National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

SeHCAT (tauroselcholic [75 selenium] acid) for investigating bile acid diarrhoea

This overview summarises the key issues for the diagnostics advisory committee's consideration. This document is intended to be read with the final scope issued by NICE for the assessment and the diagnostics assessment report. There is a glossary of terms in appendix B.

This assessment is an update of NICE's diagnostics guidance on SeHCAT (tauroselcholic [75 selenium] acid for the investigation of diarrhoea due to bile acid malabsorption in people with diarrhoea-predominant irritable bowel syndrome (IBS-D) or Crohn's disease without ileal resection. The guidance acknowledges that SeHCAT is a potentially clinically important test for diagnosing bile acid diarrhoea. But in 2012, when the guidance was published, there was not enough evidence to determine whether SeHCAT is a cost-effective option for diagnosing bile acid diarrhoea. The test is currently only recommended for use in research to collect evidence about its clinical benefits and risks and its acceptability for diagnosing and treating bile acid diarrhoea. In 2020, the evidence on SeHCAT was reviewed. The review found new evidence and changes to the care pathway, which are considered for inclusion in this updated assessment.

1 Background

1.1 Introduction

This is an assessment of the clinical and cost effectiveness of SeHCAT for investigating and diagnosing bile acid diarrhoea.

In bile acid diarrhoea, a form of chronic diarrhoea, the body's bile acids are not recycled properly. The most common form of bile acid diarrhoea is caused by overproduction of bile acid in people with no physical damage to the bile acid recycling system. Bile acid diarrhoea can also be secondary to damage to the small bowel or another part of the bile acid recycling system by disease, surgery, or a certain type of treatment such as pelvic or abdominal radiotherapy.

British Society of Gastroenterology guidelines for the investigation of chronic diarrhoea in adults recommend that bile acid diarrhoea is investigated when:

- there is persistent chronic diarrhoea without a known cause or
- diarrhoea-predominant irritable bowel syndrome (IBS-D) or functional diarrhoea is suspected or has been diagnosed.

Investigation of bile acid diarrhoea may also be considered when diarrhoea persists regardless of conventional treatment when it may be a secondary condition.

SeHCAT is a diagnostic radiopharmaceutical capsule used to measure how well the body absorbs bile acids. The result of the test shows how much SeHCAT remains in the body. Bile acid diarrhoea is typically diagnosed when around 15% or less of SeHCAT remains in the body. After diagnosis, symptoms of bile acid diarrhoea are most often controlled with bile acid sequestrants: colestyramine, colestipol and colesevelam. The treatment is likely to be long term.

Some healthcare trusts currently start bile acid sequestrant treatment for bile acid diarrhoea without a diagnostic test being done (trial of treatment). Bile acid diarrhoea may be underdiagnosed. People with bile acid diarrhoea may go through several unnecessary investigations and treatments for other conditions.

The diagnostics advisory committee will make provisional recommendations on the use of this technology at the committee meeting on 15 June 2021.

1.2 Scope of the assessment

Table 1 Scope of the assessment

Decision question	What is the clinical and cost effectiveness of SeHCAT for investigating and diagnosing bile acid diarrhoea?
Populations	• Adults presenting with chronic diarrhoea with an unknown cause, suspected or diagnosed diarrhoea-predominant irritable bowel syndrome (IBS-D) or functional diarrhoea (potential primary bile acid diarrhoea). • Adults with Crohn's disease (without ileal resection) presenting with chronic diarrhoea (potential secondary bile acid diarrhoea).
Intervention	SeHCAT test
Comparators	• No SeHCAT testing and no bile acid sequestrant treatment. • No SeHCAT testing and trial of bile acid sequestrant treatment.
Healthcare setting	Secondary care

Outcomes	Intermediate measures for consideration may include: • predictive accuracy (ability of the test to predict response to treatment, proxy measure of diagnostic accuracy) • time-to-test result • impact of test result on clinical decision making • impact of test result on treatment adherence • response to treatment • use of further tests • adverse events (during or after testing). Clinical outcomes for consideration may include: • morbidity • mortality. Patient-reported outcomes for consideration may include: • health-related quality of life • acceptability of test (such as anxiety about the testing procedure, acceptability of time-to-test result) • side effects of testing (this may also include health effects of stopping any antidiarrhoeal medication for the duration of the test) • side effects of treatment. Costs will be considered from an NHS and personal social services perspective. Costs for consideration may include: • costs of testing for bile acid diarrhoea • costs of further tests • costs of treatment and follow up. The cost effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year (ICER).

Time horizon	The time horizon for estimating clinical and cost effectiveness should be long enough to reflect any differences in costs or outcomes between the technologies being compared.

Further details, including descriptions of the intervention, comparators, care pathway and outcomes, are in the final scope for SeHCAT.

2 The evidence

This section summarises data from the external assessment group's (EAG) diagnostics assessment report.

2.1 Clinical effectiveness

To assess clinical effectiveness, the EAG did a systematic review to identify and evaluate the evidence for SeHCAT in diagnosing bile acid diarrhoea in people with:

- chronic diarrhoea with an unknown cause, suspected or diagnosed diarrhoea-predominant irritable bowel syndrome (IBS-D) or functional diarrhoea
- Crohn's disease without ileal resection, presenting with chronic diarrhoea.

Studies from the previous assessment of SeHCAT were included if they met the inclusion criteria for the current assessment (see pages 32 to 34 of the diagnostics assessment report). A search was done to find new studies published since the previous assessment. The review also included an additional search for studies on trial of bile acid sequestrant treatment in these 2 populations.

The EAG found 24 studies that met the inclusion criteria for the review (see figure 1 of the diagnostics assessment report, page 37). Only 9 of these were new studies found through the search in this assessment. The remaining 15 studies had been included in the previous assessment of SeHCAT. Of the

24 studies,15 were published as full text manuscripts in peer-reviewed journals. The remaining studies were conference abstracts and an unpublished dissertation.

All 24 included studies were observational studies. Three of these studies evaluated the ability of the SeHCAT test to predict response to bile acid treatment (predictive accuracy). The methodological quality of these studies was assessed using QUADAS-2. All the remaining evidence was the lowest level of evidence eligible for inclusion. These were studies that reported outcome data only for people who had a positive SeHCAT test result. The methodological quality of these studies was assessed using a topic-specific adaptation of a quality assessment checklist by Wedlake et al. (2009).

All the included studies provided some outcome data from people with IBS-D or functional diarrhoea. Only 1 study provided some outcome data in people with Crohn's disease. No eligible studies were found on trial of treatment in either population.

Evidence in people with IBS-D or functional diarrhoea

Predictive accuracy of SeHCAT

There were 3 small studies evaluating the predictive accuracy of SeHCAT in people with IBS-D or functional diarrhoea. These studies were included in the previous assessment. One study was done in Scotland and 2 in Italy. All 3 studies assessed the relationship between the SeHCAT test result and response to colestyramine treatment. But the study population, method of SeHCAT testing, treatment dose, definition of treatment response and follow-up period varied between the studies. For a more detailed overview of the study characteristics see table 1 (pages 40 to 52) of the diagnostics assessment report.

Table 2 summarises the predictive accuracy estimates for the different SeHCAT thresholds that the studies reported. Because of the small number of

studies, differences in study characteristics and the different test thresholds, a pooled estimate of predictive accuracy was not calculated. For a more detailed summary see table 4 (page 59) and figure 1 (page 60) of the diagnostics assessment report.

Table 2 Accuracy of SeHCAT for predicting response to bile acid sequestrant treatment in people with IBS-D or functional diarrhoea

Study	Study size	Threshold	Sensitivity	95% confidence interval (CI)	Specificity	95% CI
Merrick et al. (1985)	43	<8%	0.667	0.223 to 0.957	0.971	0.847 to 0.999
Merrick et al. (1985)	43	≤15%	1.000	0.541 to 1.000	0.912	0.763 to 0.981
Sciaretta et al. (1986)	13	<5%	0.857	0.421 to 0.996	1.000	0.541 to 1.000
Sciaretta et al. (1987)	46	<8%	0.950	0.751 to 0.999	0.962	0.804 to 0.999

Risk of bias in all 3 studies was considered unclear or high in 3 of the 4 domains (patient selection, reference standard, flow and timing) of the QUADAS-2 assessment. Only in the index test domain were 2 of the 3 studies rated at low risk of bias. There were concerns over the applicability of all 3 studies to the decision question in at least 2 of the 3 applicability domains of the QUADAS-2 assessment. Most concerns were over the applicability of the study population and the index test. All 3 studies included some people with prior cholecystectomy. No study reported previous investigations equivalent to those specified in the British Society of Gastroenterology guidelines for the investigation of chronic diarrhoea. The 3 studies were all published over 30 years ago, and were generally poorly reported. For the results of the QUADAS-2 assessment see table 2 (page 54) of the diagnostics assessment report.

Probability of response to bile acid sequestrant treatment after a positive SeHCAT test

The EAG found 21 studies that described outcomes after a positive SeHCAT test in people with IBS-D or functional diarrhoea. Of these, only 9 were new studies found through the searches in this assessment. All 21 studies were done in Europe, half in the UK. There were considerable differences in study characteristics between the studies. This included differences in the study population, the threshold used to define a positive SeHCAT test, bile acid sequestrant treatment, definition of response to treatment and follow-up period. For a more detailed overview of the study characteristics see table 1 (pages 40 to 52) of the diagnostics assessment report.

Table 3 summarises the proportion of people with a positive SeHCAT test at a 15% threshold and the probability of response to bile acid sequestrant treatment after a positive SeHCAT test in 8 of the studies. The median response rate in these studies was 68% (range 38% to 86%). The proportion of people who had bile acid sequestrant treatment after a positive SeHCAT test ranged between 70% and 100%. Only 2 of these 8 studies were new studies found through the searches in this assessment. Because of the substantial differences between studies, meta-analysis of the response rate was considered inappropriate. Pooled estimates of the proportion of people with a positive SeHCAT test and the probability of response to bile acid sequestrant treatment after a positive SeHCAT test at the 15% threshold were calculated. But this was only to provide input parameters for the cost-effectiveness modelling (table 3). The pooled estimates should be treated with caution. For a more detailed summary of these results and the treatment response probabilities at other SeHCAT thresholds see table 5 (pages 65 to 77) of the diagnostics assessment report.

Table 3 Probability of response to bile acid sequestrant treatment after a positive SeHCAT test in people with IBS-D or functional diarrhoea

Study	Study size	Proportion of people with a positive SeHCAT test	Probability of response at 15% threshold
Borghede et al. (2011)	114	0.60	0.75
Holmes et al. (2012)	8	0.99	0.50
Kumar et al. (2013)	57	0.42	0.48
Rudberg et al. (1996)	17	0.47	0.86
Sinha et al. (1998)	17	0.53	0.67
Tunney et al. (2011)	86	0.42	0.38
Wildt et al. (2003)	56	0.43	0.82
Williams et al. (1991)	181	0.33	0.69
Pooled estimate, fixed effects (95% confidence interval [CI])	Not applicable	0.416 (0.424 to 0.407)	0.642 (0.615 to 0.668)
Pooled estimate, random effects (95% CI)	Not applicable	0.454 (0.357 to 0.555)	0.638 (0.495 to 0.760)

The methodological quality of these 8 studies was generally poor. Almost all studies had a retrospective study design. None of the studies provided full outcome data for people who had a negative SeHCAT test result. There were frequent problems with reporting of a clear definition of chronic diarrhoea, enough information about the SeHCAT test procedure, a complete description of the bile acid sequestrant treatment, information on how treatment decisions were made and an objective measure of response to treatment. For the detailed results of this quality assessment of these and the other studies that described outcomes after a positive SeHCAT test, see table 3 (pages 55 to 56) of the diagnostics assessment report.

