National Institute for Health and Care Excellence

Draft for consultation

Addendum to NICE guideline CG61, Irritable bowel syndrome in adults

Diagnosis and management of irritable bowel syndrome in primary care

NICE guideline CG61.1

Methods, evidence and recommendations

October 2014

Draft for consultation

Developed by the National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

Contents

Clinical guidelines update

The NICE Clinical Guidelines Update Team update discrete parts of published clinical guidelines as requested by NICE's Guidance Executive.

Suitable topics for update are identified through the new surveillance programme (see surveillance programme interim guide).

These guidelines are updated using a standing Committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. For the duration of the update the core members of the Committee are joined by up to 5 additional members who have specific expertise in the topic being updated, hereafter referred to as 'topic-specific members'.

In this document where 'the Committee' is referred to, this means the entire Committee, both the core standing members and topic-specific members.

Where 'standing Committee members' is referred to, this means the core standing members of the Committee only.

Where 'topic-specific members' is referred to this means the recruited group of members with topic-specific expertise.

All of the standing members and the topic-specific members are fully voting members of the Committee unless stated otherwise.

Details of the Committee membership and the NICE team can be found in appendix A. The Committee members' declarations of interest can be found in appendix B.

1 Summary section

1.1 Update information

The NICE guideline on irritable bowel syndrome (IBS) in adults (NICE guideline CG61) was published in 2008. It was reviewed in 2011 and 2013 as part of NICE's routine surveillance programme to decide whether it required updating. These surveillance reports identified new evidence relating to the following areas of the guidance:

- The role of antidepressants in IBS management
- The role of relaxation therapy in IBS management.

A further two areas were identified where there was evidence suggesting that newer treatments for IBS that were not in CG61 should be included in this update:

- The use of linaclotide and lubiprostone in constipation predominant IBS (IBS-C) management
- The use of the low FODMAP (fermentable oligosacchardies, disaccahrides, monosaccharides, and polyols) diet in IBS management.

Consultation with IBS topic-specific members of the update Committee during the development of the review protocol further identified that the use of some psychological interventions (computerised CBT and mindfulness therapy) in the management of IBS should also be updated. Therefore a review question in this area (5a and 5b) was added to the update review protocol (this encompasses the relaxation therapy question).

1.2 Strength of recommendations

Some recommendations can be made with more certainty than others. The Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Committee is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

1.2.1 Interventions that must (or must not) be used

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

1.2.2 Interventions that should (or should not) be used – a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that an intervention will not be of benefit for most patients.

1.2.3 Interventions that could be used

We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The

choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

1.3 Information for consultation

You are invited to comment on the new and updated recommendations in this update. These are marked as:

- **[new 2015]** if the evidence has been reviewed and the recommendation has been added or updated
- **[2015]** if the evidence has been reviewed but no change has been made to the recommendation action

Where recommendations are shaded in grey, the evidence has not been reviewed since the original guideline. We will not be able to accept comments on this text. Where recommendations are shaded in yellow, wording changes have been made for the purpose of clarification only. Recommendations labelled [2015] have been edited into the direct style (in line with current NICE style for recommendations in clinical guidelines) where possible.

The original NICE guideline and supporting documents are available here.

1.41 Recommendations

Antidepressants

1. **Consider tricyclic antidepressants (TCAs) as second-line treatment for people with IBS if laxatives, loperamide or antispasmodics have not helped. Start treatment at a low dose (5–10 mg equivalent of amitriptyline), taken once at night and review regularly. Increase the dose if needed, but not usually beyond 30 mg. [2015][1]**

2. **Consider selective serotonin reuptake inhibitors (SSRIs) for people with IBS only if TCAs are ineffective. [2015][1]**

3. **Take into account the possible side effects when offering TCAs or SSRIs to people with IBS. Follow up people taking either of these drugs for the first time at low doses for the treatment of pain or discomfort in IBS after 4 weeks and then every 6–12 months. [2015][1]**

Low FODMAP diet

4. **If a person's IBS symptoms persist while following general lifestyle and dietary advice, offer advice on further dietary management. Such advice should:**
    - **include single food avoidance and exclusion diets (for example, a low FODMAP [fermentable oligosaccharides, disaccharides, monosaccharides and polyols] diet)**
    - **only be given by a healthcare professional with expertise in dietary management. [new 2015][2]**

Linaclotide

5. **Consider linaclotide for people with IBS only if:**
    - **they have had severe constipation for at least 12 months and**
    - **optimal or maximum tolerated doses of previous laxatives from different classes have not helped. [new 2015]**

Lubiprostone

6. **No recommendation**

Psychological interventions (relaxation, computerised CBT and mindfulness therapy)

7. **No recommendation**

[1] At the time of consultation on the guideline update (October 2014), TCAs and SSRIs did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

[2] This recommendation has been updated. However, only the low FODMAP diet was included in the evidence review. The shaded text was not reviewed for this update and so we will not be able to accept comments on this.

1.5 Patient-centred care

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. People should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If someone does not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent, the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

1.6 Methods

Please see the interim process and methods guide for updates pilot programme 2013 and the guidelines manual 2012.

2 Evidence review and recommendations

Introduction

Irritable bowel syndrome (IBS) is a chronic, relapsing and often life-long disorder. It is characterised by the presence of abdominal pain or discomfort, which may be associated with defaecation and/or accompanied by a change in bowel habit. Symptoms may include disordered defaecation (constipation or diarrhoea or both) and abdominal distension, usually referred to as bloating. Symptoms sometimes overlap with other gastrointestinal disorders such as non-ulcer dyspepsia or coeliac disease.

Treatment options include diet, physical activity, stress management, psychotherapy interventions and medication.

The NICE guideline on irritable bowel syndrome in adults was published in 2008.

The recommendations contained within this guideline can be found in the NICE pathway.

2.1 Review question 1: Antidepressants

2.1.1 Review question

Are low-dose tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) effective in the management of IBS (including which are more effective)?

2.1.2 Evidence review

The aim of the review was to assess the effectiveness of TCAs, SSRIs and SNRIs in the management of IBS compared to other antidepressants, other IBS treatments and placebo.

A systematic search was conducted (see appendix D) which identified 4662 articles. The titles and abstracts were screened and 53 articles were identified as potentially relevant. Full text versions of the articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). The review flow chart for this review is in appendix E.

One of the studies identified in the search was a Cochrane review 'Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome' (Ruepert *et al*., 2011). This Cochrane review included 15 antidepressant studies, of which 10 met the criteria for inclusion in the review protocol for this question (Masand *et al*., 2009; Talley *et al*., 2008; Vahedi *et al*., 2008; Vahedi *et al*., 2005; Tack *et al*., 2006; Tabas *et al*., 2004; Kuiken *et al*., 2003; Rajagoplanan *et al*., 1998; Vij *et al*., 1991; Myren *et al*., 1982). Of the 10 studies from the Cochrane review, 5 studies had previously been included in the evidence review in CG61 (Tabas *et al*., 2004; Kuiken *et al*., 2003; Rajagoplanan *et al*., 1998; Vij *et al*., 1991; Myren *et al*., 1982). The other 5 antidepressant papers in the Cochrane review were excluded (see appendix F for detailed reasons for exclusion). There was one study that was included in CG61, but excluded from the Cochrane review (Creed, 2003); this study has been excluded from this updated review, details for exclusion are reported in Appendix F.

Two additional studies that were not included in the Cochrane review were identified in the searches and included in this review question (Ladabaum *et al*., 2010 and Abdul-Baki *et al*.,2009). In total, 12 RCTs were included in this review question. All of the included papers were RCTs that compared TCAs or SSRIs with placebo. There were no studies identified that used any other class of antidepressant for participants with IBS.

As has been done previously in CG61 and in the Cochrane review, the comparisons have been undertaken using the drug classes (TCAs, SSRIs) and not the individual drugs; this is due to the similarities in pharmacokinetics and pharmacodynamics within the drug classes. Table 1 summarises the drug classes and drugs in the included studies.

Details of the included studies are included in evidence tables in appendix G. The quality of evidence for each critical and important outcome was appraised using a modification of the approach recommended by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group (see appendix H).

Table 1: Included comparisons

Tricyclic antidepressants (TCAs)	Selective serotonin reuptake inhibitors (SSRIs)
TCA vs placebo	SSRI vs placebo
• Amitriptyline (Rajagoplanan 1998; Vahedi 2008) • Doxepin (Vij 1991) • Trimipramine (Myren 1982) • Imipramine (Adbul-Baki 2009; Talley 2008)	• Fluoxetine (Vahedi 2005; Kuiken 2003) • Paroxetine (Masand 2009; Tabas 2004; Creed 2003) • Citalopram (Ladabaum 2010; Talley 2009; Tack 2006)

Table 2 summarises the included studies, interventions used and outcomes reported.

Table 2: Included studies summary

Reference	Participants	Intervention	Outcomes reported
Studies included in Ruepert *et al*., 2011 (**Cochrane Review), included in CG61**			
SSRIs			
Kuiken, 2003	N=40	Fluoxetine 20mg for 6 weeks	Abdominal pain, global assessment of symptoms, adverse events
Tabas, 2004	N=90	Paroxetine 10 or 20mg for 12 weeks	Abdominal pain, global assessment of symptoms, quality of life
TCAs			
Myren, 1982	N=61	Trimipramine 50mg for 4 weeks	Global assessment of symptoms
Rajagoplanan, 1998	N=22	Amitriptyline 75mg for 12 weeks	Abdominal pain
Vij, 1991	N=50	Doxepin 75mg for 6 weeks	Abdominal pain, global assessment of symptoms, adverse events
Studies included in Ruepert *et al*., 2011 (**Cochrane Review), not included in CG61**			
SSRIs			
Masand, 2009	N=72	Paroxetine 12.5-50mg for 12 weeks	Global assessment of symptoms, IBS symptoms, adverse events
Tack, 2006	N=23 (crossover)	Citalopram 20-40mg for 6 weeks	Abdominal pain, global assessment of symptoms
Vahedi, 2005	N=44	Fluoxetine 20mg for 12 weeks	Abdominal pain
TCAs			
Vahedi, 2008	N=50	Amitriptyline 10mg for 2 months	Abdominal pain, IBS symptom score, adverse events
SSRIs and TCAs			
Talley, 2008	N=51	Imipramine 50mg for	Abdominal pain, global assessment

Reference	Participants	Intervention	Outcomes reported
		12 weeks Citalopram 40mg for 12 weeks	of symptoms, quality of life, adverse events
Studies not included in Ruepert *et al*., 2011**(Cochrane Review), not included in CG61**			
Abdul-Baki, 2009	N=107	Imipramine 25mg for 12 weeks	Global assessment of symptom relief, quality of life, adverse events
Ladabaum, 2010	N=54	Citalopram 20mg for 4 weeks	Global assessment of symptom relief, quality of life, adverse events

2.1.31 Health economic evidence

2 An additional search was undertaken using the same search terms with an economic
3 evaluations filter to identify studies assessing the cost-effectiveness or cost-utility of TCAs,
4 MAOIs, SSRIs and SNRIs (see appendix D). The search retrieved 1,060 articles. The titles
5 and abstracts were screened for possible inclusion, and 6 articles were selected for further
6 examination of the full-text version. No economic evaluations were included for review. A
7 review flowchart is provided in appendix E, and the excluded studies (with reasons for
8 exclusion) are shown in appendix F.

2.1.49 Evidence statements

2.1.4.110 Abdominal pain

11 There were 6 studies in total (301 participants) that reported the numbers of participants
12 successfully treated for abdominal pain. Two TCA studies (104 participants) suggested that
13 there may be clinically significant improvement in abdominal pain, but there was very serious
14 uncertainty around the effect estimate. Four SSRI studies studies (197 participants)
15 suggested that there may be clinically significant improvement in abdominal pain, but there
16 was serious uncertainty around the effect estimate. [Very low quality].

17 There were 2 studies that reported abdominal pain scores. One TCA study showed clinically
18 significant lower pain scores with TCA compared to placebo. One SSRI study (23
19 participants) found there were clinically significant lower pain scores in the SSRI group
20 compared toplacebo groups. [Very low quality]

2.1.4.221 Global assessment of IBS symptoms

22 There were 10 studies (579 participants) that reported on the numbers of participants
23 successfully treated (responder) based on the global assessment of IBS symptoms. The 5
24 TCA studies (298 participants) suggested that TCAs may be more clinically effective than
25 placebo with regard to the number of participants successfully treated; there was some
26 uncertainty around the effect estimate. The 5 SSRI studies (281 participants) suggested that
27 SSRIs may be more clinically effective than placebo in number of people successfully
28 treated; however there is some uncertainty around the effect estimate. [Very low quality]

2.1.4.329 Symptom scores

30 There were 2 studies (126 participants) that reported on the numbers of participants
31 successfully treated (responder) based on symptom scores. One TCA study (72 participants)
32 suggested that TCAs may be more clinically effective than placebo in improving symptom
33 score, and 1 SSRI study (54 participants) suggested that SSRIs may be more clinically
34 effective than placebo in improving symptom score. In both studies there is some uncertainty
35 around the effect estimate. [Very low quality]

There were 2 studies (122 participants) that reported symptom scores. One SSRI study (50 participants) suggested that SSRIs may be more clinically effective than placebo in improvement of symptom scores, though there is some uncertainty around the result. One TCA study (72 participants) reported no difference between TCA and placebo in improvement of symptom scores. [Very low quality]

2.1.4.4 Quality of life

There were 4 studies (233 participants) that reported on quality of life.

- Two studies used SF-36 (107 participants); 1 study on TCAs (56 participants) found a statistically higher percentage difference from baseline with the TCA compared to placebo. One TCA and SSRI study (51 participants) found no difference in SF-36 components between antidepressants and placebo.[Low and very low quality]
- Two studies (126 participants) comparing SSRI to placebo reported outcomes using IBS QoL. One study (45 participants) found no difference in mean IBS QoL with the SSRI compared with placebo; the other (81 participants) found no differences in 2 of 3 IBS QoL components between SSRI and placebo. [Very low quality]

2.1.5 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The important outcomes were prioritised by the topic-specific members (TSMs) through ranking methods and further confirmed by the standing Committee before the review was carried out. They thought quality of life to be of particular importance when considering the effectiveness of antidepressant treatment for IBS. Outcomes of symptom response overall and individual symptom response (e.g. bloating, diarrhoea) were also considered important, although the impact of these factors on an individual cannot be assumed. The topic-specific Committee members noted that the improvement in a particular symptom may be viewed differently by the individuals involved. For example, some may consider improvement in their bloating symptoms to be the focal point when considering a treatment, while for others improvement in a different symptom, such as diarrhoea, would be most valuable. The Committee noted the limited reporting of adverse events in the included studies.
Trade-off between benefits and harms	The Committee agreed that the outcomes from the included studies should be presented by the class of the drugs involved, that is by TCA and SSRI class. The heterogeneity of the included studies and the differences between the pharmacokinetics and pharmacodynamics of TCAs and SSRIs was further discussed. The Committee concluded that the evidence would be most appropriately presented within their drug class rather than combining the results from all of the included studies together (as had been done previously in CG61). The Committee agreed that the results of the included studies overall showed that antidepressants have an effect to improve the symptoms of IBS. It was agreed that there was more uncertainty with the evidence on SSRIs than with TCAs. The lack of follow-up within the included studies was discussed by the Committee. It was agreed that the study length in most of the included studies was sufficient to detect a response in patients for the related outcomes. However, for consideration of any adverse effects and longer term symptom control of a fluctuating condition like IBS, further follow-up data would have been needed. The studies that had included adverse events had not reported these in detail. The Committee noted that there is limited new evidence in the use of antidepressants for those with IBS. It was further discussed that there was

	no additional evidence that provided any justification for changing the original recommendations on the use of antidepressants developed in CG61. The Committee noted that of the 12 included studies only 2 had reported on the previous IBS treatment that participants had received prior to the study. The Committee agreed that there was limited additional evidence on the use of antidepressants for those with IBS. It was noted that the results of this evidence review were consistent with the results of the evidence reviewed previously in CG61 and with the views of the topic-specific Committee members. Therefore, it was agreed that the existing recommendations for this review question from CG61 would be carried forward into this update.
Trade-off between net health benefits and resource use	The Committee determined that carrying forward the existing recommendations for this review question would not change existing resource use.
Quality of evidence	The Committee reviewed the evidence identified and noted that there are areas of concern for the applicability of the included studies to the potential users of this guideline update. The majority of the included studies used participants from non-primary care settings. The Committee discussed that this may (but not necessarily) mean that these participants had more severe IBS symptoms than those in primary care. Nevertheless, the topic-specific Committee members considered that these studies would have included a proportion of participants with symptoms that would be found within primary care; they therefore decided that it was appropriate to extrapolate the evidence. The Committee noted that the doses used within some of the included studies, particularly for the TCAs, are higher than would (at least initially) be prescribed for IBS treatment. This raised questions about the directness of these studies and this is reflected within the GRADE tables for these studies. This was not applicable with the SSRIs as they are not usually used at low dose in IBS treatment. The Committee agreed that there is low quality evidence that TCAs and SSRIs have some benefit in the treatment of the symptoms of IBS. Accepting the limitations of this evidence which are noted in the GRADE tables (appendix H), the Committee considered that there was no evidence to contradict or change the recommendations initially developed for CG61.
Other considerations	The Committee discussed the lack of recent published studies in this area. Consequently it was agreed that a modification of the research recommendation in CG61 was justified highlighting the need for further research into the treatment of IBS using antidepressants within primary care. Furthermore, they noted that the initiation of TCAs and SSRIs for IBS (for analgesic effect) currently often happens within primary care. The topic-specific Committee members considered that referral to secondary care for this therapy is not necessary, that the prescription of antidepressants could be initiated and monitored in primary care. Therefore it was agreed that the included studies have relevance for primary care and that this is an important question to be reviewed within a primary care based guideline. As currently there is still insufficient evidence on the use of antidepressants for the management of IBS, despite the existing research recommendation

	on this topic published in the original guideline, the Committee decided and agreed that the research recommendation should be relaunched as part of this update in order to promote more research in this area.

2.1.61 Recommendations

2 **1. Consider tricyclic antidepressants (TCAs) as second-line treatment for people**
3 **with IBS if laxatives, loperamide or antispasmodics have not helped. Start**
4 **treatment at a low dose (5–10 mg equivalent of amitriptyline), taken once at night**
5 **and review regularly. Increase the dose if needed, but not usually beyond 30 mg.**
6 **[2015][1]**

7 **2. Consider selective serotonin reuptake inhibitors (SSRIs) for people with IBS only**
8 **if TCAs are ineffective. [2015][1]**

9 **3. Take into account the possible side effects when offering TCAs or SSRIs to people**
10 **with IBS. Follow up people taking either of these drugs for the first time at low**
11 **doses for the treatment of pain or discomfort in IBS after 4 weeks and then every**
12 **6–12 months. [2015][1]**

13

2.1.714 Research recommendation

15 **1. What is the clinical and cost effectiveness of low-dose TCAs and SSRIs for**
16 **treating IBS in primary care?**

17 **Why this is important**

18 There is some evidence for the clinical effectiveness of low-dose TCAs and SSRIs in treating
19 the symptoms of IBS. However, this comes from studies based primarily within secondary or
20 tertiary care settings with low participation rates. There is uncertainty about whether these
21 drugs are effective for people with IBS seen in primary care. Most people with IBS are
22 treated in this setting, and may be different in a number of respects to those seen in
23 secondary and tertiary care. Therefore research on the relative short- and long-term benefits
24 of low-dose TCAs and SSRIs in primary care populations, including clarification on
25 depression as a moderator of response, would help to guide treatment.

26

[1] At the time of consultation on the guideline update (October 2014), TCAs and SSRIs did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

2.2 Review question 2: low FODMAP diet

2.2.1 Review question

Does a low FODMAP diet have an effect on the symptoms of IBS?

2.2.2 Evidence review

The aim of the review was to assess the effectiveness of a low FODMAP diet. The low FODMAP (fermentable oligo-saccharides, di-saccharides, mono-saccharides and polyols) diet restricts dietary short-chain carbohydrates which are poorly absorbed in the small intestine and fermented in the large intestine. This fermentation is not specific to those with IBS but is considered to potentially cause or worsen symptoms in those with IBS.

A systematic search was conducted (see appendix D) which identified 2063 articles. The titles and abstracts were screened and 18 articles were identified as potentially relevant. Full text versions of the articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). The review flow chart for this review is in appendix E.

There were 2 RCTs and 1 controlled trial included in this review. All of the included studies considered the use of a low FODMAP dietary intervention in participants with IBS. Two of the 3 compared thiswith habitual/typical diet and one compared this with a 'standard' IBS diet (based on current NICE recommendations). Two of the 3 studies included those with varying symptoms of IBS (diarrhoea predominant, constipation predominant, or both diarrhoea and constipation). The third study included only participants where diarrhoea and/or bloating were the predominant symptoms. There were no studies identified that considered the low FODMAP diet compared with other diets and then subsequently re-introduced foods containing FODMAPs. Those with IBS are usually advised to follow the low FODMAP diet for up to 8 weeks initially. Within the studies in this review, the time period for the low FODMAP diet was between 21 days and 4 weeks, or was unclear. For full evidence table please see appendix G; for full GRADE profiles please see appendix H.

Table 3: Included studies summary

Reference	Participants	Intervention	Outcomes reported
Halmos et al (2014) RCT, crossover	N=30 (participants with a mix of IBS symptoms)	Low FODMAP diet for 21days compared with habitual diet	GI symptoms, overall response; bloating; abdominal pain; dissatisfaction with stool consistency
Staudacher et al (2012) RCT	N=41 (participants with predominantly diarrhoea/bloating symptoms)	Low FODMAP diet for 4weeks compared with habitual diet	GI symptoms, overall response; bloating; abdominal pain; flatulence; diarrhoea; constipation
Staudacher et al (2011) Controlled trial	N=82 (participants with a mix of IBS symptoms)	Low FODMAP diet for an unclear time period compared with standard diet	GI symptoms, overall response; bloating; abdominal pain; flatulence; diarrhoea; constipation

2.2.3 Health economic evidence

An additional search was undertaken using the same search terms with an economic evaluations filter to identify studies assessing the cost-effectiveness or cost-utility of a low FODMAP diet for irritable bowel syndrome. The search retrieved 507 articles. The titles and

abstracts were screened for possible inclusion and no articles were selected for further examination of the full-text version. A review flowchart is provided in appendix E.

