National Institute for Health and Care Excellence

Irritable Bowel Syndrome (Standing Committee A)
Addendum Consultation Table
29 October – 26 November 2014

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	Almirall Ltd	1	Addendum	11	17	To include in section "Key priorities for implementation", content consistent with the guidance provided on page 17 (section Recommendations), where linaclotide is recommended after laxatives have not helped. "Consider linaclotide for people with moderate or severe symptoms of IBS with constipation only if: 1) They have had IBS symptoms for at least 12 months and 2) optimal or maximum tolerated doses of laxatives have not helped." [2015]	Thank you for your comment. The KPIs specified in the original NICE guideline were prioritised from all the recommendations by the original guideline development group in 2008. It is outside the remit of this particular update to re-prioritise previous KPIs Thank you for your comment. The Committee discussed this recommendation wording and made some amendments. The updated recommendation reads as follows: **Consider linaclotide for people with IBS only if:** • **optimal or maximum tolerated doses of previous laxatives from different classes have not helped and** • **they have had constipation for at least 12 months** **Follow-up people taking linaclotide after 3 months. [new 2015]** The Committee agreed that the stated 'at least 12 months' indicates the severity of IBS, therefore it is not necessary to state

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							'moderate' or 'severe'. There is not an internationally accepted definition of severity of IBS. .
SH	Almirall Ltd	2	Addendum	17	21	The wording regarding linaclotide should be consistent with the therapeutic indication. Suggest rewording to "Consider linaclotide for people with moderate or severe symptoms of IBS with constipation only if: 1) They have had IBS symptoms for at least 12 months and 2) optimal or maximum tolerated doses of laxatives have not helped"	Thank you for your comment. The Committee discussed this recommendation wording and made some amendments. The updated recommendation reads as follows: **Consider linaclotide for people with IBS only if:** • **optimal or maximum tolerated doses of previous laxatives from different classes have not helped and** • **they have had constipation for at least 12 months** **Follow-up people taking linaclotide after 3 months. [new 2015]** The Committee agreed that the stated 'at least 12 months' indicates the severity of IBS, therefore it is not necessary to state 'moderate' or 'severe'. There is not an internationally accepted definition of severity of IBS.
SH	Almirall Ltd	3	Addendum	22	9	Clarify use of linaclotide and benefits of treatment. "Linaclotide, a guanylate cyclase C receptor agonist is one of a relatively new class of drugs for constipation with visceral analgesic and secretory benefits. Linaclotide is licenced for adults with moderate to severe IBS with constipation at a dose of 290µg once daily."	Thank you for the information. In the implementation of guidelines, clinicians are advised to look at the SPC where they will find this information. We do not duplicate information already in the SPC. The effect of linaclotide on pain as a clinical

<table>
<tr><th>Type</th><th>Stakeholder</th><th>Order No</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments
Please insert each new comment in a new row.</th><th>Developer's Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td>It is important that the visceral analgesic property of linaclotide is reflected in the new guideline (as stated in the SmPC), as abdominal pain is a key symptom in IBS patients.</td><td>outcome formed part of the main evidence review and this has been evaluated and discussed throughout the addendum.</td></tr>
<tr><td>SH</td><td>Almirall Ltd</td><td>4</td><td>Addendum</td><td>29</td><td>42</td><td>Concerns regarding the lack of data available for potential confounders were raised:

"…Use of other medications e.g. anti-depressants, anti-spasmodics and analgesics, dietary fibre modification, fluid intake and exercise levels were not reported by study arm, leading to concerns about drug efficacy…"

Concomitant Medication usage per study arm for the two phase III trials was balanced and did not serve as a confounding factor in favour of linaclotide:

<table><tr><th>Concomitant Medication</th><th>% of patients placebo</th><th>% of patients linaclotide</th></tr><tr><td>Bulking agents/Soluble fiber(A06AC)</td><td>2.26</td><td>3.11</td></tr><tr><td>Osmotic laxatives (A06AD)</td><td>0.5</td><td>0.5</td></tr></table>Source data provided by Almirall Ltd.

The general evaluation of the quality of the clinical evidence should be reviewed considering the additional data provided above. Page 29 of the guideline should be updated to reflect this assessment, as well as pages 265, 267, 268 and 269 of the addendum (see below).</td><td>Thank you for your comment. The included studies did not report whether concomitant medication use (particularly laxatives) or rescue medication use per study arm was balanced, therefore at the time of the evidence review we could not be confident that this was the case.

This leads to uncertainty of the effect estimates and thus to the downgrading of the quality of evidence.

The data subsequently provided during stakeholder consultation includes percentages only and no statistical comparisons are performed to evaluate differences between study arms.

As such this additional data is insufficient to reduce our uncertainty of the evidence.

Nevertheless, the Committee further discussed these recommendations and made some amendments as follows:

Consider linaclotide for people with IBS only if:
• optimal or maximum tolerated doses of previous laxatives from different classes have not helped and</td></tr>
</table>

<table>
<tr><th>Type</th><th>Stakeholder</th><th>Order No</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments
Please insert each new comment in a new row.</th><th>Developer's Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>they have had constipation for at least 12 months
Follow-up people taking linaclotide after 3 months. [new 2015]</td></tr>
<tr><td>SH</td><td>Almirall Ltd</td><td>5</td><td>Addendum</td><td>29</td><td>42</td><td>Concerns regarding the lack of data available for potential confounders were raised.

Use of rescue medication (other laxatives).