Evidence on patient-reported outcomes

Effects of treatment on bowel symptoms

In addition to reporting the probability of response to treatment after a positive SeHCAT test, 3 of the studies in people with IBS-D or functional diarrhoea described the effects of bile acid sequestrants on bowel symptoms. In these studies, colestyramine was described as having a positive effect in improving stool consistency, reducing daily bowel movements and stool frequency, and removing the urgency of needing the toilet.

Tolerability of bile acid sequestrant treatment

There were 8 studies that reported the proportion of people who found bile acid sequestrant treatment difficult to tolerate or stopped their treatment for unclear reasons. Rates of intolerance and discontinuation were generally high, median 15% (range 4% to 27%). For a more detailed summary of these results see table 5 (pages 65 to 77) of the diagnostics assessment report. There was not enough information to determine whether these rates varied between the different types of bile acid sequestrants.

Health-related quality of life

There were 2 studies that reported changes in health-related quality of life in people who had bile acid sequestrant treatment after a positive SeHCAT test result. One study evaluated quality of life using the SF-36 questionnaire. This study reported improvements in the general pain domain in people with mild bile acid diarrhoea (defined as a positive SeHCAT test result at a threshold between 11% and 15%, $p<0.05$). It also reported further improvements across many other domains (emotional problems, energy or fatigue, emotional wellbeing, social functioning, general health, health change) in people with more severe bile acid diarrhoea (threshold 5% or less, $p<0.05$) after 8 weeks of colestyramine. Another study reported improvements in activity levels sub score ($p=0.00998$) using the EQ-5D questionnaire in people with a positive test result after colestyramine or colesevelam treatment. This study did not

report either the threshold used to define a positive SeHCAT test result or the duration of follow up.

Evidence in people with Crohn's disease

No evidence was found for the predictive accuracy of SeHCAT or for patient-reported outcomes in people with Crohn's disease.

Probability of response to bile acid sequestrants after a positive SeHCAT test

Only 1 small study (Smith et al. 2000) evaluated the probability of response to bile acid sequestrants (colestyramine or colestipol) after a positive SeHCAT test people with Crohn's disease. This study was included in the previous assessment, and was done in the UK. The threshold used to define a positive SeHCAT test was 10%. For a more detailed overview of the study characteristics see table 1 (pages 40 to 52) of the diagnostics assessment report.

In this study, 24 of 44 (55%) people had a positive SeHCAT test result at a 10% threshold. But only 9 of these 24 (38%) people had bile acid sequestrants. This treatment was considered to work for 8 of these 9 people (89%).

The methodological quality of this study was poor. The study had a retrospective study design, the definition of chronic diarrhoea was unclear, and no outcome data was provided for people with a negative SeHCAT test result. Fewer than 40% of the people with a positive SeHCAT test result had bile acid sequestrant treatment and the reasons for offering this treatment were not reported. The study did not report how many people had colestyramine and how many had colestipol.

2.2 Costs and cost effectiveness

To assess the cost effectiveness of SeHCAT for investigating and diagnosing bile acid diarrhoea, the external assessment group (EAG):

- did a search to find studies and
- constructed a de novo economic model.

Pragmatic review of cost-effectiveness evidence

The EAG did literature searches to find published economic evaluations, cost data and utility studies for diagnostic techniques and procedures used in investigating chronic diarrhoea, that were not in the scope of the clinical effectiveness searches. These pragmatic searches aimed to find studies to support the development of a health economic model, to estimate the model input parameters and to answer the research questions of the assessment. For search details see section 4.1 of the diagnostics assessment report (pages 81 to 82). Except for the economic model developed for the previous assessment, the searches found no published economic models.

Economic analysis

The EAG developed a de novo economic model to assess the cost effectiveness of SeHCAT for investigating and diagnosing bile acid diarrhoea. The model used 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.

Populations

The modelling was done for:

- people with diarrhoea-predominant irritable bowel syndrome (IBS-D) or functional diarrhoea and
- people with Crohn's disease.

Data from a UK study by Summers et al. (2016) was used to estimate the number of women and men, and the age of the populations. For both populations, their average age was assumed to be 50 years when they entered the model, and 75% of the population were assumed to be women.

Strategies

The SeHCAT testing strategy that was modelled used the 15% threshold value for a positive test result. Most of the studies found through the systematic review of clinical effectiveness used the 15% (or 10%) SeHCAT threshold.

SeHCAT testing using a 15% threshold value for a positive test was compared with:

- a strategy in which no SeHCAT testing was done to investigate bile acid diarrhoea and no bile acid sequestrant treatment was offered and
- a strategy in which no SeHCAT testing was done but people had a trial of bile acid sequestrant treatment.

Model structure

The economic model included 2 parts:

- a short-term decision analytic model that captured the diagnostic pathway and initial response to treatment (first 6 months) and
- a long-term Markov model that estimated the lifetime costs and effects for people having treatment.

Short-term decision analytic model in people with IBS-D or functional diarrhoea

For an outline of the short-term model structure in people with IBS-D or functional diarrhoea see figure 1. The 3 main arms and their branches in the structure represent the initial steps in the 3 strategies modelled:

- SeHCAT test at a 15% threshold
- no test and no bile acid sequestrant treatment and
- trial of bile acid sequestrant treatment.

The no test and no bile acid sequestrant treatment strategy includes the possibility of having a colonoscopy. This was included because during

scoping it was suggested that using SeHCAT could help avoid unnecessary colonoscopies. People in the SeHCAT test strategy are assumed to switch to follow the steps in the no test arm when the SeHCAT test result is negative or when the test result is positive but the bile acid sequestrant treatment did not work. Likewise, in the trial of treatment strategy, people for whom the bile acid sequestrant treatment did not work are assumed to switch to follow the steps in the no test and no bile acid sequestrant treatment strategy.

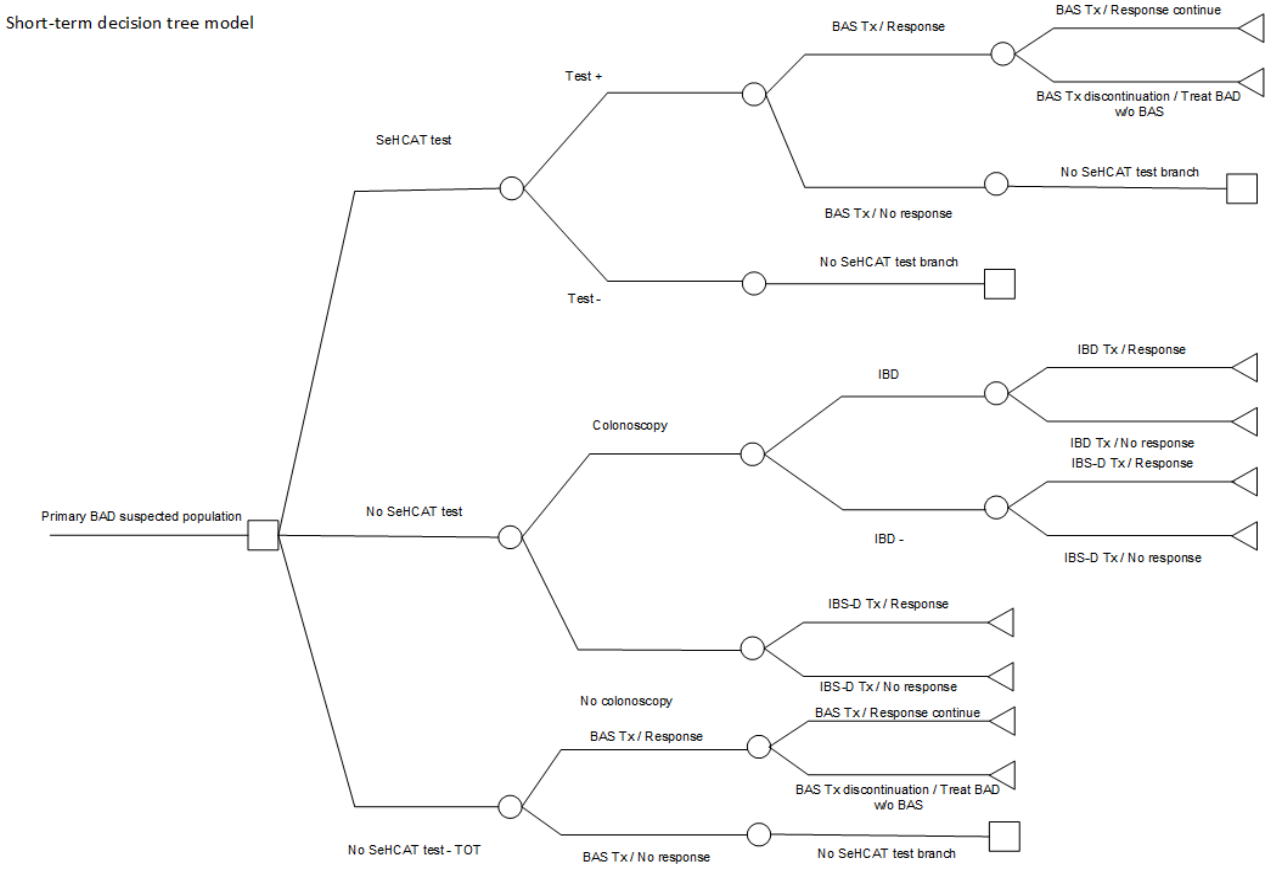
Short-term decision analytic model in people with Crohn's disease

For an outline of the short-term model structure in people with Crohn's disease see figure 2. Like the model structure for people with IBS-D or functional diarrhoea, the initial steps of the 3 strategies modelled are represented by the 3 main arms and their branches. The main difference is that the model for Crohn's disease does not include the possibility of having a colonoscopy. This is because people are assumed to have had a colonoscopy to diagnose their Crohn's disease.