2.2.4 Evidence statements

2.2.4.1 GI symptoms and abdominal pain

There were 3 studies (2 RCTS (71 participants), 1 controlled trial, (82 participants) that reported on overall GI symptom outcomes. Two studies (123 participants) reported clinically significant improvements in overall GI symptoms and in abdominal pain with a low FODMAP diet compared with the standard study diet. One study (30 participants) showed an improvement that was not clinically significant. [Very low quality]

There were 3 studies (2 RCTS, (71 participants), 1 controlled trial (82 participants)) that reported on abdominal pain. All 3 studies reported clinically significant improvements in abdominal pain on low FODMAP diet compared with the standard study diet. [Very low quality]

2.2.4.2 Bloating

There were 3 studies that reported on bloating outcomes (153 participants). All 3 studies (2 RCTS, 1 controlled trial) reported clinically significant improvements in bloating symptoms with a low FODMAP diet compared with the standard diet used in the study. [Very low quality]

2.2.4.3 Flatulence

There were 2 studies (123 participants) that reported on flatulence outcomes. One RCT (41 participants) found no clinically significant difference in incidence of flatulence between between the groups with a low FODMAP diet compared with the standard study diet. One controlled trial (82 participants) reported clinically significant improvement in flatulence symptoms with a low FODMAP diet compared with the standard study diet. [Very low quality]

2.2.4.4 Diarrhoea and constipation

There were 2 studies (123 participants) that reported on diarrhoea and constipation. Both studies (1 RCT (41 participants)withparticipants who had diarrhoea and/or bloating predominant IBS and 1 controlled trial (82 participants) found no clinical difference in diarrhoea or constipation between the groups on a low FODMAP diet compared with the standard study diet. [Very low quality]

2.2.5 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The important outcomes were prioritised by the topic-specific members (TSMs) through ranking methods and further confirmed by the standing Committee before the review was carried out. The Committee reviewed the use of the low FODMAP diet and discussed whether it would be appropriate to consider evidence where components of the diet had been modified. On the advice of the topic-specific Committee members, the Committee concluded that the low FODMAP intervention should be considered as an entity, that it would not be appropriate to consider restriction of the individual short chain carbohydrates that constitute FODMAP. In the dietary and lifestyle advice section of the original CG61, individual components such as sorbitol (which is a polyol) were mentioned and included. This review only considers the low FODMAP diet as an intervention as a whole, and its effectiveness for managing IBS symptoms. This review does not include updating the individual components included in the original

	guideline. The Committee considered that the outcomes in the included studies are relevant to those with IBS symptoms, though they noted that no quality of life outcomes were reported and that studies had reported outcomes relating to overall and/or individual symptoms. The Committee further noted that long-term outcomes for the low FODMAP diet, particularly on any potential adverse effects, will be very important. However, current included evidence did not have long enough follow-up period to capture these data.
Trade-off between benefits and harms	The Committee agreed that there is some evidence that the low FODMAP diet has an effect on reducing the symptoms of those with IBS. However, this evidence is limited to a small number of localised trials with small participant numbers. The Committee also noted the RCT including participants with diarrhoea predominant IBS had not found an improvement in diarrhoea related symptoms with the low FODMAP diet. The Committee commented that the study period of these studies did not match current practice in the NHS, which is routinely 8 weeks due to the availability of a dietitian. It was also discussed that the studies did not include further follow-up or the graded re-introduction phase of high FODMAP foods that follows the initial use of the low FODMAP diet in current practice. In recognition of the limitations of the evidence, the Committee considered whether there was sufficient evidence to enable them to make recommendations relating to the low FODMAP diet. The Committee discussed that IBS is a common condition and that there may be a considerable impact relating to any recommendation of a dietary intervention. They acknowledged that the low FODMAP diet is currently being used in those with IBS and there is increasing public awareness of this diet. Therefore, guidance in this area would be beneficial and the Committee discussed that there are other dietary and lifestyle changes currently recommended for managing IBS. The Committee commented that any new recommendations relating to the low FODMAP diet should sit within the existing recommendations to ensure that the low FODMAP diet does not get a separate predominance due to it being topical. Currently, patients using the low FODMAP diet are usually referred to a dietitian. As the Committee acknowledged the complex nature of this dietary intervention and the need to ensure that those following it have a nutritionally balanced diet, they agreed that the diet should only be undertaken under the advice of a suitably trained healthcare professional. The Committee noted the limitations of the evidence base. They also noted the importance of contextualising the low FODMAP diet with other diet and lifestyle interventions for IBS and the need for support by appropriate healthcare professionals. In consideration of these issues the Committee concluded that the optimal recommendation would be to supplement a current recommendation with the option of the low FODMAP diet. Therefore recommendation 1.2.1.8 was adapted to include this option.
Trade-off between net health benefits and resource use	The health economic review did not identify any relevant papers for the use of the low FODMAP diet in IBS. The Committee discussed that there may be future resource implications related to the low FODMAP diet as it is currently delivered through dietitian support. These resource implications were thought to be minimal due to the place of FODMAP advice as one component in the suite of diet and lifestyle interventions for IBS.
Quality of evidence	The Committee discussed the inherent difficulties with studies that consider dietary intervention, such as the difficulties with blinding the participants. Accounting for this, the Committee agreed that in assessing the studies

	using GRADE, the evidence was of very low quality. In particular the Committee highlighted the comparison of habitual or standard diet and the likelihood of a lack of consistency in what this entails. The Committee discussed that the included studies had participants who had been referred to dietitian based clinics and whether they could be considered representative of those with IBS based in primary care. It was agreed that though there may be some differences, these studies have relevance to primary care (accepting the possibility that the study participants may be those with more severe symptoms than those based in primary care). The Committee noted the difficulties in getting funding for IBS related research in general and the importance of reviewing the low FODMAP diet as it is being discussed both professionally and within patient forums. The the Committee felt that it was important to include all of the identified trial based studies and agreed with the inclusion of the controlled study as well as the two RCT based studies.
Other considerations	The Committee discussed that as the low FODMAP diet is being currently used in those with IBS and that there is very limited evidence of potential benefits and harms, a research recommendation would be appropriate. The Committee considered that this should focus on areas such as patient acceptability of the low FODMAP diet, quality of life, long-term effects and consideration of the re-introduction phase of the low FODMAP intervention.

2.2.61 Recommendations

4. If a person's IBS symptoms persist while following general lifestyle and dietary advice, offer advice on further dietary management. Such advice should:

- **include single food avoidance and exclusion diets (for example, a low FODMAP [fermentable oligosaccharides, disaccharides, monosaccharides and polyols] diet)**
- **only be given by a healthcare professional with expertise in dietary management. [new 2015][2]**

2.2.79 Research recommendation

2. For people with IBS, what is the clinical and cost effectiveness of a low FODMAP diet?

Why this is important

There is a lack of scientific research on the use of the low FODMAP diet in people with IBS. Although there is limited, very low-quality evidence of its effectiveness, anecdotal reports indicate that it is being widely used.The low FODMAP diet is complex. Adherence levels and long-term and adverse effects of the diet are unknown.

IBS-related symptoms have a considerable, negative impact on quality of life and there is a lack of evidence on the impact of the low FODMAP diet on this key outcome.

[2] This recommendation has been updated. However, only the low FODMAP diet was included in the evidence review. The shaded text was not reviewed for this update and so we will not be able to accept comments on this.

2.3 Review questions 3 and 4: Linaclotide and Lubiprostone

2.3.1 Review question

Is linaclotide effective in the treatment of constipation predominant Irritable Bowel Syndrome (IBS-C)?

Is lubiprostone effective in the treatment of IBS-C?

2.3.2 Evidence review

The aim of the review was to assess the effectiveness of linaclotide and lubiprostone against either placebo or other treatments for IBS-C.

Linaclotide, a guanylate cyclase C receptor agonist is one of a relatively new class of laxatives which is licenced for moderate to severe IBS-C at a dose of 290µg once daily.

Lubiprostone, a $5HT^4$ receptor agonist is also one of a relatively new class of laxatives and is licenced for chronic idiopathic constipation "when lifestyle changes are inadequate" at a dose of 24µg once daily to twice daily.

Both linaclotide and lubiprostone draw fluid into the gastrointestinal lumen which accelerates intestinal transit.

A systematic search was conducted (see appendix D) for both linaclotide and lubiprostone which identified 606 references. The titles and abstracts were screened and 17 articles were identified as potentially relevant. Full text versions of these 17 articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). 7 of the 17 studies were included (linaclotide n=4, lubiprostone n=3, see table below). The review flow chart for this review is in appendix E. Excluded studies are summarised in appendix F.

Only RCTs were included as they are the gold standard for drugs efficacy trials and sufficient RCT evidence has been identified for this review question. All included studies had placebo as the comparator. All linaclotide studies had a 290µg dose arm with study period of 12 weeks, plus 1 study had 12 and 26 week follow-up. Two out of 3 lubiprostone studies had a 48µg dose arm (the other, 32µg) with study periods of 6 weeks (1 study) or 12 weeks (2 studies). Meta-analyses were possible for several clinical outcomes (linaclotide) but none were possible (aside from discontinuation and safety) for lubiprostone.

Full details of the included studies are given in evidence tables in appendix G. The quality of evidence for each important outcome was appraised using the approach recommended by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group (see appendix H). A summary table of included studies is shown below.

Included studies	Population	Intervention	Outcomes
Chey (2012)	804 participants meeting Rome II criteria for IBS-C. 18+. Eligibility for randomisation: average score of ≥3 for daily abdominal pain at its worst (11 point rating scale) and an average of <3 Complete Spontaneous Bowel Movements (CSBMs) per week and ≤5 Spontaneous Bowel Movements (SBMs)/week during the baseline	Linaclotide 290µg orally once daily, 30 mins before breakfast. N=401	12 weeks and 26 weeks respectively. 1. FDA Responder (Pain ≥50% of weeks). 2. FDA Responder (Stool frequency ≥50% of weeks). 3. FDA Combined responder pain and

Included studies	Population	Intervention	Outcomes
	period (12 weeks) not necessarily consecutive, in the 12 months before the screening visit. Mean age 44yrs, Female 90%, White 78%. Significantly higher proportion of men in placebo arm than the linaclotide arm (12.7 vs 8.2% p=0.037).		stool frequency (≥50% of weeks) 4. FDA Pain Responder (≥30% improvement 75% of weeks) 5. FDA Combined responder Pain and stool frequency 75% of weeks 6. Constipation Responder (improvement in stool consistency ≥1 point on BSFS) 7. Bloating Responder (improvement ≥50% wks) Bloating severity (5 point scale).
Rao (2012)	800 participants As above (Chey 2012) Mean age 44 years, 90.5% female.	Linaclotide 290µg once daily. Timing not specified. N=405	1. FDA Responder (Pain ≥50% of weeks). 2. FDA Responder (Stool frequency ≥50% of weeks). 3. FDA Combined responder pain and stool frequency (≥50% of weeks) 4. FDA Pain Responder (≥30% improvement 75% of weeks) 5. FDA Combined responder Pain and stool frequency 75% of weeks 6. Constipation Responder (improvement in stool consistency ≥1 point on BSFS) 7. Bloating Responder (improvement ≥50% wks) 8. Constipation severity (5 point scale).
Johnston (2010)	420 participants 18+ Rome II criteria <3 SBMs per week and ≥1 of the following for at least 12 wks in the preceding 12 months: 1) Straining during ≥25% of bowel movements	Linaclotide once daily BEFORE first meal. 290µg dose arm reported only. N=84	1. QOL (IBS QOL scale) >14 point change. 2. Mean change from baseline (QOL scale) 3. IBS degree of relief responders (Equivalent to EMA

Included studies	Population	Intervention	Outcomes
	2) Lumpy or hard stools during ≥25% of bowel movements 3) Sensation of incomplete evacuation during ≥25% of bowel movements, plus Mean score of ≥2 for abdominal (non-menstrual) pain or discomfort on 5 point scale 1=none, 5=very severe) and Mean of <3 CSBMs and ≤6 SBMs per week. Discontinuation of ineligible medication (e.g. anticholinergic agents, opiods). Mean Age 44. Female 92%.		recommended outcome). 4. Constipation Severity
Quigley (2013)	803 (Trial 1, Rao (2012) as above. 805 (Trial 2, Chey (2012) as above,	Linaclotide 290µg (as above)	1. IBS QOL Mean change from baseline* (improvement) by week 12. 2. EMA 12-week abdominal pain/discomfort responders (Pain rated on 11 point NRS. Responder = those with an improvement of ≥30% for at least 6/12 weeks). 3. EMA 26-week abdominal pain/discomfort responders (as above but for 13/26 weeks) 4. EMA 12 week degree of relief responders 5. EMA 26-week degree of relief responders (as above but for at least 13/26 weeks)
Whitehead (2011)	62 patients with physician diagnosis of IBS and Rome III criteria for IBS-C. Age 18+ Baseline Characteristics: (not reported by arm) Mean age (SD) 41.95 (13.56), 85.5% Female. Average IBS Severity Score at baseline was 296 (95% CI 274,317).	Lubiprostone 48µg, one capsule twice daily. (n=62 or 60)	After treatment period 2 1. Life interference, mean difference 2. IBS-SS Mean difference 3. Pain (0–10 scale) Mean difference 4. Days with hard/lumpy stools or no stools (%)

Included studies	Population	Intervention	Outcomes
	Percentage per score category: Mild (score<175) - 8.1% Moderate (175-300) - 46.7% Severe (>300) - 45.2%		5. Bloating (0–10 scale) mean difference.
Drossman (2009)	Combined n= 1171 Study A n=590 Study B n=581 Rome II diagnosis of IBS-C. Age 18+. Compliance with daily diary completion ≥70% during the 4 week baseline period. Min 2 of the following 1. <3 SBMs / week 2. At least 25% SBMs accompanied by at least moderate straining 3. At least 25% SBMs associated with stool consistency rating. Mean Age 47years, 91.6% female.	Lubiprostone 16µg (8µg twice daily) with breakfast and dinner and with 8oz water Study A n=390 Study B N=379	1. IBS QOL, mean difference 2. Overall responders (degree of relief over time) 3. Spontaneous Bowel Movements (frequency) Mean difference. Statistically significant result for outcome 2 only (favouring lubiprostone).
Johanson (2008)	195 18-80 years old, not pregnant, not lactating. Rome II diagnostic criteria for IBS Rome II modular questionnaire criteria for IBS-C Sigmoidoscopy or colonoscopy within 5 years to rule out other causes/diseases. In 4 week initiation period Avoidance of disallowed medications (not specified) Satisfactorily complete electronic diary Min 2 of the following 1. <3 SBMs / week 2. At least 25% SBMs accompanied by at least moderate straining 3. At least 25% SBMs associated with stool consistency rating Mean Age 44, 91% female.	Lubiprostone 16, 32, 48µg per day, Split into 8µg twice daily (n=51), 16µg twice daily (n=49) or 24µg twice daily (n=45) with breakfast and dinner and 8oz H^20.	1. IBS-QOL mean difference 2. Spontaneous bowel movements (weekly frequency) – mean difference 3. Constipation Severity (5 point scale) mean difference.

1

2

2.3.31 Health economic evidence

2 An additional search was undertaken using the same search terms with an economic
3 evaluations filter to identify studies assessing the cost-effectiveness or cost-utility of
4 Linaclotide or Lubiprostone for the treatment of IBS-C. The search retrieved 239 articles.
5 The titles and abstracts were screened for possible inclusion and no articles were selected
6 for further examination of the full-text version. A review flowchart is provided in appendix E.

2.3.47 Evidence statements

2.3.4.18 Linaclotide

9 Quality of life

10 One RCT (139 participants) evaluated quality of life using responder criteria in linaclotide vs.
11 placebo in IBS-C, reported no significant differences between study arms [very low quality].

12 Three RCTs (1743 participants) evaluated quality of life (mean change) in linaclotide vs.
13 placebo in IBS-C. Two individual studies detected significant and clinically important
14 improvements after twelve weeks of study drug [moderate and low quality]. The third study
15 provided no statistical evaluation [very low quality].

16 FDA and EMA responder criteria

17 Two RCTs (1604 participants) reported FDA responder criteria for IBS symptoms. Meta-
18 analyses suggested people on linaclotide were more likely to achieve improvement
19 (responder status) compared to placebo for the following:

20 • Composite pain and stool frequency (≥75% of study weeks) (2 RCTs) [moderate quality]
21 • Pain (for both ≥50% and 75% of study weeks) (2 RCTs) [low and very low quality]
22 • Stool frequency (≥50% of study weeks) (2 RCTs) [low quality]

23 However, only the composite outcome and stool frequency had reached clinical important
24 significance.

25 Three RCTs (1773 participants) evaluated IBS-C symptoms on linaclotide vs. placebo per
26 EMA criteria. Meta-analysis suggested statistically significant improvements in global
27 responders and pain/discomfort responders (2 RCTs 1604 participants), but the latter was
28 not clinically significant [low quality].

29 Severity and bloating

30 Two RCTs (1604 participants) evaluated constipation severity using responder status
31 (percentage with >1point change on Bristol Stool Form Scale). Meta-analysis detected an
32 increase in BSFS responder status in IBS-C participants receiving linaclotide vs. placebo
33 [moderate quality].

34 Two RCTs (1604 participants) evaluated bloating using responder status (% with >30%
35 improvement for ≥ half the study weeks). Meta-analysis detected a significant increase in
36 bloating responder status in IBS-C participants receiving linaclotide vs. placebo [moderate
37 quality].

38 Discontinuation and adverse events

39 Meta-analysis (two RCTs, 1608 participants) showed no clinically significant increase in
40 study discontinuation (for all reasons) in linaclotide vs. placebo; [low quality]

Meta-analysis of 3 RCTs (1778 participants) and 2 RCTs (1607 participants) respectively, detected there was no clinically significant increase in discontinuation due to diarrhoea and flatulence in linaclotide vs. placebo. Discontinuation due to adverse events (abdominal pain (three RCTs, 1777 participants), abdominal distension (2 RCTs, 1607 participants), nausea and UTIs (1 RCT, 170 participants) were not different in linaclotide vs. placebo. [moderate – low quality]

There were no clinically significant differences in serious adverse events (meta-analysis of three RCTs, 1777 participants) in linaclotide vs. placebo. [moderate quality]

2.3.4.2 Lubiprostone

Quality of life

Three RCTs (1467 participants) reported on QOL but pooling was not possible due to missing data in 2 of the 3 studies. Thus, there is a lack of RCTs of sufficient quality to enable evaluation of the effect of lubiprostone on the QOL of participants with IBS-C.

Severity and abdominal pain

Two RCTs (1278 participants) individually evaluated IBS symptoms (symptom severity and overall responder status respectively) in IBS-C participants receiving lubiprostone vs. placebo. No clinically significant difference in symptom severity was found, but a clinically significant improvement in overall responder status was detected in lubiprostone vs. placebo arms. [low quality]

One RCT (120 participants) evaluated abdominal pain in IBS-C participants receiving lubiprostone vs. placebo but detected no clinical difference between study arms. [very low quality]

Bowel movement, constipation and bloating

Two RCTs (1347 participants) evaluated frequency of spontaneous bowel movements in participants with IBS-C receiving lubiprostone vs. placebo. One study (193 participants) detected a clinically significant improvement in frequency of bowel movements in lubiprostone vs. placebo. The other study (1154 participants) detected no clinically significant improvement. [low and very low quality]

One RCT (193 participants) detected no clinically significant improvement in constipation severity. [very low quality]

One RCT (120 participants) evaluated bloating in participants receiving lubiprostone vs. placebo but detected no clinically significant difference by study arm. [moderate quality]

Discontinuation and adverse events

Meta-analysis of 3 RCTs (1256 participants) evaluated discontinuation (for all reasons) in lubiprostone vs. placebo and detected no clinically significant difference in discontinuation by study arm. [low quality]

Meta-analysis of 2 RCTs evaluated adverse events (1260 participants) and serious adverse events (1266 participants) and detected no clinically significant differences by study arm [low and moderate quality respectively] with the exception of nausea which was significantly higher in the lubiprostone arm. [moderate quality].

