OF BIAS

All patients received treatment with 2-8g colestyramine, twice daily for at least 10 days. When colestyramine was not effective in relieving symptoms, therapy was discontinued. Where colestyramine was effective, therapy was stopped for seven days and started again if symptoms returned. A positive test was defined as symptom resolution on treatment and return of symptoms when treatment was discontinued. Stool frequency was taken as the average number of bowel actions per day over a one week period and was recorded before and after colestyramine administration.

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING
A. RISK OF BIAS

All patients received the index test and were treated with colestyramine. The follow-up period was not reported.

Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes

Was response to treatment assessed over an adequate period?	Unclear
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: Unclear**

APPENDIX 4: DETAILS OF EXCLUDED STUDIES WITH RATIONALE

To be included in the review studies had to fulfil the following criteria:

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

OR

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

Setting: Secondary care

Index Test: SeHCAT (Tauroselcholic [^{75}Selenium] acid) test, (GE Healthcare Limited, UK)

Comparator: No SeHCAT test

(RCTs, CCTs and comparative observational studies)

Reference Standard: Response to treatment with BAS

(predictive accuracy and response rate studies)

Outcome: 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

Treatment outcome in patients with a positive SeHCAT result (i.e. sufficient data to calculate positive predictive value)

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: RCTs, CCT, comparative observational studies, multi-variable regression modelling studies, predictive accuracy studies, observational studies reporting response to treatments in patients with a positive SeHCAT test.

Table 56 summarises studies which were screened for inclusion based on full text publication but did not fulfil one or more of the above criteria. Table 57 Summarises studies which were included in our previous systematic review, but which did not meet the inclusion criteria for this assessment. Studies were assessed sequentially against criteria; as soon as a study had failed based on one of the criteria it was not assessed against subsequent criteria. The table shows which of the criteria each study fulfilled ("Y") and on which item it failed ("N") or was unclear.

Table 56: Studies excluded based on full text screening

Study Details	Study Design	Setting	Population	Intervention/Index Test	Comparator	Reference Standard	Outcome
Albireo, 2014[85]	Yes	Yes	Unclear	No			
Appleby, 2017[86]	Yes	Yes	Yes	Yes	NA	No	
Arms-Williams, 2016[87]	Yes	Yes	No[◊*]	Yes	NA	Yes	Unclear[*]
Aujla, 2014[88]	Yes	Yes	No[◊*]	Yes	NA	Yes	Unclear[*]
Baena Garcia, 2019[89]	No						
Bajor 2015[90]	Yes	Yes	No[◊*]	Yes	NA	Yes	Unclear[*]
Barber Caselles, 2017[91]	Yes	Yes	No[◊*]	Yes	NA	Yes	Unclear[*]
Beigel, 2014[76]	No						
Bronte, 2020[92]	Yes	Yes	No				
Carrasco-Labra, 2019[93]	No						
Damsgaard, 2018[94]	Yes	Yes	Yes	Yes	NA	Unclear[*]	Unclear[*]
Fernandes, 2018[95]	No						
Fraccascia, 2020[96]	Yes	Yes	Yes	Yes	NA	Unclear[$]	Unclear[$]
Fullard, 2019[97]	Yes	Yes	No				
Hendy, 2015[74]	No						
Kok, 2013[98]	Yes	Yes	No[◊*]	Yes	NA	Yes	Unclear[*]
Kurien, 2014[99]	No						

Study Details	Study Design	Setting	Population	Intervention/Index Test	Comparator	Reference Standard	Outcome
Mayo Clinic, 2019[100]	No						
Moayyedi, 2019[101]	No						
Orekoya, 2015[102]	Yes	Yes	No [◊*]	Yes	NA	Yes	Yes
Pierry, 2019[103]	Yes	Yes	No [◊$]	Yes	NA	Yes	Unclear[$]
Reid, 2016[104]	Yes	Yes	Yes	Yes	NA	Yes	No
Sanchez, 2016[105]	Yes	Yes	No [◊$]	Yes	NA	Yes	Yes
Siu, 2018[106]	Yes	Yes	No[◊*]	Yes	NA	Yes	Unclear[*]
Slattery, 2015[72]	No						
Smith, 2013[68]	No						
Talavera Rubio, 2018[107]	Yes	Yes	No[◊*]	Yes	NA	Yes	Unclear[*]
Valentin, 2016[73]	No						
Vijayvargiya, 2019[108]	No						
Wenzel, 2019[75]	No						
Woolson, 2014[109]	Yes	Yes	No[◊*]	Yes	NA	Yes	Unclear[*]

[◊]Mixed population, no separate data for either specified population
[*]Study authors contacted, no additional information received
[$]Study authors could not be contacted (no contact details identified)
NA: Not applicable

Table 57: Studies included in our previous systematic review which did not meet the inclusion criteria for this assessment

Study Details	Study Design	Setting	Population	Intervention/Index Test	Comparator	Reference Standard	Outcome
Dyson 2011[48]	Yes	Yes	No				
Eusufzai[49]	Yes	Yes	No				
Eusufzai 1993[50]	Yes	Yes	No				
Ford 1992[51]	Yes	Yes	No				
Nyhlin 1994[52]	Yes	Yes	No				
Odunsi-Shiyanbade 2010[53]	Yes	Yes	No				

APPENDIX 5: PRISMA CHECK LIST

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Preceding table of contents
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Section 2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Section 1
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Section 3.1.2 and paragraph 1 of section 3.1.5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Section 3.1.1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Section 3.1.3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Section 3.1.3
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Sections 3.1.2 and 3.1.3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Section 3.1.3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Section 3.1.4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Section 3.1.3
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Section 3.1.5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data	NA (narrative

Section and Topic	Item #	Checklist item	Location where item is reported
		conversions.	synthesis)
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Section 3.1.5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Section 3.1.5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA (narrative synthesis)
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA (narrative synthesis)
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA (narrative synthesis)
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA (narrative synthesis)
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1 and section 3.2.1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Appendix 4
Study characteristics	17	Cite each included study and present its characteristics.	Section 3.2.1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Section 3.2.2 and Appendix 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Sections 3.2.3 and 3.2.4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Section 3.2.2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA (narrative synthesis)
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA (narrative synthesis)
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA (narrative synthesis)
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA (narrative synthesis)
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA (narrative synthesis)

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Section 5.1.1
	23b	Discuss any limitations of the evidence included in the review.	Sections 5.2.1 and 5.3.1
	23c	Discuss any limitations of the review processes used.	Section 5.2.1
	23d	Discuss implications of the results for practice, policy, and future research.	Section 6.2
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	PROSPERO registration: CRD42020223877
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	PROSPERO
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA (no amendments)
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funded by NIHR
Competing interests	26	Declare any competing interests of review authors.	None
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	None

APPENDIX 6: QUESTIONNAIRE SENT TO CLINICAL EXPERTS

Questionnaire - treatment of patients with suspected bile acid diarrhoea

Introduction

KSR has been commissioned by NICE to evaluate the clinical and cost effectiveness of [^{75}Se] tauroselcholic acid (SeHCAT) in diagnosing bile acid diarrhoea (BAD). The current BSG guideline for chronic diarrhoea lists 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.

After the scoping phase, it was decided that the current evaluation should address the following two populations:

1. Adults presenting with chronic diarrhoea with unknown cause, suspected or diagnosed IBS-D or functional diarrhoea (i.e., people with suspected primary BAD)
2. Adults presenting with chronic diarrhoea and a diagnosis of Crohn's disease, who have not undergone ileal resection (i.e., people with suspected secondary BAD)

Our systematic review has revealed little published evidence is available to inform this evaluation, and therefore your expert opinion is of critical importance. To this end, we have prepared this structured questionnaire, which we kindly invite you to fill in where possible. This questionnaire is rather long (16 pages) but given the lack of formal evidence this was unavoidable. If you are aware of other relevant sources, such as published literature, conference abstracts, databases, etc. that provide information on one or more of the questions, we would be grateful if you could indicate them. We highly value your time and effort, which is key to the success of this project.