Long-term Markov model in people with IBS-D or functional diarrhoea and in people with Crohn's disease

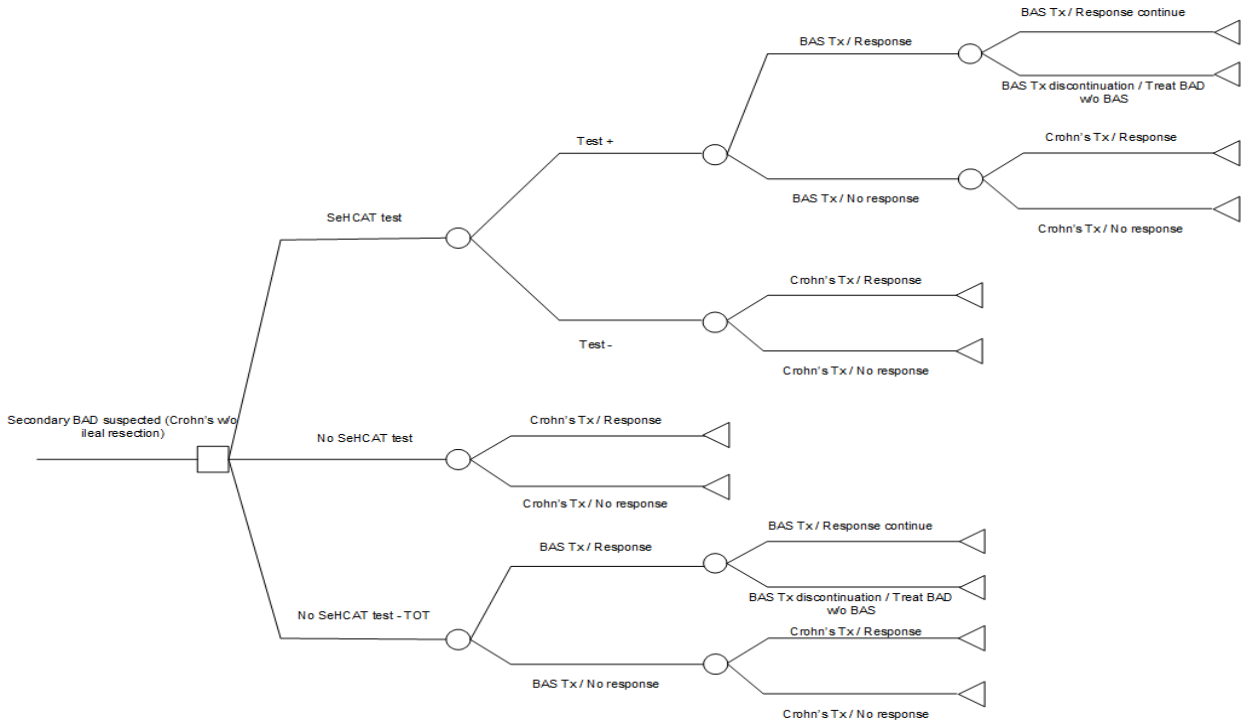
After the initial steps in the short-term diagnostic and treatment path, both populations enter a model representing their care pathway in the long term. For the structure of this model see figure 3. People for whom treatment worked in the short-term model enter the model in the health state called 'no diarrhoea'. People for whom treatment has not worked start in this model in the health state called 'diarrhoea'. Because the model has a lifetime time horizon, it includes a further health state called 'death' where people from the other 2 health states move when they die. The assumptions about the moves between the 'no diarrhoea' and 'diarrhoea' health states in the model for people with IBS-D or functional diarrhoea and the model for people with Crohn's disease are explained in the section about model inputs. The cycle length between transitions in the model is 6 months.

Figure 1 Decision analytic model in people with IBS-D or functional diarrhoea



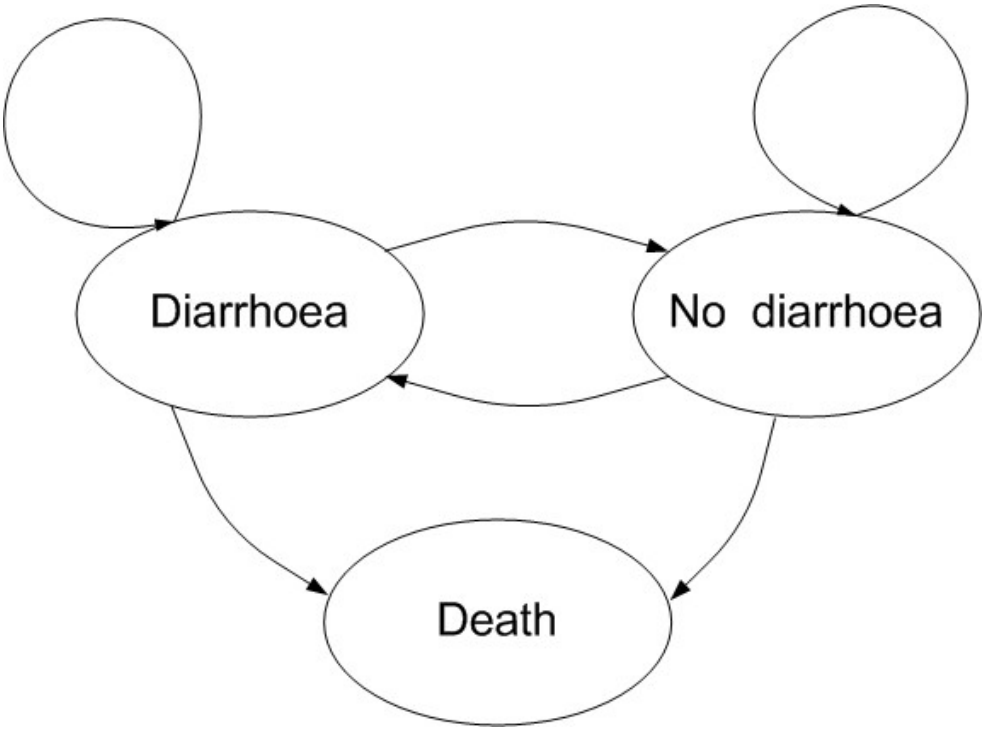
Abbreviations: BAD, bile acid diarrhoea; TOT, trial of bile acid sequestrant treatment; BAS Tx, bile acid sequestrant treatment; IBS-D Tx, diarrhoea-prominent irritable bowel syndrome treatment; IBD Tx, inflammatory bowel disease treatment

Figure 2 Decision analytic model in people with Crohn's disease



Abbreviations: BAD, bile acid diarrhoea; TOT, trial of bile acid sequestrant treatment; BAS Tx, bile acid sequestrant treatment; Crohn's Tx, diarrhoea treatment in Crohn's disease

Figure 3 Markov model for people with IBS-D or functional diarrhoea and for people with Crohn's disease



Model inputs

When possible, model inputs were based on the clinical effectiveness systematic review (described in section 2.1), other published literature found through the further pragmatic searches, and UK databases. When such evidence was not available, expert opinion was used. The EAG sent out a questionnaire to the specialist committee members for the assessment and their answers were used to inform the input parameters for which data were lacking. For the full questionnaire see appendix 6 of the diagnostics assessment report. When experts were not able to provide estimates, modelling assumptions were made.

Only health effects for patients were included. All costs and effects were discounted by 3.5%. Alternative parameter values for most model inputs were considered in scenario analyses.

Model inputs for people with IBS-D or functional diarrhoea

Positive SeHCAT test result

The clinical effectiveness systematic review found 8 studies that reported the probability of response to bile acid sequestrant treatment after a positive SeHCAT test at a 15% threshold. The probability of a positive SeHCAT test result in the base case was the pooled estimate of 45.4% calculated from the data in these studies (see table 2).

Type of bile acid sequestrant treatment

Everyone with a positive SeHCAT test result was assumed to be offered bile acid sequestrants, either colestyramine or colesevelam. Based on the responses to EAG's questionnaire, it was assumed in the base case that 50% of people started colestyramine and 50% started colesevelam.

In the trial of treatment strategy, everyone was also assumed to be offered either colestyramine or colesevelam. But based on the experts' responses, 85% of people started colestyramine and 15% started colesevelam. The higher proportion of colestyramine used in this strategy might be because of its lower costs.

Response to bile acid sequestrant treatment

The probability of response to treatment after a positive SeHCAT test result in the base case was a pooled estimate of 63.8%. This was calculated from the data in the same 8 studies that provided data for estimating the probability of a positive SeHCAT test result (see table 13 on page 93 of the diagnostics assessment report).

In the trial of treatment strategy, because people with and without bile acid diarrhoea would be having bile acid sequestrants the treatment response was expected to be lower than in the SeHCAT strategy. Because the clinical effectiveness systematic review found no trial of treatment studies, the probability of treatment response for the base case of 30% was estimated

based on expert opinion (see table 17 on page 97 of the diagnostics assessment report).

The experts' responses to the questionnaire also suggested that, in general, the initial treatment response happens within 6 months from the start of the treatment. The experts also suggested that a lifetime treatment effect may be assumed. Based on the available evidence, it was not possible to distinguish between the response to colestyramine and colesevelam.

Tolerability of bile acid sequestrant treatment and the probability of switching to an alternative bile acid sequestrant

Half of the studies that provided data for the probability of response to bile acid sequestrant treatment reported that some people found the treatment difficult to tolerate. The rates of treatment discontinuation in these studies were high. Because these studies already implicitly included the effect of low tolerability of bile acid sequestrant treatment, in the model none of the people having this treatment were assumed to stop because it was difficult to tolerate.

The experts' responses to the EAG's questionnaire suggested that colestyramine may be more difficult to tolerate than other types of bile acid sequestrant. If so, the experts explained that people may be offered colesevelam instead. This switch is likely to happen quite early in treatment, and for simplicity was assumed to happen at the beginning of treatment. The impact of this assumption is expected to be small because it would only affect the treatment costs and utilities for less than 6 months.

The probability of switching from colestyramine to colesevelam in the base case was estimated to be 50% based on the experts' responses (see table 14 on page 94 of the diagnostics assessment report). This same probability of switching treatment was also assumed in the base case for the trial of treatment strategy.

Colonoscopy

The proportions of people who may have a colonoscopy in the model were estimated based on the experts' responses to the EAG's questionnaire. When bile acid diarrhoea is not investigated and a trial of bile acid sequestrant treatment is not offered, the probability of having a colonoscopy in the base case was estimated to be 74%.

The probability of having a colonoscopy after a negative SeHCAT test result or after the SeHCAT test result has been positive but bile acid sequestrant treatment has not worked was much lower. This was estimated to be 49% in the base case (see table 15 on page 95 of the diagnostics assessment report).

The highest probability of having a colonoscopy was estimated for people who have had a trial of treatment but it has not worked. Based on the experts' responses, this proportion in the base case was estimated to be 90% (see table 18 on page 97 of the diagnostics assessment report).

IBD prevalence and response to IBD treatment

The probability of being diagnosed with inflammatory bowel disease (IBD) after the colonoscopy was likely to be very small. This was supported by the experts, and a study (Patel et al. 2015) that reported the number of people with IBS-D-like symptoms who were eventually diagnosed with IBD. Based on this, the proportion of people who would be diagnosed with IBD after colonoscopy in the base case was estimated to be 5.3%.

Based on the experts' input, the response to IBD treatment in the base case was estimated to be 72% (see table 10 on page 90 of the diagnostics assessment report). Although this estimate is uncertain, alternative estimates were not explored in scenario analyses. This was because the number of people who would be offered IBD treatment was estimated to be very low. So the impact of the IBD medication costs on the model results was expected to be small.

As with bile acid sequestrant treatment, the initial treatment response was assumed to happen within 6 months of the start of treatment. But according to the experts the time to initial response with IBD treatment may vary more and a lifetime effect with IBD treatment should not be assumed. Relapses are expected after the initial response.