2.3.51 Evidence to recommendations

Relative value of different outcomes	The important outcomes were prioritised by the topic-specific members (TSMs) through ranking methods and further confirmed by the standing Committee before the review was carried out. The relative value of different outcomes was discussed, and the prioritised, important outcomes were as follows: Quality of life, symptoms, pain, patient preferences, deterioration, stool score/change in bowel habit and relapse, flatulence or bloating. Across the included studies (n=7), more than 50 different outcome measures/metrics were reported that were relevant to the 7 agreed important outcomes. There were also differences in the way outcomes were reported between linaclotide and lubiprostone to decide which of these were the most clinically relevant and important to patients. The TSMs were again consulted, and a total of 21 outcomes were subsequently selected. These were:- *Linaclotide* **Quality of Life** 1. Quality of Life (IBS QOL Scale) 2. Quality of Life responder (>14 point change on IBS QOL Scale) **Symptoms** 3. Improvement of ≥ 30% from baseline in average daily worst abdominal **pain** score 50% of the time (calculated weekly) (FDA suggested) 4. Rate increase in **stool frequency** - ≥1 complete spontaneous bowel movement (CSBM) per week from baseline (FDA suggested) 5. Combined weekly FDA responder (improvements in both **pain** and **stool frequency**) (FDA suggested) 6. Improvement of ≥ 30% from baseline in average daily worst abdo **pain** score 75% of the time (calculated wkly) (FDA suggested) 7. Combined end point defined a responder (improvements in **pain** and **stool frequency** (≥3 CBSMs and increase of ≥1 CSBM from baseline) 75% of the time (FDA suggested) 8. 12-week abdominal pain/discomfort responders (≥30% reduction in mean abdominal pain and/or discomfort (11 point scale) *with neither worsening from baseline* for ≥6 weeks) (EMA suggested) 9. 12-week IBS degree of relief responders (symptoms 'considerably' or 'completely' relieved for ≥6/12wks) (EMA suggested) **Stool Score/Bowel habits** 10. Constipation Severity (% with decrease in ≥ 1 point on BSFS for ≥ 50% weeks) 11. Mean change in constipation (5 point scale, 1 = none, 5=very severe) **Relapse or flatulence or bloating** 12. Abdominal bloating (% of patients with ≥30% decrease in discomfort for ≥50% of weeks) *Lubiprostone* **Quality of Life** 13. Quality of Life (IBS QOL Scale) 14. Life interference (0-10 scale) **Symptoms** 15. IBS Symptom severity (Score out of 500) 16. Overall Relief Responder Status (based on reported 7-point relief scale) **Pain** 17. Pain (0-10 scale) **Stool Score/Bowel habits** 18. Spontaneous Bowel Movements (SBMs) (Frequency) 19. Constipation severity (5 point scale) (0= absent, 4=very severe) 20. Stool output (days with hard/lumpy stools or no stools %)

	Relapse or flatulence or bloating 21. Bloating (0-10 point scale) The Committee was advised of the agreed sub outcomes prior to further analysis. As the FDA and EMA suggested outcomes included individual and composite outcomes for pain and stool frequency, these were reported once under the outcome 'symptoms' and not separately under 'pain' or 'stool frequency'. The FDA and EMA recommended that clinical relevance for continuous outcomes should be considered as ≥30% improvement. This figure was therefore used to assess clinical relevance for each continuous outcome. The Committee considered the recent EMA recommendations not to use 'overall relief' as an outcome measure, and thus decided that this information weakened the suggested benefit of lubiprostone. The Committee advised that changes to stool consistency should equate to a minimum of two points on the BSFS to be clinically important.
Quality of evidence	*There was variation in how outcomes were reported for both drugs and several composite outcome reported. For all included studies, the reviewer had to back-calculate statistics to obtain results of sufficient quality before evaluation could begin.* *Linaclotide* Effects favouring linaclotide vs. placebo were both statistically and clinically significant in 7 out of 12 selected clinical outcomes. Six of these 7 outcomes included a meta-analysis of at least 2 studies. Quality ratings were moderate (3 pooled outcomes), low (2 pooled outcomes) and very low (1 pooled outcome). One outcome included 3 individual studies that could not be pooled (moderate to very low quality). Moderate, low or very low quality evidence suggests that linaclotide may improve quality of life, stool frequency, combination of pain and stool frequency, degree of relief, constipation and bloating in people with IBS-C. Potential confounders cannot be excluded. Use of rescue medication (other laxatives), use of concomitant laxatives (bulk forming and stool softeners), 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. As such the overall evidence quality was rated down due to risk of bias. The Committee acknowledged that we could not be sure whether it was the study drug, the rescue medication or concomitant medication that had a positive effect on the outcomes. The efficacy of linaclotide was discussed in detail, taking into account the evidence quality and the risk of bias for the above reasons. It was acknowledged that many people have tried multiple laxatives without adequate symptom relief and that in practice, for some patients, they would welcome the opportunity to try these new laxatives. The Committee decided that a weak recommendation would be appropriate for this drug, taking into account individual patient symptoms (severity and duration) and previous treatment options that may not have induced sufficient or long-lasting relief.

	Lubiprostone Effects favouring lubiprostone vs. placebo were both statistically and clinically significant in only 2 out of 9 selected important outcomes (overall relief and spontaneous bowel movements) and the evidence rating for these outcomes was low. One of these outcomes was reported by 2 studies - 1 small study was both statistically and clinically significant, the other larger study was not. As the evidence for efficacy of lubiprostone was low quality the Committee decided there was insufficient evidence to warrant a recommendation for the use of lubiprostone in this update.
Trade-off between benefits and harms	*Linaclotide* Benefits of linaclotide identified in the evidence review were improvements in quality of life, stool frequency, combination of pain and stool frequency, degree of relief, constipation and bloating. The outcome quality ratings were from moderate to very low. Diarrhoea was the only adverse event that was both statistically and clinically worse in the linaclotide arm. The Committee acknowledged diarrhoea is an adverse event common to all laxatives. CG61 recommends dose titration and monitoring of laxatives according to clinical response. Taking multiple laxatives from different classes could contribute to polypharmacy which may be undesirable for some people and therefore affect adherence to prescribed doses. *Lubiprostone* Benefits of lubiprostone were more uncertain than those for linaclotide and were limited to an improvement in overall relief only (low quality evidence). Nausea was more likely in the lubiprostone vs. placebo arms and this could be considered by some people as a minor harm, although nausea is also a potential consequence of constipation.
Trade-off between net health benefits and resource use	No existing economic evaluations of linaclotide or lubiprostone were identified. The Committee considered the unit costs of linaclotide and lubiprostone and compared these to the lower unit costs of various classes of laxatives currently used in the NHS. The Committee considered that there may be a reduction in resource use due to a decrease in presentations to healthcare if symptomatic relief is achieved.
Other considerations	The Committee decided that the predominantly female population across all the included studies (86-92%) was reasonable as it reflected the epidemiology of the IBS population. The Committee discussed the timing and setting for potential prescribing of linaclotide. It was agreed that prescribing recommendations should not be limited to secondary care, and that other conventional laxative classes recommended by the original guideline should be tried first, taking individual patient preferences into account. The Committee further discussed whether a research recommendation was required for this topic. They agreed that further efficacy trials for linaclotide were not necessary. Regarding lubiprostone, as it is off-label for treating IBS and there is already a licensed and indicated alternative (linaclotide) for which a positive recommendation has been made, the Committee felt that a further research recommendation on this was not necessary.

2.3.6 Recommendations

5. Consider linaclotide for people with IBS only if:

- **they have had severe constipation for at least 12 months and**
- **optimal or maximum tolerated doses of previous laxatives from different classes have not helped. [new 2015]**

2.3.7 Research recommendation

The Committee did not prioritise the need for research recommendation in this area.

2.4 Review question 5: Psychological interventions

This first part of this section (review question part 5a) will update the evaluation of relaxation compared to other interventions in the management of IBS undertaken in CG61.

The second part of the section (review question 5b) will evaluate the effectiveness of computerised cognitive behavioural therapy and mindfulness therapy compared to usual care and other interventions; this will not not supercede the separate recommendation about hypnotherapy, Cognitive Behavioural Therapy and psychological interventions originally made in CG61 (recommendation 1.2.3.1).

2.4.1 Review question 5a

Do psychotherapies (relaxation therapy) have an effect on symptoms of IBS?

2.4.2 Evidence review

2.4.2.1 Relaxation therapies

The aim of the review was to assess the clinical and cost- effectiveness of relaxation therapies compared to other interventions in the management of IBS.

A systematic search was conducted (see appendix D) which identified 2553 articles. The titles and abstracts were screened and 19 articles were identified as potentially relevant. Full text versions of the articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). The review flow chart for this review is in appendix E.

In addition, a Cochrane Review assessing the psychological treatments for the management of irritable bowel syndrome was identified (Zijdenbos et al., 2009), along with 4 studies from the original CG61 guideline (Blanchard et al., 1993; Keefer 2001; Forbes et al., 2000; Boyce et al., 2003). One study from the previous guideline that was included in this review (Forbes et al., 2000) was a three-armed trial comprising CBT, relaxation and placebo, and was not previously included in the relaxation comparison. Of the 23 studies identified, 19 studies were excluded, including 2 which were originally included in the evidence review in CG61; these were excluded because 1 broke randomisation and was therefore no longer considered an RCT (Blanchard 1993) and for the other study there was insufficient information about the study to classify it as randomised controlled trial (Keefer, 2001). The Cochrane Review was excluded because it included relaxation and other CBT- based therapies as the intervention.

Details of the included studies are given in evidence tables in appendix G. The quality of evidence for each important outcome was appraised using the approach recommended by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group (see appendix H).

Four RCTs were subsequently included in this review. Two studies compared relaxation to routine clinical care or control, 1 study compared relaxation to enhanced medical care and 1 study compared relaxation to hypnotherapy.

Studies reported outcomes at multiple time points. As IBS is considered to be a chronic condition, the results from the longest follow-up point were used to assess clinical effectiveness of the intervention. Where more than 1 study reported the same outcome and the results could be meta- analysed, more than one time point has been used. This is so that both pooled results and results from the longest follow- up point were available for analysis.

Table 4: Included studies summary

Reference	Participants	Intervention	Outcomes reported
Boyce et al. (2003) RCT	N=44 (participants diagnosed with IBS according to Rome I criteria)	Relaxation therapy compared to routine clinical care for 8 weeks.	Quality of Life outcomes: SF36, HADS, ATQ, LCB Symptom score: BSS
Shinozaki (2010)	N=21 (participants diagnosed with IBS according to Rome II criteria, all non-responders to previous treatment)	Autogenic training compared to control for 8 weeks.	Quality of Life outcomes: SIBSQ, SDS, STAI, SF36, Automatic thoughts, locus of control, HAD (total) Symptom score: BSSS (frequency, distress, interference),
Lahman (2010)	N=80 (participants diagnosed with IBS according to Rome II criteria within prior 2 years)	Functional relaxation compared to enhanced medical care for 5 weeks.	Symptom score: score, IBS symptoms, Abdominal pain, deterioration (diarrhoea and constipation), bloating
Forbes (2000)	N=25 (participants diagnosed with IBS according to Rome I criteria, symptomatic for at least 6 months failed to respond to conventional therapy)	Relaxation compared to hypnotherapy for 12 weeks	Quality of Life outcomes: GHQ, HADS, SF36. Symptom score: Overall symptom score

2.4.3 Health economic evidence

2.4.3.1 Relaxation therapies

An additional search was undertaken using the same search terms with an economic evaluations filter to identify studies assessing the cost-effectiveness or cost-utility of relaxation therapies (see appendix D). The search retrieved 1,153 articles. The titles and abstracts were screened for possible inclusion, and 14 articles were selected for further examination of the full-text version. No economic evaluations were included for review. A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

2.4.4 Evidence statements

2.4.4.1 Relaxation therapies

2.4.4.1.1 Relaxation/ autogenic training vs routine clinical care/ control

Quality of life

One study (21 participants) reported the quality of life outcomes SIBSQ, SDS and STAI; there is no clinically significant improvement in any of these outcomes within either group or between the relaxation or control groups at 8 weeks follow up. [very low quality]

Two studies (65 participants) reported SF36 individual domain scores at 8 weeks follow up; there is no clinically significant improvement in any SF36 domain within either group or

between the relaxation or control groups at 8 weeks follow up [very low quality]. One study (n=34) reported SF36 individual domain scores at 52 weeks follow up; there is only clinically significant improvement in the domain “role physical” within the relaxation group and there is considerable uncertainty [very low quality], the difference between relaxation and control groups at 52 weeks follow up does not reach clinical significance. [very low quality]

One study (34 participants) reported the quality of life outcomes ATQ, LCB and HADS; there is no clinically significant improvement in any of these outcomes within groups or between relaxation therapy and control groups at 52 weeks follow up. [very low quality]

Symptom scores

One study (21 participants) reporting adequate relief at 8 weeks follow up suggests that relaxation therapy may be more clinically effective than control, but there is some uncertainty. [very low quality]

One study reported Bowel Symptom Severity Score (BSSS) domains of frequency, interference and distress (34 participants) at 52 weeks follow up; there is no clinically significant improvement in any BSSS domain within groups or between relaxation therapy and control groups at 52 weeks follow up. [very low quality]

No studies were identified that reported the outcomes patient preference, stool score/ general changes in bowel habit, relapse or flatulence.

2.4.4.1.2 Relaxation vs enhanced medical care

Quality of life

One study (80 participants) reported impairment severity score domains of bodily impairment, psychic impairment and social impairment; there is no clinically significant improvement in any of these outcomes within groups or between relaxation therapy and control groups at 12 weeks follow up. [low quality]

Abdominal pain and deterioration

One study (80 participants) reported abdominal pain, diarrhoea and constipation [very low quality outcomes], bloating and overall IBS symptoms [low quality outcomes]; there is no clinically significant improvement in any of these outcomes within groups or between relaxation therapy and control groups at 12 weeks follow up.

No studies were identified that reported the outcomes patient preference, stool score/ general changes in bowel habit, relapse or flatulence.

2.4.4.1.3 Relaxation vs hypnotherapy

Quality of life

One study (25 participants) reported the quality of life outcomes GHQ, HADS and individual domains of SF36. There was no clinically significant difference within groups or between relaxation and hypnotherapy groups for GHQ and HADS (anxiety and depression domains) at 12 weeks follow up. [very low quality]

There was clinically significant improvement in SF36 “role physical” domain between relaxation and hypnotherapy (favouring hypnotherapy) at 12 weeks follow up [very low quality], the improvement within the hypnotherapy group did not reach clinical significance. No other domain of the SF36 showed clinically significant improvement within groups or between relaxation and hypnotherapy groups at 12 weeks follow up [very low quality]. All other SF36 domains except health change had higher baseline scores in the relaxation group

than the hypnotherapy group. As baseline scores between groups were not comparable, there is uncertainty about the IBS population of this study and the effect of the intervention.

Symptom score

One study (25 participants) reported outcome overall symptom score; the data suggests that there is no clinically significant improvement within groups or between relaxation or hypnotherapy groups at 12 weeks follow up. The uncertainty around this result cannot be interpreted due to the way that the data is presented. [very low quality]

No studies were identified that reported the outcomes abdominal pain, patient preferences, deterioration, stool score/ general changes in bowel habit and relapse or flatulence.

2.4.5 Evidence to recommendations

Relaxation therapies

	Committee discussions
Relative value of different outcomes	Important outcomes were prioritised through ranking by the topic-specific members (TSMs) of the Committee and agreed by other standing Committee members before the review was carried out. The following outcomes were considered important in decision making: Quality of Life, symptom scores, abdominal pain, patient preferences, deterioration, stool score/ general changes in bowel habit, relapse or flatulence or bloating. The Committee discussed and agreed that quality of life would be the most critical patient-important outcome as IBS is a chronic condition. However, the Committee noted that 2 of the included studies reported SF36 (quality of life scale) as individual domains. The Committee noted that there was uncertainty around the interpretation of the scores of individual domains of SF36 and that conclusions could not be drawn from the results reported in the studies. The Committee did not identify any adverse events specifically relating to relaxation therapy and no adverse events were identified from the studies included in the evidence review. The Committee noted that due to the nature of the intervention, adverse events are unlikely.
Quality of evidence	All outcomes for the included comparisons of relaxation vs routine care, relaxation vs enhanced medical care and relaxation vs hypnotherapy were assessed as either low or very low quality evidence using the GRADE methodology. The Committee reviewed the evidence, taking into account the low and very low quality evidence available for this review. The Committee noted that the 4 interventions included were very different, that currently there is still no agreed definition for relaxation therapy in the NHS and components of relaxation were usually adopted as part of CBT rather than a stand- alone intervention. The Committee decided that due to the limited and poor quality evidence, it was not possible to make a recommendation about relaxation as a stand-alone therapy that would apply to the wider population with IBS.
Trade-off between benefits and harms	Using a 30% change from baseline score for continuous outcome (as clinical minimal important difference) as outlined in the EMA document[3], 2 of the 30 separate outcomes suggested that there was possible clinical

3 Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome (2013). European Medicines Agency. [Accessed 03/10/2014 at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500173457.pdf]

	benefit for relaxation and one outcome suggested possible clinical benefit for hypnotherapy compared to placebo. There was considered to be possible clinical benefit with relaxation compared to routine care with regards to obtaining adequate relief and improvement in SF36 role 'physical domain', but there was some uncertainty around both of the results. For the comparison of relaxation vs hypnotherapy there was possible clinical benefit for hypnotherapy compared to relaxation at follow up, though there was uncertainty around the result. All of the outcomes showing clinical benefit were very low quality evidence. For the remainder of the outcomes (13 symptom- related outcomes and 17 quality of life related outcomes) the evidence suggested that there was no difference between relaxation and routine care, enhanced medical care or hypnotherapy (all low and very low quality evidence). No serious adverse events were identified. There was insufficient evidence to indicate clinical effectiveness for relaxation in the management of IBS, and there was no evidence identified that indicated relaxation caused clinical harm.
Trade-off between net health benefits and resource use	No economic evaluations were identified on relaxation therapies. The Committee considered that the cost of delivering relaxation therapy was quite low compared to other psychological interventions although there was variation in the mode of delivery.
Other considerations	The Committee discussed that there was not sufficient evidence to make a recommendation regarding relaxation therapy in the management of IBS in adults in primary care. The Committee further discussed whether a research recommendation was required to further investigate the effectiveness of relaxation therapy. The Committee agreed that currently there was no standard definition for relaxation therapy which will make research in this area difficult. Moreover, the Committee also acknowledged that relaxation therapy was not routinely used for managing IBS on its own, rather, some elements of relaxation therapy were aften incorporated into standard CBT instead. For these reasons, the Committee felt that further research recommendation was not necessary.

2.4.6 Recommendations

No recommendation.

2.4.7 Research recommendation

The Committee did not prioritise the need for research recommendation for this area.

2.4.8 Review question 5b

Do psychotherapies (computerised cognitive behavioural therapy, CBT, and mindfulness therapy) have an effect on the symptoms of IBS?

2.4.9 Evidence review

A systematic search was conducted (see appendix D) which identified 3704 articles. The titles and abstracts were screened and 76 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). Of these, 67 were excluded as they did not meet the

criteria. Seven studies reported in 9 publications met the criteria and were included (3 publications out of the 9 were of the same study).

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F. Overall, the reasons for exclusion are:

- Interventions were outside the update remit
- Studies were not RCT
- Inappropriate study population (other GI conditions)
- Duplication of publications.

Overall summary of evidence

From the 9 included publications (7 studies, of which 3 publications were of the same study), evidence was identified for the following relevant interventions:

- Internet-based CBT using both mindfulness and exposure principles (ICBT-Mindfulness/Exposure)
- Internet-based CBT using exposure principles (ICBT-Exposure)
- Mindfulness group training
- Mindfulness-based stress reduction programme (MBSR)

Most of the evidence identified was of low to very low quality due to the following reasons:

- The study populations from 6 included studies (3 publications are from the same study) were self-referred, which indicated the risk of selection bias. The potential risk of selection bias together with the lack of blinding due to the nature of the interventions may overestimate the treatment effects.
- All of the included studies have unclear baselines (not reported) regarding any concomitant treatments for the treatment of IBS (e.g. unclear whether the study population was on pharmacological treatments, lifestyle management or other psychological interventions for IBS).
- Reasons for withdrawal or lost to follow-up in some studies were not reported.
- The details of the comparators of 2 included studies (Zernicke 2012, TAU) and Hunt (2009, Waitlist control) was unclear.

It is of note that all of the included studies were non-UK based (6 publications of 4 studies were from the same research group (Ljotsson et al., Sweden). The generalisability of the evidence to UK population and UK practice are therefore questionable.

For the full evidence tables and full GRADE profiles please see appendices G and H.

Table 5: Included studies summary

Reference	Participants	Intervention and comparator	Outcomes reported
Ljotsson (2010) ID: 2511 Andersson (2011) ID: 252 Ljotsson (2011)c ID: 295 (a)	85 self-referred IBS-patients who self-declared to have had a previous diagnosis of IBS given by a physician and if they presently fulfilled the Rome III criteria for IBS. Stockholm.	Intervention: CCBT-Mindfulness/ Exposure (10-week CBT-protocol) With online therapist contact Comparator: Waitlist (online discussion forum) With online therapist	10-week treatment period with 3-month follow-up online assessment. Outcomes (10-week and 3-month follow-up): • IBS-QoL • GSRS-IBS responder • GSRS-IBS scores • The GI symptom diary (only at 10-week)

Reference	Participants	Intervention and comparator	Outcomes reported
		contact	All outcomes reported statistical significant difference between groups at 10-week, but no difference in all outcomes at 3-month follow-up.
Ljotsson (2011)b ID: 209	61 IBS-patients consecutively recruited at a single gastroenterological clinic located in Stockholm, Sweden. Patients came to the clinic by referral or by self-referral. Stockholm.	Intervention: CCBT-Mindfulness/ Exposure (10-week CBT-protocol) With online therapist contact Comparator: Waitlist (online discussion forum) With online therapist contact	10-week treatment period with 12-month follow-up online assessment. • IBS-QoL • GSRS-IBS scores All outcomes reported statistical significant difference between groups at 10-week, but no difference in all outcomes at 12-month follow-up.
Ljotsson (2011) ID: 226	195 self-referred IBS-patients who self-declared to have had a previous diagnosis of IBS given by a physician and if they presently fulfilled the Rome III criteria for IBS. Stockholm.	Intervention: CCBT-Mindfulness/ Exposure (10-week CBT-protocol) With online therapist contact Comparator: Internet-delivered stress management (ISM) With online therapist contact	10-week treatment period with 6-month follow-up online assessment. Outcomes (10-week and 3-month follow-up): • ISB-QoL (statistical significant between groups at 10-week but not at 6-month) • GSRS-IBS scores (statistical significant between groups at both time points) • Adequate relief (responder) (not statistical significant between groups at 10-week but significant at 6-month)
Gaylord (2011) ID: 219	75 women with IBS under the care of a physician recruited through an existing registry of IBS patients interested in participating in research studies. USA.	Intervention: Mindfulness-based stress and pain management program (8 weekly 2-hour group session, plus one half-day retreat) Comparator: Social-support group	8 weeks treatment period with 10-week post-outcome assessment and then 3-month follow-up. • IBS-QoL (not statistical significant between groups at both time points) • IBS-SS responder (statistical significant between groups at 10-week but not at 3-month) • IBS-SS scores (mixed results for different individual symptoms at different time points).
Zernicke (2012) ID: 1579	90 people who received a diagnosis of IBS by a gastroenterologist 90 people who received a diagnosis of IBS by a gastroenterologist Canada.	Intervention: Mindfulness-Based Stress Reduction (MBSR) (8 weekly group sessions) Comparator: Treatment as usual (TAU) (b)	8-week treatment period with 6 months follow-up. • IBS-QoL(statistical significant between groups at 8-week but not at 6-month) • IBS-SS responder (not statistical significant between groups at 8-week) • IBS-SS scores (not statistical significant between groups at 6-

Reference	Participants	Intervention and comparator	Outcomes reported
			month)
Hunt (2009) ID: 454	54 IBS patients who self-reported that they had been diagnosed with IBS by a medical professional, but were not currently diagnosed with any other GI disorder. USA.	Intervention: CCBT-Exposure (5-week treatment) Comparator: Waitlist control (basic self-monitoring, no other information provided)	5-week treatment with 3-month follow-up (only incomplete 3-month data was reported). At 6-week assessment: • IBS-QoL (statistical significant between groups at 6-week) • GSRS-IBS scores (statistical significant between groups at 6-week).
Ljotsson (2014) ID: 1535	311 self-referred IBS patients who declared to have had a previous diagnosis of IBS given by a physician, presently fulfilled the Rome III-criteria for IBS. Sweden.	Intervention: CCBT-Mindfulness (10-week CBT protocol) Comparator: CCBT-Mindfulness/ Exposure (10-week CBT protocol)	10-week treatment with 6-month follow-up. • IBS-QoL (statistical significant between groups at both time points). • GSRS-IBS scores (statistical significant between groups at both time points). Adverse events (not statistical significant between groups at both time points).