First population – adults with suspected primary bile acid diarrhoea

The place for SeHCAT that is currently under investigation is in adults (age ≥18 years) referred to a GI clinic for investigation and diagnosis of possible BAD, who have previously undergone primary clinical assessment/investigations (as recommended in the BSG guidelines) 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).

Specifically, we aim to compare the current scenario without SeHCAT, in which these patients, who possibly already receive treatment, for their suspected BAD-1, with a new scenario in which these patients undergo a diagnostic test for BAD using SeHCAT or trial of treatment with bile acid sequestrants (BAS).

In the current scenario, many treatment options are possible for patients with a suspected diagnosis of BAD-1. Your expert knowledge is required regarding the typical approach in the clinical management of these patients.

No SeHCAT available

1. Through the use of SeHCAT invasive diagnostic procedures such as colonoscopy are expected to be avoided. Therefore, we have assumed in our economic model that when SeHCAT is not available patients with suspected BAD-1 undergo colonoscopy to detect inflammatory bowel disease (IBD). Please provide an estimate of the percentage (average value and/or range) of patients with suspected BAD-1 that currently undergo colonoscopy for IBD. Additionally, please indicate what alternatives, if any, to colonoscopy and in what proportions are presented to these patients.

Colonoscopy: %
Range: % - %
Alternative 1 (please name it): %
Range: % - %
Please add more alternatives if needed

Patients who test negative for IBD with colonoscopy or who did not undergo colonoscopy are assumed to be treated as IBS-D patients

2. What percentage of patients with IBS-D receive a pharmaceutical treatment? (please also provide a range reflecting your uncertainty about the percentage).

%

Range: % - %

3. Please provide more details about the pharmaceutical treatments.

Type drug	dosage	Duration (If indefinite, please indicate. If limited period, please indicate duration)	% of patients	range
Please add rows if needed				

4. What percentage of patients with IBS-D will be given diet instructions at some point? (please also provide a range reflecting your uncertainty about the percentage)

% Range: % - %

5. Regarding the diet instructions, will these be simple instructions regarding e.g., the use of fibre intake, or do they entail visits to a dietician for more extensive dietary advice? In the latter case, please provide an estimate of the frequency of such referrals.

Visits dietician (as opposed to simple instructions)	%
Number of visits to dietician	…. visits

6. What percentage of patients with IBS-D receives some form of psychological treatment (e.g., cognitive behavioural therapy, hypnotherapy, etc.) at some point? (please also provide a range reflecting your uncertainty about the percentage)

% Range: % - %

7. Please provide more details about the psychological treatment.

Type of therapy	% of patients	range	Number of sessions

Please add rows if needed			

8. Please indicate what percentage of IBS-D patients will eventually be considered "successfully treated" i.e., responders.

% Range: % - %

9. Please indicate the average duration of the process to determine if treatment succeeds or not (e.g., 6 months, 1 year, longer than a year).

Time: Range:

10. How long do patients remain responders i.e., how long does it take until relapse?

Time: Range:

11. How many of these periods of response/relapse might be expected over a patient lifetime?

Time: Range:

Patients who test positive for IBD with colonoscopy are assumed to be treated as IBD patients

12. What percentage of IBD patients receives a pharmaceutical treatment? (please also provide a range reflecting your uncertainty about the percentage).

% Range: % - %

13. Please provide more details about the pharmaceutical treatments.

Type drug	dosage	Duration (If indefinite,	% of patients	range

		please indicate. If limited period, please indicate duration)		
Please add rows if needed				

14. What percentage of patients with IBD receive diet instructions? (please also provide a range reflecting your uncertainty about the percentage)

% Range: % - %

15. Regarding the diet instructions, will these be simple instructions regarding e.g., the use of fibre intake, or do they entail visits to a dietician for more extensive dietary advice? In the latter case, please provide an estimate of the frequency of such referrals.

Only simple diet instructions during regular consultation	%
Visits dietician	% …. visits

16. What percentage of patients with IBD receive some form of psychological treatment (e.g., cognitive behavioural therapy, hypnotherapy) at some point? (please also provide a range reflecting your uncertainty about the percentage)

% Range: % - %

17. Please provide more details about the psychological treatments.

Type of therapy	% of patients	range	Duration
Please add rows if needed			

18. Please indicate what percentage of IBD patients will eventually be considered as "successfully treated" i.e., responders?

% Range: % - %

19. Please indicate the average duration of the process to determine if treatment succeeds or not (e.g., 6 months, 1 year, longer than a year)?

Time: Range:

20. How long do patients remain responders i.e., how long does it take until relapse?

Time: Range:

21. How many of these periods of response/relapse might be expected over a patient lifetime?

Time: Range:

SeHCAT available

Until now, we have considered the situation that SeHCAT is not a diagnostic option. In the following questions, we will assume the new scenario, i.e. patients have had a SeHCAT test.

What is the threshold that you typically use to determine SeHCAT test positive (the decision threshold for offering treatment with BAS)?

SeHCAT BAD negative patients

Assume that the test finding was negative (i.e., the percentage bile acid absorption was above a threshold e.g., > 15%). However, the SeHCAT test does not have a 100% sensitivity and specificity (in respect of the test's ability to predict response to treatment with BAS), so it is reasonable to assume that some of these 'negative' patients do in fact have BAD. However, because of the negative test

result, they are now considered to have IBS-D. **Note: if some of the answers below depend on the SeHCAT threshold used, please specify your answer per threshold**.

22. What percentage of patients (if any) with a negative SeHCAT would undergo an invasive diagnostic procedure such as colonoscopy analogous to the scenario in which SeHCAT was not available?

Colonoscopy: %
Range: % - %
Alternative 1 (please name it): %
Range: % - %
Please add more alternatives if needed

23. Is the treatment of the negative SeHCAT patients the same as above in the situation without SeHCAT? If no, please describe?

Type drug	dosage	Duration (If indefinite, please indicate. If limited period, please indicate duration)	% of patients	range
Please add rows if needed				

24. Please indicate what percentage of IBS-D or IBD patients **with a SeHCAT negative** result will eventually be considered "successfully treated".

%
Range: % - %

25. Please indicate the average duration of the process to determine if treatment succeeds or not (e.g., 6 months, 1 year, longer than a year).

Time: Range:

26. How long do patients remain responders i.e., how long does it take until relapse?

Time: Range:

27. How many of these periods of response/relapse might be expected over a patient lifetime?

Time: Range:

28. What percentage of misdiagnosed patients (if any) would eventually be correctly diagnosed with BAD?

% Range: % - %

29. If eventually the patient is diagnosed with BAD, please indicate approximately the time period from first assessment to correct diagnosis (e.g., 6 months, 1 year, 3 years).

Time: Range:

SeHCAT BAD positive patients

We consider below the patients with a positive test result. We have assumed that these patients are treated with bile acid sequestrants (BAS). **Note: if some of the answers below depend on the SeHCAT threshold used, please specify your answer per threshold**.

30. Please provide details about the BAS treatments that are available to these patients.

Type drug	Dosage	Duration (If indefinite, please indicate. If limited period, please	% of patients	range

		indicate duration)		
cholestyramine				
colestipol				
colesevelam				
If anything else, please add.				

31. Results in the literature indicate that a certain percentage of patients with a diagnosis of BAD who are treated with BAS are unwilling or unable to take them Please provide the percentage of patients who would discontinue treatment due to intolerance. **Note: if the answer below depends on the BAS drug used, please specify your answer per BAS drug**.

% Range: % - %

32. When cholestyramine, colestipol or colesevelam are not an option or are not tolerated, are other (BAS or no BAS) treatments considered for BAD patients? If so, please indicate them.

Option 1: % Range: % - % Option 2: % Range: % - % Please add more alternatives if needed

33. What percentage of SeHCAT positive patients are "successfully" treated? **If this changes per SeHCAT threshold and treatment option, please indicate them separately**.

% Range: % - %

34. How long do patients remain responders i.e., how long does it take until relapse?

Time: Range:

35. How many of these periods of response/relapse might be expected over a patient lifetime?

Time: Range:

BAS trial of treatment patients

Finally, we consider the scenario of trial of treatment with BAS (no SeHCAT involved, therefore, it is unknown whether patients have BAD or not).