Rescue medication usage per study arm for the two phase III trials did not serve as a confounding factor in favour of linaclotide:

<table><tr><td>Class of Rescue Medication</td><td>% of pts</td><td>% of pts</td></tr><tr><td></td><td>Placebo</td><td>Linaclotide</td></tr><tr><td>Stimulant Laxatives</td><td>75.16</td><td>56.27</td></tr></table>Source data provided by Almirall Ltd.

The general evaluation of the quality of the clinical evidence should be reviewed considering the additional data provided above. Page 29 of the guideline should be updated to reflect this assessment, as well as pages 265, 267, 268 and 269 of the addendum.</td><td>Thank you for your comment. The included studies did not report whether concomitant medication use (particularly laxatives) or rescue medication use per study arm was balanced, therefore at the time of the evidence review we could not be confident that this was the case.

This leads to the uncertainty of the effect estimates and thus to the downgrading of the quality of evidence.

The data subsequently provided during stakeholder consultation includes percentages only and no statistical comparisons are performed to evaluate differences between study arms.

As such this additional data is insufficient to reduce our uncertainty of the evidence.

Nevertheless, the Committee further discussed these recommendations and made some amendments as follows:

Consider linaclotide for people with IBS only if:
optimal or maximum tolerated doses of previous laxatives from different classes have not helped and</td></tr>
</table>

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							• **they have had constipation for at least 12 months** **Follow-up people taking linaclotide after 3 months. [new 2015]**
SH	Almirall Ltd	6	Addendum	31	2	To make wording consistent throughout the guideline. Consider linaclotide for people with moderate or severe symptoms of IBS with constipation only if: 1) They have had IBS symptoms for at least 12 months and 2) optimal or maximum tolerated doses of laxatives have not helped. [2015]	This comment is a duplication of comment ID18 and 19 and suggests the addition of the word 'moderate' when describing constipation severity. After further discussion by the Committee, these recommendations have been amendments as follows: **Consider linaclotide for people with IBS only if:** • **optimal or maximum tolerated doses of previous laxatives from different classes have not helped and** • **they have had constipation for at least 12 months** **Follow-up people taking linaclotide after 3 months. [new 2015]** The Committee agreed that the stated 'at least 12 months' indicates the severity of IBS, therefore it is not necessary to state 'moderate' or 'severe'. There is not an internationally accepted definition of severity of IBS. Moreover, the 12-month time frame is based on the evidence (entry criteria from the included studies [Chey 2012; Rao 2012; Johnston 2010]).

<table>
<tr><th>Type</th><th>Stakeholder</th><th>Order No</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments
Please insert each new comment in a new row.</th><th>Developer's Response
Please respond to each comment</th></tr>
<tr><td>SH</td><td>Almirall Ltd</td><td>7</td><td>Addendum</td><td>265</td><td>7 - 10</td><td>Concerns regarding the lack of data available for potential confounders were raised.

Concomitant Medication usage per study arm for the two phase III trials was balanced and did not serve as a confounding factor in favour of linaclotide:

<table>
<tr><td>Concomitant Medication (ATC Code)</td><td>% of patients placebo</td><td>% of patients linaclotide</td></tr>
<tr><td>Bulking agents/Soluble fibre (A06AC)</td><td>2.26</td><td>3.11</td></tr>
<tr><td>Osmotic laxatives (A06AD)</td><td>0.5</td><td>0.5</td></tr>
</table>
Source data provided by Almirall Ltd.

Use of rescue medication (other laxatives):

Rescue Medication usage per study arm for the two phase III trials (pooled analysis) was balanced and did not serve as a confounding factor:

<table>
<tr><td>Class of Rescue Medication</td><td>% of pts Placebo</td><td>% of pts linaclotide</td></tr>
<tr><td>Stimulant Laxatives</td><td>75.16</td><td>56.27</td></tr>
</table>
Source data provided by Almirall Ltd.
.

The general evaluation of the quality of the clinical evidence for linaclotide should be reviewed considering this additional data. Page 29 of the guideline should be updated to reflect this assessment, as well as pages 265, 267, 268 and 269 of the addendum.</td><td>Thank you for your comment. The included studies did not report whether concomitant medication use (particularly laxatives) or rescue medication use per study arm was balanced, therefore at the time of the evidence review we could not be confident that this was the case.

This leads to the uncertainty of the effect estimates and thus to the downgrading of the quality of evidence.

The data subsequently provided during stakeholder consultation includes percentages only and no statistical comparisons are performed to evaluate differences between study arms.

As such this additional data is insufficient to reduce our uncertainty of the evidence.

Nevertheless, the Committee further discussed these recommendations and made some amendments as follows:

Consider linaclotide for people with IBS only if:
• optimal or maximum tolerated doses of previous laxatives from different classes have not helped and
• they have had constipation for at least 12 months

Follow-up people taking linaclotide after 3 months. [new 2015]</td></tr>
</table>

<table>
<tr><th>Type</th><th>Stakeholder</th><th>Order No</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments
Please insert each new comment in a new row.</th><th>Developer's Response
Please respond to each comment</th></tr>
<tr><td>SH</td><td>Almirall Ltd</td><td>8</td><td>Addendum</td><td>267</td><td>2 - 3</td><td>Concerns regarding the lack of data available for potential confounders were raised.

Use of rescue medication (other laxatives):

Rescue medication usage per study arm for the two phase III trials (pooled analysis) was balanced and did not serve as a confounding factor:

<table>
<tr><td>Class of Rescue Medication</td><td>% of pts Placebo</td><td>% of pts linaclotide</td></tr>
<tr><td>Stimulant Laxatives</td><td>75.16</td><td>56.27</td></tr>
</table>
Source data provided by Almirall Ltd.