(a) 3 publications of one study; (b) No definition for treatment as usual.

2.4.10 Health economic evidence

2.4.10.1 Mindfulness therapy

An additional search was undertaken using the same search terms with an economic evaluations filter to identify studies assessing the cost-effectiveness or cost-utility of mindfulness techniques or computer-based cognitive behavioural therapy (see appendix D). The search retrieved 1,407 articles. The titles and abstracts were screened for possible inclusion, and no articles on mindfulness were selected for further examination of the full-text version. A review flowchart is provided in appendix E.

2.4.10.2 Computer-based cognitive behavioural therapy

An additional search was undertaken using the same search terms with an economic evaluations filter to identify studies assessing the cost-effectiveness or cost-utility of mindfulness techniques or computer-based cognitive behavioural therapy (see appendix D). The search retrieved 1,407 articles. The titles and abstracts were screened for possible inclusion and two articles were selected for further examination of the full-text version. No economic evaluations were included for review. A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

2.4.11 Evidence statements

Four RCTs investigated the effectiveness of CCBT-Mindfulness/Exposure and 1 RCT investigated the effectiveness of CCBT-Exposure.

2.4.11.1 When compared CCBT-Mindfulness/Exposure to online discussion forum

Two RCTs (135 particpants) suggested that people in the CCBT-Mindfulness/Exposure programme were more likely to achieve improvement on quality of life (IBS-QoL scale) and IBS symptoms (GSRS-IBS) at 10-wks. However, only the quality of life outcome has reached the clinical minimum important difference. [low and very low quality]

One RCT (85 participants) also suggested that people in the CCBT-Mindfulness/Exposure programme were more likely to be a responder (GSRS-IBS scale) at 10-wks. This effect reached clinical minimum important difference. [low quality]

One RCT (85 participants) suggested that people in the CCBT-Mindfulness/Exposure programme were more likely to achieve improvement on abdominal pain, tenderness, constipation (composite), total pain, constipation, bloating and flatulence at 10-wks. However, there were no differences between the 2 interventions on diarrhoea and belching. None of the effects reached the clinical minimum important difference. [very low quality]

2.4.11.2 When compared CCBT-Mindfulness/Exposure to Internet delivered stress management (ISM)

One RCT (195 participants) suggested that people in the CCBT-Mindfulness/Exposure programme were more likely to achieve improvement on quality of life (IBS-QoL scale) and IBS symptoms (GSRS-IBS) at both 10-wks and 6-mths follow-up. However, only the quality of life outcome has reached the clinical minimum important difference. The RCT also suggested that people in the CCBT-Mindfulness/Exposure programme were more likely to achieve adequate relief at 6-mths follow-up but not at 10-wks. This effect did not reach the clinical minimum important difference. [low to very low quality]

2.4.11.3 When compared CCBT-Exposure to waitlist control

One RCT (31 participants) suggested that people in the CCBT-Exposure programme were more likely to achieve improvement on quality of life (IBS-QoL scale) and IBS symptoms (GSRS-IBS) at 6-wks. However, only the quality of life outcome has reached the clinical minimum important difference. [low to very low quality]

2.4.11.4 When compared CCBT-Mindfulness/Exposure to CCBT-Mindfulness

One RCT (292 participants) suggested that people in the CCBT-Mindfulness/Exposure programme were more likely to achieve improvement on quality of life (IBS-QoL scale) and IBS symptoms (GSRS-IBS) at both 10-wks and 6-mths follow up. However, only the quality of life outcome has reached the clinical minimum important difference. The RCT also suggested that there was no difference between the 2 interventions on adverse events (cluster). [moderate to low quality]

2.4.11.5 When compared mindfulness group training to social support group

One RCT (75 participants) suggested that people in the mindfulness group training were more likely to be a responder based on the IBS-SS scale (at 10-wks only), and more likely to achieve improvement on the IBS-SS composite outcome (abdominal pain, dissatisfaction with bowel habit, at both 10-wks and 3-mth) compared to those in social support group. However, none of the effects reached clinical minimum important difference. The RCT also suggested there was no difference between interventions for the quality of life outcome (IBS-QoL) and bloating (IBS-SS). [very low quality]

2.4.11.6 When compared mindfulness-based stress reduction programme (MBSR) to treatment as usual

One RCT (90 participants) suggested that people in the mindfulness-based stress reduction programme were more likely to achieve QoL improvement (IBS-QoL scale) at 8-wks compared to those in treatment as usual. However, this effect did not retain at the 6-mths follow-up. None of these effects reached clinical minimum important difference. The RCT also suggested there was no difference between interventions for the IBS symptoms outcomes (IBS-SS responder and total scores) at both time points. [very low quality]

2.4.12 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The important outcomes were prioritised by the topic-specific members (TSMs) through ranking methods and further confirmed by the standing Committee before the review was carried out. The Committee discussed the outcomes data and agreed that patient's quality of life is the most important outcome as IBS is a chronic condition. The Committee also agreed that the use of the IBS-QoL scale for this outcome in the evidence was appropriate as it has been validated and used widely in practice and research. The Committee discussed the importance of assessing the magnitude of improvement from baseline for the quality of life outcome (mean change from baseline scores) rather than just focussing on the difference between treatment groups (mean difference at endpoint). The Committee noted that outcomes for IBS symptoms (as reported using the GSRS-IBS scale and the ISB-SS scale) were not useful in evaluating effectiveness of psychological interventions. This is because the aim of psychological interventions is to equip people with skills and techniques to manage their IBS symptoms better in the long-term to improve their quality of life overall. They are not aimed at reducing IBS symptoms.
Quality of evidence	The Committee agreed that the quality of evidence was mostly of low to very low quality due to a number of factors. All of the included studies have unclear baselines regarding any concomitant treatments for IBS; the study populations of all included studies, apart from 1 (Gaylord 2011), were self-referred, which was subject to selection bias; most included studies did not report reasons for withdrawal or lost to follow-up; finally the definition of the comparator in 2 included studies (Zernicke 2012, Treatment as usual) and (Hunt 2009, Waitlist control) was unclear. The Committee also discussed the directness of the 6 included publications of 4 studies (3 of which were multiple publications of the same research) on the Computerised Cognitive Behavioural Therapy with Mindfulness and Exposure principles (CCBT-Mindfulness/Exposure) as these were conducted in Sweden. The Committee considered and agreed that the procedures of this particular intervention may not be applicable to UK setting for a number of reasons. The intervention package was in Swedish, and that translating the online materials into English may not be practical and there may be uncertainty around its effectiveness when delivered in different languages. Moreover, in this particular CCBT-Mindfulness/Exposure intervention, the participants have online access to a therapist or psychologist to gain detailed one-to-one advice, which was different to how the CCBT programme (for depression) was delivered in the UK. The Committee moved on to discuss the 1 included study (Hunt 2009) on Computerised Cognitive Behavioural Therapy with Exposure principles

	(CCBT-Exposure) and another included study on Mindfulness-based stress reduction (MBSR) (Zernicke 2012). As the definition of the comparator in these 2 studies (waitlist control and treatment as usual, respectively) was unclear, the Committee agreed that the quality of the evidence was of very low quality and there was high uncertainty of the results reported in these 2 studies. Finally, the Committee agreed that the evidence on Mindfulness group training was very limited (1 small study) and of very low quality due to the unclear baseline and reporting issues on reasons for withdrawal and lost to follow-up.
Trade-off between benefits and harms	The Committee discussed the potential benefits of the psychological interventions where only limited evidence was identified. CCBT-Mindfulness/Exposure: The Committee acknowledged that the evidence suggested some benefits on quality of life and IBS symptoms at 10-week post treatment, but it failed to illustrate longer-term benefit (12-month follow-up). This could be due to potentially unsustainable benefits of the intervention or due to participants from the comparison group crossing over to the treatment arm after the 10-week treatment period. Also, the limited evidence for this intervention was from the same study (with multiple publications across different time points) carried out in Sweden. As discussed above, the Committee agreed that currently there is still insufficient evidence to recommend such complex intervention in the UK. A member of the Committee commented that, Ljotsson 2014 was a study of 'mechanisms' where a complex intervention that has found to be effective was "dismantled" to investigate the effectiveness of each component part. As such, it is not an efficacy or effectiveness study comparing intervention with a control. CCBT-Exposure, MBSR and Mindfulness group training 1 very small study (n=31) suggested a small benefit at 6-weeks on quality of life and IBS symptoms without any further longer term data. The Committee agreed that currently there is still insufficient evidence to recommend CCBT-Exposure. 1 small study (n=75) on Mindfulness group training failed to illustrate benefits on quality of life for both the 10-week and 3-month follow-up time points. The Committee again agreed that currently there is still insufficient evidence to recommend Mindfulness group training. Finally, 1 small study (n=75) on MBSR illustrated small benefit on the quality of life outcome at 8-week time-point, but the study failed to illustrate benefits on both quality of life and IBS symptoms at 6-month follow-up. The Committee again agreed that currently there is still insufficient evidence to recommend MBSR. The Committee noted that due to the nature of psychological interventions, there was unlikely to be any treatment-related adverse effects.
Trade-off between net health benefits and resource use	No economic evaluations of mindfulness were identified. The Committee considered that mindfulness is usually delivered as part of cognitive behavioural therapy and therefore unlikely to involve any substantial impact

	on resource use. No economic evaluations of computer-based cognitive behavioural therapy were included in the review of cost-effectiveness. The Committee considered that CCBT is likely to cost less than other psychological interventions.
Other considerations	The Committee acknowledged that although there is currently insufficient research evidence to recommend CCBT and Mindfulness therapy for the management of IBS, Mindfulness therapy has become increasingly popular in private practice, and widely available and free or commercial self-help websites. The Committee felt strongly that urgent UK-based good quality research on Mindfulness therapy is crucial to provide good quality accurate research data to inform both healthcare professionals and patients regarding the effectiveness of such interventions, so that appropriate standards and recommendations could be made for the NHS. Therefore, the Committee agreed that a research recommendation should be made for investigating the effectiveness of Mindfulness therapy.

2.4.13 Recommendations

No recommendation.

2.4.14 Research recommendation

3. What is the clinical and cost effectiveness of computerised CBT and mindfulness therapy for the management of IBS in adults?

Why this is important

There is currently insufficient research evidence to recommend either computerised CBT or mindfulness therapy for the management of IBS. There is limited, low-quality evidence that these interventions may have some benefit in the short-term, but the long-term effects are unknown.

Mindfulness therapy has become increasingly popular in private practice, and is widely available free-of-charge on commercial self-help websites.

Both self-help computerised CBT and mindfulness therapy should be further evaluated with an adequate follow-up period to establish the longer-term effects of these interventions.

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4 Glossary and abbreviations

Please refer to the NICE glossary.

CCBT

Computerised cognitive behavioural therapy

CBT

Cognitive behavioural therapy

FDA

Food and Drug Administration

EMA

European Medicines Agency

1 Appendices

2 Appendix A: Committee members and 3 NICE teams

A.1 4 Standing Committee members

Name	Role
Damien Longson (Chair)	Consultant Liaison Psychiatrist, Manchester Mental Health and Social Care Trust
Catherine Briggs	GP Principal, Bracondale Medical Centre, Stockport
John Cape	Director of Psychological Therapies Programme, University College London
Alun Davies	Professor of Vascular Surgery and Honorary Consultant Surgeon, Charing Cross & St Mary's Hospital & Imperial College NHS Trust
Alison Eastwood	Senior Research Fellow, Centre for Reviews and Dissemination, University of York
Sarah Fishburn	Lay Member
Jim Gray	Consultant Medical Microbiologist, The Birmingham Children's Hospital NHS Foundation Trust
Nuala Lucas	Consultant Anaesthetist, Northwick Park Hospital, Middlesex
Kath Nuttall	Director, Lancashire & South Cumbria Cancer Network (- April 2013)
Tilly Pillay	Consultant Neonatologist, Staffordshire, Shropshire and Black Country Newborn Network, Royal Wolverhampton Hospitals Trust
Nick Screaton	Radiologist, Papworth Hospital NHS Foundation Trust
Lindsay Smith	Principal in General Medical Practice, Somerset PCT
Philippa Williams	Lay Member
Sophie Wilne	Paediatric Oncologist, Nottingham Children's Hospital

A.2 5 Topic-specific Committee members

Name	Role
Mark Follows	GPwSI gastroenterology, St James' Medical Practice, Norfolk
Elspeth Guthrie	Professor of Psychological Medicine & Medical Psychotherapy , Manchester University
Yvonne McKenzie	Dietitian, Department of Health
Marion Saunders	Lay Member
Simon Smale	Consultant Gastroenterologist, York Hospitals NHS Foundation Trust
Peter Whorwell	Professor of Medicine and Gastroenterology, Wythenshawe Hospital

A.3 6 Clinical guidelines update team

Name	Role
Phil Alderson	Clinical Advisor
Sara Buckner	Technical Analyst
Paul Crosland	Health Economist
Nicole Elliott	Associate Director
Cheryl Hookway	Technical Analyst
Jenny Kendrick	Information Specialist

Name	Role
Susannah Moon	Programme Manager
Rebecca Parsons	Project Manager
Roberta Richey	Technical Analyst
Charlotte Purves	Administrator
Toni Tan	Technical Advisor

A.41 NICE project team

Name	Role
Mark Baker	Clinical Advisor
Christine Carson	Guideline Lead
Sarah Catchpole	Senior Medical Editor
Bhash Naidoo	Technical Lead (Health Economics)
Laura Norburn	Public Involvement Advisor
Katie Prickett	Senior Medical Editor
Beth Shaw	Technical Lead
Louise Shires	Guideline Commissioning Manager
Jennifer Wells	Guideline Co-ordinator

1Appendix B: Declarations of interest

Member name	Interest declared	Date declared	Type of interest	Decision
Standing committee members				
Damien Longson	Family member employee of NICE	29/05/13	Personal family non-specific	Declare and participate
Damien Longson	Director of Research & Innovation, Manchester Mental Health & Social Care NHS Trust	29/05/13	Personal non-specific pecuniary	Declare and participate
Catherine Briggs	Husband is a consultant anaesthetist at the University Hospital of South Manchester.	08/07/13	Personal family non-specific	Declare and participate
Catherine Briggs	Member of the Royal College of Surgeons, the Royal College of General Practitioners, the Faculty of Sexual and Reproductive Health and the BMA.	08/07/13	Personal non-specific pecuniary	Declare and participate
John Cape	Trustee of the Anna Freud Centre, a child and family mental health charity which applies for and receives grants from the department of health and the national institute for health research.	10/07/13	Personal non-specific non-pecuniary	Declare and participate
John Cape	Member of British Psychological Society & British Association for Behaviour & Cognitive Psychotherapists who seek to influence policy towards psychology & psychological therapies.	10/07/13	Personal non-specific non-pecuniary	Declare and participate
Alun Davies	Research grant funding: Commercial: Vascular Insights; Acergy Ltd; Firstkind; URGO laboritoire; Sapheon Inc (terminated 2013). All administered by Imperial College London as Sponsor and Prof Davies as CI.	04/11/13	Personal non-specific pecuniary	Declare and participate
Alun Davies	Non-commercial: NIHR, BHF, Royal College of Surgeons, Circulation foundation, European Venous Forum.	04/11/13	Personal non-specific pecuniary	Declare and participate
Alun Davies	Non-commercial: Attendance at numerous	04/11/13	Personal non-specific	Declare and participate

Member name	Interest declared	Date declared	Type of interest	Decision
	national & international meetings as an invited guest to lecture where the organising groups receive funding from numerous sources including device and pharmaceutical manufacturers. Organising groups pay expenses and occasionally honoraria - the exact source of funding is often not known.		pecuniary	
Alun Davies	Non-commercial: Has received travel expenses to attend the Veith Meeting NY 2013 November to give lectures by Vascutek.	04/11/13	Personal non-specific pecuniary	Declare and participate
Alison Eastwood	Member of an independent academic team at Centre for Review & Dissemination, University of York commissioned by NICE through NIHR to undertake technology assessment reviews.	10/07/13	Non-personal non-specific pecuniary	Declare and participate
Sarah Fishburn	Organises workshops for physiotherapists treating pelvic girdle pain. Paid for this work.	11/11/13	Personal non-specific pecuniary	Declare and participate
Sarah Fishburn	Receives payment and expenses from the Nursing and Midwifery Council as a lay panellist of the Fitness to Practise Investigating Committee.	11/11/13	Personal non-specific pecuniary	Declare and participate
Sarah Fishburn	Lay reviewed with the Local Supervising Authority auditing supervision of midwives - receives payment and expenses for this work.	11/11/13	Personal non-specific pecuniary	Declare and participate
Sarah Fishburn	Lay reviewer for the NIHR; has reviewed a number of research proposals being considered for funding. Paid for carrying out these reviews.	11/11/13	Personal non-specific pecuniary	Declare and participate
Sarah Fishburn	Chair of the Pelvic Partnership, a support group for women with pregnancy-related pelvic	11/11/13	Personal non-specific pecuniary	Declare and participate

Member name	Interest declared	Date declared	Type of interest	Decision
	girdle pain. This is a voluntary position.			
Sarah Fishburn	Trained as a chartered physiotherapist and qualified in 1988 but have not been in clinical practice since 1997. Remains a non-practicing member of the Chartered Society of Physiotherapy.	11/11/13	Personal non-specific pecuniary	Declare and participate
Sarah Fishburn	Recently appointed by Mott MacDonald to carry out reviews as a lay reviewer on behalf to the Nursing and Midwifery Council of Local Supervising Authorities and Universities providing courses for nurses and midwives. This is paid work.	11/11/13	Personal non-specific pecuniary	Declare and participate
Jim Gray	None	10/07/13		No action
Nuala Lucas	Member Obstetric Anaesthetists' Association Executive Committee	08/01/14	Personal non-specific non-pecuniary	Declare and participate
Nuala Lucas	Member NICE – Intra-partum Care GDG	08/01/14	Personal non-specific non-pecuniary	Declare and participate
Nuala Lucas	Member, Editorial Board, International Journal of Obstetric Anesthesia	08/01/14	Personal non-specific non-pecuniary	Declare and participate
Kath Nuttall	None	02/07/13		No action
Tilly Pillay	None	11/07/13		No action
Nick Screaton	Attended Thorax meeting – travel expenses paid.	10/04/14	None specific personal pecuniary	No action
Lindsay Smith	None	09/10/13		No action
Philippa Williams	None	27/06/13		No action
Sophie Wilne	Recipient of NHS Innovation Challenge Award for clinical awareness campaign to reduce delays in diagnosis of brain tumours in children & young adults. Award will be used to develop the campaign.	08/06/13	Personal non-specific non-pecuniary	Declare and participate
Sophie Wilne	Co-investigator for RFPB grant to undertake systematic reviews in childhood brain tumours.	08/06/13	Personal non-specific non-pecuniary	Declare and participate

Member name	Interest declared	Date declared	Type of interest	Decision
Sophie Wilne	Co-investigator for grant awards from charity to evaluate impact of brain tumour awareness campaign.	08/06/13	Personal non-specific non-pecuniary	Declare and participate
Sophie Wilne	Speaker at conferences to talk about TS – invited by Novatis – travel expenses only.	08/06/13	Personal non-specific non-pecuniary	Declare and participate
Sophie Wilne	Presented at educational meetings sponsored by drug companies – not paid for educational events.	08/06/13	Personal non-specific non-pecuniary	Declare and participate
Topci specific members				
Mark Follows	None	13/12/13		No action
Elspeth Guthrie	None	28/11/13		No action
Yvonne McKenzie	Voluntary role – Clinical Lead in IBS for the Gastroenterology Specialist Group of the British Dietetic Association. Role has received honoraria	09/07/14	Personal non-pecuniary	Declare and participate
Yvonne McKenzie	Chair of team of 9 GSG dietetians, systematically reviewing the BDA's 2010 guidelines on the dietary management of IBS, includes SR on FODMAPs with clinical practice recommendations on FODMAPs, currently pre draft stage. Will go out for full peer review, likely to be in early 2015. This review will be transferred to the PEN data base, a global dietetic resource for dietitians. Small amount of funding by PEN and honorarium will be received at the end. May gain funding to cover some of the personal time for writing up this guideline document. Travel, meeting refreshments and telephone expenses have been paid by the GSG.	09/07/14	Personal non-pecuniary	Declare and participate
Yvonne McKenzie	Developing dietetic outcomes for IBS	09/07/14	Personal non-pecuniary	Declare and participate

Member name	Interest declared	Date declared	Type of interest	Decision
	management. Travel, meeting refreshments and telephone expenses have been paid by the GSG.			
Yvonne McKenzie	Developing an IBS key fact sheet that will provide guidance on the value of the role of the dietitian in IBS management, for GPs, therapy management, CCGs.	09/07/14	Personal non-pecuniary	Declare and participate
Yvonne McKenzie	Wrote a chapter on IBS for the Manual of Dietetic Practice. Published in June 14 – 5th Edition	09/07/14	Personal non-pecuniary	Declare and participate
Yvonne McKenzie	Presentation to be filmed "Can probiotics help with IBS-type gut problems?" Yakult HCP study day at RCP. Stand alone paid educational work.	09/07/14	Personal non-pecuniary	Declare and participate
Yvonne McKenzie	Part of editorial panel for Dietetics Today, the BDA's official magazine.	09/07/14	Personal non-pecuniary	Declare and participate
Yvonne McKenzie	Write articles on IBS for clinical dietetic practice and CPD purposes (on FODMAPS – issued Jan 13 and further article due Oct 14)	09/07/14	Personal non-pecuniary	Declare and participate
Yvonne McKenzie	Planning to write further article for to encourage dietitians who are BDA members to have stronger leadership roles in gastroenterology, may include sections on supporting dietetic-led IBS management in the community	09/07/14	Personal non-pecuniary	Declare and participate
Yvonne McKenzie	My dietetic gastro clinics are in 2 hospitals and I hire a room in my local town (to reduce travel costs)	09/07/14		
Marion Saunders	Patient member on the Psychological Therapies/GI advisory group at BUPA	04/11/13		No action
Simon Smale	None	14/01/14		No action
Peter Whorwell (non-voting expert)	Advisory board member for Almirall	27/10/13	Specific personal non-pecuniary	Not be involved in discussions

Member name	Interest declared	Date declared	Type of interest	Decision
				and decisions on linaclotide due to member's involvement with Almirall.
Peter Whorwell (non-voting expert)	Research grants from Almirall, Danone, Salix (Published on hypnotherapy, acupuncture, probiotics)	27/10/13	Specific personal non-pecuniary	Not be involved in discussions and decsions on linaclotide due to member's involvement with Almirall.