IBS-D prevalence and response to treatment

The estimated probabilities of having a colonoscopy and a diagnosis of IBD (5.3% of the people having a colonoscopy) meant that most people, about 96%, would be offered IBS-D treatment. But no clear data from the literature was found on how well IBS-D treatment works. So, the probability of IBS-D treatment response, after a colonoscopy that ruled out IBD, was estimated based on the experts' input. For people with a negative SeHCAT test result, this probability was estimated to be 56% (see table 16 on page 96 of the diagnostics assessment report). For people who had not had a SeHCAT test or a trial of bile acid sequestrant treatment, the probability was estimated to be 46% (see table 11 on page 91 of the diagnostics assessment report). A modelling assumption was made that when bile acid sequestrant treatment had not worked, the probability of IBS-D treatment would be between these 2 probabilities, so it would be 50%.

Based on these estimates, the EAG calculated that the probability of IBS-D treatment response would be slightly lower for people who had not had a colonoscopy to rule out IBD. For people with a negative SeHCAT test this was estimated to be 53%. For people who had not had a test or a trial of treatment it was estimated to be 44%. When bile acid sequestrants had not worked it was estimated to be 47%.

As with bile acid sequestrant treatment, the initial treatment response was assumed to happen within 6 months of the start of treatment. In practice this may vary. The experts indicated that a lifetime effect with IBS-D treatment in general could be assumed.

Transition between health states

No evidence was found on the long-term effectiveness of bile acid sequestrants, or IBS-D or IBD treatment in the systematic review of clinical effectiveness studies. So the assumptions about people moving between the 'diarrhoea' and 'no diarrhoea' health states in the long-term Markov model were informed by the experts' responses. The experts suggested that, in general, the response to bile acid sequestrants and to IBS-D treatment is expected to last, so no relapses in the long term should be expected. Therefore, for the base case it was assumed that when bile acid sequestrants or IBS-D treatment initially work, people will start the Markov model in the 'no diarrhoea' health state. The only possible transition from this health state is to the 'death' health state.

With IBD treatment, the experts indicated that relapses are expected to occur after the initial response to treatment. Therefore, in the long-term Markov model it was assumed that people having IBD treatment would move between the 'diarrhoea' and 'no diarrhoea' health states. Based on the experts' responses, the EAG assumed people having IBD treatment would on average have 1 relapse every 5 years. Based on this, the base-case probability of people on IBD treatment moving from the 'no diarrhoea' to 'diarrhoea' health state was estimated as 0.45%.

Mortality

The base case assumed that no excess mortality is associated with bile acid diarrhoea.

Resource use and costs

The following costs were considered in the model:

- the cost of a SeHCAT test
- the cost of bile acid diarrhoea treatment with bile acid sequestrants
- the cost of IBS-D treatment
- the cost of IBD treatment and

- the cost of a colonoscopy.

Cost of a SeHCAT test

The company provided the cost of SeHCAT, which was £195 per capsule. The cost for administering this diagnostic test in the NHS was taken from the NHS national tariff for 2021/22 (HRG code RN14Z). This was £282 per test. Therefore, the total cost of a SeHCAT test in the base case was £477 per test.

Cost of bile acid diarrhoea treatment with bile acid sequestrants

The prices of colestyramine and colesevelam were taken from the BNF. The cost of treatment was estimated using the average dosages reported by the experts. The total cost of colestyramine in the base case was £0.35 per day per person. The total cost of colesevelam was £2.56 per day per person. For details of medication use, dosage and the proportion of people having treatment see appendix 7 of the diagnostics assessment report.

Cost of IBS-D treatment

For IBS-D treatment, the model included 3 types of resource use and cost based on expert opinion: medication, diet therapy and psychological therapy. The costs were estimated using national pricing and expert estimates of dosage or healthcare visits and the proportion of people who would have treatment. Costs in the base case were as follows:

- The cost of medication (loperamide, codeine, and tricyclic antidepressants) was £0.06 per day per person.
- The cost of diet therapy was £12.24 per day per person.
- The cost of psychological therapy (cognitive behavioural therapy, counselling and hypnotherapy) was £35.74 per day per person.

See the diagnostics assessment report, table 20 (page 100) for more details on medication costs, table 21 (page 100) for the costs of diet therapy and table 22 (page 101) for the costs of psychological therapy.

Cost of IBD treatment

For IBD treatment, the model also considered 3 types of resource use and cost based on expert opinion: medication, diet therapy and psychological therapy. As with the costs of IBS-D treatment, the costs of IBD treatment were estimated using national pricing and expert estimates of dosage or healthcare visits and the proportion of people who would have treatment. Costs in the base case were as follows:

- The cost of medication was £21.73 per day per person.
- The cost of diet therapy was £149 per day per person.
- The cost of psychological therapy was £289.33 per day per person.

See the diagnostics assessment report, table 23 (page 101) for more details on medication costs, table 24 (page 102) for the costs of diet therapy and table 25 (page 102) for the costs of psychological therapy.

Cost of colonoscopy

The cost of colonoscopy in the model was calculated based on an expert's suggestion that 90% of people would have a conventional colonoscopy and 10% of people would have a CT colonoscopy. The cost of conventional colonoscopy in the base case, £469, was taken from the NHS national tariff for diagnostic colonoscopy. The cost of CT colonoscopy was calculated as the average of the following elements: Single Photon Emission Computed Tomography with CT (SPECT-CT) of 1 area, SPECT-CT of 2 or 3 areas, and SPECT-CT of more than 3 areas for people 18 years old and older. Therefore, the total cost of CT colonoscopy in the base case was £175.75.

Health-related quality of life

None of the new studies on health-related quality of life of people with IBS-D or functional diarrhoea reported on the utility values:

- for the health states without diarrhoea (when the treatment worked) and with diarrhoea (when the treatment did not work) or

- measured using the EQ-5D questionnaire.

Because of this, the utility values identified during the previous assessment were used also in this assessment.

The utility values used in the base case and the sources they were derived from are summarised in table 4. The 2 studies that provided data for the pooled estimates included people with IBS. No evidence was found on the effect of bile acid sequestrants or IBD treatment on the utility values. So, it was assumed that the people for whom the colesevelam or IBD treatment worked had the same utility gain as the people for whom the treatment for IBS worked. Because of the potentially worse tolerability of colestyramine, it was assumed that people for whom colestyramine worked have a slightly lower utility gain from their treatment. This was estimated to be 75% of the utility gain of people whose condition responded to the other treatments.

The model did not include utility loss for colonoscopy. For more details on the utility estimates see pages 98 to 99 of the diagnostics assessment report.

Table 4 Utility values used in the base case in people with IBS-D or functional diarrhoea

Health state	Subpopulation	Utility value	Source
No diarrhoea	People for whom colesevelam, IBS-D or IBD treatment works (treatment response)	0.776	Pooled estimate from data in Mearin et al. (2004) and Spiegel et al. (2009)
No diarrhoea	People for whom colestyramine treatment works (treatment response)	0.760	Assumption
Diarrhoea	People for whom bile acid sequestrant, IBS-D or IBD treatment does not work (no treatment response)	0.712	Pooled estimate from data in Mearin et al. (2004) and Spiegel et al. (2009)

Abbreviations: IBS-D, diarrhoea-predominant irritable bowel syndrome; IBD, inflammatory bowel disease

Base-case assumptions in the model for people with IBS-D or functional diarrhoea

The following key assumptions were applied in the base-case analysis:

- People whose condition responds to bile acid sequestrant treatment have bile acid diarrhoea.
- Treatment for bile acid diarrhoea includes only bile acid sequestrants, either colestyramine or colesevelam.
- Some people who initially have colestyramine will switch to colesevelam early in the treatment because colestyramine may be difficult to tolerate.
- People for whom bile acid sequestrant or IBS-D treatment works in the short term will continue with the treatment and will benefit from it for the rest of their life.

- People who take colesevelam will have better quality of life compared with people who take colestyramine.
- Some people who have not had a SeHCAT test, or their SeHCAT test result is negative, or when the bile acid sequestrant has not worked in the short term, will have a colonoscopy to detect IBD.
- Some people for whom IBD treatment works in the short term will have relapses throughout their life.
- People for whom none of the treatments offered in the short term have worked, are assumed to take loperamide for the rest of their life.
- All the resource use estimates are based on expert opinion.

Model inputs for people with Crohn's disease

Positive SeHCAT test result

The clinical effectiveness systematic review found only 1 study that reported the probability of a positive SeHCAT test in people with Crohn's disease. This probability of 55% was used in the base case.

Type of bile acid sequestrant treatment

Everyone with a positive SeHCAT test result was assumed to be offered bile acid sequestrants, either colestyramine or colesevelam. Based on the experts' responses to EAG's questionnaire, it was assumed in the base case that 63% of people were initially offered colestyramine and 37% colesevelam.

In the trial of treatment strategy, everyone was assumed to be offered either colestyramine or colesevelam. Based on the experts' responses, 58% of people started with colestyramine and 42% with colesevelam (see table 31 on page 109 of the diagnostics assessment report). It was unclear why the proportion of people starting with colestyramine in this strategy was estimated to be lower than in the SeHCAT strategy.

Response to bile acid sequestrant treatment

The probability of response to treatment after a positive SeHCAT test result at a 15% threshold in the base case was estimated as 89%. This came from the same small study that provided data for the probability of a positive SeHCAT test result. This probability was higher than the maximum 70% probability of response estimated by the experts.

In the trial of treatment strategy, because both people with and without bile acid diarrhoea would be having treatment, the treatment response was expected to be lower than in the SeHCAT strategy. Because the clinical effectiveness systematic review found no studies on trial of treatment, the probability of treatment response for the base case (33%) was estimated based on expert opinion (see table 32 on page 109 of the diagnostics assessment report).

Experts' responses to the questionnaire also suggested that, in general, the initial treatment response happens within 6 months of the start of the treatment. The experts were less certain about the duration of the treatment effect. Without further evidence and for consistency with the base case in people with IBS-D or functional diarrhoea, the treatment effect was assumed to last a lifetime. Based on the available evidence, it was not possible to distinguish between the response to colestyramine and colesevelam.

Tolerability of bile acid sequestrants and probability of switching to an alternative bile acid sequestrant

No evidence was available about the tolerability of bile acid sequestrants in people with Crohn's disease. Following the approach taken for modelling people with IBS-D or functional diarrhoea, it was assumed that the study providing treatment response data already implicitly included the effect of low tolerability of the treatment. Nobody having bile acid sequestrants was assumed to stop their treatment in the model.

As with the model for people with IBS-D or functional diarrhoea, switching from colestyramine to colesevelam was assumed to happen. The probability of switching was estimated to be 44% based on the experts' responses (see table 29 on page 107 of the diagnostics assessment report). This same probability of switching was also assumed in the base case for the trial of treatment strategy.

Response to diarrhoea treatment in Crohn's disease

Treatment options for diarrhoea in Crohn's disease may vary depending on whether the diarrhoea is because of relapse or to prevent diarrhoea during remission. Because of this, it was not possible to find data from the literature showing how well diarrhoea treatment in Crohn's disease might work. Therefore, based on the experts' input, the response to diarrhoea treatment was estimated as 40% (see table 26 on page 105 of the diagnostics assessment report).