Concomitant Medication usage per study arm for the two phase III trials was balanced and did not serve as a confounding factor in favour of linaclotide:

<table>
<tr><td>Concomitant Medication (ATC Code)</td><td>% of patients placebo</td><td>% of patients linaclotide</td></tr>
<tr><td>Bulking agents/Soluble fibre (A06AC)</td><td>2.26</td><td>3.11</td></tr>
<tr><td>Osmotic laxatives (A06AD)</td><td>0.5</td><td>0.5</td></tr>
</table>
Source data provided by Almirall Ltd.
.

The general evaluation of the quality of the clinical evidence for linaclotide should be reviewed considering this additional data. Page 29 of the guideline should be updated to reflect this, as well as pages 265, 267, 268 and 269 of the addendum.</td><td>Thank you for your comment. The included studies did not report whether concomitant medication use (particularly laxatives) or rescue medication use per study arm was balanced, therefore at the time of the evidence review we could not be confident that this was the case.

This leads to the uncertainty of the effect estimates and thus to the downgrading of the quality of evidence.

The data subsequently provided during stakeholder consultation includes percentages only and no statistical comparisons are performed to evaluate differences between study arms.

As such this additional data is insufficient to reduce our uncertainty of the evidence.

Nevertheless, the Committee further discussed these recommendations and made some amendments as follows:

Consider linaclotide for people with IBS only if:
• optimal or maximum tolerated doses of previous laxatives from different classes have not helped and
• they have had constipation for at least 12 months
Follow-up people taking linaclotide after 3 months. [new 2015]</td></tr>
</table>

<table>
<tr><th>Type</th><th>Stakeholder</th><th>Order No</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments
Please insert each new comment in a new row.</th><th>Developer's Response
Please respond to each comment</th></tr>
<tr><td>SH</td><td>Almirall Ltd</td><td>9</td><td>Addendum</td><td>268</td><td>3 - 4</td><td>Concerns regarding the lack of data available for potential confounders were raised.

Use of rescue medication (other laxatives):

Rescue medication usage per study arm for the two phase III trials (pooled analysis) was balanced and did not serve as a confounding factor:

<table><tr><td>Class of Rescue Medication</td><td>% of pts Placebo</td><td>% of pts linaclotide</td></tr><tr><td>Stimulant Laxatives</td><td>75.16</td><td>56.27</td></tr></table>Source data provided by Almirall Ltd.

Concomitant Medication usage per study arm for the two phase III trials was balanced and did not serve as a confounding factor in favour of linaclotide:

<table><tr><td>Concomitant Medication (ATC Code)</td><td>% of patients placebo</td><td>% of patients linaclotide</td></tr><tr><td>Bulking agents/Soluble fibre (A06AC)</td><td>2.26</td><td>3.11</td></tr><tr><td>Osmotic laxatives (A06AD)</td><td>0.5</td><td>0.5</td></tr></table>Source data provided by Almirall Ltd.

The general evaluation of the quality of the clinical evidence for linaclotide should be reviewed considering this additional data. Page 29 of the guideline should be updated to reflect this, as well as pages 265, 267, 268 and 269 of the addendum.</td><td>Thank you for your comment. The included studies did not report whether concomitant medication use (particularly laxatives) or rescue medication use per study arm was balanced, therefore at the time of the evidence review we could not be confident that this was the case.

This leads to the uncertainty of the effect estimates and thus to the downgrading of the quality of evidence.

The data subsequently provided during stakeholder consultation includes percentages only and no statistical comparisons are performed to evaluate differences between study arms.

As such this additional data is insufficient to reduce our uncertainty of the evidence.

Nevertheless, the Committee further discussed these recommendations and made some amendments as follows:

Consider linaclotide for people with IBS only if:
optimal or maximum tolerated doses of previous laxatives from different classes have not helped and
they have had constipation for at least 12 months
Follow-up people taking linaclotide after 3 months. [new 2015]</td></tr>
</table>

<table>
<tr><th>Type</th><th>Stakeholder</th><th>Order No</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments
Please insert each new comment in a new row.</th><th>Developer's Response
Please respond to each comment</th></tr>
<tr><td>SH</td><td>Almirall Ltd</td><td>10</td><td>Addendum</td><td>269</td><td>9 – 10</td><td>Concerns regarding the lack of data available for potential confounders were raised.

Use of rescue medication (other laxatives):

Rescue medication usage per study arm for the two phase III trials (pooled analysis) was balanced and did not serve as a confounding factor:

<table><tr><td>Class of Rescue Medication</td><td>% of pts Placebo</td><td>% of pts linaclotide</td></tr><tr><td>Stimulant Laxatives</td><td>75.16</td><td>56.27</td></tr></table>Source data provided by Almirall Ltd.

The general evaluation of the quality of the clinical evidence for linaclotide should be reviewed considering this additional data. Page 29 of the guideline should be updated to reflect this, as well as pages 265, 267, 268 and 269 of the addendum.</td><td>Thank you for your comment. The included studies did not report whether concomitant medication use (particularly laxatives) or rescue medication use per study arm was balanced, therefore at the time of the evidence review we could not be confident that this was the case.

This leads to the uncertainty of the effect estimates and thus to the downgrading of the quality of evidence.

The data subsequently provided during stakeholder consultation includes percentages only and no statistical comparisons are performed to evaluate differences between study arms.

As such this additional data is insufficient to reduce our uncertainty of the evidence.