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1 Appendix C: Review protocol

	Details
Review Question	1.Are low-dose tricyclic antidepressants (TCAs), MAOIs, SSRIs and SNRIs effective in the management of IBS (including which are more effective)? 2.Does a low FODMAP diet have an effect on the symptoms of IBS? 3.Is linaclotide effective in the treatment of IBS-C? 4.Is lubiprostone effective in the treatment of IBS-C? 5.a Do psychotherapies (CCBT and mindfulness therapy) have an effect on the symptoms of IBS? 5.b Does relaxation therapy have an effect on the symptoms of IBS?
Original	CG61 did not include questions relating to low FODMAP, linaclotide or lubiprostone Review questions from CG61; • Are low-dose tricyclic antidepressants (TCAs), SSRIs and SNRIs effective in the treatment of IBS, and which is the more effective and the safer option? • Does relaxation therapy have a role in managing symptoms? • Do exclusion diets improve IBS or related symptoms? • Does psychotherapy have a role in managing symptoms?
Type of Review	Intervention
Language	English
Study Design	RCTs, controlled trials, systematic review of RCTs (if there is sufficient RCT evidence then controlled trials will not be included)
Status	Published papers (full text only)
Population	Adults with IBS (≥18 years)
Intervention	Antidepressants; - TCAs (amitriptyline, clomipramine, dosulephin, doxepin, imipremaine, lofepramine, nortriptyline, trimipramine, miansnerin, trazodone) - SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) - MAOIs (phenelzine, isocarboxazid, tranylcypromine) - Reversible MAOIs (moclobemide) - Others including SNRIs (duloxetine, flupentixol, mirtazapine, reboxetine, L-tryptophan, venlafaxine) Low FODMAP diet; - Restriction of FODMAPs Pharmacological treatment (both for IBS-C); - Linaclotide - Lubiprostone Psychotherapies; CCBT and Mindfulness therapy Relaxation therapy; - Relaxation therapy -
Comparator	Antidepressants; - Comparisons with other antidepressants - In addition to other IBS treatments - Placebo Low FODMAP diet; - Normal diet

	Details
	- Diet high in FODMAPs Pharmacological treatment (both for IBS-C); - Comparison with other IBS-C treatments - Placebo Psychotherapies (CCBT and Mindfulness therapy); - Usual care Other interventions Relaxation therapy; - Other intervention -
Outcomes	Outcomes (ranked by the topic specific committee members in the following order); - Quality of life (IBS and/or generic) - Symptoms scores - Abdominal pain - Patient preferences - Deterioration - Stool score/general changes in bowel habit - Relapse or Flatulence or Bloating (all had the same ranking)
Other criteria for inclusion / exclusion of studies	Include; - Adults with IBS Exclude[a]; - Those with other co-existing bowel conditions - Observational studies, narrative reviews, case series, case studies
Review strategies	Data on all included studies will be extracted into evidence tables Where statistically possible, a meta-analytical approach will be used to give an overall effect All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarised in evidence statements. All treatments are available within primary care (although some psychotherapies may be delivered through intermediate care)

[a] Systematic reviewer judgement meant exclusion criteria relating to inadequate duration (2 days in FODMAPs and 5 days in Linaclotide studies) was subsequently applied. This was in the context of other RCTs which were of longer follow-up.

Appendix D: Search strategy

D.1 Review question 1

D.1.1 Clinical search summary

Databases that were searched, search dates and the number of articles retrieved from each databaseare shown in Table 6. Databases were searched from inception or date specified below. The MEDLINE search strategy is shown in Table 7. The same strategy was translated for the other databases listed.

Table 6: Clinical search summary

Database	Date searched	Version/files	Number search)
CDSR (Wiley)	15/08/13 and again 10/02/2014	Issue 2 of 12, February 2014	31, (5)
Database of Abstracts of Reviews of Effects – DARE (Wiley)	15/08/13 and again 10/02/2014	Issue 1 of 4, January 2014	10, (0)
HTA database (Wiley)	15/08/13 and again 10/02/2014	Issue 1 of 4, January 2014	0, (0)
CENTRAL (Wiley)	15/08/13 and again 10/02/2014	Issue 1 of 12, January 2014	127, (42)
MEDLINE (Ovid)	15/08/13 and again 10/02/2014	1946 to January Week 5 2014	483, (34)
MEDLINE In-Process (Ovid)	15/08/13 and again 10/02/2014	February 07, 2014	28, (4)
EMBASE (Ovid)	15/08/13 and again 10/02/2014	1980 to 1987	5852, (18
PsycINFO (Ovid)	15/08/13 and again 10/02/2014	2002 to January Week 3 2014	223, (20)
Pub Med	10/02/2014 only	n/a	(6)

Table 7: Clinical search terms (MEDLINE)

Line number	Search term	Number retrieved
	Search Strategy: --- 1 Irritable Bowel Syndrome/ (4182) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (7398) 3 (Irritable* adj4 colon*).tw. (515) 4 IBS.tw. (4547) 5 exp Gastrointestinal Motility/ (32900) 6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (415649) 7 Flatulence/ (1209) 8 (Flatu* or bloat*).tw. (4815) 9 Fecal Incontinence/ (7744) 10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or	411

soil* or seep* or impact*)).tw. (22857)
11 FI.tw. (4914)
12 Encopres*.tw. (548)
13 Diarrhea/ (39254)
14 (Diarrhoea* or diarrhea*).tw. (75897)
15 Constipation/ (10460)
16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (14744)
17 Colonic Diseases, Functional/ (3648)
18 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (1018)
19 Dyspepsia/ (7289)
20 (Dyspeps* or Indigest*).tw. (9512)
21 or/1-20 (545849)
22 exp Antidepressive Agents/ (121498)
23 (Antidepress* or anti-depress*).tw. (46017)
24 exp Serotonin Uptake Inhibitors/ (31350)
25 ((Select* or serotonin*) adj4 (uptake* or up-take* or reuptake* or re-uptake*) adj4 inhibitor*).tw. (12764)
26 SSRI.tw. (4040)
27 exp Antidepressive Agents, Tricyclic/ (29036)
28 Tricyclic*.tw. (12605)
29 or/22-28 (146268)
30 21 and 29 (3325)
31 Animals/ not Humans/ (3926191)
32 30 not 31 (2670)
33 Meta-Analysis.pt. (49881)
34 Meta-Analysis as Topic/ (13930)
35 Review.pt. (1894357)
36 exp Review Literature as Topic/ (7544)
37 (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw. (57298)
38 (review$ or overview$).ti. (260353)
39 (systematic$ adj4 (review$ or overview$)).tw. (51252)
40 ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw. (3697)
41 ((studies or trial$) adj1 (review$ or overview$)).tw. (7679)
42 (integrat$ adj2 (research or review$ or literature)).tw. (3592)
43 (pool$ adj1 (analy$ or data)).tw. (9452)
44 (handsearch$ or (hand adj2 search$)).tw. (6555)
45 (manual$ adj2 search$).tw. (2963)
46 or/33-45 (2043448)
47 animals/ not humans/ (3926191)
48 46 not 47 (1908855)
49 Randomized Controlled Trial.pt. (382120)
50 Controlled Clinical Trial.pt. (88870)
51 Clinical Trial.pt. (499567)
52 exp Clinical Trials as Topic/ (292503)
53 Placebos/ (33370)
54 Random Allocation/ (80818)
55 Double-Blind Method/ (129386)
56 Single-Blind Method/ (19108)
57 Cross-Over Studies/ (35341)
58 ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw.

	(648974) 59 (random$ adj2 allocat$).tw. (20247) 60 placebo$.tw. (158578) 61 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (127154) 62 (crossover$ or (cross adj over$)).tw. (58157) 63 or/49-62 (1331078) 64 animals/ not humans/ (3926191) 65 63 not 64 (1246049) 66 48 or 65 (2918027) 67 32 and 66 (1603) 68 limit 67 to english language (1416) 69 limit 68 to ed=20070601-20130815 (483)	

1 **Table 8: Clinical search terms (EMBASE)**

Line number	Search term	Number retrieved
	Strategy used: --- 1 irritable colon/ (14846) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (11222) 3 (Irritable* adj4 colon*).tw. (591) 4 IBS.tw. (7748) 5 exp gastrointestinal motility/ (26586) 6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (532130) 7 flatulence/ (7730) 8 (Flatu* or bloat*).tw. (7215) 9 feces incontinence/ (13079) 10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (33309) 11 FI.tw. (11942) 12 Encopres*.tw. (715) 13 diarrhea/ (143830) 14 (Diarrhoea* or diarrhea*).tw. (93843) 15 constipation/ (52395) 16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (22949) 17 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (1468) 18 dyspepsia/ (23969) 19 (Dyspeps* or Indigest*).tw. (13193) 20 or/1-19 (784150) 21 exp antidepressant agent/ (293399) 22 (Antidepress* or anti-depress*).tw. (63838) 23 exp serotonin uptake inhibitor/ (136512) 24 ((Select* or serotonin*) adj4 (uptake* or up-take* or reuptake* or re-uptake*) adj4 inhibitor*).tw. (17291) 25 SSRI.tw. (6313) 26 exp tricyclic antidepressant agent/ (89925)	5826

	27 Tricyclic*.tw. (17397) 28 or/21-27 (308297) 29 20 and 28 (20297) 30 Nonhuman/ not Human/ (3300306) 31 29 not 30 (19578) 32 Systematic Review/ (62942) 33 Meta Analysis/ (74817) 34 Review/ (1988330) 35 Review.pt. (1983739) 36 (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw. (73560) 37 (review$ or overview$).ti. (326275) 38 (systematic$ adj4 (review$ or overview$)).tw. (65620) 39 ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw. (4460) 40 ((studies or trial$) adj1 (review$ or overview$)).tw. (8951) 41 (integrat$ adj2 (research or review$ or literature)).tw. (4333) 42 (pool$ adj1 (analy$ or data)).tw. (12265) 43 (handsearch$ or (hand adj2 search$)).tw. (6237) 44 (manual$ adj2 search$).tw. (3582) 45 or/32-44 (2288525) 46 nonhuman/ not human/ (3300306) 47 45 not 46 (2171333) 48 exp Clinical Trials/ (73406) 49 Randomization/ (63137) 50 Placebo/ (223384) 51 Double Blind Procedure/ (116998) 52 Single Blind Procedure/ (18070) 53 Crossover Procedure/ (38092) 54 ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw. (821449) 55 (random$ adj2 allocat$).tw. (24383) 56 placebo$.tw. (193467) 57 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (154960) 58 (crossover$ or (cross adj over$)).tw. (67284) 59 or/48-58 (1171258) 60 nonhuman/ not human/ (3300306) 61 59 not 60 (1125411) 62 47 or 61 (3054757) 63 31 and 62 (12688) 64 limit 63 to english language (11734) 65 limit 64 to em=200700-201332 (6333) 66 limit 65 to embase (6220) 67 limit 66 to (conference abstract or conference paper) (368) 68 66 not 67 (5852)	

1 **Table 9: Clinical search terms (PsyINFO)**

Line number	Search term	Number retrieved
	Search Strategy: --- 1 Irritable Bowel Syndrome/ (515) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (655)	221

	3 (Irritable* adj4 colon*).tw. (1) 4 IBS.tw. (479) 5 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (5290) 6 (Flatu* or bloat*).tw. (115) 7 Fecal Incontinence/ (153) 8 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (2865) 9 FI.tw. (490) 10 Encopres*.tw. (156) 11 Diarrhea/ (137) 12 (Diarrhoea* or diarrhea*).tw. (840) 13 Constipation/ (148) 14 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (754) 15 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (52) 16 Dyspepsia/ (47) 17 (Dyspeps* or Indigest*).tw. (223) 18 or/1-17 (10210) 19 exp Antidepressant Drugs/ (13695) 20 (Antidepress* or anti-depress*).tw. (16246) 21 exp serotonin reuptake inhibitors/ (5695) 22 ((Select* or serotonin*) adj4 (uptake* or up-take* or reuptake* or re-uptake*) adj4 inhibitor*).tw. (5603) 23 SSRI.tw. (2166) 24 Tricyclic*.tw. (1479) 25 or/19-24 (23517) 26 18 and 25 (398) 27 limit 26 to (english language and yr="2007 -Current")	

1 **Table 10: Clinical search terms (Cochrane, CENTRAL, DARE, HTA)**

Line number	Search term	Number retrieved
	Search Strategy: --- #1 MeSH descriptor: [Irritable Bowel Syndrome] this term only 373 #2 (Irritable* near/4 bowel* near/4 syndrome*):ti,ab,kw 997 #3 (Irritable* near/4 colon*):ti,ab,kw 221 #4 IBS:ti,ab,kw 518 #5 MeSH descriptor: [Gastrointestinal Motility] explode all trees 2352 #6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) near/4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)):ti,ab,kw 31534 #7 MeSH descriptor: [Flatulence] this term only 207 #8 (Flatu* or bloat*):ti,ab,kw 1296 #9 MeSH descriptor: [Fecal Incontinence] this term only 373 #10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or	123

	double or defecat* or defaecat*) near/4 (incontinen* or urge* or leak* or soil* or seep* or impact*)):ti,ab,kw 1918 #11 FI:ti,ab,kw 299 #12 Encopres*:ti,ab,kw 50 #13 MeSH descriptor: [Diarrhea] this term only 1991 #14 (Diarrhoea* or diarrhea*):ti,ab,kw 8149 #15 MeSH descriptor: [Constipation] this term only 805 #16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*):ti,ab,kw 2817 #17 MeSH descriptor: [Colonic Diseases, Functional] this term only 308 #18 (Function* near/4 (colon* or bowel*) near/4 (disease* or disorder*)):ti,ab,kw 0 #19 MeSH descriptor: [Dyspepsia] this term only 862 #20 (Dyspeps* or Indigest*):ti,ab,kw 2182 #21 {or #1-#20} 42187 #22 MeSH descriptor: [Antidepressive Agents] explode all trees 4545 #23 (Antidepress* or anti-depress*):ti,ab,kw 8946 #24 MeSH descriptor: [Serotonin Uptake Inhibitors] explode all trees 2202 #25 ((Select* or serotonin*) near/4 (uptake* or up-take* or reuptake* or re-uptake*) near/4 inhibitor*):ti,ab,kw 3406 #26 SSRI:ti,ab,kw 806 #27 MeSH descriptor: [Antidepressive Agents, Tricyclic] explode all trees 973 #28 Tricyclic*:ti,ab,kw 1892 #29 {or #22-#28} 10958 #30 #21 and #29 from 2007 to 2013 173	

D.1.21 Health economics search summary

2 **Table 11: Health economics search summary**

Database	Date searched	Number retrieved
MEDLINE (Ovid)	04/03/14	120
MEDLINE In-Process (Ovid)	04/03/14	11
EMBASE (Ovid)	04/03/14	1331
NHS Economic Evaluation Database - NHS EED (Wiley)	04/03/14	3
Health Economic Evaluations Database – HEED (Wiley)	04/03/14	2
PubMed	04/03/14	27

3 **Table 12: Health economics search terms (MEDLINE)**

Line number	Search term	Number retrieved
	1 Irritable Bowel Syndrome/ (4019) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (7184) 3 (Irritable* adj4 colon*).tw. (508) 4 IBS.tw. (4391) 5 exp Gastrointestinal Motility/ (32407) 6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or	

Line number	Search term	Number retrieved
	gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (405110) 7 Flatulence/ (1179) 8 (Flatu* or bloat*).tw. (4729) 9 Fecal Incontinence/ (7704) 10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (22170) 11 FI.tw. (4807) 12 Encopres*.tw. (545) 13 Diarrhea/ (37920) 14 (Diarrhoea* or diarrhea*).tw. (71461) 15 Constipation/ (10490) 16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (14576) 17 Colonic Diseases, Functional/ (3652) 18 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (975) 19 Dyspepsia/ (7156) 20 (Dyspeps* or Indigest*).tw. (9279) 21 or/1-20 (530494) 22 exp Antidepressive Agents/ (118882) 23 (Antidepress* or anti-depress*).tw. (44569) 24 exp Serotonin Uptake Inhibitors/ (30486) 25 ((Select* or serotonin*) adj4 (uptake* or up-take* or reuptake* or re-uptake*) adj4 inhibitor*).tw. (12232) 26 SSRI.tw. (3809) 27 exp Antidepressive Agents, Tricyclic/ (28745) 28 Tricyclic*.tw. (12302) 29 or/22-28 (142771) 30 21 and 29 (3255) 31 Animals/ not Humans/ (3791956) 32 30 not 31 (2617) 33 Economics/ (26480) 34 exp "Costs and Cost Analysis"/ (177305) 35 Economics, Dental/ (1853) 36 exp Economics, Hospital/ (19186) 37 exp Economics, Medical/ (13502) 38 Economics, Nursing/ (3886) 39 Economics, Pharmaceutical/ (2494) 40 Budgets/ (9601) 41 exp Models, Economic/ (9810) 42 Markov Chains/ (9289) 43 Monte Carlo Method/ (19163) 44 Decision Trees/ (8623) 45 econom$.tw. (148965) 46 cba.tw. (8589) 47 cea.tw. (15673) 48 cua.tw. (765) 49 markov$.tw. (10800) 50 (monte adj carlo).tw. (19769)	

Line number	Search term	Number retrieved
	51 (decision adj3 (tree$ or analys$)).tw. (7902) 52 (cost or costs or costing$ or costly or costed).tw. (291345) 53 (price$ or pricing$).tw. (22087) 54 budget$.tw. (16665) 55 expenditure$.tw. (33375) 56 (value adj3 (money or monetary)).tw. (1274) 57 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3281) 58 or/33-57 (627005) 59 "Quality of Life"/ (113179) 60 quality of life.tw. (129386) 61 "Value of Life"/ (5372) 62 Quality-Adjusted Life Years/ (6608) 63 quality adjusted life.tw. (5450) 64 (qaly$ or qald$ or qale$ or qtime$).tw. (4531) 65 disability adjusted life.tw. (1072) 66 daly$.tw. (1071) 67 Health Status Indicators/ (19485) 68 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (14277) 69 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (952) 70 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2357) 71 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (20) 72 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (323) 73 (euroqol or euro qol or eq5d or eq 5d).tw. (3373) 74 (qol or hql or hqol or hrqol).tw. (22620) 75 (hye or hyes).tw. (53) 76 health$ year$ equivalent$.tw. (37) 77 utilit$.tw. (104758) 78 (hui or hui1 or hui2 or hui3).tw. (797) 79 disutili$.tw. (185) 80 rosser.tw. (71) 81 quality of wellbeing.tw. (5) 82 quality of well-being.tw. (312) 83 qwb.tw. (159) 84 willingness to pay.tw. (1997) 85 standard gamble$.tw. (622) 86 time trade off.tw. (680) 87 time tradeoff.tw. (197) 88 tto.tw. (536) 89 or/59-88 (300440) 90 58 or 89 (886587) 91 32 and 90 (280) 92 limit 91 to ed=20070601-20140304 (135) 93 limit 92 to english language (120)	

Table 13: Health economics search terms (EMBASE)