Transition between health states

No evidence on the long-term effectiveness of bile acid sequestrants was found in the clinical effectiveness systematic review. So the assumptions about people moving between the 'diarrhoea' and 'no diarrhoea' health states in the long-term Markov model were informed by the experts' responses. The experts suggested that, in general, the response to bile acid sequestrants is expected to last. No relapses in the long term are expected.

For diarrhoea treatment for Crohn's disease, the experts indicated that relapses are expected to occur after the initial response to treatment. Therefore, in the long-term Markov model it was assumed that people having this treatment would move between the 'diarrhoea' and 'no diarrhoea' health states. As with people having IBD treatment in IBS-D or functional diarrhoea model, it was assumed that people having diarrhoea treatment for Crohn's disease would have on average 1 relapse every 5 years. Based on this, the base-case probability of people on this treatment moving from the 'no diarrhoea' to 'diarrhoea' health state was estimated as 0.575%.

Mortality

The base case assumed that no excess mortality is associated with bile acid diarrhoea. For the base case, a pooled standardised mortality ratio estimate from a meta-analysis of mortality in Crohn's disease by Canavan et al. (2007) was then applied to the overall mortality estimates in the UK.

Resource use and costs

The following costs were considered in the model:

- the cost of a SeHCAT test
- the cost of bile acid diarrhoea treatment with bile acid sequestrants and
- the cost of diarrhoea treatment in Crohn's disease.

Cost of a SeHCAT test

The total cost of SeHCAT in the base-case model was £477 per test, the same as in the IBS-D or functional diarrhoea model.

Cost of bile acid diarrhoea treatment with bile acid sequestrants

The prices and dosage of colestyramine and colesevelam were the same as in the IBS-D or functional diarrhoea model.

Cost of diarrhoea treatment in Crohn's disease

For treating diarrhoea in Crohn's disease, the model considered the following medications: loperamide, codeine, corticosteroids, adalimumab, mesalazine, azathioprine and bile acid sequestrants. These were included based on expert input in the previous assessment. The cost of medication in the base case, £5.76 per day per person, was estimated using BNF prices, and the average dosages and proportion of people having treatment reported by the experts in the previous assessment. See table 34 (page 111) of the diagnostic assessment report for the base-case costs of medication per day per person having treatment.

Health-related quality of life

The utility values used in the base case and the sources they were derived from are summarised in table 5. No studies on health-related quality of life in people with Crohn's disease and diarrhoea were found. The estimate from a study providing utilities for people with active Crohn's disease (Buxton et al. 2007) was assumed to also reflect quality of life in the diarrhoea health state. To estimate the utility gain for people for whom the treatment worked, it was then assumed that the utility loss because of diarrhoea was the same as for people with IBS-D or functional diarrhoea. As in the IBS-D or functional diarrhoea model, it was assumed that the utility gain from colestyramine would be slightly lower than from the other treatments.

Table 5 Utility values used in the base case in people with Crohn's disease

Health state	Subpopulation	Utility value	Source
No diarrhoea	People for whom colesevelam or treatment of diarrhoea in Crohn's disease works (treatment response)	0.764	Assumption
No diarrhoea	People for whom colestyramine treatment works (treatment response)	0.748	Assumption
Diarrhoea	People for whom bile acid sequestrants or treatment of diarrhoea in Crohn's disease does not work (no treatment response)	0.700	Estimate from data in Buxton et al. (2007)

Base-case assumptions in the model for people with Crohn's disease

Except for the assumption about colonoscopy, the key assumptions used in the base-case analysis for people with IBS-D or functional diarrhoea were also applied in the base-case analysis for people with Crohn's disease. In addition, the following key assumptions were applied:

- Everyone has had a colonoscopy to diagnose Crohn's disease.
- People who have not had a SeHCAT test, or who have a negative SeHCAT test result, or when bile acid treatment has not worked in the short term, will be offered treatment for diarrhoea in Crohn's disease.
- Some people with Crohn's disease for whom the diarrhoea treatment works in the short term, will have relapses throughout their life.

Base-case results in people with IBS-D or functional diarrhoea

For decision making, the incremental cost-effectiveness ratios (ICERs) per quality-adjusted life year (QALY) gained or lost will be considered.

The deterministic and probabilistic cost-effectiveness results for the base-case scenario in people with IBS-D or functional diarrhoea are in table 6 and table 7.

The SeHCAT strategy was more effective and less expensive (dominant) compared with the strategy of offering a trial of bile acid sequestrant treatment. It was also more effective but more expensive than the strategy in which bile acid diarrhoea was not investigated or treated. The ICER for the SeHCAT strategy compared with this strategy was £9,661 per QALY gained (probabilistic base-case analysis).

In the short term, the SeHCAT strategy had the lowest rate of colonoscopies and the lowest cost per colonoscopy avoided. It also had the highest rate of treatment response (any type of treatment). The initial costs of the SeHCAT strategy were the highest because of the costs of the SeHCAT test. The results are consistent for both the deterministic and probabilistic analysis.

Table 6 Deterministic cost-effectiveness results for the base-case scenario in people with IBS-D or functional diarrhoea

Strategy	Colonoscopies avoided	Treatment response	Initial costs	Total QALYs	Total costs	Incremental QALYs	Incremental costs	ICER
No SeHCAT	26%	47%	£557	13.8242	£4,720	–	–	–
Trial of treatment	37%	65%	£507	14.0096	£7,449	–	–	Dominated by SeHCAT
SeHCAT	65%	68%	£786	14.0550	£6,956	0.2308	£2,236	£9,688

Table 7 Probabilistic cost-effectiveness results for the base-case scenario in people with IBS-D or functional diarrhoea

Strategy	Colonoscopies avoided	Treatment response	Initial costs	Total QALYs	Total costs	Incremental QALYs	Incremental costs	ICER
No SeHCAT	26%	46%	£560	13.8236	£4,687	–	–	–
Trial of treatment	37%	66%	£564	14.0151	£7,431	–	–	Dominated by SeHCAT
SeHCAT	65%	68%	£826	14.0623	£6,993	0.2387	£2,306	£9,661

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

Secondary analysis in people with IBS-D or functional diarrhoea

The deterministic and probabilistic cost-effectiveness results for the secondary analysis in people with IBS-D or functional diarrhoea are shown in table 8 and table 9. In this analysis, it was assumed that colonoscopy was not offered to people who had no SeHCAT test or who had a negative SeHCAT test result or for whom the bile acid treatment did not work.

As with the base-case analysis, the SeHCAT strategy provided the highest QALYs. But in this analysis, it was more expensive than the strategy in which no testing and no bile acid sequestrant was offered and the strategy in which a trial of treatment was offered. The ICER for the SeHCAT strategy compared with the trial of treatment strategy was £21,036 per QALY gained (probabilistic base-case analysis).

In the short term, as in the base-case scenario, the SeHCAT strategy had the highest rate of treatment response. Initial costs of the SeHCAT strategy were again the highest because of the costs of the SeHCAT test. The results of the deterministic and probabilistic analysis are similar.

Analysis of alternative scenarios people with IBS-D or functional diarrhoea

Robustness of the cost-effectiveness results to alternative model assumptions was considered in several scenario analyses. For more details see table 10 and pages 121 to 124 of the diagnostics assessment report. In nearly all the scenarios, the cost-effectiveness results were similar to the base case or SeHCAT produced ICERs at around or below £20,000 per QALY gained. In the scenarios (1 and 2, table 10) in which another strategy could be considered the most cost-effective option, the model assumptions were likely to be unrealistic.

Table 8 Deterministic cost-effectiveness results for the secondary analysis in people with IBS-D or functional diarrhoea

Strategy	Colonoscopies avoided	Treatment response	Initial costs	Total QALYs	Total costs	Incremental QALYs	Incremental costs	ICER
No SeHCAT	NA	44%	£59	13.8026	£374	–	–	–
Trial of treatment	NA	63%	£85	13.9825	£3,767	0.1799	£3,393	£18,860
SeHCAT	NA	67%	£553	14.0408	£4,922	0.0583	£1,115	£19,125

Table 9 Probabilistic cost-effectiveness results for the secondary analysis in people with IBS-D or functional diarrhoea

Strategy	Colonoscopies avoided	Treatment response	Initial costs	Total QALYs	Total costs	Incremental QALYs	Incremental costs	ICER
No SeHCAT	NA	44%	£62	13.8021	£374	–	–	–
Trial of treatment	NA	63%	£143	13.9893	£3,806	0.1871	£3,432	£18,343
SeHCAT	NA	67%	£596	14.0539	£5,168	0.0647	£1,361	£21,036

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

Table 10 Results of the scenario analyses in people with IBS-D or functional diarrhoea

Scenario	Area of uncertainty investigated	Summary of analyses	Results
1	Probability of having a colonoscopy	The probability of having a colonoscopy was set to 0% (none of the people who may have colonoscopy in the base case will have a colonoscopy, as in the secondary analysis) or to 100% (everyone who has not had an investigation of bile acid diarrhoea or bile acid sequestrants or for whom bile acid sequestrants have not worked will have a colonoscopy).	Compared with the trial of treatment strategy, the SeHCAT strategy provides the most quality-adjusted life years (QALYs) for the highest cost, with incremental cost-effectiveness ratios (ICERs) around £20,000 per QALY gained. Depending on the threshold set for cost effectiveness, trial of treatment may be considered the most cost-effective strategy if everyone is assumed to have a colonoscopy. This may be an unrealistic assumption.
2	Probability of response to diarrhoea-predominant irritable bowel syndrome (IBS-D) treatment	Probability of response to IBS-D treatment in the no testing and the trial of treatment strategies were set closer to, the same or above the probability of response assumed in the SeHCAT strategy.	SeHCAT can be considered the most cost-effective strategy and provides ICERs below £20,000 per QALY gained in most scenarios. Only when people in the no testing strategy are assumed to have a much higher probability of IBS-D treatment response (70%) than people who have had a SeHCAT test (56%), can the no testing strategy be considered the most cost-effective strategy. This may be an unrealistic assumption.

3	Probability of a positive SeHCAT result and response to bile acid sequestrant treatment	Probability of a positive SeHCAT result and response to treatment were changed at the same time to the lowest and to the highest values within the 95% confidence intervals from their base-case values. In 2 further scenarios, the probability of response to the trial of treatment was decreased and increased from the base case value by 10%.	SeHCAT can be considered the most cost-effective strategy and provides ICERs below £13,000 per QALY gained in all the scenarios.

4	Distribution of bile acid sequestrant treatment	In 1 scenario, everyone with a positive SeHCAT test was assumed to be offered colestyramine and in another scenario, colesevelam. In 2 further scenarios, it was assumed that the distribution of colestyramine and colesevelam treatment in the trial of treatment matched their distribution in the SeHCAT strategy either using the base-case distribution from the trial of treatment strategy or the SeHCAT strategy.	Results were similar to the base case. Trial of treatment was dominated by the SeHCAT strategy. All ICERs for SeHCAT compared with the no testing strategy were below £13,500 per QALY gained.
5	Health state utilities	Response to colestyramine treatment was assumed to lead to full utility gain. In further scenarios, utility values from individual literature sources were explored but with a 75% utility gain similar to the base case assumption. One scenario also looked at using utility without an adjustment for age.	Results were similar to the base case. Trial of treatment was dominated by the SeHCAT strategy. All ICERs for SeHCAT compared with the no testing strategy were below £12,500 per QALY gained.
6	Cost inputs	All costs in the model were varied by 20% from the base case.	Results were similar to the base case. Trial of treatment was dominated by the SeHCAT strategy. All ICERs for SeHCAT compared with the no testing strategy were below £13,500 per QALY gained.