Nevertheless, the Committee further discussed these recommendations and made some amendments as follows:

Consider linaclotide for people with IBS only if:
optimal or maximum tolerated doses of previous laxatives from different classes have not helped and
they have had constipation for at least 12 months
Follow-up people taking linaclotide after 3 months. [new 2015]</td></tr>
</table>

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	British Acupuncture Council	1	General	General	General	There has been substantial new evidence on acupuncture and irritable bowel syndrome published since the original guideline, in particular the UK-based RCT from MacPherson et al (2012). Why then is acupuncture not part of the new evidence review in this addendum? The most recent meta-analysis (Chao and Zhang 2014) on the subject found a statistically significant beneficial effect. The adverse events data also need updating.	Thank you for your comment. Acupuncture for irritable bowel syndrome was outside the scope of this update. The review protocol specifies the interventions that were reviewed in this update. Your feedback will however be passed on to our surveillance team for the next review.
SH	British Dietetic Association	4	General	General	General	Should anything be included regarding assessing social circumstances/ understanding, before consideration of commencement of fodmap diet - to help improve adherence	Thank you for your comment. From the evidence point of view, none of the included studies for the low FODMAP diet mentioned social circumstances or level of understanding in their baseline characteristics, and therefore there is no evidence to support the suggestion that assessment would improve adherence. However, the Committee did acknowledge the in importance of individual differences and patient-centred care, therefore the Committee has made a new recommendation that the dietary advice should ***"only be given by a healthcare professional with expertise in dietary management"***, to ensure individual circumstances and understanding of the diet would be addressed. These may include the availability and choices of different food sources, as well as advice to implement the diet.
SH	British Dietetic Association	17	General	General	General	A very recent review indicates that NNT is 2.2 for a low FODMAP diet so it may be worth looking at this review paper for further details. Khan et al 2014 Low-FODMAP Diet for Irritable Bowel Syndrome: Is It Ready for Prime Time?Dig Dis Sci DOI 10.1007/s10620-014-3436-4	Thank you for the information. We have obtained and assessed this article but it doesn't meet the inclusion criteria of the systematic review as it is not a primary research study and it is not a systematic review of RCTs.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	British Dietetic Association	18	Addendum	10		Change 'a healthcare professional' to a 'Registered Dietitian' – the research shows a low FODMAP diet to be successful when delivered by a Registered Dietitian	Thank you for your comment. This was discussed further by the Committee. They took into account your comments, as well as other differing comments from the British Gastroenterology Society. On balance, and the fact that this is a primary care guideline, the Committee agreed to keep the current recommendation because a dietitian is a healthcare professional with expertise in dietary management. The Committee felt they could not be more specific than the current recommendation.
SH	British Dietetic Association	9	Addendum	18	9	We would suggest that fermentation does not cause the symptoms of IBS. It worsens or provokes symptoms in patients with IBS who have visceral hypersensitivity	Thank you. We have made the suggested change in the addendum.
SH	British Dietetic Association	10	Addendum	18	18	We suggest '…with varying subtypes (diarrhoea predominant, …)' would be more accurate than what is currently stated regarding the participants included in the studies.	Thank you. We have made the suggested change in the addendum.
SH	British Dietetic Association	11	Addendum	18	19	This is not entirely correct. This study included patients with bloating and diarrhoea, it was not specified that these were predominant symptoms, as suggested. The predominant symptom for each patient was not recorded in this study	Thank you. We have reworded as suggested in the addendum.
SH	British Dietetic Association	12	Addendum	19		Urgency was not considered in the evidence statement section. This is a major symptom that affects quality of life in these patients and should be included (measured in the controlled trial).	Thank you for your comment. We agree that this is a major symptom for some people with IBS. At the protocol development stage, the topic specific committee members were asked to identify and prioritise patient important outcomes. Examples of those identified include pain, overall symptoms, stool frequency and quality of life (full list is available in the review protocol). Urgency was not an outcome that was prioritised by the experts