Line number	Search term	Number retrieved
	1 Irritable Bowel Syndrome/ (4019) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (7184) 3 (Irritable* adj4 colon*).tw. (508) 4 IBS.tw. (4391) 5 exp Gastrointestinal Motility/ (32407) 6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (405110) 7 Flatulence/ (1179) 8 (Flatu* or bloat*).tw. (4729) 9 Fecal Incontinence/ (7704) 10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (22170) 11 FI.tw. (4807) 12 Encopres*.tw. (545) 13 Diarrhea/ (37920) 14 (Diarrhoea* or diarrhea*).tw. (71461) 15 Constipation/ (10490) 16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (14576) 17 Colonic Diseases, Functional/ (3652) 18 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (975) 19 Dyspepsia/ (7156) 20 (Dyspeps* or Indigest*).tw. (9279) 21 or/1-20 (530494) 22 exp Antidepressive Agents/ (118882) 23 (Antidepress* or anti-depress*).tw. (44569) 24 exp Serotonin Uptake Inhibitors/ (30486) 25 ((Select* or serotonin*) adj4 (uptake* or up-take* or reuptake* or re-uptake*) adj4 inhibitor*).tw. (12232) 26 SSRI.tw. (3809) 27 exp Antidepressive Agents, Tricyclic/ (28745) 28 Tricyclic*.tw. (12302) 29 or/22-28 (142771) 30 21 and 29 (3255) 31 Animals/ not Humans/ (3791956) 32 30 not 31 (2617) 33 Economics/ (26480) 34 exp "Costs and Cost Analysis"/ (177305) 35 Economics, Dental/ (1853) 36 exp Economics, Hospital/ (19186) 37 exp Economics, Medical/ (13502) 38 Economics, Nursing/ (3886) 39 Economics, Pharmaceutical/ (2494) 40 Budgets/ (9601) 41 exp Models, Economic/ (9810) 42 Markov Chains/ (9289)	

Line number	Search term	Number retrieved
	43 Monte Carlo Method/ (19163) 44 Decision Trees/ (8623) 45 econom$.tw. (148965) 46 cba.tw. (8589) 47 cea.tw. (15673) 48 cua.tw. (765) 49 markov$.tw. (10800) 50 (monte adj carlo).tw. (19769) 51 (decision adj3 (tree$ or analys$)).tw. (7902) 52 (cost or costs or costing$ or costly or costed).tw. (291345) 53 (price$ or pricing$).tw. (22087) 54 budget$.tw. (16665) 55 expenditure$.tw. (33375) 56 (value adj3 (money or monetary)).tw. (1274) 57 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3281) 58 or/33-57 (627005) 59 "Quality of Life"/ (113179) 60 quality of life.tw. (129386) 61 "Value of Life"/ (5372) 62 Quality-Adjusted Life Years/ (6608) 63 quality adjusted life.tw. (5450) 64 (qaly$ or qald$ or qale$ or qtime$).tw. (4531) 65 disability adjusted life.tw. (1072) 66 daly$.tw. (1071) 67 Health Status Indicators/ (19485) 68 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (14277) 69 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (952) 70 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2357) 71 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (20) 72 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (323) 73 (euroqol or euro qol or eq5d or eq 5d).tw. (3373) 74 (qol or hql or hqol or hrqol).tw. (22620) 75 (hye or hyes).tw. (53) 76 health$ year$ equivalent$.tw. (37) 77 utilit$.tw. (104758) 78 (hui or hui1 or hui2 or hui3).tw. (797) 79 disutili$.tw. (185) 80 rosser.tw. (71) 81 quality of wellbeing.tw. (5) 82 quality of well-being.tw. (312) 83 qwb.tw. (159) 84 willingness to pay.tw. (1997) 85 standard gamble$.tw. (622) 86 time trade off.tw. (680) 87 time tradeoff.tw. (197)	

Line number	Search term	Number retrieved
	88 tto.tw. (536) 89 or/59-88 (300440) 90 58 or 89 (886587) 91 32 and 90 (280) 92 limit 91 to ed=20070601-20140304 (135) 93 limit 92 to english language (120)	

1 **Table 14: Health economics search terms (NHS EED)**

Line number	Search term	Number retrieved
	#1 MeSH descriptor: [Irritable Bowel Syndrome] this term only 406 #2 (Irritable* near/4 bowel* near/4 syndrome*):ti,ab,kw 1099 #3 (Irritable* near/4 colon*):ti,ab,kw 293 #4 IBS:ti,ab,kw 597 #5 MeSH descriptor: [Gastrointestinal Motility] explode all trees 2410 #6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) near/4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)):ti,ab,kw 34703 #7 MeSH descriptor: [Flatulence] this term only 213 #8 (Flatu* or bloat*):ti,ab,kw 1610 #9 MeSH descriptor: [Fecal Incontinence] this term only 391 #10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) near/4 (incontinen* or urge* or leak* or soil* or seep* or impact*)):ti,ab,kw 2232 #11 FI:ti,ab,kw 375 #12 Encopres*:ti,ab,kw 52 #13 MeSH descriptor: [Diarrhea] this term only 2061 #14 (Diarrhoea* or diarrhea*):ti,ab,kw 9938 #15 MeSH descriptor: [Constipation] this term only 844 #16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*):ti,ab,kw 3622 #17 MeSH descriptor: [Colonic Diseases, Functional] this term only 311 #18 (Function* near/4 (colon* or bowel*) near/4 (disease* or disorder*)):ti,ab,kw 401 #19 MeSH descriptor: [Dyspepsia] this term only 889 #20 (Dyspeps* or Indigest*):ti,ab,kw 2551 #21 {or #1-#20} 47428 #22 MeSH descriptor: [Antidepressive Agents] explode all trees 4744 #23 (Antidepress* or anti-depress*):ti,ab,kw 9494 #24 MeSH descriptor: [Serotonin Uptake Inhibitors] explode all trees 2313 #25 ((Select* or serotonin*) near/4 (uptake* or up-take* or reuptake* or re-uptake*) near/4 inhibitor*):ti,ab,kw 3675 #26 SSRI:ti,ab,kw 851 #27 MeSH descriptor: [Antidepressive Agents, Tricyclic] explode all trees 998 #28 Tricyclic*:ti,ab,kw 1969	

Line number	Search term	Number retrieved
	#29 {or #22-#28} 11677 #30 #21 and #29 from 2007 to 2014 256	

1

2 **Table 15: Health economics search terms (HEED)**

Line number	Search term	Number retrieved
	All data: 'IBS' or Irritable* bowel* syndrome* or Irritable* colon* or IBS AND All data: 'ANTIDEPRESSANT' or 'ANTIDEPRESSANTS' or Antidepress* or anti-depress* or uptake* inhibitor* or up-take* inhibitor* or reuptake* inhibitor* or re-uptake* inhibitor* or SSRI or Tricyclic*	

3 **Table 16: Health economics search terms (Pubmed)**

Line number	Search term			
	Search	Add to builder	Query	Items found
	#5	Add	Search (#3 and #4)	27
	#4	Add	Search (Econom* or Markov Chains or Monte Carlo Method or Decision Trees or quality of life or quality adjusted life or qaly* or qald* or qale* or qtime*)	738347
	#3	Add	Search (#1 and #2)	142
	#2	Add	Search (Antidepress* or anti-depress* or uptake* inhibitor* or up-take* inhibitor* or reuptake* inhibitor* or re-uptake* inhibitor* or SSRI or Tricyclic*[Title/Abstract])	99211
	#1	Add	Search ('IBS' or Irritable* bowel* syndrome* or Irritable* colon* or IBS[Title/Abstract])	7345

D.24 Review question 2

D.2.15 Clinical search summary

6 **Table 17: Clinical search summary**

Database	Date searched	Number retrieved
CDSR (Wiley)	27/02/14	10
Database of Abstracts of Reviews of Effects – DARE (Wiley)	27/04/14	7
HTA database (Wiley)	27/02/14	0

Database	Date searched	Number retrieved
CENTRAL (Wiley)	27/02/14	741
MEDLINE (Ovid)	27/02/14	1123
MEDLINE In-Process (Ovid)	27/02/14	32
EMBASE (Ovid)	27/02/14	989
PubMed	27/02/14	27

1 **Table 18: Clinical search terms (MEDLINE, MEDLINE in process)**

Line number	Search term	Number retrieved
	Search Strategy: --- 1 Irritable Bowel Syndrome/ (4064) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (7236) 3 (Irritable* adj4 colon*).tw. (510) 4 IBS.tw. (4441) 5 exp Gastrointestinal Motility/ (32495) 6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (406671) 7 Flatulence/ (1179) 8 (Flatu* or bloat*).tw. (4753) 9 Fecal Incontinence/ (7722) 10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (22296) 11 FI.tw. (4830) 12 Encopres*.tw. (547) 13 Diarrhea/ (38031) 14 (Diarrhoea* or diarrhea*).tw. (71789) 15 Constipation/ (10523) 16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (14650) 17 Colonic Diseases, Functional/ (3658) 18 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (980) 19 Dyspepsia/ (7184) 20 (Dyspeps* or Indigest*).tw. (9315) 21 or/1-20 (532575) 22 Fodmap*.tw. (26) 23 "fermentable oligo* di* monosaccharides and polyols".tw. (8) 24 "fermentable oligo* di* mono-saccharides and polyols".tw. (2) 25 "fermentable oligo* di* and monosaccharides and polyols".tw. (10) 26 "fermentable oligo* di* and mono-saccharides and polyols".tw. (5) 27 Dietary Carbohydrates/ or Diet, Carbohydrate-Restricted/ (22239) 28 ((short-chain* or shortchain* or short chain* or low-digest* or lowdigest* or low digest* or non-digest* or nondigest* or nondigest* or fermentable*) adj4 carbohydrate*).tw. (607)	1155

	29 ((carbohydrate* or sugar*) adj4 malabsorpt*).tw. (372) 30 (fructose* or oligosaccharide* or fructo-oligosacchride* or galactan* or galacto-oligosaccharide* or oligofructose* or fructan* or inulin* or sorbitol* or polyol* or xylitol* or mannitol* or maltitol* or raffinose* or stachyose* or nystose* or kestose* or lactose* or ordisaccharide* or monosaccharide*).tw. (94481) 31 Fructose/ or Oligosaccharides/ or Galactans/ or Fructans/ or Inulin/ or Sorbitol/ or Xylitol/ or Mannitol/ or Raffinose/ or Lactose/ or Monosaccharides/ or Disaccharides/ (77492) 32 or/22-31 (150894) 33 21 and 32 (7268) 34 Controlled Clinical Trial.pt. (87769) 35 Clinical Trial.pt. (484436) 36 exp Clinical Trials as Topic/ (276232) 37 Placebos/ (32313) 38 Double-Blind Method/ (124067) 39 Single-Blind Method/ (18635) 40 Cross-Over Studies/ (33501) 41 placebo$.tw. (148340) 42 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (121488) 43 (crossover$ or (cross adj over$)).tw. (55285) 44 ((control$ or clinical$) adj3 (trial$ or stud$)).tw. (609050) 45 or/34-44 (1197542) 46 33 and 45 (1272) 47 Animals/ not Humans/ (3807921) 48 46 not 47 (1214) 49 limit 48 to english language (1123)	

1 **Table 19: Clinical search terms (Embase)**

Line number	Search term	Number retrieved
	Search Strategy: --- 1 irritable colon/ (15705) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (11897) 3 (Irritable* adj4 colon*).tw. (604) 4 IBS.tw. (8319) 5 exp gastrointestinal motility/ (27169) 6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (555764) 7 flatulence/ (8198) 8 (Flatu* or bloat*).tw. (7755) 9 feces incontinence/ (13705) 10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (35893) 11 FI.tw. (12928) 12 Encopres*.tw. (734) 13 diarrhea/ (151580) 14 (Diarrhoea* or diarrhea*).tw. (98710) 15 constipation/ (55736)	989

	16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (24556) 17 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (1512) 18 dyspepsia/ (25050) 19 (Dyspeps* or Indigest*).tw. (13777) 20 or/1-19 (821040) 21 Fodmap*.tw. (79) 22 "fermentable oligo* di* monosaccharides and polyols".tw. (19) 23 "fermentable oligo* di* mono-saccharides and polyols".tw. (8) 24 "fermentable oligo* di* and monosaccharides and polyols".tw. (24) 25 "fermentable oligo* di* and mono-saccharides and polyols".tw. (18) 26 carbohydrate diet/ (14536) 27 low carbohydrate diet/ (1486) 28 ((short-chain* or shortchain* or short chain* or low-digest* or lowdigest* or low digest* or non-digest* or nondigest* or nondigest* or fermentable*) adj4 carbohydrate*).tw. (773) 29 ((carbohydrate* or sugar*) adj4 malabsorpt*).tw. (451) 30 (fructose* or oligosaccharide* or fructo-oligosacchride* or galactan* or galacto-oligosaccharide* or oligofructose* or fructan* or inulin* or sorbitol* or polyol* or xylitol* or mannitol* or maltitol* or raffinose* or stachyose* or nystose* or kestose* or lactose* or ordisaccharide* or monosaccharide*).tw. (110879) 31 fructose/ or oligosaccharide/ or galactan/ or galactose oligosaccharide/ or fructose oligosaccharide/ or fructan/ or inulin/ or sorbitol/ or polyol/ or xylitol/ or mannitol/ or maltitol/ or raffinose/ or lactose/ or monosaccharide/ or disaccharide/ (102047) 32 or/21-31 (167776) 33 20 and 32 (9743) 34 exp Clinical Trials/ (94542) 35 Placebo/ (235971) 36 Double Blind Procedure/ (120717) 37 Single Blind Procedure/ (19074) 38 Crossover Procedure/ (40030) 39 placebo$.tw. (202397) 40 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (161252) 41 (crossover$ or (cross adj over$)).tw. (70115) 42 ((control$ or clinical$) adj3 (trial$ or stud$)).tw. (861369) 43 or/34-42 (1187311) 44 33 and 43 (1500) 45 Nonhuman/ not Human/ (3387770) 46 44 not 45 (1458) 47 limit 46 to english language (1362) 48 limit 47 to embase (1191) 49 limit 48 to (conference abstract or conference paper) (198) 50 48 not 49 (993)	

1 **Table 20: Clinical search terms (CDSR, HTA, Central, DARE)**

Line number	Search term	Number retrieved
	Search Strategy:	758

#1 MeSH descriptor: [Irritable Bowel Syndrome] this term only 406

#2 (Irritable* near/4 bowel* near/4 syndrome*):ti,ab,kw 1099

#3 (Irritable* near/4 colon*):ti,ab,kw 293

#4 IBS:ti,ab,kw 597

#5 MeSH descriptor: [Gastrointestinal Motility] explode all trees 2410

#6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) near/4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)):ti,ab,kw 34703

#7 MeSH descriptor: [Flatulence] this term only 213

#8 (Flatu* or bloat*):ti,ab,kw 1610

#9 MeSH descriptor: [Fecal Incontinence] this term only 391

#10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) near/4 (incontinen* or urge* or leak* or soil* or seep* or impact*)):ti,ab,kw 2231

#11 FI:ti,ab,kw 375

#12 Encopres*:ti,ab,kw 52

#13 MeSH descriptor: [Diarrhea] this term only 2061

#14 (Diarrhoea* or diarrhea*):ti,ab,kw 9936

#15 MeSH descriptor: [Constipation] this term only 844

#16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*):ti,ab,kw 3622

#17 MeSH descriptor: [Colonic Diseases, Functional] this term only 311

#18 (Function* near/4 (colon* or bowel*) near/4 (disease* or disorder*)):ti,ab,kw 401

#19 MeSH descriptor: [Dyspepsia] this term only 889

#20 (Dyspeps* or Indigest*):ti,ab,kw 2551

#21 {or #1-#20} 47425

#22 Fodmap*:ti,ab,kw 2

#23 "fermentable oligo* di* monosaccharides and polyols":ti,ab,kw 0

#24 "fermentable oligo* di* mono-saccharides and polyols":ti,ab,kw 0

#25 "fermentable oligo* di* and monosaccharides and polyols":ti,ab,kw 0

#26 "fermentable oligo* di* and mono-saccharides and polyols":ti,ab,kw 0

#27 MeSH descriptor: [Dietary Carbohydrates] this term only 2221

#28 MeSH descriptor: [Diet, Carbohydrate-Restricted] this term only 157

#29 ((short-chain* or shortchain* or short chain* or low-digest* or lowdigest* or low digest* or non-digest* or nondigest* or nondigest* or fermentable*) near/4 carbohydrate*):ti,ab,kw 55

#30 ((carbohydrate* or sugar*) near/4 malabsorpt*):ti,ab,kw 60

#31 (fructose* or oligosaccharide* or fructo-oligosacchride* or galactan* or galacto-oligosaccharide* or oligofructose* or fructan* or inulin* or sorbitol* or polyol* or xylitol* or mannitol* or maltitol* or raffinose* or stachyose* or nystose* or kestose* or lactose* or ordisaccharide* or monosaccharide*):ti,ab,kw 4373

#32 MeSH descriptor: [Fructose] this term only 576

#33 MeSH descriptor: [Oligosaccharides] this term only 238

	#34	MeSH descriptor: [Galactans] this term only 151	
	#35	MeSH descriptor: [Fructans] this term only 11	
	#36	MeSH descriptor: [Inulin] this term only 135	
	#37	MeSH descriptor: [Sorbitol] this term only 218	
	#38	MeSH descriptor: [Xylitol] this term only 191	
	#39	MeSH descriptor: [Mannitol] this term only 388	
	#40	MeSH descriptor: [Raffinose] this term only 73	
	#41	MeSH descriptor: [Lactose] this term only 257	
	#42	MeSH descriptor: [Monosaccharides] this term only 11	
	#43	MeSH descriptor: [Disaccharides] this term only 114	
	#44	{or #22-#43} 6600	
	#45	#21 and #44 1059	

1 **Table 21: Clinical search terms (Pubmed)**

Line number	Search term	Number retrieved
	Search Strategy: --- #7 Add Search (#2 or #3 or #4 or #5 or #6) 29 #6 Add Search (fermentable oligo* di* and mono-saccharides and polyols[Title/Abstract]) 0 #5 Add Search (fermentable oligo* di* and monosaccharides and polyols[Title/Abstract]) 0 #4 Add Search (fermentable oligo* di* mono-saccharides and polyols[Title/Abstract]) 0 #3 Add Search (fermentable oligo* di* monosaccharides and polyols[Title/Abstract]) 0 #2 Add Search Fodmap[Title/Abstract] 29	27

D.2.2 Health economics search summary

3 **Table 22: Health economics search summary**

Databases	Date searched	No. retrieved
MEDLINE (Ovid)	06/03/14	187
MEDLINE In-Process (Ovid)	06/03/14	18
EMBASE (Ovid)	06/03/14	413

Databases	Date searched	No. retrieved
NHS Economic Evaluation Database - NHS EED (Wiley)	06/03/14	1
Health Economic Evaluations Database – HEED (Wiley)	06/03/14	0
PubMed	06/03/14	1

1

2 **Table 23: Health economic search terms (Medline and Medline in Process)**

Search term
Search Strategy: --- 1 Irritable Bowel Syndrome/ (4064) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (7236) 3 (Irritable* adj4 colon*).tw. (510) 4 IBS.tw. (4441) 5 exp Gastrointestinal Motility/ (32495) 6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (406671) 7 Flatulence/ (1179) 8 (Flatu* or bloat*).tw. (4753) 9 Fecal Incontinence/ (7722) 10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (22296) 11 FI.tw. (4830) 12 Encopres*.tw. (547) 13 Diarrhea/ (38031) 14 (Diarrhoea* or diarrhea*).tw. (71789) 15 Constipation/ (10523) 16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (14650) 17 Colonic Diseases, Functional/ (3658) 18 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (980) 19 Dyspepsia/ (7184) 20 (Dyspeps* or Indigest*).tw. (9315) 21 or/1-20 (532575) 22 Fodmap*.tw. (26) 23 "fermentable oligo* di* monosaccharides and polyols".tw. (8) 24 "fermentable oligo* di* mono-saccharides and polyols".tw. (2) 25 "fermentable oligo* di* and monosaccharides and polyols".tw. (10) 26 "fermentable oligo* di* and mono-saccharides and polyols".tw. (5) 27 Dietary Carbohydrates/ or Diet, Carbohydrate-Restricted/ (22239) 28 ((short-chain* or shortchain* or short chain* or low-digest* or lowdigest* or low digest* or non-digest* or nondigest* or nondigest* or fermentable*) adj4 carbohydrate*).tw. (607) 29 ((carbohydrate* or sugar*) adj4 malabsorpt*).tw. (372) 30 (fructose* or oligosaccharide* or fructo-oligosacchride* or galactan* or galacto-oligosaccharide* or oligofructose* or fructan* or inulin* or sorbitol* or polyol* or xylitol* or mannitol* or maltitol* or raffinose* or stachyose* or nystose* or kestose* or lactose* or ordisaccharide* or monosaccharide*).tw. (94481) 31 Fructose/ or Oligosaccharides/ or Galactans/ or Fructans/ or Inulin/ or Sorbitol/ or Xylitol/ or Mannitol/ or Raffinose/ or Lactose/ or Monosaccharides/ or Disaccharides/ (77492) 32 or/22-31 (150894)

Search term
33 21 and 32 (7268)
34 Economics/ (26508)
35 exp "Costs and Cost Analysis"/ (178069)
36 Economics, Dental/ (1853)
37 exp Economics, Hospital/ (19221)
38 exp Economics, Medical/ (13508)
39 Economics, Nursing/ (3887)
40 Economics, Pharmaceutical/ (2507)
41 Budgets/ (9617)
42 exp Models, Economic/ (9913)
43 Markov Chains/ (9437)
44 Monte Carlo Method/ (19364)
45 Decision Trees/ (8650)
46 econom$.tw. (150098)
47 cba.tw. (8624)
48 cea.tw. (15744)
49 cua.tw. (779)
50 markov$.tw. (10981)
51 (monte adj carlo).tw. (19965)
52 (decision adj3 (tree$ or analys$)).tw. (7950)
53 (cost or costs or costing$ or costly or costed).tw. (293286)
54 (price$ or pricing$).tw. (22220)
55 budget$.tw. (16720)
56 expenditure$.tw. (33620)
57 (value adj3 (money or monetary)).tw. (1287)
58 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3319)
59 or/34-58 (630780)
60 "Quality of Life"/ (113933)
61 quality of life.tw. (130420)
62 "Value of Life"/ (5381)
63 Quality-Adjusted Life Years/ (6754)
64 quality adjusted life.tw. (5583)
65 (qaly$ or qald$ or qale$ or qtime$).tw. (4634)
66 disability adjusted life.tw. (1089)
67 daly$.tw. (1088)
68 Health Status Indicators/ (19623)
69 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (14442)
70 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (954)
71 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2383)
72 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (20)
73 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (323)
74 (euroqol or euro qol or eq5d or eq 5d).tw. (3455)
75 (qol or hql or hqol or hrqol).tw. (22792)
76 (hye or hyes).tw. (53)
77 health$ year$ equivalent$.tw. (38)
78 utilit$.tw. (105910)
79 (hui or hui1 or hui2 or hui3).tw. (811)