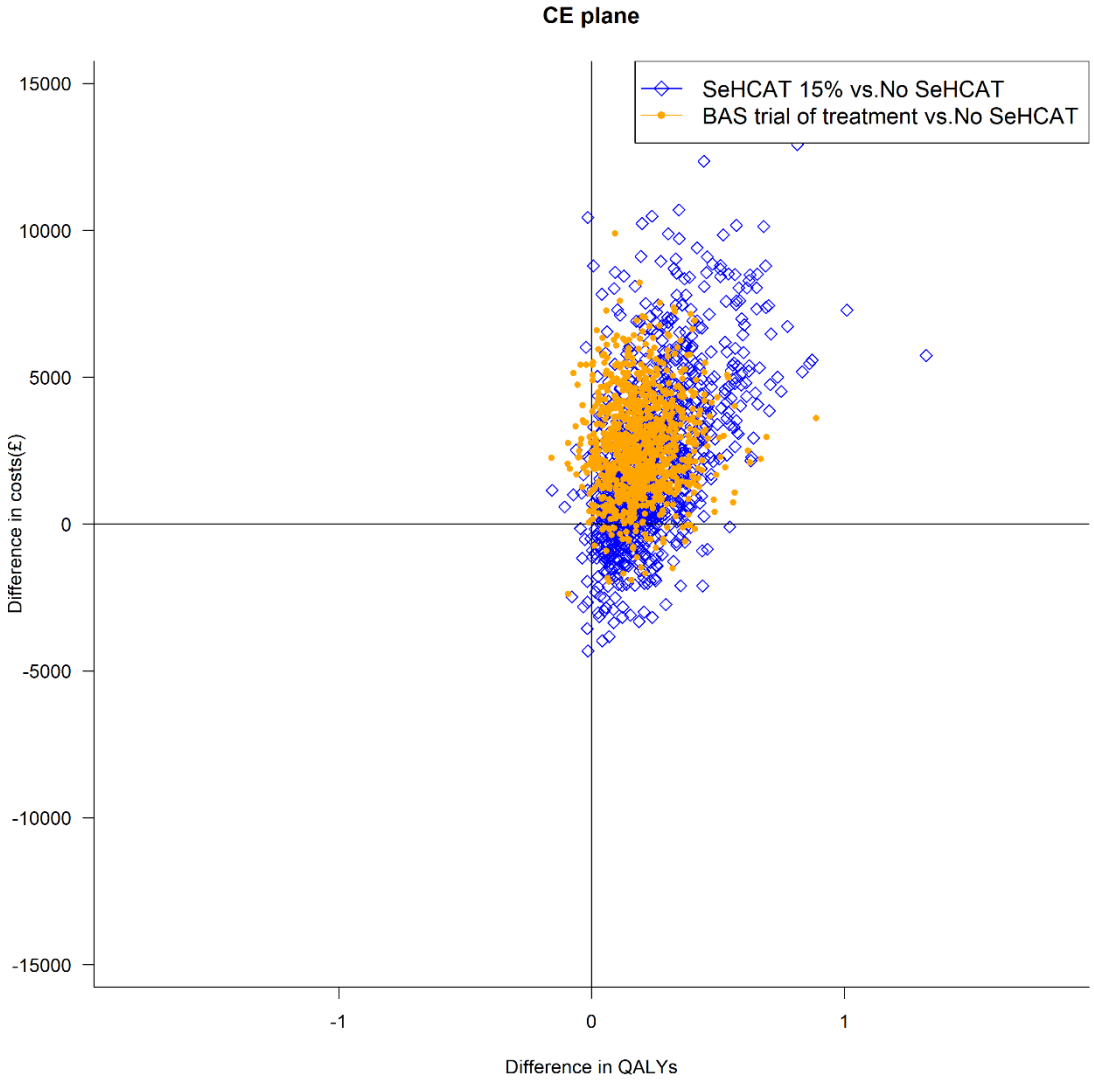
7	Transition probabilities	Probability of moving from the 'no diarrhoea' to the 'diarrhoea' health state (relapse) in the long-term Markov model was included also for people on IBS-D treatment and people having bile acid sequestrants. In further scenarios, this probability was increased. One scenario also included the probability of moving from the 'no diarrhoea' back to the 'diarrhoea' health state (remission).	Results were similar to the base case. Trial of treatment was dominated by the SeHCAT strategy. All ICERs for SeHCAT compared with the no testing strategy were below £10,000 per QALY gained.
8	Mortality estimates	Probability of death was set higher than in the base case.	Results were similar to the base case. Trial of treatment was dominated by the SeHCAT strategy. All strategies provided less QALYs and costs but the ICER for SeHCAT compared with the no testing strategy was only £70 lower than in the base case.

Probabilistic sensitivity analysis

Uncertainty in the model input values was explored through probabilistic sensitivity analysis. See figure 4 for the cost-effectiveness plane from the analysis in the base case. In most simulations, the SeHCAT testing strategy was more effective than the strategy in which testing or bile acid sequestrant treatment was not offered. See figure 5 for the cost-effectiveness acceptability curves from the same analysis. This shows that when the maximum acceptable ICER is £10,000 per QALY gained or above, SeHCAT testing is the strategy that is most likely to be cost effective. At a maximum acceptable ICER of £20,000 per QALY gained, SeHCAT has a 67% probability of being the most cost-effective option. At a maximum acceptable ICER of £30,000 per QALY gained, this probability is 73%.

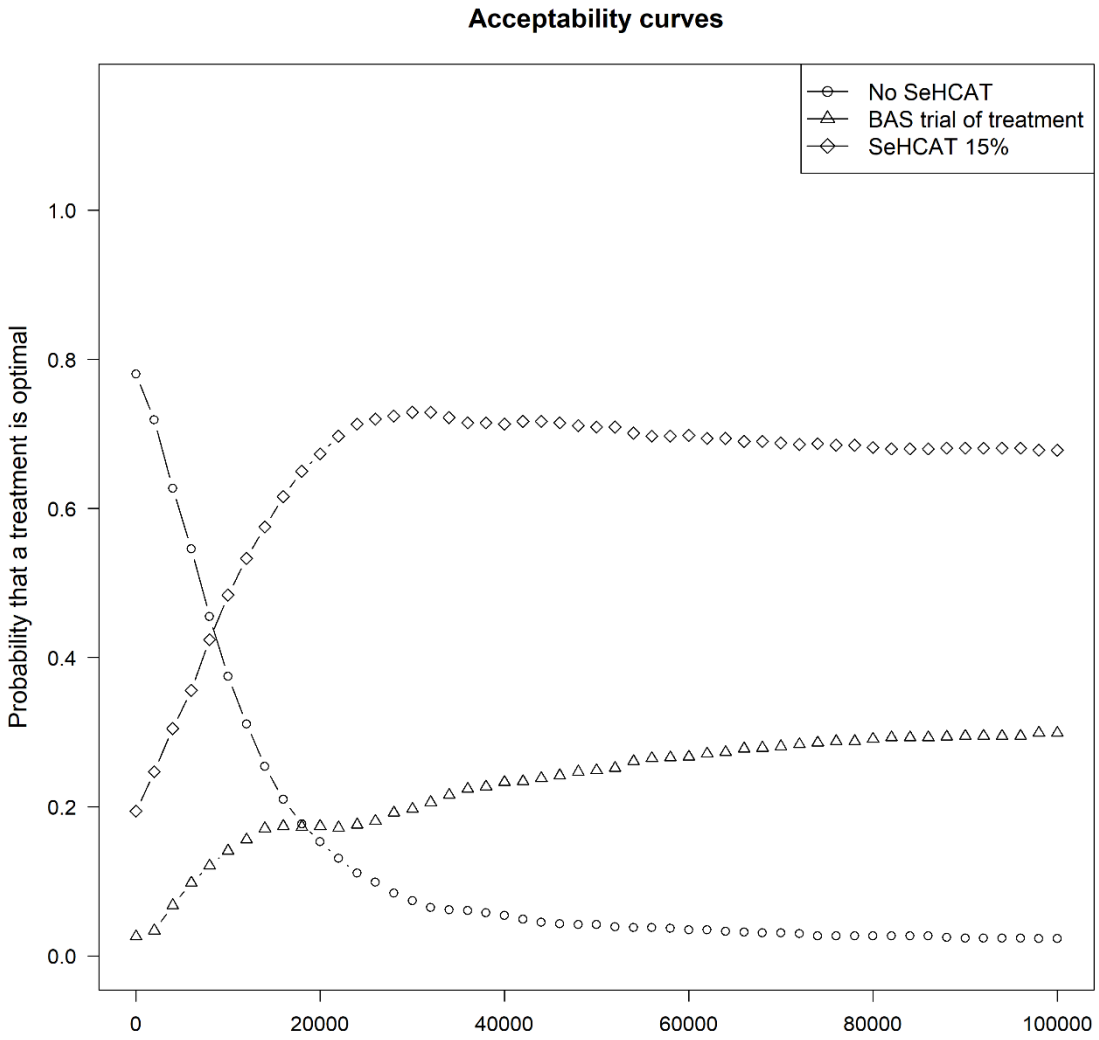
Likewise, in most simulations of the probabilistic sensitivity analysis in the secondary analysis (in which the model did not include the possibility of having a colonoscopy), the SeHCAT testing strategy was more effective than the strategy in which testing or bile acid sequestrant treatment was not offered. SeHCAT testing is the strategy that is most likely to be cost effective at a maximum acceptable ICER of £20,000 per QALY gained or higher. At a maximum acceptable ICER of £30,000 per QALY gained, SeHCAT has a 50% probability of being cost effective. The cost-effectiveness plane and the cost-effectiveness acceptability curve from this analysis are presented in figures 8 and 9 (pages 132 to 133) of the diagnostics assessment report.

Figure 4 Cost-effectiveness plane from the probabilistic sensitivity analysis of the base case for people with IBS-D or functional diarrhoea



Abbreviations: BAS, bile acid sequestrant; QALY, quality-adjusted life year

Figure 5 Cost-effectiveness acceptability curves from the probabilistic sensitivity analysis of the base case for people with IBS-D or functional diarrhoea



Abbreviation: BAS, bile acid sequestrant

Base-case results in people with Crohn's disease

The deterministic and probabilistic cost-effectiveness results for the base-case scenario in people with Crohn's disease are shown in table 11 and table 12.

In both the deterministic and probabilistic base-case analyses, the SeHCAT strategy was the most cost-effective strategy. In the deterministic analysis, it was more expensive but also more effective than the strategy of offering a trial of a bile acid sequestrant. The ICER for the SeHCAT strategy compared with this strategy was £1,727 per QALY gained (deterministic base-case analysis). In the probabilistic analysis, it was both more effective and less expensive compared with the trial of treatment strategy. In both analyses, the strategy in which bile acid diarrhoea was not investigated or treated was more expensive and less effective than the other strategies. The total costs of all the strategies in the probabilistic analysis were higher than the total costs in the deterministic analysis. This can be explained by the skewness of the distributions chosen to parameterise the cost inputs of the model.