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							hence it was not included in the review protocol. The evidence review only includes outcomes specified in the review protocol and the evidence statements can only reflect the evidence reviewed. As such it is not possible to consider urgency in the evidence statements.
SH	British Dietetic Association	13	Addendum	19	27	This population group did not have diarrhoea and/or bloating predominant IBS. The paper states that they experienced the symptom, not that it was predominant. Please note there was a significant change in satisfaction with bowel habit in both IBS-D and IBS-C in Halmos et al 2014. This was not mentioned in the evidence statements for diarrhoea and constipation.	Thank you the wording has been amended and this point was verbally reiterated to the Committee. Patient satisfaction with bowel habit was not prioritised as an important outcome in the review protocol which is why this outcome is not mentioned in the evidence statement.
SH	British Dietetic Association	16	Addendum	19		The evidence statements for each symptom have been graded 'very low quality'. According to GRADE this means that any estimate of effect is very uncertain. All 3 studies considered report beneficial effects of the low FODMAP diet on symptoms. Certainly, there are limitations to the studies, including the lack of blinding, which is almost impossible in dietary intervention studies (Yao et al 2013, Design of Clinical Trials Evaluating Dietary Interventions in Patients With Functional Gastrointestinal Disorders, Gastroenterology)	Quality ratings for each outcome are rated based on 5 criteria. The GRADE profiles illustrate how the quality ratings were assigned and the corresponding footnotes provide the rationale for the judgement. GRADE methodology does not simply assess whether an intervention reported beneficial effects or not, it also assesses the certainty/uncertainty around the effect estimates from the included studies. These are 2 separate quality assessments. Thank you for your comment. We acknowledged that it is difficult to blind trials on dietary intervention. However, the impossibility to blind does not eliminate the potential placebo effects particularly if the outcomes are self-report measurements. The essence of GRADE is to be explicit and transparent.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						For dietary intervention studies, the participant numbers are not particularly small and have been powered appropriately.	The sample size of the included studies may be sufficient for testing a hypothesis (power-based sample size calculation); however it wasn't sufficient to be certain about the precision of the effect estimates (precision-based sample size calculation). Please refer to: *Bland M. BMJ 2009;339:b3985* *doi: 10.1136/bmj.b3985*
						GRADE recommends that grade should be increased if there is evidence of a dose response gradient. Please refer to Shepherd et al 2008 Dietary Triggers of Abdominal Symptoms in Patients With Irritable Bowel Syndrome: Randomized Placebo-Controlled Evidence. Clin Gastroenterol Hepatol 6:765–771 for a double blind quadruple arm placebo-controlled randomised controlled trial demonstrating a dose response effect for FODMAPs in inducing IBS symptoms. Finally, and importantly, studies should not be downgraded based on the statement that 'FODMAP diet usually advised for 8 weeks'. Clinical guidelines should be developed and graded based on the evidence, not on current practice.	Thank you for your comment. In GRADE methodology, the criteria for upgrading only apply to observational studies if they have not been downgraded for any other reasons (based on the 4 criteria). This is explained fully here. The paper you refer to (Shepherd 2008 was identified in our systematic review but was excluded (see F.33, P139) as it did not meet the inclusion criteria in the review protocol (the baseline was previous FODMAP responders rather than a comparison of low FODMAP diet with other diets). The evidence on specific outcomes was downgraded because the duration of the included studies meant that there was no data available on the reintroduction of low FODMAP diet or its long term effects.
SH	British Dietetic	14	Addendum	20		As above. The Staudacher et al 2012 paper did not	Thank you this has been amended.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
	Association					include IBS-D patients.	
SH	British Dietetic Association	15	Addendum	20		Regarding the statement 'the committee commented that the study period of these studies did not match current practice in the NHS…' The purpose of the guidelines is to guide practice based on the evidence. Therefore, although I see consideration of current practice is important in this process, it should not influence the development of the guidelines.	Thank you for your comment. This statement is just a record of the discussion that took place. The evidence was downgraded because the duration of the included studies meant that there was no data available on reintroduction of low FODMAP diet or its long term effects.
SH	British Dietetic Association	1	NICE	16		Resistant starch is still in there???	Thank you for your comment. This section was not in the scope of this guideline update
SH	British Dietetic Association	6	NICE	16		Suggest amending the point around fibre in diet – there appears to be limited evidence for this	Thank you for your comment. This section was not in the scope of this guideline update
SH	British Dietetic Association	7	NICE	16 - 17		I welcome the inclusion of using the Low FODMAP exclusion diet as a next steps dietary intervention for those not responding to general diet and lifestyle advice. This may not be available to all ethnic backgrounds and minority groups, as current Low FODMAP resources available in the UK do not reflect the dietary foods common to some ethnic minorities and are only available in written English language.	Thank you for your comment. The issue of culturally specific foods for low FODMAP diet has been further discussed by the Committee. This has now being captured in the LETR table in the full addendum. The Committee acknowledged that the current dietary resources available for implementing the low FODMAP diet only includes a list of foods that are common in a typical western diet, and that information on culturally specific foods are very limited. Therefore, the Committee emphasized that healthcare professionals need to have an appropriate discussion with people with IBS who wish to go on a dietary intervention, particularly people who consumed culturally specific foods. Full information on available food sources for low FODMAP diet needs to be provided and discussed with people with IBS so that they can make an informed