36. Please indicate what percentage receives each BAS as a trial of treatment.

Type drug	% of patients	range	dosage	Duration (If indefinite, please indicate. If limited period, please indicate duration)
cholestyramine				
colestipol				
colesevelam				
If anything else, please add.				

37. Please provide an estimate of the percentage of patients who would be "successfully treated" i.e., respond to BAS treatment. **<u>If this changes per treatment option, please indicate them separately.</u>**

% Range: % - %

38. How long do patients remain responders i.e., how long does it take until relapse?

Time: Range:

39. How many of these periods of response might be expected over a patient lifetime?

Time: Range:

40. What percentage of patients (if any) not responding to BAS treatment would undergo colonoscopy (or an alternative investigation), as in the scenario in which SeHCAT was not available?

Colonoscopy: % Range: % - % Alternative 1 (please name it): % Range: % - % Please add more alternatives if needed

Patients continuing to have chronic diarrhoea

41. For patients not responding to any form of previous treatment (IBS-D, IBD or BAS) and continuing to have chronic diarrhoea, what alternatives (and in what proportions) are offered as long-term treatment?

Alternative 1: % Range: % - % Alternative 2: % Range: % - % Please add more alternatives if needed

Second population – Crohn's disease without ileum resection

The second population for which SeHCAT testing is under consideration is for patients with Crohn's disease without ileal resection who have suspected (secondary) bile acid diarrhoea (BAD-2). For this population we have found less data (no additional data since the last assessment of SeHCAT), therefore, your input is even more valuable.

We start with the current scenario, in which we presume that patients with Crohn's disease without ileal resection have been referred to secondary care for investigation of possible BAD-2. We aim to compare the current scenario without SeHCAT, in which these patients, who possibly already receive treatment, for their suspected BAD-2, with a new scenario in which these patients undergo a diagnostic test for BAD using SeHCAT or trial of treatment with BAS.

We have some questions that are similar to the earlier questions, but now pertaining to this very different second population. One of the main differences with respect to the previous population is that now patients are known to have Crohn's disease. Therefore, it is assumed that these patients would not undergo any (additional) colonoscopy.

No SeHCAT available

1. What percentage of patients with suspected BAD-2 in Crohn's disease (without ileal resection) receives a pharmaceutical treatment? (please also provide a range reflecting your uncertainty about the percentage)

% Range: % - %

2. Please provide more details about the pharmaceutical treatments.

Type drug	% of patients	range	dosage	Duration (If indefinite, please indicate. If limited period, please indicate duration)
Please add rows if needed				

3. Are there any non-pharmaceutical treatment options available for these patients?

Option 1: %

Range: % - %   Option 2: %   Range: % - %   Please add more alternatives if needed

4. Can you indicate what percentage of Crohn's patients (without ileal resection) will eventually be considered "successfully treated" for BAD-2 i.e., responders?

%   Range: % - %

5. Please indicate the average duration of the process of reaching success (e.g., 1 months, 3 months, a year).

Duration: Range:

6. How long do patients remain responders i.e., how long does it take until relapse?

Time: Range:

7. How many of these periods of response might be expected over a patient lifetime?

Time: Range:

SeHCAT available

Until now, we have considered the situation that SeHCAT is not a diagnostic option. In the following questions, we will assume the <u>new scenario</u>, i.e. patients have had a SeHCAT test.

What is the threshold that you typically use to determine SeHCAT test positive?

SeHCAT BAD negative patients

Assume that the test finding was negative (i.e., the percentage bile acid absorption was above a threshold e.g. > 15%). However, the SeHCAT test does not have a 100% sensitivity and specificity (with respect to the ability of the test to predict response to treatment with BAS), so it is reasonable to assume that some of these 'negative' patients do in fact have BAD. However, because of the negative test result, they are now considered to have Crohn's disease and diarrhoea without a known cause. **Note: if some of the answers below depend on the SeHCAT threshold used, please specify your answer per threshold**.

8. Is the treatment of the negative SeHCAT patients the same as above in the situation without SeHCAT? If no, please describe.

Type drug	dosage	Duration (If indefinite, please indicate. If limited period, please indicate duration)	% of patients	range
Please add rows if needed				

9. Please indicate what percentage of these patients will eventually be considered "successfully treated".

%

Range: % - %

10. Please indicate the average duration of the process to determine if treatment succeeds or not (e.g., 6 months, 1 year, longer than a year).

Time:

Range:

11. How long do patients remain responders i.e., how long does it take until relapse?

Time: Range:

12. How many of these periods of response/relapse might be expected over a patient lifetime?

Time: Range:

13. What percentage of misdiagnosed patients (if any) would eventually be correctly diagnosed with BAD?

% Range: % - %

14. If eventually the patient is diagnosed with BAD, please indicate approximately the time period from first assessment to correct diagnosis (e.g., 6 months, 1 year, 3 years).

Time: Range:

SeHCAT BAD positive patients

We consider below the patients with a positive test result. We have assumed that these patients are treated with bile acid sequestrants (BAS). **Note: if some of the answers below depend on the SeHCAT threshold used, please specify your answer per threshold**.

15. Please provide details about the BAS treatments that are available to these patients.

Type drug	Dosage	Duration (If indefinite, please indicate. If limited period, please indicate duration)	% of patients	range
cholestyramine				
colestipol				
colesevelam				
If anything else, please add.				

16. Results in the literature indicate that a certain percentage of patients with a diagnosis of BAD who are treated with BAS are unwilling or unable to take them Please provide the percentage of patients who would discontinue treatment due to intolerance. **Note: if the answer below depends on the BAS drug used, please specify your answer per BAS drug.**

% Range: % - %

17. When cholestyramine, colestipol or colesevelam are not an option or are not tolerated, are other (BAS or no BAS) treatments considered for BAD patients? If so, please indicate them.

Option 1: % Range: % - % Option 2: % Range: % - % Please add more alternatives if needed

18. What percentage of Crohn's patients with SeHCAT positive are "successfully" treated? **If this changes per SeHCAT threshold and treatment option, please indicate them separately**.

% Range: % - %

19. How long do patients remain responders i.e., how long does it take until relapse?

Time: Range:

20. How many of these periods of response/relapse might be expected over a patient lifetime?

Time:

Range:

BAS trial of treatment patients

Finally, we consider the scenario of trial of treatment with BAS (no SeHCAT involved, therefore, it is unknown whether patients have BAD or not).

21. Please indicate what percentage receives each BAS as a trial of treatment.

Type drug	% of patients	range	dosage	Duration (If indefinite, please indicate. If limited period, please indicate duration)
cholestyramine				
colestipol				
colesevelam				
If anything else, please add.				

22. Please provide an estimate of the percentage of patients who would be "successfully treated" i.e., respond to BAS treatment. **If this changes per treatment option, please indicate them separately.**

% Range: % - %

23. How long do patients remain responders i.e., how long does it take until relapse?

Time: Range:

24. How many of these periods of response might be expected over a patient lifetime?

Time: Range:

Patients continuing to have chronic diarrhoea

25. For patients not responding to any form of previous treatment (Crohn's or BAS) and continuing to have chronic diarrhoea, what alternatives (and in what proportions) are offered as long-term treatment?

Alternative 1: %
Range: % - %
Alternative 2: %
Range: % - %
Please add more alternatives if needed

APPENDIX 7: DETAILS ON ESTIMATION MEDICATION COSTS BAS, IBS-D, IBD AND DIARRHOEA IN CROHN'S WITHOUT ILEAL RESECTION

Table 58: Responses expert to question which drugs are given to patients from the first population diagnosed as BAM

Expert	Drug	% of patients (lowest-highest)	Dosage/frequency	Total dosage per day (expert)	Dosage per day (model)*	Price per unit	Costs per day
A	cholestyramine	50	2-8g/day	2-8g	5g	£0.28 per 4g	£0.35
A	colesevelam	50	625mg twice a day or 4 doses a day	1250-2500mg	2500mg	£0.64 per 625mg	£2.56
B	cholestyramine	50 (40-60)	2-8g daily	2-8g	5g	£0.28 per 4g	£0.35
B	colesevelam	50 (40-60)	625mg upto 6/day	3750mg	2500mg	£0.64 per 625mg	£2.56
C	colesevelam	100	625mg tds	1875mg	2500mg	£0.64 per 625mg	£2.56

* Dosage per day is taken as average of all expert's answers
Abbreviations: g = grams; mg = milligrams; tds = three times a day.