In the short term, the SeHCAT strategy had the highest treatment response rate to any type of medication. But the initial costs were higher than in the trial of treatment strategy because of the costs of the SeHCAT test. Cost per response was the lowest for the trial of treatment strategy.

Analysis of alternative scenarios in people with Crohn's disease

Robustness of the cost-effectiveness results to alternative model assumptions and parameters was considered in several scenario analyses. For more details see table 13 and pages 143 to 147 of the diagnostics assessment report. In nearly all the scenarios, the cost-effectiveness results were similar to the base case or SeHCAT produced ICERs at below £9,500 per QALY gained. In the scenarios (see 10, in table 13) in which another strategy could be considered the most cost-effective option, the model assumptions were likely to be unrealistic.

Table 11 Deterministic cost-effectiveness results for the base-case scenario in people with Crohn's disease

Strategy	Treatment response	Initial costs	Total QALYs	Total costs	Incremental QALYs	Incremental costs	ICER
No SeHCAT	40%	£1,052	12.6863	£14,419	–	–	Dominated by trial of treatment
Trial of treatment	60%	£756	12.9008	£13,946	–	–	–
SeHCAT	71%	£1,061	13.0079	£14,131	0.1071	£185	£1,727

Table 12 Probabilistic cost-effectiveness results for the base-case scenario in people with Crohn's disease

Strategy	Treatment response	Initial costs	Total QALYs	Total costs	Incremental QALYs	Incremental costs	ICER
No SeHCAT	40%	£1,180	12.6857	£15,686	–	–	Dominated by trial of treatment
Trial of treatment	60%	£895	12.9006	£14,880	–	–	Dominated by SeHCAT
SeHCAT	71%	£1,172	13.0084	£14,795	–	–	–

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

Table 13 Results of the scenario analyses in people with Crohn's disease

Scenario	Area of uncertainty investigated	Summary of analyses	Results
9	Probability of response to diarrhoea treatment in Crohn's disease	Probability of response to diarrhoea treatment in the no testing and the trial of treatment strategies were set to the same or above the probability of response assumed in the SeHCAT strategy.	SeHCAT can be considered the most cost-effective strategy in all scenarios.
10	Probability of positive SeHCAT result and response to bile acid sequestrant treatment	Probability of a positive SeHCAT result and response to treatment were changed at the same time to the lowest and to the highest values within the 95% confidence intervals from their base-case values. In 2 further scenarios, the probability of response to the trial of treatment was decreased and increased from the base case value by 10%.	SeHCAT can be considered the most cost-effective strategy except when both the probability of the positive SeHCAT result and response to bile acid sequestrants was set lower than the base case and in a scenario where the response to trial of treatment was increased to 50%. In these scenarios trial of treatment may be considered a cost-effective strategy. The assumptions in these scenarios may be unrealistic.
11	Distribution of bile acid sequestrant treatment	In 1 scenario, everyone with a positive SeHCAT test was assumed to be offered colestyramine and in another scenario, colesevelam. In 2 further scenarios, it was assumed that the	No testing strategy was no longer dominated in all the scenarios explored but all the ICERs for SeHCAT compared with the trial

		distribution of colestyramine and colesevelam treatment in the trial of treatment matched their distribution in the SeHCAT strategy either using the base-case distribution from the trial of treatment strategy or the SeHCAT strategy.	of treatment strategy were below £9,500 per QALY gained.

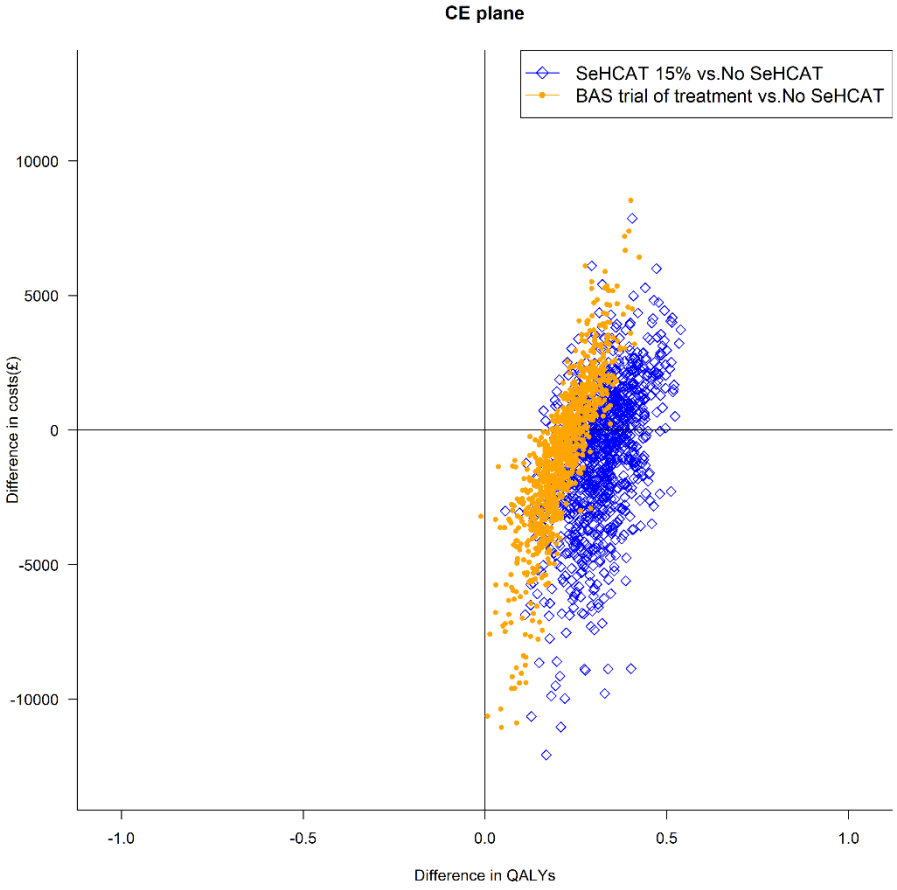
12	Health state utilities	Response to colestyramine treatment was assumed to lead to full utility gain. In further scenarios, utility values from individual literature sources were explored but with a 75% utility gain similar to the base-case assumption. One scenario also looked at using utility without an adjustment for age.	Results were similar to the base case. No testing strategy was dominated. All ICERs for SeHCAT compared with the trial of treatment strategy were below £3,000 per QALY gained.
13	Cost inputs	Costs of bile acid sequestrant treatment or Crohn's disease treatment in the model were varied by 20% from the base case.	No testing strategy was no longer dominated but all the ICERs for SeHCAT compared with the trial of treatment strategy were below £6,000 per QALY gained.
14	Transition probabilities	Probability of moving from the 'no diarrhoea' to the 'diarrhoea' health state (relapse) in the long-term Markov model was also included for people having bile acid sequestrants. In further scenarios, this probability was increased.	Results were similar to the base case. SeHCAT was dominant in all scenarios except in the scenario with the highest probability of relapse. In this scenario, all strategies resulted in lower costs and QALYs than in the base case but the ICER for SeHCAT at £1,459 per QALY gained remained almost the same.

15	Mortality estimates	Probability of death was set higher and lower than in the base case.	Results were similar to the base case. No testing-no treatment strategy was dominated. All ICERs for SeHCAT compared with the trial of treatment strategy remained practically unchanged.

Probabilistic sensitivity analysis

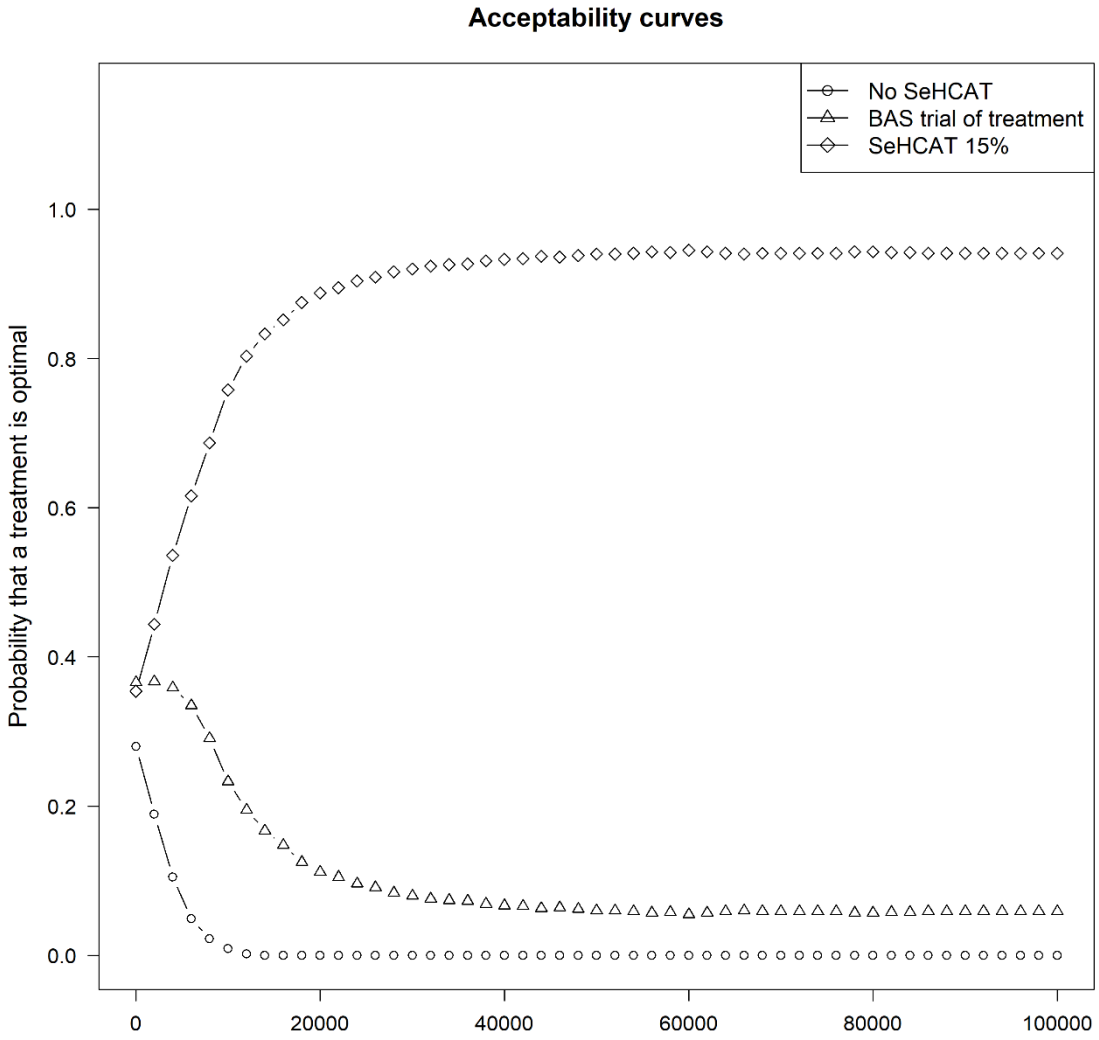
See figure 6 for the cost-effectiveness plane from the probabilistic sensitivity analysis in the base case. In all the simulations, the SeHCAT testing strategy was more effective than the strategy in which testing or a bile acid sequestrant was not offered. In half of the simulations, it was also less costly. See figure 7 for the cost-effectiveness acceptability curves from the same analysis. At a maximum acceptable ICER of £20,000 per QALY gained, SeHCAT has an 89% probability of being the most cost-effective option. At a maximum acceptable ICER of £30,000 per QALY gained, this probability is 92%.