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							decision.
SH	British Dietetic Association	8	NICE	17		The text... only be given by a healthcare professional with expertise in dietary management ...is ambiguous. The research thus far is based on advice provided by an experienced dietitian. Given the potential adverse effects on dietary intake of this exclusion diet, this should be specified as 'only be given by a dietitian'.	Thank you for your comment. This was discussed further by the Committee. The Committee took into account your comments, as well as other differing comments from the British Gastroenterology Society. On balance, and the fact that this is a primary care guideline, the Committee agreed to keep the current recommendation as a dietitian is a healthcare professional with expertise in dietary management. The Committee felt they could not be more specific than the current recommendation.
SH	British Dietetic Association	2	NICE	18	16	Space needed between 'this with'	Thank you, this has been done.
SH	British Dietetic Association	3	NICE	18	27	Space needed between 'with participants'	Thank you, this has been done.
SH	British Dietetic Association	5	NICE	21	1	Line 1: suggest adding the words recommend State Registered Dietitian	Thank you for your comment. This was discussed further by the Committee. The Committee took into account your comments, as well as other differing comments from the British Gastroenterology Society. On balance, and the fact that this is a primary care guideline, the Committee agreed to keep the existing recommendation as a dietitian is a healthcare professional with expertise in dietary management. The Committee felt they could not be more specific than current recommendations.
SH	British Pain Society	1	General	Gene ral	Gener al	The British Pain Society welcomes the guidance as many patients with IBS also have other chronic pain conditions. The clarification regarding investigations, diagnosis and treatment is useful.	Thank you.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	British Society of Gastroenterology	2	Addendum	13	13	The committee has recommended that low dose TCA's and SSRI's should be considered as second line treatment for IBS patients that have not fully responded to laxatives, loperamide or anti-spasmodics. However, there is no recommendation for which type of IBS patient may benefit best from this treatment. There is no recommendation as to whether this should be taken as an additional medication (in addition to laxatives for instance). Could clarification be given?	Thank you for your comment. The committee did not recommend antidepressants as first line treatment due to the low quality evidence (See LETR table of addendum, p.16). Because there is insufficient new evidence to change current recommendations the Committee decided to carry forward the original guideline recommendations. There is also insufficient evidence on the use of antidepressants (TCAs and SSRIs) by IBS type, thus the recommendations do not make reference to IBS subtypes. (Of the 13 studies in the original full guideline, 6 identified IBS subtype as "mixed", the remainder did not specify. In this update, of the additional 4 studies that were reviewed, only one study reported outcomes by IBS subtype). There was no evidence identified on the use of antidepressants as monotherapy vs combination therapy. Therefore in the absence of clarity in the evidence, clinical judgement will need to be applied on a case-by-case basis. In addition, it is stated in the LETR table that of the 12 included studies, only 2 reported on the previous IBS treatment (one included participants who had previously failed to respond to anti-spasmodics n=107 and the other excluded those currently on antispasmodics n=81). Thank you for your support.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						We would support the committee's view to 're-launch' their support for further clinical research to support the case for the use of this class of drugs for the treatment of IBS. These comments are endorsed by the Royal College of Physicians.	
SH	British Society of Gastroenterology	3	Addendum	19	General	Data from limited trials of a low FODMAP diet in IBS is somewhat encouraging and anecdotal evidence is growing from NHS services but evidence to support the use of this intervention is still of low quality. Because of the increased interest of this dietary intervention both within the (predominantly) dietetic community and with IBS patients it is good that guidance is given. There are a few issues. The first is patient selection. It is not clear which type of IBS patient would benefit most from a low FODMAP diet but the best evidence suggests those with bloating and abdominal distension or those with proven intolerance to specific carbohydrate absorption would do best but this intervention maybe deleterious to IBS-C patients.	Thank you. Thank you for your comments. Your point regarding patient selection is well made. Having reviewed the evidence in full it was not possible to stratify data by IBS sub-groups for the outcome of bloating (nor any other outcomes) as this data was not available. Therefore, the Committee felt the recommendation could not be more specific based on current available evidence. The Committee would expect the clinical judgement of a qualified healthcare professional with expertise in dietary management to tailor dietary advice to the symptom profile of the individual, taking into account the physiological plausibility of the effects of the low FODMAP diet in different symptom profiles.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						At present the guidance seems to suggest that a general diagnosis of IBS would be enough to merit a referral to a 'qualified healthcare professional' (presumably a dietician but the qualification is not specified) for administration of a low FODMAP diet.	Thank you for your comment. We disagree with your interpretation as the beginning of the recommendation does clearly state: *If a person's IBS symptoms persist while following general lifestyle and dietary advice, offer advice on further dietary management…* Hence, the current recommendation does not suggest that a general diagnosis of IBS would be enough to merit a referral to a *'qualified healthcare professional with expertise in dietary management'*. The Committee felt that they could not be more specific about the qualification and job title because this should be commissioned and decided by local CCGs how they would want to set up local services.
						The question as to whether an IBS patient trying out the low FODMAP diet needs to see a trained healthcare professional any more than when being asked to try any other dietary intervention (such as low fibre for example) is up for debate. It is not clear that the low FODMAP diet poses any undue risks (as patients usually swap one type of fruits and vegetable for another equally healthy option, for example). There are excellent 'self-help' booklets / mobile phone	Thank you for your comments. As mentioned above, the recommendation as a whole covers other dietary components, requiring qualified healthcare professionals with expertise in dietary management, not just for the low FODMAP diet. The Committee discussed the lack of long term effects of low FODMAP diet (this is now captured in the LETR table). Due to this uncertainty, the Committee felt it's important to have the input from a qualified healthcare professional with expertise in dietary management. This qualified healthcare professional may or may not be

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						'apps' available to patients to try this diet initially and then could get a referral to a dietician upon review if unsuccessful or if they were finding it difficult to maintain nutritional balance. Introducing a dietician led primary care service would potentially increase costs and waiting times considerably and needs further justification with clinical trials. The committee have made a recommendation for further research in this area which we would strongly support. These comments are endorsed by the Royal College of Physicians.	a dietitian depending on local service configuration. The Committee were not convinced that current freely available self-help materials and 'apps' would be consistently high quality and have no assurance that they will have been properly developed and validated. Again, due to the uncertainty of the long term effects of low FODMAP diet, it is important to have input from a qualified healthcare professional with expertise in dietary management. Thank you for your comment. The current recommendation does not suggest introduction of a dietitian led primary care service. It will be down to local CCGs to decide how they want to commission services. Thank you.
SH	British Society of Gastroenterology	1	Addendum	23	11	Lubiprostone is not a 5-HT4 agonist it is a chloride channel (CIC-2) agonist.	Thank you we have amended this.
SH	British Society of Gastroenterolog	4	Addendum	23	General	Linaclotide is a new class of drug which has been shown to effectively treat dual features (pain and bowel frequency) of IBS in a clearly defined (IBS-C) population	Thank you for your comment. A decision was made by the Committee not to make linaclotide a first line treatment taking into