Table 59: Responses expert to question which BAS trial of treatment drugs are given to patients

Expert	Drug	% of patients (lowest-highest)	Dosage/frequency	Total dosage per day (expert)	Dosage per day (model)**	Price per unit	Costs per day
D	Cholestyramine	85 (70-95)	2g-8g/day	5g	5g	£0.28 per 4g	£0.35
	Colesevelam	10 (10-20)	1250mg-2500mg	2500mg	2500mg	£0.64 per 625mg	£2.56
F	Colesevelam	100	1875mg*	2500mg	2500mg	£0.64 per 625mg	£2.56

*Dosage assumed to be the same as BAS treatment with SeHCAT available
** Dosage per day is taken as average of all expert's answers
Abbreviations: g = grams; mg = milligrams.

Table 60: Responses experts to question which drugs are given to patients diagnosed as IBS-D

Expert	Drug	% of patients (lowest-highest)	Dosage/frequency	Total dosage per day (expert)	Dosage per day (model)*	Price per unit	Costs per day
G	buscopan	10 (1-15)	10 BD PRN	20mg	20mg	0.05 per 10 mg	0.11
G	loperamide	20 (2-25)	1-2 per day	1-2 per day	2mg	0.05 per 2 mg	0.05
G	amitriptyline	20 (15-35)	5-10mg	5-10mg	11mg	0.04 per 10mg	0.04
H	loperamide	50 (20-75)	2mg prn	2mg	2mg	0.05 per 2 mg	0.05
H	codeine	5 (2-10)	30mg prn	30mg	75mg	0.05 per 30 mg	0.12
H	amitriptyline	3 (1-5)	10mg+	10mg	11mg	0.21 per 4 mg	0.04
H	buscopan	20 (10-40)	NR		20mg	0.05 per 10 mg	0.11
I	loperamide	100	2mg	2mg	2mg	0.05 per 2 mg	0.05
I	TCA, assume amitriptyline	50	NR	8mg	11mg	0.04 per 10mg	0.04
J	amitriptyline	NR	10-20mg	10-20mg	11mg	0.04 per 10mg	0.04
J	loperamide	NR	2mg prn. Max 16mg/d		2mg	0.05 per 2 mg	0.05
J	Codeine	NR	30mg qds prn	120mg	75mg	0.05 per 30 mg	0.12

* Dosage per day is taken as average of all expert's answers

Abbreviations: BD = twice a day; PRN = pro re nata (prescription is taken as needed); qds = four times a day; mg = milligram; NR = not reported

Note: Alverine and mebeverine were excluded, as full information was not reported.

Table 61: Responses experts to question which drugs are given to patients diagnosed as IBD

Expert	Drug	% of patients (lowest-highest)	Dosage/frequency	Total dosage per day (expert)	Dosage per day (model)***	Price per unit	Costs per day
K	asacol	80 (70-90)	4.8 grams	4.8 grams	4.8g	0.65 per 0.8g	3.92
K	octasa	80 (70-90)	4.8 grams	4.8 grams	4.8g	0.45 per 0.8g	2.69
K	pentasa	80 (70-90)	4 grams	4 grams	4g	0.61 per 1g	2.46
K	azathioprine	50 (40-60)	2.5mg/kg weight adjusted	2.5mg/kg weight adjusted	2.3mg/kg	0.06 per 50mg	0.20
K	Infliximab*	20 (10-30)	10mg/kg every 8 weeks	14mg	14mg	377 per 100mg	49.01
K	Adalimumab**	20 (10-30)	40mg EOW	3mg	3mg	316.80 per 40mg	22.88
L	azathioprine	50 (40-60)	2mg/kg	2mg/kg	2.3mg/kg	0.06 per 50mg	0.20

* Maintenance schedule of infusions every 8 weeks was assumed

** Maintenance schedule of infusions every 2 weeks was assumed

***Dosage per day is taken as average of all expert's answers

Abbreviations: g = grams; mg = milligrams; kg = kilograms; EOW = every other week.

Note: Answers without full information were not reported. For weight-adjusted medication, a body weight of 78 kg was assumed, based on previous SeHCAT report.

Table 62: Responses expert to question which drugs are given to patients from the second population diagnosed as BAM

Expert	Drug	% of patients (lowest-highest)	Dosage/frequency	Total dosage per day (expert)	Dosage per day (model)*	Price per unit	Costs per day
M	cholestyramine	30 (10-50)	2-4g	2-8g	5g	£0.28 per 4g	£0.35
M	colesevelam	50	625mg 2 to 4 a day	1250-2500mg	2500mg	£0.64 per 625mg	£2.56
N	cholestyramine	70 (50-80)	2-8g daily	2-8g	5g	£0.28 per 4g	£0.35
N	colesevelam	30 (20-50)	625mg upto 6/day	3750mg	2500mg	£0.64 per 625mg	£2.56
O	colesevelam	10	625mg tds	1875mg	2500mg	£0.64 per 625mg	£2.56

* Dosage per day is taken as average of all expert's answers
Abbreviations: g = grams; mg = milligrams; tds = three times a day.

Table 63: Responses experts to question which drugs are given to patients with Crohn's without ileal resection with chronic diarrhoea

Expert	Drug	% of patients (lowest-highest)	Dosage/frequency	Total dosage per day (expert)	Dosage per day (model)*	Price per unit	Costs per day
P	loperamide	80 (50-100)	2–16 mg	2–16 mg	5 mg	0.05 per 2 mg	0.13
P	codeine	20 (0-50)	30–120 mg	30–120 mg	75 mg	0.05 per 30 mg	0.12
P	corticosteroids	70 (50-100)	40 mg prednisolone/ 9 mg budesonide	40 mg prednisolone/ 9 mg budesonide	40 mg prednisolone/ 9 mg budesonide	0.13 per 20mg predsnisolone 2.50 per 9mg budesonide	1.38
P	Anti-TNF-α adalimumab	10 (0-30)	40 mg EOW**	3mg	3mg	316.80 per 40mg	22.88
Q	Pentasa® (Ferring)	0.6 (0.4–0.7)	4 g per day	4g	4g	0.61 per 1 g	2.46
Q	Azathioprine	0.5 (0.2–0.7)	2 mg/kg per day	156 mg (assume average weight 78)	156 mg (assume	0.06 per 50mg	0.17

Expert	Drug	% of patients (lowest-highest)	Dosage/frequency	Total dosage per day (expert)	Dosage per day (model)*	Price per unit	Costs per day
					average weight 78)		
Q	Corticosteroids	0.8 (0.6–1)	40 mg prednisolone/ 9 mg budesonide	40 mg prednisolone/ 9 mg budesonide	40 mg prednisolone/ 9 mg budesonide	0.13 per 20mg predsnisolone 2.50 per 9mg budesonide	1.38
Q	Anti-TNF-α adalimumab	0.1 (0–0.15)	40 mg EOW**	3mg	3mg	316.80 per 40mg	22.88
Q	BAS	0.2 (0.05–0.4)			5g cholestyramine / 2.5g colesevelam	0.28 per 4g cholestyramine 0.64 per 625mg colesevelam	1.46
R	Codeine	0.5 (0.4–0.8)	30–120 mg	30–120 mg	75 mg	0.05 per 30 mg	0.12
R	Loperamide	0.5 (0.4–0.8)	2–8 mg	5mg	5mg	0.05 per 2 mg	0.13
S	BAS	0.8 (0.7–0.9)			5g cholestyramine / 2.5g colesevelam	0.28 per 4g cholestyramine 0.64 per 625mg colesevelam	1.46
S	Loperamide	0.3 (0.25–0.35)	2–4 mg OD–t.i.d.	2–12 mg	5mg	0.05 per 2 mg	0.13
T	Codeine	0.5 (0.4–0.8)	30–120 mg	30–120 mg	75 mg	0.05 per 30 mg	0.12
T	Loperamide	0.8 (0.5–1)	2–4 mg OD–t.i.d.	2–12 mg	5mg	0.05 per 2 mg	0.13

Expert	Drug	% of patients (lowest-highest)	Dosage/frequency	Total dosage per day (expert)	Dosage per day (model)*	Price per unit	Costs per day
T	Corticosteroids	0.8 (0.6–1)	40 mg prednisolone/ 9 mg budesonide	40 mg prednisolone/ 9 mg budesonide	40 mg prednisolone/ 9 mg budesonide	0.13 per 20mg predsnisolone 2.50 per 9mg budesonide	1.38
T	BAS	0.8 (0.7–0.9)			5g cholestyramine / 2.5g colesevelam	0.28 per 4g cholestyramine 0.64 per 625mg colesevelam	1.46

***** Dosage per day is taken as average of all expert's answers

** Maintenance schedule of infusions every 2 weeks was assumed

Abbreviations: g = grams; mg = milligrams; tds = three times a day; OD = once a day; t.i.d. = ter in die (three times a day).