Search term
80 disutili$.tw. (188)
81 rosser.tw. (71)
82 quality of wellbeing.tw. (5)
83 quality of well-being.tw. (316)
84 qwb.tw. (159)
85 willingness to pay.tw. (2025)
86 standard gamble$.tw. (634)
87 time trade off.tw. (689)
88 time tradeoff.tw. (198)
89 tto.tw. (543)
90 or/60-89 (303013)
91 59 or 90 (892441)
92 33 and 91 (229)
93 limit 92 to english language (203)
94 Animals/ not Humans/ (3807921)
95 93 not 94 (187)

1 **Table 24: Health economic search terms (EMBASE)**

Search term
Search Strategy:
1 irritable colon/ (15719)
2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (11913)
3 (Irritable* adj4 colon*).tw. (604)
4 IBS.tw. (8332)
5 exp gastrointestinal motility/ (27185)
6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (556859)
7 flatulence/ (8214)
8 (Flatu* or bloat*).tw. (7775)
9 feces incontinence/ (13731)
10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (36027)
11 FI.tw. (12965)
12 Encopres*.tw. (734)
13 diarrhea/ (151868)
14 (Diarrhoea* or diarrhea*).tw. (98930)
15 constipation/ (55832)
16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (24607)
17 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (1516)
18 dyspepsia/ (25080)
19 (Dyspeps* or Indigest*).tw. (13796)
20 or/1-19 (822645)
21 Fodmap*.tw. (82)
22 "fermentable oligo* di* monosaccharides and polyols".tw. (21)
23 "fermentable oligo* di* mono-saccharides and polyols".tw. (8)
24 "fermentable oligo* di* and monosaccharides and polyols".tw. (26)
25 "fermentable oligo* di* and mono-saccharides and polyols".tw. (18)
26 carbohydrate diet/ (14550)
27 low carbohydrate diet/ (1487)

Search term
28 ((short-chain* or shortchain* or short chain* or low-digest* or lowdigest* or low digest* or non-digest* or nondigest* or nondigest* or fermentable*) adj4 carbohydrate*).tw. (773)
29 ((carbohydrate* or sugar*) adj4 malabsorpt*).tw. (451)
30 (fructose* or oligosaccharide* or fructo-oligosacchride* or galactan* or galacto-oligosaccharide* or oligofructose* or fructan* or inulin* or sorbitol* or polyol* or xylitol* or mannitol* or maltitol* or raffinose* or stachyose* or nystose* or kestose* or lactose* or ordisaccharide* or monosaccharide*).tw. (111002)
31 fructose/ or oligosaccharide/ or galactan/ or galactose oligosaccharide/ or fructose oligosaccharide/ or fructan/ or inulin/ or sorbitol/ or polyol/ or xylitol/ or mannitol/ or maltitol/ or raffinose/ or lactose/ or monosaccharide/ or disaccharide/ (102166)
32 or/21-31 (167942)
33 20 and 32 (9762)
34 exp Health Economics/ (618525)
35 exp "Health Care Cost"/ (202322)
36 exp Pharmacoeconomics/ (173338)
37 Monte Carlo Method/ (21775)
38 Decision Tree/ (6029)
39 econom$.tw. (208490)
40 cba.tw. (9620)
41 cea.tw. (21866)
42 cua.tw. (908)
43 markov$.tw. (15866)
44 (monte adj carlo).tw. (27447)
45 (decision adj3 (tree$ or analys$)).tw. (11603)
46 (cost or costs or costing$ or costly or costed).tw. (423443)
47 (price$ or pricing$).tw. (32451)
48 budget$.tw. (23596)
49 expenditure$.tw. (45197)
50 (value adj3 (money or monetary)).tw. (1927)
51 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (6246)
52 or/34-51 (1113042)
53 "Quality of Life"/ (248870)
54 Quality Adjusted Life Year/ (12158)
55 Quality of Life Index/ (1569)
56 Short Form 36/ (11409)
57 Health Status/ (85076)
58 quality of life.tw. (214253)
59 quality adjusted life.tw. (8778)
60 (qaly$ or qald$ or qale$ or qtime$).tw. (8673)
61 disability adjusted life.tw. (1569)
62 daly$.tw. (1665)
63 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (23235)
64 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1457)
65 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (4177)
66 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (36)
67 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (323)
68 (euroqol or euro qol or eq5d or eq 5d).tw. (6777)
69 (qol or hql or hqol or hrqol).tw. (42243)

Search term
70 (hye or hyes).tw. (91)
71 health$ year$ equivalent$.tw. (43)
72 utilit$.tw. (153308)
73 (hui or hui1 or hui2 or hui3).tw. (1261)
74 disutili$.tw. (360)
75 rosser.tw. (90)
76 quality of wellbeing.tw. (19)
77 quality of well-being.tw. (378)
78 qwb.tw. (195)
79 willingness to pay.tw. (3331)
80 standard gamble$.tw. (791)
81 time trade off.tw. (1011)
82 time tradeoff.tw. (228)
83 tto.tw. (888)
84 or/53-83 (532598)
85 52 or 84 (1559824)
86 33 and 85 (654)
87 Nonhuman/ not Human/ (3391370)
88 86 not 87 (617)
89 limit 88 to embase (537)
90 limit 89 to (conference abstract or conference paper) (93)
91 89 not 90 (444)
92 limit 91 to english language (413)

1 **Table 25: Health economic search terms (NHS EED)**

Search term
Search Strategy:

#1 MeSH descriptor: [Irritable Bowel Syndrome] this term only 406
#2 (Irritable* near/4 bowel* near/4 syndrome*):ti,ab,kw 1100
#3 (Irritable* near/4 colon*):ti,ab,kw 293
#4 IBS:ti,ab,kw 597
#5 MeSH descriptor: [Gastrointestinal Motility] explode all trees 2410
#6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) near/4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)):ti,ab,kw 34704
#7 MeSH descriptor: [Flatulence] this term only 213
#8 (Flatu* or bloat*):ti,ab,kw 1611
#9 MeSH descriptor: [Fecal Incontinence] this term only 391
#10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) near/4 (incontinen* or urge* or leak* or soil* or seep* or impact*)):ti,ab,kw 2232
#11 FI:ti,ab,kw 375
#12 Encopres*:ti,ab,kw 52
#13 MeSH descriptor: [Diarrhea] this term only 2061
#14 (Diarrhoea* or diarrhea*):ti,ab,kw 9939
#15 MeSH descriptor: [Constipation] this term only 844
#16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*):ti,ab,kw 3622
#17 MeSH descriptor: [Colonic Diseases, Functional] this term only 311
#18 (Function* near/4 (colon* or bowel*) near/4 (disease* or disorder*)):ti,ab,kw 401
#19 MeSH descriptor: [Dyspepsia] this term only 889
#20 (Dyspeps* or Indigest*):ti,ab,kw 2551

Search term
#21 {or #1-#20} 47430
#22 Fodmap*:ti,ab,kw 2
#23 "fermentable oligo* di* monosaccharides and polyols":ti,ab,kw 0
#24 "fermentable oligo* di* mono-saccharides and polyols":ti,ab,kw 0
#25 "fermentable oligo* di* and monosaccharides and polyols":ti,ab,kw 0
#26 "fermentable oligo* di* and mono-saccharides and polyols":ti,ab,kw 0
#27 MeSH descriptor: [Dietary Carbohydrates] this term only 2221
#28 MeSH descriptor: [Diet, Carbohydrate-Restricted] this term only 157
#29 ((short-chain* or shortchain* or short chain* or low-digest* or lowdigest* or low digest* or non-digest* or nondigest* or nondigest* or fermentable*) near/4 carbohydrate*):ti,ab,kw 55
#30 ((carbohydrate* or sugar*) near/4 malabsorpt*):ti,ab,kw 60
#31 (fructose* or oligosaccharide* or fructo-oligosacchride* or galactan* or galacto-oligosaccharide* or oligofructose* or fructan* or inulin* or sorbitol* or polyol* or xylitol* or mannitol* or maltitol* or raffinose* or stachyose* or nystose* or kestose* or lactose* or ordisaccharide* or monosaccharide*):ti,ab,kw 4374
#32 MeSH descriptor: [Fructose] this term only 577
#33 MeSH descriptor: [Oligosaccharides] this term only 238
#34 MeSH descriptor: [Galactans] this term only 151
#35 MeSH descriptor: [Fructans] this term only 11
#36 MeSH descriptor: [Inulin] this term only 135
#37 MeSH descriptor: [Sorbitol] this term only 218
#38 MeSH descriptor: [Xylitol] this term only 191
#39 MeSH descriptor: [Mannitol] this term only 388
#40 MeSH descriptor: [Raffinose] this term only 73
#41 MeSH descriptor: [Lactose] this term only 257
#42 MeSH descriptor: [Monosaccharides] this term only 11
#43 MeSH descriptor: [Disaccharides] this term only 114
#44 {or #22-#43} 6601
#45 #21 and #44 1

1 **Table 26: Health economic search terms (HEED)**

Search term
Search Strategy:

All data: Fodmap OR
All data: fermentable oligo di monosaccharides and polyols OR
All data: fermentable oligo di mono-saccharides and polyols OR
All data: fermentable oligo di and monosaccharides and polyols OR
All data: fermentable oligo di and mono-saccharides and polyols

2 **Table 27: Health economic search terms (PubMed)**

Search term				
Search	Add to builder	Query	Items found	Time
#7	Add	Search (#6) AND ("2014/03/01"[Date - Entrez] : "3000"[Date - Entrez])	1	11:26:12
#6	Add	Search (#1 or #2 or #3 or #4 or #5)	30	11:25:36

Search term				
#5	Add	Search (fermentable oligo* di* and mono-saccharides and polyols[Title/Abstract])	0	11:25:10
#4	Add	Search (fermentable oligo* di* and monosaccharides and polyols[Title/Abstract])	0	11:24:54
#3	Add	Search (fermentable oligo* di* mono-saccharides and polyols[Title/Abstract])	0	11:24:28
#2	Add	Search (fermentable oligo* di* monosaccharides and polyols[Title/Abstract])	0	11:24:14
#1	Add	Search Fodmap[Title/Abstract]	30	

D.3 Review questions 3 and 4

D.3.1 Clinical search summary

Table 28: Clinical search summary

Database	Date searched	Number retrieved
CDSR (Wiley)	24/02/2014	0
Database of Abstracts of Reviews of Effects – DARE (Wiley)	24/02/2014	0
HTA database (Wiley)	24/02/2014	3
CENTRAL (Wiley)	24/02/2014	30
MEDLINE (Ovid)	24/02/2014	149
MEDLINE In-Process (Ovid)	24/02/2014	29
EMBASE (Ovid)	24/02/2014	575
PsycINFO (Ovid)	24/02/2014	90
PubMed	24/02/2014	0

Table 29: Clinical search terms (MEDLINE)

Line number	Search term	Number retrieved
	1 Irritable Bowel Syndrome/ (4003) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (7169) 3 (Irritable* adj4 colon*).tw. (508) 4 IBS.tw. (4385) 5 exp Gastrointestinal Motility/ (32395) 6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (404749)	149

	7 Flatulence/ (1175) 8 (Flatu* or bloat*).tw. (4715) 9 Fecal Incontinence/ (7699) 10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (22138) 11 FI.tw. (4803) 12 Encopres*.tw. (545) 13 Diarrhea/ (37897) 14 (Diarrhoea* or diarrhea*).tw. (71408) 15 Constipation/ (10472) 16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (14556) 17 Colonic Diseases, Functional/ (3652) 18 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (974) 19 Dyspepsia/ (7151) 20 (Dyspeps* or Indigest*).tw. (9273) 21 or/1-20 (530021) 22 (Linaclotid* or Constella or Linzess).tw. (71) 23 (Lubiproston* or Amitiza).tw. (216) 24 or/22-23 (261) 25 21 and 24 (225) 26 Meta-Analysis.pt. (44135) 27 Meta-Analysis as Topic/ (13223) 28 Review.pt. (1830363) 29 exp Review Literature as Topic/ (7207) 30 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (52539) 31 (review$ or overview$).ti. (255871) 32 (systematic$ adj5 (review$ or overview$)).tw. (48201) 33 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (3941) 34 ((studies or trial$) adj2 (review$ or overview$)).tw. (23166) 35 (integrat$ adj3 (research or review$ or literature)).tw. (4986) 36 (pool$ adj2 (analy$ or data)).tw. (12729) 37 (handsearch$ or (hand adj3 search$)).tw. (4842)	

	38 (manual$ adj3 search$).tw. (2838) 39 or/26-38 (1981673) 40 animals/ not humans/ (3789994) 41 39 not 40 (1849996) 42 Randomized Controlled Trial.pt. (362550) 43 Controlled Clinical Trial.pt. (87486) 44 Clinical Trial.pt. (483076) 45 exp Clinical Trials as Topic/ (273772) 46 Placebos/ (32159) 47 Random Allocation/ (79100) 48 Double-Blind Method/ (123169) 49 Single-Blind Method/ (18475) 50 Cross-Over Studies/ (33200) 51 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (698402) 52 (random$ adj3 allocat$).tw. (19672) 53 placebo$.tw. (147043) 54 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (120661) 55 (crossover$ or (cross adj over$)).tw. (54899) 56 or/42-55 (1322728) 57 animals/ not humans/ (3789994) 58 56 not 57 (1232791) 59 41 or 58 (2858373) 60 25 and 59 (155) 61 animals/ not humans/ (3789994) 62 60 not 61 (155) 63 limit 62 to english language (149)	

1 **Table 30: Clinical search terms (Embase)**

Line number	Search term	Number retrieved
	Search Strategy: --- 1 irritable colon/ (15705) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (11897) 3 (Irritable* adj4 colon*).tw. (604) 4 IBS.tw. (8319) 5 exp gastrointestinal motility/ (27169)	575

	6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (555764) 7 flatulence/ (8198) 8 (Flatu* or bloat*).tw. (7755) 9 feces incontinence/ (13705) 10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (35893) 11 FI.tw. (12928) 12 Encopres*.tw. (734) 13 diarrhea/ (151580) 14 (Diarrhoea* or diarrhea*).tw. (98710) 15 constipation/ (55736) 16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (24556) 17 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (1512) 18 dyspepsia/ (25050) 19 (Dyspeps* or Indigest*).tw. (13777) 20 or/1-19 (821040) 21 linaclotide/ (338) 22 (Linaclotid* or Constella or Linzess).tw. (253) 23 lubiprostone/ (598) 24 (Lubiproston* or Amitiza).tw. (351) 25 or/21-24 (848) 26 20 and 25 (773) 27 exp Clinical Trials/ (94542) 28 Randomization/ (64919) 29 Placebo/ (235971) 30 Double Blind Procedure/ (120717) 31 Single Blind Procedure/ (19074) 32 Crossover Procedure/ (40030) 33 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (1000852) 34 (random$ adj3 allocat$).tw. (26387) 35 placebo$.tw. (202397) 36 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (161252) 37 (crossover$ or (cross adj over$)).tw. (70115) 38 or/27-37 (1341064) 39 nonhuman/ not human/ (3387770) 40 38 not 39 (1285702) 41 Systematic Review/ (70658) 42 Meta Analysis/ (80923) 43 Review/ (2048024) 44 Review.pt. (2043949) 45 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (82061) 46 (review$ or overview$).ti. (343399) 47 (systematic$ adj5 (review$ or overview$)).tw. (74354) 48 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (5572) 49 ((studies or trial$) adj2 (review$ or overview$)).tw. (31707)	

	50 (integrat$ adj3 (research or review$ or literature)).tw. (6854) 51 (pool$ adj2 (analy$ or data)).tw. (19617) 52 (handsearch$ or (hand adj3 search$)).tw. (6729) 53 (manual$ adj3 search$).tw. (4076) 54 or/41-53 (2376673) 55 nonhuman/ not human/ (3387770) 56 54 not 55 (2254976) 57 40 or 56 (3270144) 58 26 and 57 (592) 59 Nonhuman/ not Human/ (3387770) 60 58 not 59 (592) 61 limit 60 to english language (575)	

1 **Table 31: Clinical search terms (DARE, Central, HTA, CDRS)**

Line number	Search term	Number retrieved
	Search Strategy: --- #1 MeSH descriptor: [Irritable Bowel Syndrome] this term only 406 #2 (Irritable* near/4 bowel* near/4 syndrome*):ti,ab,kw 1099 #3 (Irritable* near/4 colon*):ti,ab,kw 293 #4 IBS:ti,ab,kw 597 #5 MeSH descriptor: [Gastrointestinal Motility] explode all trees 2410 #6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) near/4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)):ti,ab,kw 34703 #7 MeSH descriptor: [Flatulence] this term only 213 #8 (Flatu* or bloat*):ti,ab,kw 1610 #9 MeSH descriptor: [Fecal Incontinence] this term only 391 #10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) near/4 (incontinen* or urge* or leak* or soil* or seep* or impact*)):ti,ab,kw 2231 #11 FI:ti,ab,kw 375 #12 Encopres*:ti,ab,kw 52 #13 MeSH descriptor: [Diarrhea] this term only 2061 #14 (Diarrhoea* or diarrhea*):ti,ab,kw 9936 #15 MeSH descriptor: [Constipation] this term only 844 #16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*):ti,ab,kw 3622 #17 MeSH descriptor: [Colonic Diseases, Functional] this term only 311 #18 (Function* near/4 (colon* or bowel*) near/4 (disease* or disorder*)):ti,ab,kw 401 #19 MeSH descriptor: [Dyspepsia] this term only 889 #20 (Dyspeps* or Indigest*):ti,ab,kw 2551 #21 {or #1-#20} 47425 #22 (Linaclotid* or Constella or Linzess):ti,ab,kw 9 #23 (Lubiproston* or Amitiza):ti,ab,kw 25 #24 {or #22-#23} 34 #25 #21 and #24 33	33

Table 32: Clinical search terms (Pubmed)

Line number	Search term	Number retrieved
	Search Strategy: --- #5 Add Search (#1 and #4) 90 #4 Add Search (#2 or #3) 308 #3 Add Search (Lubiproston* or Amitiza[Title/Abstract]) 178 #2 Add Search (Linaclotid* or Constella or Linzess[Title/Abstract]) 162 #1 Add Search (Irritable* bowel* syndrome* or Irritable* colon* or IBS[Title/Abstract]) 7318	0

D.3.2 Health economics search summary

Table 33: Health economics search summary

Databases	Date searched	No. retrieved
MEDLINE (Ovid)	07/03/14	49
MEDLINE In-Process (Ovid)	07/03/14	8
EMBASE (Ovid)	07/03/14	208
NHS Economic Evaluation Database - NHS EED (Wiley)	07/03/14	0
Health Economic Evaluations Database – HEED (Wiley)	07/03/14	0
PubMed	07/03/14	0

Table 34: Health economic search terms (Medline and Medline in Process)

Search term
Search Strategy: --- 1 Irritable Bowel Syndrome/ (4064) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (7236) 3 (Irritable* adj4 colon*).tw. (510) 4 IBS.tw. (4441) 5 exp Gastrointestinal Motility/ (32495) 6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (406671) 7 Flatulence/ (1179)

Search term
8 (Flatu* or bloat*).tw. (4753)
9 Fecal Incontinence/ (7722)
10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (22296)
11 FI.tw. (4830)
12 Encopres*.tw. (547)
13 Diarrhea/ (38031)
14 (Diarrhoea* or diarrhea*).tw. (71789)
15 Constipation/ (10523)
16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (14650)
17 Colonic Diseases, Functional/ (3658)
18 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (980)
19 Dyspepsia/ (7184)
20 (Dyspeps* or Indigest*).tw. (9315)
21 or/1-20 (532575)
22 (Linaclotid* or Constella or Linzess).tw. (75)
23 (Lubiproston* or Amitiza).tw. (217)
24 or/22-23 (266)
25 21 and 24 (230)
26 Economics/ (26508)
27 exp "Costs and Cost Analysis"/ (178069)
28 Economics, Dental/ (1853)
29 exp Economics, Hospital/ (19221)
30 exp Economics, Medical/ (13508)
31 Economics, Nursing/ (3887)
32 Economics, Pharmaceutical/ (2507)
33 Budgets/ (9617)
34 exp Models, Economic/ (9913)
35 Markov Chains/ (9437)
36 Monte Carlo Method/ (19364)
37 Decision Trees/ (8650)
38 econom$.tw. (150098)
39 cba.tw. (8624)
40 cea.tw. (15744)
41 cua.tw. (779)
42 markov$.tw. (10981)
43 (monte adj carlo).tw. (19965)
44 (decision adj3 (tree$ or analys$)).tw. (7950)
45 (cost or costs or costing$ or costly or costed).tw. (293286)
46 (price$ or pricing$).tw. (22220)
47 budget$.tw. (16720)
48 expenditure$.tw. (33620)
49 (value adj3 (money or monetary)).tw. (1287)
50 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3319)
51 or/26-50 (630780)
52 "Quality of Life"/ (113933)
53 quality of life.tw. (130420)
54 "Value of Life"/ (5381)
55 Quality-Adjusted Life Years/ (6754)
56 quality adjusted life.tw. (5583)
57 (qaly$ or qald$ or qale$ or qtime$).tw. (4634)

