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, please indicate. If limited period, please indicate duration)	% of patients	range
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 <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 (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	% of patients	range

		period, please 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. **<u>If this changes per treatment option, please indicate them separately.</u>**

% 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