APPENDIX 8: FULL COST EFFECTIVENESS RESULTS (TABLES ONLY)

Cost effectiveness results for all scenarios in both populations are summarised in this appendix.

Population 1

Table 64: Base-case cost effectiveness results, population 1

	Colo. avoided	Response	Initial costs	QALYs	Total Costs	Inc. QALYs	Inc. costs	ICER
No SeHCAT	26%	47%	£557	13.8242	£4,720			
BAS TOT	37%	65%	£507	14.0096	£7,449	Dominated by SeHCAT 15%		
SeHCAT 15%	65%	68%	£786	14.0550	£6,956	0.2308	£2,236	£9,688

Abbreviations: BAS = bile acid sequestrants, Colo. = colonoscopy, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, SeHCAT = Tauroselcholic [^{75}Selenium] acid, TOT = trial of treatment.

Note: Percentage of colonoscopies avoided per patient. Percentage of response to any medication (thus, IBS-D, IBD or BAS). Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

Table 65: Secondary analysis cost effectiveness results (no colonoscopy), population 1

	Colo. avoided	Response	Initial costs	QALYs	Total Costs	Inc. QALYs	Inc. Costs	ICER
No SeHCAT	NA	44%	£59	13.8026	£374			
BAS TOT	NA	63%	£85	13.9825	£3,767	0.1799	£3,393	£18,860
SeHCAT 15%	NA	67%	£553	14.0408	£4,922	0.0583	£1,115	£19,125

Abbreviations: BAS = bile acid sequestrants, Colo. = colonoscopy, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, SeHCAT = Tauroselcholic [^{75}Selenium] acid, TOT = trial of treatment.

Note: Percentage of colonoscopies avoided per patient. Percentage of response to any medication (thus, IBS-D, IBD or BAS). Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

Table 66: PSA base-case cost effectiveness results, population 1

	Colo. Avoided	Response	Initial costs	QALYs	Total Costs	Inc. QALYs	Inc. costs	ICER
No SeHCAT	26%	46%	£560	13.8236	£4,687			
BAS TOT	37%	66%	£564	14.0151	£7,431	Dominated by SeHCAT 15%		
SeHCAT 15%	65%	68%	£826	14.0623	£6,993	0.2387	£2,306	£9,661

Abbreviations: BAS = bile acid sequestrants, Colo. = colonoscopy, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, SeHCAT = Tauroselcholic [^{75}Selenium] acid, TOT = trial of treatment.

Note: Percentage of colonoscopies avoided per patient. Percentage of response to any medication (thus, IBS-D, IBD or BAS). Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

Table 67: PSA secondary analysis cost effectiveness results (no colonoscopy), population 1

	Colo. Avoided	Response	Initial costs	QALYs	Total Costs	Inc. QALYs	Inc. Costs	ICER
No SeHCAT	NA	44%	£62	13.8021	£374			
BAS TOT	NA	63%	£143	13.9893	£3,806	0.1871	£3,432	£18,343
SeHCAT 15%	NA	67%	£596	14.0539	£5,168	0.0647	£1,361	£21,036

Abbreviations: BAS = bile acid sequestrants, Colo. = colonoscopy, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, SeHCAT = Tauroselcholic [^{75}Selenium] acid, TOT = trial of treatment.

Note: Percentage of colonoscopies avoided per patient. Percentage of response to any medication (thus, IBS-D, IBD or BAS). Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

Table 68: Results of colonoscopy scenarios, population 1

	Colo. avoided	Response	Initial costs	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
Base-case (No SeHCAT = 74%, SeHCAT 15% = 49%, BAS TOT = 90%)								
No SeHCAT	26%	47%	£557	13.8242	£4,720			
BAS TOT	37%	65%	£507	14.0096	£7,449	Dominated by SeHCAT 15%		
SeHCAT 15%	65%	68%	£786	14.0550	£6,956	0.2308	£2,236	£9,688
Colonoscopy scenario 1 (secondary analysis, no colonoscopy)								
No SeHCAT	NA	44%	£59	13.8026	£374			
BAS TOT	NA	63%	£85	13.9825	£3,767	0.1799	£3,393	£18,860
SeHCAT 15%	NA	67%	£553	14.0408	£4,922	0.0583	£1,115	£19,125
Colonoscopy scenario 2 (No SeHCAT = 100%, SeHCAT 15% = 100%, BAS TOT = 100%)								
No SeHCAT	0%	47%	£727	13.832	£6,210			
BAS TOT	30%	66%	£554	14.013	£7,863	0.181	£1,653	£9,136
SeHCAT 15%	29%	69%	£1,028	14.070	£9,069	0.057	£1,206	£21,140

Abbreviations: BAS = bile acid sequestrants, Colo. = colonoscopy, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.

Note: Percentage of colonoscopies avoided per patient. Percentage of response to any medication (thus, IBS-D, IBD or BAS). Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

Table 69: Results of IBS-D response scenarios, population 1

	Response	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
Base-case						
No SeHCAT	47%	13.8242	£4,720			
BAS TOT	65%	14.0096	£7,449	Dominated by SeHCAT 15%		
SeHCAT 15%	68%	14.0550	£6,956	0.2308	£2,236	£9,688
IBS-D scenario 1 (response No SeHCAT increased = response BAS TOT)						
No SeHCAT	50%	13.8660	£4,728			
BAS TOT	65%	14.0096	£7,449	Dominated by SeHCAT 15%		
SeHCAT 15%	68%	14.0550	£6,956	0.189	£2,228	£11,788
IBS-D scenario 2 (response BAS TOT increased = response No SeHCAT, response No SEHCAT as in scenario 1)						
No SeHCAT	50%	13.8660	£4,728			
SeHCAT 15%	68%	14.0550	£6,956	0.1890	£2,228	£11,788
BAS TOT	69%	14.0558	£7,458	0.0008	£502	£627,500
IBS-D scenario 3 (equal response in the three strategies, equal to SeHCAT 15%)						
No SeHCAT	56%	13.9323	£4,741			
SeHCAT 15%	68%	14.0550	£6,956	0.1227	£2,215	£18,052
BAS TOT	69%	14.0558	£7,458	0.0008	£502	£627,500
IBS-D scenario 4 (No SeHCAT = 70%, SeHCAT and BAS TOT per base-case)						
BAS TOT	65%	14.0096	£7,449	Dominated by SeHCAT 15%		
SeHCAT 15%	68%	14.0550	£6,956	Dominated by No SeHCAT		
No SeHCAT	69%	14.0892	£4,771			

Abbreviations: BAS = bile acid sequestrants, Colo. = colonoscopy, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment. Note: Percentage of colonoscopies avoided per patient. Percentage of response to any medication (thus, IBS-D, IBD or BAS). Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