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
	y					of patients. It is peripherally restricted and therefore has an excellent safety profile. The committee have recommended that Linaclotide should be available in primary care but only offered as an option when patient have been suffering from severe constipation for 12-months and have not responded to other laxatives. IBS-C is different to chronic constipation in several ways and by definition if patients IBS-C patients have had severe constipation for 12-months they will also have been suffering from abdominal pain for this period. It This seems like a very long period to make patients suffer and is at odds with guidance for prucalopride for instance which is 6-months. There does not seem to be a clear rationale as to why clinicians should wait for such a long period if there is an effective treatment available for a clearly defined sub-group of patients (unlike the majority of the other treatment options described). These comments are endorsed by the Royal College of Physicians.	account the uncertainty about the treatment effects, evidence quality and risk of bias (See LETR table, p29). It was also acknowledged that people with constipation would likely have tried multiple other laxatives already and thus a recommendation was made to offer linaclotide to people without sufficient symptom relief after twelve months. The 12-month time frame is based on the evidence available (the entry criteria from the included studies [Chey 2012; Rao 2012; Johnston 2010]). However this point has been discussed by the Committee. The Committee subsequently made some amendments to the recommendation wording but decided not to change the 12 month duration because it was evidence based. The updated recommendation is as follows: **Consider linaclotide for people with IBS only if:** • **optimal or maximum tolerated doses of previous laxatives from different classes have not helped and** • **they have had constipation for at least 12 months** **Follow-up people taking linaclotide after 3 months. [new 2015]**

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	British Society of Gastroenterology	5	Addendum	33	General	There is an extensive review of the use of different psychological interventions in IBS. Whilst the committee have not made any recommendations for the use of techniques such as relaxation therapy, Cognitive behavioural therapy and Mindfulness therapy due to lack of strong evidence, they have made a research recommendation for further work in this area to assess cost effectiveness which we would support. These comments are endorsed by the Royal College of Physicians.	Thank you for your comment and support.
SH	British Society of Gastroenterology	6	Addendum	General	General	Probiotics: There is growing evidence to suggest that dysbiosis in the GI tract contributes to IBS symptoms and that pro-biotic therapies can be effective but there is no review, update or research recommendations for this approach. These comments are endorsed by the Royal College of Physicians.	Thank you for your comment. Probiotics were not in the scope for this update. Probiotics were evaluated in the original Full Guideline (see section 7.4)
SH	British Society of Gastroenterology	7	Addendum	General	General	Diagnostic testing: There is no update of the use of simple tests such as hydrogen and methane breath testing to identify patients with conditions such as small intestinal bacterial overgrowth or specific carbohydrate mal-absorption (and not IBS) which are cost effective and could provide objective evidence for inexpensive, targeted treatments. These comments are endorsed by the Royal College of Physicians.	Thank you for your comment. Diagnostic testing for other conditions was outside the scope for this update.
SH	Department of Health	1	General	General	General	I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you.
SH	Digital Assessment Service, NHS Choices	1	General	General	General	DAS welcome the guidance and have no comments on its content.	Thank you.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	NHS England	1	General	General	General	I wish to confirm that NHS England has no substantive comments to make regarding this consultation.	Thank you.
SH	Royal College of Nursing	1	General	General	General	Nurses working in this area have reviewed the addendum for the above guidelines and have no comments to submit.	Thank you.
SH	The Royal College of Pathologists	1	General	General	General	The Royal College of Pathologists does not have any comments on the following clinical addendum.	Thank you.

These organisations were approached but did not respond:

AbbVie

Alder Hey Children's NHS Foundation Trust

Allocate Software PLC

Alpha Laboratories Limited

Amgen UK

anglia community leisure

Anxiety UK

Association for Continence Advice

Association for Psychoanalytic Psychotherapy in the NHS

Association of Anaesthetists of Great Britain and Ireland

Association of British Healthcare Industries

Association of Child Psychotherapists, the

Association of Clinical Pathologists

Association of Coloproctology of Great Britain and Ireland

Association of Directors of Children's Services

B. Braun Medical Ltd

Belfast Health and Social Care Trust

Birmingham & Brunel Consortium

Bladder and Bowel Foundation

Blood Pressure UK

Boehringer Ingelheim

Bradford District Care Trust

British Acupuncture Council

British Association for Counselling and Psychotherapy

British Association for Parenteral & Enteral Nutrition

British Association of Behavioural and Cognitive Psychotherapies

British Geriatrics Society - Gastro-enterology and Nutrition Special Interest Group

British Heart Foundation Health Promotion Research Group

British Medical Association

British Medical Journal

British National Formulary

British Nuclear Cardiology Society

British Nuclear Medicine Society

British Pharmacological Society

British Psychological Society

British Red Cross

British Society of Gastroenterology

British Society of Paediatric Gastroenterology Hepatology and Nutrition

BSPGHAN

BUPA Foundation

Cambridge University Hospitals NHS Foundation Trust

Camden Link

Capsulation PPS

Cardiff and Vale NHS Trust

Care Quality Commission
Central & North West London NHS Foundation Trust
CHKS Ltd
CIS' ters
CLEAR Cannabis Law Reform
Cochrane Depression Anxiety and Neurosis Group
Coeliac UK
Coloplast Limited
Continence Advisory Service
Covidien Ltd.
Crohn's and Colitis UK
Croydon Council
Croydon University Hospital
Cumbria Partnership NHS Foundation Trust
CWHHE Collaborative CCGs
David Lewis Centre, The
Department for Communities and Local Government
Department of Gastroenterology
Department of Health, Social Services and Public Safety - Northern Ireland
Ealing Hospital NHS Trust
East and North Hertfordshire NHS Trust
Equalities National Council
Ethical Medicines Industry Group
Faculty of Public Health
Faculty of Sexual and Reproductive Healthcare
Ferring Pharmaceuticals
Fibroid Network Charity