Figure 6 Cost-effectiveness plane from the probabilistic sensitivity analysis of the base case for people with Crohn's disease



Abbreviations: BAS, bile acid sequestrant; QALY, quality-adjusted life year

Figure 7 Cost-effectiveness acceptability curves from the probabilistic sensitivity analysis of the base case for people with Crohn's disease



Abbreviation: BAS, bile acid sequestrant

3 Summary

Clinical effectiveness

The external assessment group (EAG) did a systematic review to identify and evaluate evidence for SeHCAT in diagnosing bile acid diarrhoea in people with:

- suspected or diagnosed diarrhoea-predominant irritable bowel syndrome (IBS-D) or functional diarrhoea and
- Crohn's disease without ileal resection, presenting with chronic diarrhoea.

The EAG identified 24 studies that met the inclusion criteria for the review. Only 9 of these were new studies found in the searches for this assessment. Most of the studies were of the lowest level of evidence eligible for inclusion: observational studies that reported outcome data only after a positive SeHCAT test result. Heterogeneity between studies was high and the quality of the studies was considered low. All the included studies provided some outcome data in people with IBS-D or functional diarrhoea. Only 1 small study provided data in people with Crohn's disease.

In total, 21 studies described outcomes after a positive SeHCAT test in people with IBS-D or functional diarrhoea. The probability of response to bile acid sequestrant treatment after a positive SeHCAT test result at a 15% threshold was estimated in 8 of these studies. The probability ranged from 38% to 86%. In the study in people with Crohn's disease, bile acid sequestrants were considered to have worked for 8 of the 9 people (89%) with a positive SeHCAT test result who were offered this treatment.

Very limited evidence exists on health-related quality of life of people with bile acid diarrhoea. No evidence was found on the long-term effects of bile acid sequestrants. No eligible studies were found on trial of treatment in either of the populations.

Cost effectiveness

The EAG developed a de novo economic model to investigate the cost effectiveness of SeHCAT testing using a 15% threshold for a positive test result. Since the publication of NICE's diagnostics guidance on SeHCAT, the place of SeHCAT in the care pathway has changed. The updated model reflects this and for people with suspected or diagnosed diarrhoea-predominant irritable bowel syndrome (IBS-D) or functional diarrhoea,

colonoscopy is placed after SeHCAT testing. This may generate different costs and outcomes compared with the original assessment. The modelling approach has also been simplified, with only the 15% threshold modelled to reduce the number of analyses and plausible ranges of results.

The results show that SeHCAT at a 15% threshold could be considered cost effective for investigating and diagnosing bile acid diarrhoea in people with IBS-D or functional diarrhoea and in people with Crohn's disease. In the base-case analyses, the ICER for SeHCAT testing for people in IBS-D or functional diarrhoea was below £10,000 per QALY gained. Also, in the base-case analyses for people with Crohn's disease, SeHCAT was the most cost-effective strategy (ICER below £2,000 per QALY gained in the deterministic analysis and dominating in the probabilistic analysis). Regardless of the SeHCAT test result, people who had a SeHCAT test were more likely to benefit from any treatment they were offered than people who were offered a trial of bile acid sequestrant or people who were not offered a SeHCAT test or a trial of treatment. A potential additional benefit of SeHCAT testing in people with IBS-D or functional diarrhoea could be that fewer colonoscopies are done. The cost-effectiveness results for this population show that SeHCAT was the strategy in which the lowest number of people had a colonoscopy.

The EAG varied the base-case assumptions in several scenarios. In most scenarios, the cost-effectiveness results for both populations were robust to the alternative assumptions. However, 1-way and multiway-sensitivity analyses could not be done because of a lack of published distributions on which to base estimates. The EAG caution that the model results depend heavily on expert opinion and are subject to many uncertainties, described in section 4.

4 Issues for consideration

Clinical effectiveness

In the previous assessment of SeHCAT, only limited evidence on its clinical effectiveness was found. Since then, only 9 new studies have been published and the evidence base remains very limited.

The existing evidence describes outcomes for people who have had a positive SeHCAT test result. But not everyone with a positive test result in these studies had a bile acid sequestrant and it is not certain what happens to people who have had a negative SeHCAT test result. So, the evidence is too limited to estimate SeHCAT's accuracy and how much bile acid sequestrants might benefit people who have a positive test result at different SeHCAT thresholds. The optimal SeHCAT threshold for clinical decision making remains uncertain.

The available evidence is of low quality. There are differences between the studies and unclear reporting about the initial assessment for people in the studies. So it is not certain how generalisable the evidence is to the target populations in this assessment. Very limited or no evidence is available on patient-reported outcomes such as health-related quality of life of people with bile acid diarrhoea, acceptability of SeHCAT testing and tolerability of bile acid sequestrants. There is still a lack of evidence on safety, efficacy and long-term effects of bile acid sequestrants.

Cost effectiveness

Because of the lack of evidence on the accuracy of SeHCAT testing, test accuracy had to be modelled based on treatment response after a positive SeHCAT test. This meant that it was not possible to indicate or account for the consequences of any incorrect test results. It is possible that some people with a negative test result may have bile acid diarrhoea but because of the test result they may not be offered the best treatment for the condition.

Likewise, it is possible that with a bile acid sequestrant, some people with a positive test result could have some improvement in their diarrhoea without having bile acid diarrhoea. Again, these people may not be offered another potentially more suitable treatment.

Very limited evidence was found to inform the model inputs. So, most of the inputs were based on expert opinion and many modelling assumptions had to be made. There was substantial uncertainty, particularly about what steps are taken, what resources may be used and what outcomes might follow a negative SeHCAT test result or a trial of bile acid sequestrant.

SeHCAT testing was included in the models with the 15% threshold value for a positive test. The threshold value used in clinical practice may vary. The available clinical effectiveness evidence shows that the threshold used to define a positive SeHCAT test affects the probability of treatment response. Treatment response was a key driver of the cost-effectiveness results. It is uncertain how the cost-effectiveness results would change if other thresholds were included in the analyses.

One-way or multi-way sensitivity analyses could not be done because of the lack of published uncertainty data for model input parameters. Although model results were robust to the various scenario analyses that were run, it is not certain that the full extent of the uncertainty in the decision question has been explored because of the limitations in the available data.

5 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

IBS is twice as common in women as in men. It may be that the prevalence distribution of bile acid diarrhoea follows a similar pattern. Symptoms of bile acid diarrhoea often appear in people between 20 and 30 years. Fewer

people from black, Asian and minority ethnic groups than expected are seen for investigation of bile acid diarrhoea. People who are pregnant, breast feeding or considering having a baby may need to delay SeHCAT because the test involves exposure to radiation.

Chronic diarrhoea, including bile acid diarrhoea, has a substantial and long-term adverse effect on a person's ability to carry out normal day-to-day activities. Therefore, people with chronic diarrhoea may be protected under the disability provision of the Equality Act 2010.

6 Implementation

SeHCAT is in routine clinical use in many NHS acute trusts. The test has a healthcare resource group code (RN14Z) and an NHS tariff. The equipment used for taking the scan is also used for other common nuclear medicine procedures and is widely available in nuclear medicine departments. Adoption of the test does not need extensive additional training.

There are logistic considerations for high-throughput nuclear medicine departments because other concurrent studies may result in background radiation, which could affect SeHCAT testing. For nuclear medicine departments that are running at or close to capacity in terms of staff or equipment or both, additional funding may be needed to increase capacity.

7 Authors

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

A. The diagnostics assessment report for this assessment was prepared by Kleijnen Systematic Reviews Ltd:

- Westwood ME, Corro Ramos I, Armstrong N et al. (2021) SeHCAT (Tauroselcholic [75 selenium] acid) for the investigation of bile acid diarrhoea: a systematic review and cost-effectiveness analysis. A Diagnostic Assessment Report. Kleijnen Systematic Reviews Ltd.

B. The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

Manufacturer(s) of technologies included in the final scope:

- GE Healthcare Ltd

Other commercial organisations:

- BIOHIT HealthCare Ltd
- Immundiagnostik AG

Professional groups and patient/carer groups:

- British Nuclear Medicine Society
- British Society of Gastroenterology (BSG)
- Royal College of Physicians
- BAD-UK (Bile Acid Diarrhoea – UK)
- Guts UK Charity
- Pelvic Radiation Disease Association
- The IBS Network

Research groups:

- UK Bile Acid Related Diarrhoea Network

Associated guideline groups:

- None

Others:

- Department of Health and Social Care
- Healthcare Improvement Scotland
- Medicines and Healthcare products Regulatory Agency
- NHS England
- Welsh Government

Appendix B: Glossary of terms

Bile acid diarrhoea

A form of chronic diarrhoea. In bile acid diarrhoea, bile acids in the body are not recycled properly. Excess bile travels from the small bowel to the colon, stimulates salt and water secretion and bowel movements and results in diarrhoea.

Bile acid malabsorption

Another term for bile acid diarrhoea.

Bile acid sequestrants

Medication for treating bile acid diarrhoea.

Chronic diarrhoea

Chronic diarrhoea is the persistent alteration from the norm with stool consistency between types 5 and 7 on the Bristol stool chart and increased frequency greater than 4 weeks' duration (British Society for Gastroenterology guidelines for investigation of chronic diarrhoea in adults).

Diarrhoea-predominant irritable bowel syndrome (IBS-D)

A type of IBS characterised by chronic diarrhoea (see also irritable bowel syndrome). This is the most common type of IBS.

Functional diarrhoea

Functional diarrhoea is a type of chronic diarrhoea in which no structural or biochemical abnormalities have been identified as a cause for the symptoms in people whose condition does not meet the symptom profile for IBS.

Incremental cost-effectiveness ratio (ICER)

The difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest.

Irritable bowel syndrome (IBS)

A chronic, relapsing and often lifelong disorder. IBS is characterised by abdominal pain or discomfort, which may be associated with a bowel movement, with or without a change in bowel habit. Symptoms may include constipation or diarrhoea or both, and abdominal distension, usually referred to as bloating. Symptoms sometimes overlap with other gastrointestinal disorders.

Predictive accuracy

Ability of a test to predict a future outcome such as response to treatment. To assess this, predictive accuracy studies use an accuracy-type study design. But because predictive accuracy studies do not account for other potential predictors of the outcome (they are not true prediction modelling studies), their results may not reflect the true predictive ability of the test.

Quality-adjusted life year (QALY)

A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a person having a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance.

Reference standard

The best currently available diagnostic test, against which the technology under assessment is compared.