Table 70: Results of SeHCAT positive and response to BAS scenarios, population 1

	Colo. avoided	Response	Initial costs	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
Base-case (SeHCAT + = 0.454, BAS response | SeHCAT + = 0.638, BAS TOT response = 0.299)								
No SeHCAT	26%	47%	£557	13.8242	£4,720			
BAS TOT	37%	65%	£507	14.0096	£7,449	Dominated by SeHCAT 15%		
SeHCAT 15%	65%	68%	£786	14.0550	£6,956	0.2308	£2,236	£9,688
Scenario 1 (SeHCAT + = 0.357, BAS response | SeHCAT + = 0.495, BAS TOT response = 0.299)								
No SeHCAT	26%	47%	£557	13.8242	£4,720			
SeHCAT 15%	60%	63%	£819	14.0031	£5,702	0.1789	£982	£5,489
BAS TOT	37%	65%	£507	14.0096	£7,449	0.0064	£1,747	£272,969
BAS scenario 2 (SeHCAT + = 0.555, BAS response | SeHCAT + = 0.760, BAS TOT response = 0.299)								
No SeHCAT	26%	47%	£557	13.8242	£4,720			
BAS TOT	37%	65%	£507	14.0096	£7,449	Ext. dominated by SeHCAT 15%		
SeHCAT 15%	72%	74%	£748	14.1156	£8,423	0.2914	£3,703	£12,708
BAS scenario 3 (SeHCAT + = 0.454, BAS response | SeHCAT + = 0.638, BAS TOT response = 0.20)								
No SeHCAT	26%	47%	£557	13.8242	£4,720			
BAS TOT	28%	61%	£566	13.9644	£6,857	Ext. dominated by SeHCAT 15%		
SeHCAT 15%	65%	68%	£786	14.0550	£6,956	0.2307	£2,236	£9,692
BAS scenario 4 (SeHCAT + = 0.454, BAS response | SeHCAT + = 0.638, BAS TOT response = 0.40)								
No SeHCAT	26%	47%	£557	13.8242	£4,720			
SeHCAT 15%	65%	68%	£786	14.0550	£6,956	0.2307	£2,236	£9,692
BAS TOT	46%	70%	£446	14.0561	£8,059	0.0012	£1,103	£919,167

Abbreviations: BAS = bile acid sequestrants, Colo. = colonoscopy, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment. Note: Percentage of colonoscopies avoided per patient. Percentage of response to any medication (thus, IBS-D, IBD or BAS). Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

Table 71: Results of distribution of BAS treatment scenarios, population 1

	Colo. avoided	Response	Initial costs	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
Base-case (SeHCAT = 50/50, BAS TOT = 85/15)								
No SeHCAT	26%	47%	£557	13.8242	£4,720			
BAS TOT	37%	65%	£507	14.0096	£7,449	Dominated by SeHCAT 15%		
SeHCAT 15%	65%	68%	£786	14.0550	£6,956	0.2308	£2,236	£9,688
Scenario 1 (cholestyramine only, SeHCAT = 100/0, BAS TOT = 100/0)								
No SeHCAT	26%	47%	£557	13.8242	£4,720			
BAS TOT	37%	65%	£504	14.0027	£7,077	Dominated by SeHCAT 15%		
SeHCAT 15%	65%	68%	£779	14.0339	£5,813	0.2097	£1,094	£5,217
BAS scenario 2 (colesevelam only, SeHCAT = 0/100, BAS TOT = 0/100)								
No SeHCAT	26%	47%	£557	13.8242	£4,720			
BAS TOT	37%	65%	£520	14.0461	£9,432	Dominated by SeHCAT 15%		
SeHCAT 15%	65%	68%	£794	14.0760	£8,098	0.252	£3,378	£13,405
BAS scenario 3 (SeHCAT = 50/50, BAS TOT = 50/50)								
No SeHCAT	26%	47%	£557	13.8242	£4720			
BAS TOT	37%	65%	£512	14.0244	£8255	Dominated by SeHCAT 15%		
SeHCAT 15%	65%	68%	£786	14.0550	£6956	0.2307	£2,236	£9,692
BAS scenario 4 (SeHCAT = 85/15, BAS TOT = 85/15)								
No SeHCAT	26%	47%	£557	13.8242	£4720			
BAS TOT	37%	65%	£506	14.0092	£7430	Dominated by SeHCAT 15%		
SeHCAT 15%	65%	68%	£781	14.0402	£6156	0.2160	£1,436	£6,648

Abbreviations: BAS = bile acid sequestrants, Colo. = colonoscopy, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment. Note: Percentage of colonoscopies avoided per patient. Percentage of response to any medication (thus, IBS-D, IBD or BAS). Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

Table 72: Utility scenario results, population 1

	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
Base-case					
No SeHCAT	13.8242	£4720			
BAS TOT	14.0096	£7449	Dominated by SeHCAT 15%		
SeHCAT 15%	14.0550	£6956	0.2308	2236	£9,688
Cholestyramine BAS response equal to full diarrhoea decrement					
No SeHCAT	13.8242	£4720			
BAS TOT	14.0472	£7449	Dominated by SeHCAT 15%		
SeHCAT 15%	14.0771	£6956	0.2529	2236	£8,841
Utility values based on Mearin et al. (2004)[58]					
No SeHCAT	13.7360	£4720			
BAS TOT	13.9440	£7449	Dominated by SeHCAT 15%		
SeHCAT 15%	13.9950	£6956	0.259	2236	£8,633
Utility values based on Spiegel et al. (2009)[57]					
No SeHCAT	14.0395	£4720			
BAS TOT	14.1860	£7449	Dominated by SeHCAT 15%		
SeHCAT 15%	14.2218	£6956	0.1823	2236	£12,265
No age adjustment					
No SeHCAT	14.7992	£4720			
BAS TOT	14.9977	£7449	Dominated by SeHCAT 15%		
SeHCAT 15%	15.0464	£6956	0.2472	2236	£9,045

Abbreviations: BAS = bile acid sequestrants, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment. Note: Percentage of colonoscopies avoided per patient. Percentage of response to any medication (thus, IBS-D, IBD or BAS). Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

Table 73: Cost scenario results, population 1

	QALYs	Costs	Incr. QALYs	Incr. Costs	ICER
Base-case					
No SeHCAT	13.8242	£4720			
BAS TOT	14.0096	£7449	Dominated by SeHCAT 15%		
SeHCAT 15%	14.055	£6956	0.2308	£2236	£9,688
Decrease cost of BAS treatment by 20%					
No SeHCAT	13.8242	£4720			
BAS TOT	14.0096	£6749	Dominated by SeHCAT 15%		
SeHCAT 15%	14.055	£6123	0.2308	£1403	£6,079
Increase cost of BAS treatment by 20%					
No SeHCAT	13.8242	£4720			
BAS TOT	14.0096	£8149	Dominated by SeHCAT 15%		
SeHCAT 15%	14.055	£7789	0.2308	£3069	£13,297
Decrease cost of colonoscopy by 20%					
No SeHCAT	13.8242	£4654			
BAS TOT	14.0096	£7394	Dominated by SeHCAT 15%		
SeHCAT 15%	14.055	£6925	0.2308	£2271	£9,840
Increase cost of colonoscopy by 20%					
No SeHCAT	13.8242	£4785			
BAS TOT	14.0096	£7504	Dominated by SeHCAT 15%		
SeHCAT 15%	14.055	£6987	0.2308	2202	£9,541
Decrease cost of IBD dietician by 20%					
No SeHCAT	13.8242	£4719			
BAS TOT	14.0096	£7448	Dominated by SeHCAT 15%		
SeHCAT 15%	14.055	£6955	0.2308	£2236	£9,688

	QALYs	Costs	Incr. QALYs	Incr. Costs	ICER
Increase cost of IBD dietician by 20%					
No SeHCAT	13.8242	£4721			
BAS TOT	14.0096	£7450	Dominated by SeHCAT 15%		
SeHCAT 15%	14.055	£6957	0.2308	£2236	£9,688
Decrease cost of IBD medication by 20%					
No SeHCAT	13.8242	£3918			
BAS TOT	14.0096	£6770	Dominated by SeHCAT 15%		
SeHCAT 15%	14.055	£6581	0.2308	£2663	£11,538
Increase cost of IBD medication by 20%					
No SeHCAT	13.8242	£5522			
BAS TOT	14.0096	£8128	Dominated by SeHCAT 15%		
SeHCAT 15%	14.055	£7331	0.2308	£1809	£7,838
Decrease cost of IBD psychological treatment by 20%					
No SeHCAT	13.8242	£4718			
BAS TOT	14.0096	£7447	Dominated by SeHCAT 15%		
SeHCAT 15%	14.055	£6955	0.2308	£2237	£9,692
Increase cost of IBD psychological treatment by 20%					
No SeHCAT	13.8242	£4722			
BAS TOT	14.0096	£7451	Dominated by SeHCAT 15%		
SeHCAT 15%	14.055	£6957	0.2308	£2235	£9,684
Decrease cost of IBS-D dietician by 20%					
No SeHCAT	13.8242	£4718			
BAS TOT	14.0096	£7447	Dominated by SeHCAT 15%		
SeHCAT 15%	14.055	£6954	0.2308	£2236	£9,688
Increase cost of IBS-D dietician by 20%					
No SeHCAT	13.8242	£4722			