Five Boroughs Partnership NHS Trust

Forte Medical

GE Healthcare

George Eliot Hospital NHS Trust

Gloucestershire County Council

Gloucestershire Hospitals NHS Foundation Trust

Gloucestershire LINk

GP update / Red Whale

Great Western Hospitals NHS Foundation Trust

Greater Manchester & Beyond Coalition of PLW & HIV

H & R Healthcare Limited

Health and Care Professions Council

Health and Social Care Information Centre

Healthcare Improvement Scotland

Healthcare Infection Society

Healthcare Quality Improvement Partnership

Healthwatch East Sussex

Herts Valleys Clinical Commissioning Group

Hindu Council UK

Hockley Medical Practice

HQT Diagnostics

Humber NHS Foundation Trust

Institute of Biomedical Science

Institute of Psychiatry

International Neuromodulation Society

Johnson & Johnson

Joint Royal Colleges Ambulance Liaison Committee

KCARE

Kimal PLC

Lactation Consultants of Great Britain

Lancashire Care NHS Foundation Trust

Leeds North Clinical Commisioning Group

Local Government Association

ME Association, The

Medical Directorate Services

Medicines and Healthcare products Regulatory Agency

Mental Health Act Commission

Ministry of Defence

Muslim Doctors and Dentists Association

National Clinical Guideline Centre

National Collaborating Centre for Cancer

National Collaborating Centre for Mental Health

National Collaborating Centre for Women's and Children's Health

National Deaf Children's Society

National Institute for Health Research Health Technology Assessment Programme

National Institute for Health Research

National Patient Safety Agency

National Pharmacy Association

National Public Health Service for Wales

Neuromodulation Society of the United Kingdom and Ireland

Newham University Hospital NHS Trust

NHS Barnsley Clinical Commissioning Group

NHS Choices

NHS Clinical Knowledge Summaries

NHS Connecting for Health
NHS Derbyshire county
NHS England
NHS Hardwick CCG
NHS Havering CCG
NHS Health at Work
NHS Improvement
NHS Kirklees
NHS Luton CCG
NHS North Somerset CCG
NHS Plus
NHS Sheffield CCG
NHS South Cheshire CCG
NHS South Norfolk CCG
NHS Wakefield CCG
NHS Warwickshire North CCG
NHS West Cheshire CCG
Norgine Limited
North of England Commissioning Support
North West London Hospitals NHS Trust
Northern Health and Social Care Trust
Northern Ireland Chest, Heart & Stroke
Northern Region Endoscopy Group
Northwick Park and St Mark's Hospitals
Nottingham City Hospital
Novartis Pharmaceuticals
Nursing and Midwifery Council

Nutricia Advanced Medical Nutrition

Nutrition and Diet Resources UK

Obesity Action Campaign

Ovarian Cancer Action

Oxford Nutrition Ltd

Oxfordshire Clinical Commissioning Group

Pancreatic Cancer UK

Pathfinders Specialist and Complex Care

Peckforton Pharmaceuticals Ltd

Pelvic Obstetric and Gynaecological Physiotherapy

Pelvic Pain Support Network

PERIGON Healthcare Ltd

Pernicious Anaemia Society

PharmaPlus Ltd

Pilgrim Projects

PrescQIPP NHS Programme

Primary Care Pharmacists Association

Primary Care Society for Gastroenterology

Primary Care Society for Gastroenterology

Primrose Bank Medical Centre

PromoCon

Public Health England

Public Health Wales NHS Trust

Quality Institute for Self Management Education and Training

RioMed Ltd.

Roche Products

Royal Berkshire NHS Foundation Trust

Royal College of Anaesthetists
Royal College of General Practitioners
Royal College of General Practitioners in Wales
Royal College of Midwives
Royal College of Obstetricians and Gynaecologists
Royal College of Paediatrics and Child Health
Royal College of Paediatrics and Child Health , Gastroenetrology, Hepatology and Nutrition
Royal College of Pathologists
Royal College of Physicians
Royal College of Physicians of Edinburgh
Royal College of Psychiatrists
Royal College of Radiologists
Royal College of Speech and Language Therapists
Royal College of Surgeons of Edinburgh
Royal College of Surgeons of England
Royal Cornwall Hospitals NHS Trust
Royal Free Hospital NHS Foundation Trust
Royal Pharmaceutical Society
Royal Society of Medicine
Scottish Intercollegiate Guidelines Network
SEE BETSI CADWALADR - North Wales NHS Trust
Self Management UK
Sheffield Children's Hospital
Sheffield Children's NHS Trust
Sheffield Teaching Hospitals NHS Foundation Trust
Shire Pharmaceuticals Ltd
SNDRi

Social Care Institute for Excellence

Society and College of Radiographers

Solvay

South Eastern Health and Social Care Trust

South London & Maudsley NHS Trust

South West Yorkshire Partnership NHS Foundation Trust

Southern Health & Social Care Trust

St Mary's Hospital

Staffordshire and Stoke on Trent Partnership NHS Trust

Stockport Clinical Commissioning Group

Symprove Ltd

Teva UK

The British Homeopathic Association & Faculty of Homeopathy 131134

The British In Vitro Diagnostics Association

The IBS Network

The Neurological Alliance

The Patients Association

The Rotherham NHS Foundation Trust

The University of Birmingham

The Urology Trade Association

UK Clinical Pharmacy Association

University College London Hospital NHS Foundation Trust

University Hospital Birmingham NHS Foundation Trust

University Hospitals Birmingham

University of Salford

University of York

Urology User Group Coalition

Warner Chilcott UK
Welsh Government
Welsh Scientific Advisory Committee
West Midlands Ambulance Service NHS Trust
Western Health and Social Care Trust
Western Sussex Hospitals NHS Trust
Whipps Cross University Hospital NHS Trust
Worcestershire Acute Hospitals Trust
Wyreside Products Ltd
York Hospitals NHS Foundation Trust