	QALYs	Costs	Incr. QALYs	Incr. Costs	ICER
BAS TOT	14.0096	£7451	Dominated by SeHCAT 15%		
SeHCAT 15%	14.055	£6958	0.2308	£2236	£9,688
Decrease cost of IBS-D medication by 20%					
No SeHCAT	13.8242	£4679			
BAS TOT	14.0096	£7418	Dominated by SeHCAT 15%		
SeHCAT 15%	14.055	£6921	0.2308	£2242	£9,714
Increase cost of IBS-D medication by 20%					
No SeHCAT	13.8242	£4761			
BAS TOT	14.0096	£7480	Dominated by SeHCAT 15%		
SeHCAT 15%	14.055	£6991	0.2308	£2230	£9,662
Decrease cost of IBS-D psychological treatment by 20%					
No SeHCAT	13.8242	£4713			
BAS TOT	14.0096	£7444	Dominated by SeHCAT 15%		
SeHCAT 15%	14.055	£6951	0.2308	£2238	£9,697
Increase cost of IBS-D psychological treatment by 20%					
No SeHCAT	13.8242	£4727			
BAS TOT	14.0096	£7454	Dominated by SeHCAT 15%		
SeHCAT 15%	14.055	£6961	0.2308	£2234	£9,679
Decrease SeHCAT cost by 20%					
No SeHCAT	13.8242	£4720			
BAS TOT	14.0096	£7449	Dominated by SeHCAT 15%		
SeHCAT 15%	14.055	£6861	0.2308	£2141	£9,276
Increase SeHCAT cost by 20%					
No SeHCAT	13.8242	£4720			
BAS TOT	14.0096	£7449	Dominated by SeHCAT 15%		
SeHCAT 15%	14.055	£7051	0.2308	£2331	£10,100

	QALYs	Costs	Incr. QALYs	Incr. Costs	ICER
Abbreviations: BAS = bile acid sequestrants, IBD = irritable bowel disease, IBS-D = irritable bowel syndrome with diarrhoea, ICER = incremental cost effectiveness ratio, Incr. = incremental, QALY = quality adjusted life year, SeHCAT = Tauroselcholic [^{75}Selenium] acid, ToT = trial of treatment.					

Table 74: Results of transition probability scenarios, population 1

	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
Base-case (relapse in IBD model only, p = 0.0045)					
No SeHCAT	13.8242	£4,720			
BAS TOT	14.0096	£7,449	Dominated by SeHCAT 15%		
SeHCAT 15%	14.0550	£6,956	0.2308	£2,236	£9,688
Scenario 1 (relapse in IBD, IBS-D and BAS models, p = 0.0045)					
No SeHCAT	13.7687	£4,708			
BAS TOT	13.9335	£7,048	Dominated by SeHCAT 15%		
SeHCAT 15%	13.9728	£6,475	0.2041	£1,767	£8,658
BAS scenario 2 (relapse and remission in IBD, IBS-D and BAS models, p = 0.0045)					
No SeHCAT	13.8358	£4,944			
BAS TOT	13.9803	£7,278	Dominated by SeHCAT 15%		
SeHCAT 15%	14.0171	£6,628	0.1813	£1,684	£9,288
BAS scenario 3 (relapse in IBD, IBS-D and BAS models, p = 0.0045*2)					
No SeHCAT	13.7193	£4,281			
BAS TOT	13.8674	£6,361	Dominated by SeHCAT 15%		
SeHCAT 15%	13.9028	£5,881	0.1834	£1,600	£8,724
BAS scenario 4 (relapse in IBD, IBS-D and BAS models, p = 0.0045*5)					
No SeHCAT	13.6124	£3,366			
BAS TOT	13.7244	£4,890	Dominated by SeHCAT 15%		
SeHCAT 15%	13.7511	£4,608	0.1387	£1,243	£8,962

Abbreviations: BAS = bile acid sequestrants, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.

Table 75: Results of mortality scenario, population 1

	QALYs	Total Costs	Inc. QALYs	Inc. Costs	ICER
Base-case (no excess mortality)					
No SeHCAT	13.8242	£4,720			
BAS TOT	14.0096	£7,449	Dominated by SeHCAT 15%		
SeHCAT 15%	14.0550	£6,956	0.2308	£2,236	£9,688
Scenario 1 (SMR = 1.52, per Crohn's disease)					
No SeHCAT	13.0241	£4,478			
BAS TOT	13.1986	£7,021	Dominated by SeHCAT 15%		
SeHCAT 15%	13.2413	£6,567	0.2172	£2,089	£9,618

Abbreviations: BAS = bile acid sequestrants, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.

Population 2

Table 76: Base-case results, population 2

	Response	Initial costs	QALYs	Total Costs	Inc. QALYs	Inc. costs	ICER
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	60%	£756	12.9008	£13,946			
SeHCAT 15%	71%	£1,061	13.0079	£14,131	0.1071	£185	£1,727

Abbreviations: BAS = bile acid sequestrants, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, TOT = trial of treatment, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.

Note: Percentage of response to any medication. Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

Table 77: PSA base-case results, population 2

	Response	Initial costs	QALYs	Total Costs	Inc. QALYs	Inc. costs	ICER
No SeHCAT	40%	£1,180	12.6857	£15,686	Dominated by BAS TOT		
BAS TOT	60%	£895	12.9006	£14,880	Dominated by SeHCAT 15%		
SeHCAT 15%	71%	£1,172	13.0084	£14,795			

Abbreviations: BAS = bile acid sequestrants, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, TOT = trial of treatment, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.

Note: Percentage of response to any medication. Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

Table 78: Results of response to diarrhoea treatment without BAS scenarios, population 2

	Response	Initial costs	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
Base-case (No SeHCAT = 40%, SeHCAT 15% = 42%, BAS TOT = 41%)							
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	60%	£756	12.9008	£13,946			
SeHCAT 15%	71%	£1,061	13.0079	£14,131	0.1071	£185	£1,727
Diarrhoea treatment w/o BAS scenario 1 (No SeHCAT = 42%, SeHCAT 15% = 42%, BAS TOT = 42%)							
No SeHCAT	42%	£1,052	12.7059	£15,078	Dominated by BAS TOT		
BAS TOT	61%	£756	12.9075	£14,171	Dominated by SeHCAT 15%		
SeHCAT 15%	71%	£1,061	13.0079	£14,131			
Diarrhoea treatment w/o BAS scenario 2 (No SeHCAT = 70%, SeHCAT 15% = 42%, BAS TOT = 70%)							
No SeHCAT	70%	£1,052	12.9809	£24,295	Dominated by SeHCAT 15%		
SeHCAT 15%	71%	£1,061	13.0079	£14,131			
BAS TOT	80%	£756	13.0925	£20,373	0.0847	£6,241	£73,684

Abbreviations: BAS = bile acid sequestrants, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, TOT = trial of treatment, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.

Note: Percentage of response to any medication. Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

Table 79: Results of SeHCAT positive and response to BAS scenarios, population 2

	Response	Initial costs	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
Base-case (SeHCAT + = 0.55, BAS response | SeHCAT + = 0.89, BAS TOT response = 0.339)							
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	60%	£756	12.9008	£13,946			
SeHCAT 15%	71%	£1,061	13.0079	£14,131	0.1071	£185	£1,727
Scenario 1 (SeHCAT + = 0.39, BAS response | SeHCAT + = 0.67, BAS TOT response = 0.33)							
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by BAS TOT		
SeHCAT 15%	58%	£1,282	12.8700	£14,893	Dominated by BAS TOT		
BAS TOT	60%	£756	12.9008	£13,946			
BAS scenario 2(SeHCAT + = 0.71, BAS response | SeHCAT + = 1, BAS TOT response = 0.33)							
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	60%	£756	12.9008	£13,946	Dominated by SeHCAT 15%		
SeHCAT 15%	83%	£848	13.1411	£13,396			
BAS scenario 3 (SeHCAT + = 0.55, BAS response | SeHCAT + = 0.89, BAS TOT response = 0.23)							
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	55%	£852	12.8399	£14,190	Dominated by SeHCAT 15%		
SeHCAT 15%	71%	£1,061	13.0079	£14,131			
BAS scenario 4 (SeHCAT + = 0.55, BAS response | SeHCAT + = 0.89, BAS TOT response = 0.5)							
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by SeHCAT 15%		
SeHCAT 15%	71%	£1,061	13.0079	£14,131	Dominated by BAS TOT		
BAS TOT	70%	£586	13.0090	£13,511			

Abbreviations: BAS = bile acid sequestrants, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, TOT = trial of treatment, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.
Note: Percentage of response to any medication. Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

Table 80: Results of distribution of BAS treatment scenarios, population 2

	Response	Initial costs	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
Base-case (SeHCAT = 63/37, BAS TOT = 58/42)							
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	60%	£756	12.9008	£13,946			
SeHCAT 15%	71%	£1,061	13.0079	£14,131	0.1071	£185	£1,727
Scenario 1 (cholestyramine only, SeHCAT = 100/0, BAS TOT = 100/0)							
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	60%	£748	12.8798	£12,825	Dominated by SeHCAT 15%		
SeHCAT 15%	71%	£1,050	12.9792	£12,601			
BAS scenario 2 (colesevelam only, SeHCAT = 0/100, BAS TOT = 0/100)							
No SeHCAT	40%	£1,052	12.6863	£14,419			
BAS TOT	60%	£767	12.9307	£15,539	0.2444	£1120	£4,581
SeHCAT 15%	71%	£1,079	13.0553	£16,662	0.1247	£1123	£9,009
BAS scenario 3 (SeHCAT = 63/37, BAS TOT = 63/37)							
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	60%	£755	12.8989	£13,847			
SeHCAT 15%	71%	£1,061	13.0079	£14,131	0.189	£284	£2,608
BAS scenario 4 (SeHCAT = 58/42, BAS TOT = 58/42)							
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	60%	£756	12.9008	£13,946			
SeHCAT 15%	71%	£1,062	13.0106	£14,279	0.1098	£333	£3,030

Abbreviations: BAS = bile acid sequestrants, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, TOT = trial of treatment, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.
Note: Percentage of response to any medication. Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

Table 81: Utility scenario results, population 2

	QALYs	Costs	Inc. QALYs	Inc. Costs	ICER
Base-case					
No SeHCAT	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	12.9008	£13,946			
SeHCAT 15%	13.0079	£14,131	0.1071	185	£1,727
Cholestyramine BAS response equal to full diarrhoea utility decrement					
No SeHCAT	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	12.932	£13,946			
SeHCAT 15%	13.0573	£14,131	0.1253	185	£1,476
Utility values based on Mearin er al. (2004)[58]					
No SeHCAT	12.7292	£14,419	Dominated by BAS TOT		
BAS TOT	12.9672	£13,946			
SeHCAT 15%	13.086	£14,131	0.1188	185	£1,557
Utility values based on Spiegel et al. 2009[57]					
No SeHCAT	12.6003	£14,419	Dominated by BAS TOT		
BAS TOT	12.7679	£13,946			
SeHCAT 15%	12.8516	£14,131	0.0837	185	£2,210
No age adjustment					
No SeHCAT	13.4956	£14,419	Dominated by BAS TOT		
BAS TOT	13.7247	£13,946			
SeHCAT 15%	13.839	£14,131	0.1143	185	£1,619

Abbreviations: BAS = bile acid sequestrants, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, TOT = trial of treatment, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.

Table 82: Cost scenario results, population 2

	QALYs	Costs	Inc. QALYs	Inc. Costs	ICER
Base-case					
No SeHCAT	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	12.9008	£13,946			
SeHCAT 15%	13.0079	£14,131	0.1071	£185	£1,727
Decrease cost of BAS treatment by 20%					
No SeHCAT	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	12.9008	£13,140	Dominated by SeHCAT 15%		
SeHCAT 15%	13.0079	£12,961			
Increase cost of BAS treatment by 20%					
No SeHCAT	12.6863	£14,419			
BAS TOT	12.9008	£14,751	0.2145	£332	£1,548
SeHCAT 15%	13.0079	£15,302	0.1071	£551	£5,143
Decrease SeHCAT cost by 20%					
No SeHCAT	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	12.9008	£13,946			
SeHCAT 15%	13.0079	£14,036	0.1071	£90	£840
Increase SeHCAT cost by 20%					
No SeHCAT	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	12.9008	£13,946			
SeHCAT 15%	13.0079	£14,227	0.1071	£281	£2,623
Decrease cost of Crohns medication by 20%					
No SeHCAT	12.6863	£11,516			
BAS TOT	12.9008	£11,979	0.2145	£463	£2,159
SeHCAT 15%	13.0079	£12,584	0.1071	£605	£5,647
Increase cost of Crohns medication by 20%					

	QALYs	Costs	Inc. QALYs	Inc. Costs	ICER
No SeHCAT	12.6863	£17,277	Dominated by BAS TOT		
BAS TOT	12.9008	£15,912	Dominated by SeHCAT 15%		
SeHCAT 15%	13.0079	£15,679			

Abbreviations: BAS = bile acid sequestrants, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, TOT = trial of treatment, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.

Table 83: Results of transition probability scenarios, population 2

	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
Base-case (relapse in non-BAS model only, p = 0. 00575)					
No SeHCAT	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	12.9008	£13,946			
SeHCAT 15%	13.0079	£14,131	0.1071	£185	£1,727
Scenario 1 (relapse in non-BAS and BAS models, p = 0. 00575)					
No SeHCAT	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	12.8582	£13,417	Dominated by SeHCAT 15%		
SeHCAT 15%	12.9446	£13,360			
BAS scenario 2 (relapse and remission in non-BAS and BAS models, p = 0. 00575)					
No SeHCAT	12.7686	£17,403	Dominated by BAS TOT		
BAS TOT	12.9169	£15,449	Dominated by SeHCAT 15%		
SeHCAT 15%	12.9911	£14,904			
BAS scenario 3 (relapse in non-BAS and BAS models, p = 0. 00575*2)					
No SeHCAT	12.6404	£12,768	Dominated by BAS TOT		
BAS TOT	12.7922	£11,854	Dominated by SeHCAT 15%		
SeHCAT 15%	12.8684	£11,843			
BAS scenario 4 (relapse in non-BAS and BAS models, p = 0. 00575*5)					
No SeHCAT	12.5462	£9,412	Dominated by BAS TOT		
No SeHCAT and BAS TOT	12.6565	£8,678			
SeHCAT 15%	12.7119	£8,759	0.0054	£81	£1,459

Abbreviations: BAS = bile acid sequestrants, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, TOT = trial of treatment, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.

Table 84: Results of mortality scenarios, population 2

	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
Base-case (SMR = 1.52)					
No SeHCAT	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	12.9008	£13,946			
SeHCAT 15%	13.0079	£14,131	0.1071	£185	£1,727
Scenario 1 (SMR = 1.32)					
No SeHCAT	12.9594	£14,697	Dominated by BAS TOT		
BAS TOT	13.1790	£14,234			
SeHCAT 15%	13.2886	£14,424	0.1096	£190	£1,732
Scenario 2 (SMR = 1.74)					
No SeHCAT	12.4134	£14,141	Dominated by BAS TOT		
BAS TOT	12.6229	£13,658			
SeHCAT 15%	12.7275	£13,840	0.1046	£182	£1,740

Abbreviations: BAS = bile acid sequestrants, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, TOT = trial of treatment, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.