Search term
58 disability adjusted life.tw. (1089)
59 daly$.tw. (1088)
60 Health Status Indicators/ (19623)
61 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (14442)
62 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (954)
63 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2383)
64 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (20)
65 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (323)
66 (euroqol or euro qol or eq5d or eq 5d).tw. (3455)
67 (qol or hql or hqol or hrqol).tw. (22792)
68 (hye or hyes).tw. (53)
69 health$ year$ equivalent$.tw. (38)
70 utilit$.tw. (105910)
71 (hui or hui1 or hui2 or hui3).tw. (811)
72 disutili$.tw. (188)
73 rosser.tw. (71)
74 quality of wellbeing.tw. (5)
75 quality of well-being.tw. (316)
76 qwb.tw. (159)
77 willingness to pay.tw. (2025)
78 standard gamble$.tw. (634)
79 time trade off.tw. (689)
80 time tradeoff.tw. (198)
81 tto.tw. (543)
82 or/52-81 (303013)
83 51 or 82 (892441)
84 25 and 83 (49)
85 Animals/ not Humans/ (3807921)
86 84 not 85 (49)
87 limit 86 to english language (48)

1 **Table 35: Health economic search terms (EMBASE)**

Search term
Search Strategy:
---
1 irritable colon/ (15719)
2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (11913)
3 (Irritable* adj4 colon*).tw. (604)
4 IBS.tw. (8332)
5 exp gastrointestinal motility/ (27185)
6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (556859)
7 flatulence/ (8214)
8 (Flatu* or bloat*).tw. (7775)
9 feces incontinence/ (13731)
10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*)

Search term
adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (36027)
11 FI.tw. (12965)
12 Encopres*.tw. (734)
13 diarrhea/ (151868)
14 (Diarrhoea* or diarrhea*).tw. (98930)
15 constipation/ (55832)
16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (24607)
17 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (1516)
18 dyspepsia/ (25080)
19 (Dyspeps* or Indigest*).tw. (13796)
20 or/1-19 (822645)
21 linaclotide/ (339)
22 (Linaclotid* or Constella or Linzess).tw. (254)
23 lubiprostone/ (599)
24 (Lubiproston* or Amitiza).tw. (352)
25 or/21-24 (850)
26 20 and 25 (775)
27 exp Health Economics/ (618525)
28 exp "Health Care Cost"/ (202322)
29 exp Pharmacoeconomics/ (173338)
30 Monte Carlo Method/ (21775)
31 Decision Tree/ (6029)
32 econom$.tw. (208490)
33 cba.tw. (9620)
34 cea.tw. (21866)
35 cua.tw. (908)
36 markov$.tw. (15866)
37 (monte adj carlo).tw. (27447)
38 (decision adj3 (tree$ or analys$)).tw. (11603)
39 (cost or costs or costing$ or costly or costed).tw. (423443)
40 (price$ or pricing$).tw. (32451)
41 budget$.tw. (23596)
42 expenditure$.tw. (45197)
43 (value adj3 (money or monetary)).tw. (1927)
44 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (6246)
45 or/27-44 (1113042)
46 "Quality of Life"/ (248870)
47 Quality Adjusted Life Year/ (12158)
48 Quality of Life Index/ (1569)
49 Short Form 36/ (11409)
50 Health Status/ (85076)
51 quality of life.tw. (214253)
52 quality adjusted life.tw. (8778)
53 (qaly$ or qald$ or qale$ or qtime$).tw. (8673)
54 disability adjusted life.tw. (1569)
55 daly$.tw. (1665)
56 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (23235)
57 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1457)
58 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (4177)

Search term
59 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (36)
60 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (323)
61 (euroqol or euro qol or eq5d or eq 5d).tw. (6777)
62 (qol or hql or hqol or hrqol).tw. (42243)
63 (hye or hyes).tw. (91)
64 health$ year$ equivalent$.tw. (43)
65 utilit$.tw. (153308)
66 (hui or hui1 or hui2 or hui3).tw. (1261)
67 disutili$.tw. (360)
68 rosser.tw. (90)
69 quality of wellbeing.tw. (19)
70 quality of well-being.tw. (378)
71 qwb.tw. (195)
72 willingness to pay.tw. (3331)
73 standard gamble$.tw. (791)
74 time trade off.tw. (1011)
75 time tradeoff.tw. (228)
76 tto.tw. (888)
77 or/46-76 (532598)
78 45 or 77 (1559824)
79 26 and 78 (266)
80 Nonhuman/ not Human/ (3391370)
81 79 not 80 (266)
82 limit 81 to embase (257)
83 limit 82 to (conference abstract or conference paper) (46)
84 82 not 83 (211)
85 limit 84 to english language (208)

1 **Table 36: Health economic search terms (NHS EED)**

Search term
Search Strategy:
#1 MeSH descriptor: [Irritable Bowel Syndrome] this term only 406
#2 (Irritable* near/4 bowel* near/4 syndrome*):ti,ab,kw 1100
#3 (Irritable* near/4 colon*):ti,ab,kw 293
#4 IBS:ti,ab,kw 597
#5 MeSH descriptor: [Gastrointestinal Motility] explode all trees 2410
#6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) near/4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)):ti,ab,kw 34704
#7 MeSH descriptor: [Flatulence] this term only 213
#8 (Flatu* or bloat*):ti,ab,kw 1611
#9 MeSH descriptor: [Fecal Incontinence] this term only 391
#10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) near/4 (incontinen* or urge* or leak* or soil* or seep* or impact*)):ti,ab,kw 2232
#11 FI:ti,ab,kw 375
#12 Encopres*:ti,ab,kw 52
#13 MeSH descriptor: [Diarrhea] this term only 2061
#14 (Diarrhoea* or diarrhea*):ti,ab,kw 9939
#15 MeSH descriptor: [Constipation] this term only 844

Search term		
#16	(Constipat* or costiveness* or dyschezia* or colonic* inertia*):ti,ab,kw	3622
#17	MeSH descriptor: [Colonic Diseases, Functional] this term only	311
#18	(Function* near/4 (colon* or bowel*) near/4 (disease* or disorder*)):ti,ab,kw	401
#19	MeSH descriptor: [Dyspepsia] this term only	889
#20	(Dyspeps* or Indigest*):ti,ab,kw	2551
#21	{or #1-#20}	47430
#22	(Linaclotid* or Constella or Linzess):ti,ab,kw	9
#23	(Lubiproston* or Amitiza):ti,ab,kw	25
#24	{or #22-#23}	34
#25	#21 and #24	0

Table 37: Health economic search terms (HEED)

Search term	
Search Strategy:	

All data: 'IBS' or Irritable* bowel* syndrome* or Irritable* colon* or IBS	AND
All data: Linaclotid* or Constella or Linzess or Lubiproston* or Amitiza	

Table 38: Health economic search terms (PubMed)

Search term			
Search Strategy:			

Search	Add to builder	Query	Items found
#4	Add	Search (#3) AND ("2014/03/01"[Date - Entrez] : "3000"[Date - Entrez])	0
#3	Add	Search (#1 and #2)	90
#2	Add	Search (Linaclotid* or Constella or Linzess or Lubiproston* or Amitiza)	308
#1	Add	Search (Irritable* bowel* syndrome* or Irritable* colon* or IBS[Title/Abstract])	7345

D.43 Review question 5a (relaxation)

D.4.14 Clinical search summary

Table 39: Clinical search summary (further update search)

Database	Date searched	Number retrieved
CDSR (Wiley)	16/08/13	49
Database of Abstracts of Reviews of Effects – DARE (Wiley)	16/08/13	16
HTA database (Wiley)	16/08/13	0
CENTRAL (Wiley)	16/08/13	165

Database	Date searched	Number retrieved
MEDLINE (Ovid)	16/08/13	496
MEDLINE In-Process (Ovid)	16/08/13	14
EMBASE (Ovid)	16/08/13	997/804
PsycINFO (Ovid)	16/08/13	308

1 **Table 40: Clinical search terms (Medline and Medline in process)**

Line number	Search term	Number retrieved
	Search Strategy: --- 1 Irritable Bowel Syndrome/ (4182) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (7398) 3 (Irritable* adj4 colon*).tw. (515) 4 IBS.tw. (4547) 5 exp Gastrointestinal Motility/ (32900) 6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (415649) 7 Flatulence/ (1209) 8 (Flatu* or bloat*).tw. (4815) 9 Fecal Incontinence/ (7744) 10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (22857) 11 FI.tw. (4914) 12 Encopres*.tw. (548) 13 Diarrhea/ (39254) 14 (Diarrhoea* or diarrhea*).tw. (75897) 15 Constipation/ (10460) 16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (14744) 17 Colonic Diseases, Functional/ (3648) 18 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (1018) 19 Dyspepsia/ (7289) 20 (Dyspeps* or Indigest*).tw. (9512) 21 or/1-20 (545849) 22 exp Hypnosis/ (10588) 23 Hypno*.tw. (17355) 24 exp psychotherapy/ (149510) 25 Psychotherap*.tw. (29703) 26 ((Psychodynamic* or interpersonal*) adj4 (therap* or treat* or techni* or manag* or train*)).tw. (2726) 27 Relaxation Therapy/ (5744) 28 (Relax* adj4 (therap* or treat* or techni* or manag* or train*)).tw. (5783) 29 Stress, Psychological/ (86317) 30 (Stress* adj4 (therap* or treat* or techni* or manag* or train*)).tw. (21578)	510

	31 or/22-30 (266914) 32 21 and 31 (5286) 33 Animals/ not Humans/ (3926191) 34 32 not 33 (4429) 35 Meta-Analysis.pt. (49881) 36 Meta-Analysis as Topic/ (13930) 37 Review.pt. (1894357) 38 exp Review Literature as Topic/ (7544) 39 (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw. (57298) 40 (review$ or overview$).ti. (260353) 41 (systematic$ adj4 (review$ or overview$)).tw. (51252) 42 ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw. (3697) 43 ((studies or trial$) adj1 (review$ or overview$)).tw. (7679) 44 (integrat$ adj2 (research or review$ or literature)).tw. (3592) 45 (pool$ adj1 (analy$ or data)).tw. (9452) 46 (handsearch$ or (hand adj2 search$)).tw. (6555) 47 (manual$ adj2 search$).tw. (2963) 48 or/35-47 (2043448) 49 animals/ not humans/ (3926191) 50 48 not 49 (1908855) 51 Randomized Controlled Trial.pt. (382120) 52 Controlled Clinical Trial.pt. (88870) 53 Clinical Trial.pt. (499567) 54 exp Clinical Trials as Topic/ (292503) 55 Placebos/ (33370) 56 Random Allocation/ (80818) 57 Double-Blind Method/ (129386) 58 Single-Blind Method/ (19108) 59 Cross-Over Studies/ (35341) 60 ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw. (648974) 61 (random$ adj2 allocat$).tw. (20247) 62 placebo$.tw. (158578) 63 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (127154) 64 (crossover$ or (cross adj over$)).tw. (58157) 65 or/51-64 (1331078) 66 animals/ not humans/ (3926191) 67 65 not 66 (1246049) 68 50 or 67 (2918027) 69 34 and 68 (1841) 70 limit 69 to english language (1567) 71 limit 70 to ed=20070601-20130816 (595)	

1 **Table 41: Clinical search terms (Embase)**

Line number	Search term	Number retrieved
	Strategy used: --- 1 irritable colon/ (14846) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (11222) 3 (Irritable* adj4 colon*).tw. (591)	804

	4 IBS.tw. (7748) 5 exp gastrointestinal motility/ (26586) 6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (532130) 7 flatulence/ (7730) 8 (Flatu* or bloat*).tw. (7215) 9 feces incontinence/ (13079) 10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (33309) 11 FI.tw. (11942) 12 Encopres*.tw. (715) 13 diarrhea/ (143830) 14 (Diarrhoea* or diarrhea*).tw. (93843) 15 constipation/ (52395) 16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (22949) 17 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (1468) 18 dyspepsia/ (23969) 19 (Dyspeps* or Indigest*).tw. (13193) 20 or/1-19 (784150) 21 exp hypnosis/ (13072) 22 Hypno*.tw. (21934) 23 exp psychotherapy/ (176804) 24 Psychotherap*.tw. (43934) 25 ((Psychodynamic* or interpersonal*) adj4 (therap* or treat* or techni* or manag* or train*)).tw. (3847) 26 relaxation training/ (8218) 27 (Relax* adj4 (therap* or treat* or techni* or manag* or train*)).tw. (7553) 28 mental stress/ (58394) 29 (Stress* adj4 (therap* or treat* or techni* or manag* or train*)).tw. (28080) 30 or/21-29 (289442) 31 20 and 30 (8470) 32 Nonhuman/ not Human/ (3300306) 33 31 not 32 (8124) 34 Systematic Review/ (62942) 35 Meta Analysis/ (74817) 36 Review/ (1988330) 37 Review.pt. (1983739) 38 (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw. (73560) 39 (review$ or overview$).ti. (326275) 40 (systematic$ adj4 (review$ or overview$)).tw. (65620) 41 ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw. (4460) 42 ((studies or trial$) adj1 (review$ or overview$)).tw. (8951) 43 (integrat$ adj2 (research or review$ or literature)).tw. (4333) 44 (pool$ adj1 (analy$ or data)).tw. (12265) 45 (handsearch$ or (hand adj2 search$)).tw. (6237) 46 (manual$ adj2 search$).tw. (3582)	

	47 or/34-46 (2288525) 48 nonhuman/ not human/ (3300306) 49 47 not 48 (2171333) 50 exp Clinical Trials/ (73406) 51 Randomization/ (63137) 52 Placebo/ (223384) 53 Double Blind Procedure/ (116998) 54 Single Blind Procedure/ (18070) 55 Crossover Procedure/ (38092) 56 ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw. (821449) 57 (random$ adj2 allocat$).tw. (24383) 58 placebo$.tw. (193467) 59 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (154960) 60 (crossover$ or (cross adj over$)).tw. (67284) 61 or/50-60 (1171258) 62 nonhuman/ not human/ (3300306) 63 61 not 62 (1125411) 64 49 or 63 (3054757) 65 33 and 64 (4254) 66 limit 65 to english language (3821) 67 limit 66 to em=200700-201332 (2060) 68 limit 67 to embase (1938) 69 limit 68 to (conference abstract or conference paper) (135) 70 68 not 69 (1803)	

1 **Table 42: Clinical search terms (PsyINFO)**

Line number	Search term	Number retrieved
	Search Strategy: --- 1 Irritable Bowel Syndrome/ (515) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (655) 3 (Irritable* adj4 colon*).tw. (1) 4 IBS.tw. (479) 5 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (5290) 6 (Flatu* or bloat*).tw. (115) 7 Fecal Incontinence/ (153) 8 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (2865) 9 FI.tw. (490) 10 Encopres*.tw. (156) 11 Diarrhea/ (137) 12 (Diarrhoea* or diarrhea*).tw. (840) 13 Constipation/ (148) 14 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (754) 15 (Function* adj4 (colon* or bowel*) adj4 (disease* or	308

	disorder*)).tw. (52) 16 Dyspepsia/ (47) 17 (Dyspeps* or Indigest*).tw. (223) 18 or/1-17 (10210) 19 exp Hypnosis/ (1782) 20 Hypno*.tw. (4476) 21 exp Psychotherapy/ (71104) 22 Psychotherap*.tw. (36185) 23 ((Psychodynamic* or interpersonal*) adj4 (therap* or treat* or techni* or manag* or train*)).tw. (3936) 24 Relaxation Therapy/ (333) 25 (Relax* adj4 (therap* or treat* or techni* or manag* or train*)).tw. (1383) 26 Psychological Stress/ (2729) 27 (Stress* adj4 (therap* or treat* or techni* or manag* or train*)).tw. (6708) 28 or/19-27 (93761) 29 18 and 28 (606) 30 limit 29 to (english language and yr="2007 -Current") (310)	

1 **Table 43: Clinical search terms (DARE, HTA, Central, CDRS)**

Line number	Search term	Number retrieved
	Search Strategy: --- #1 MeSH descriptor: [Irritable Bowel Syndrome] this term only 373 #2 (Irritable* near/4 bowel* near/4 syndrome*):ti,ab,kw 997 #3 (Irritable* near/4 colon*):ti,ab,kw 221 #4 IBS:ti,ab,kw 518 #5 MeSH descriptor: [Gastrointestinal Motility] explode all trees 2352 #6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) near/4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)):ti,ab,kw 31534 #7 MeSH descriptor: [Flatulence] this term only 207 #8 (Flatu* or bloat*):ti,ab,kw 1296 #9 MeSH descriptor: [Fecal Incontinence] this term only 373 #10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) near/4 (incontinen* or urge* or leak* or soil* or seep* or impact*)):ti,ab,kw 1918 #11 FI:ti,ab,kw 299 #12 Encopres*:ti,ab,kw 50 #13 MeSH descriptor: [Diarrhea] this term only 1991 #14 (Diarrhoea* or diarrhea*):ti,ab,kw 8149 #15 MeSH descriptor: [Constipation] this term only 805 #16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*):ti,ab,kw 2817 #17 MeSH descriptor: [Colonic Diseases, Functional] this term only 308 #18 (Function* near/4 (colon* or bowel*) near/4 (disease* or disorder*)):ti,ab,kw 389 #19 MeSH descriptor: [Dyspepsia] this term only 862	230

	#20 (Dyspeps* or Indigest*):ti,ab,kw 2182 #21 {or #1-#20} 42188 #22 MeSH descriptor: [Hypnosis] explode all trees 560 #23 Hypno*:ti,ab,kw 4702 #24 MeSH descriptor: [Psychotherapy] explode all trees 13737 #25 Psychotherap*:ti,ab,kw 5932 #26 ((Psychodynamic* or interpersonal*) near/4 (therap* or treat* or techni* or manag* or train*)):ti,ab,kw 730 #27 MeSH descriptor: [Relaxation Therapy] this term only 1113 #28 (Relax* near/4 (therap* or treat* or techni* or manag* or train*)):ti,ab,kw 2472 #29 MeSH descriptor: [Stress, Psychological] this term only 3055 #30 (Stress* near/4 (therap* or treat* or techni* or manag* or train*)):ti,ab,kw 3682 #31 {or #22-#30} 25438 #32 #21 and #31 from 2007 to 2013 294	

1 **Table 44: Clinical search summary (further update search)**

Database	Date searched	Number retrieved
CDSR (Wiley)	10/02/2014	6
Database of Abstracts of Reviews of Effects – DARE (Wiley)	10/02/2014	6
HTA database (Wiley)	10/02/2014	1
CENTRAL (Wiley)	10/02/2014	37
MEDLINE (Ovid)	10/02/2014	36
MEDLINE In-Process (Ovid)	10/02/2014	2
EMBASE (Ovid)	10/02/2014	5
PsycINFO (Ovid)	10/02/2014	39
PubMed	10/02/2014	17

2 **Table 45: Clinical search terms (MEDLINE)**

Line number	Search term	Number retrieved
1	Irritable Bowel Syndrome/	(3960)
2	(Irritable* adj4 bowel* adj4 syndrome*).tw.	(7088)
3	(Irritable* adj4 colon*).tw.	(507)
4	IBS.tw.	4335
5	exp Gastrointestinal Motility/	(32269)
6	((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw.	(402152)
7	Flatulence/	(1170)
8	(Flatu* or bloat*).tw.	(4682)
9	Fecal Incontinence/	(7657)

Line number	Search term	Number retrieved
10	((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw.	(22005)
11	FI.tw.	(4773)
12	Encopres*.tw.	(542)
13	Diarrhea/	(37693)
14	(Diarrhoea* or diarrhea*).tw.	(70921)
15	Constipation/	(10401)
16	(Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw.	(14466)
17	Colonic Diseases, Functional/	(3616)
18	(Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw.	(963)
19	Dyspepsia/	(7086)
20	(Dyspeps* or Indigest*).tw.	(9183)
21	or/1-20	(526688)
22	exp Hypnosis/	(10510)
23	Hypno*.tw.	(16988)
24	exp psychotherapy/	(146219)
25	Psychotherap*.tw.	(29216)
26	((Psychodynamic* or interpersonal*) adj4 (therap* or treat* or techni* or manag* or train*)).tw.	(2639)
27	Relaxation Therapy/	(5635)
28	(Relax* adj4 (therap* or treat* or techni* or manag* or train*)).tw.	(5578)
29	Stress, Psychological/	(83211)
30	(Stress* adj4 (therap* or treat* or techni* or manag* or train*)).tw.	(20586)
31	or/22-30	(259291)
32	21 and 31	(5117)
33	Animals/ not Humans/	(3778831)
34	32 not 33	(4294)
35	Meta-Analysis.pt.	(43521)
36	Meta-Analysis as Topic/	(13143)
37	Review.pt.	(1821724)
38	exp Review Literature as Topic/	(7171)
39	(metaanaly$ or metanaly$ or (meta adj2 analy$)).tw.	(51820)
40	(review$ or overview$).ti.	(254165)
41	(systematic$ adj4 (review$ or overview$)).tw.	(47362)
42	((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw.	(3433)
43	((studies or trial$) adj1 (review$ or overview$)).tw.	(6969)
44	(integrat$ adj2 (research or review$ or literature)).tw.	(3407
45	(pool$ adj1 (analy$ or data)).tw.	(8458)
46	(handsearch$ or (hand adj2 search$)).tw.	(4743)
47	(manual$ adj2 search$).tw.	(2681)
48	or/35-47	(1965877)
49	animals/ not humans/	(3778831)
50	48 not 49	(1835212)
51	Randomized Controlled Trial.pt.	(359956)

Line number	Search term	Number retrieved
52	Controlled Clinical Trial.pt.	(86949)
53	Clinical Trial.pt.	(481258)
54	exp Clinical Trials as Topic/	(271943)
55	Placebos/	(31933)
56	Random Allocation/	(78719)
57	Double-Blind Method/	(122345)
58	Single-Blind Method/	(18322)
59	Cross-Over Studies/	(32947)
60	((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw.	(601767)
61	(random$ adj2 allocat$).tw.	(19078)
62	placebo$.tw.	(146022)
63	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.	(119902)
64	(crossover$ or (cross adj over$)).tw.	(54551)
65	or/51-64	(1253677)
66	animals/ not humans/	(3778831)
67	65 not 66	(1171810)
68	50 or 67	(2792424)
69	34 and 68	(1753)
70	limit 69 to english language	(1481)
71	limit 70 to ed=20070601-20130816	(505)
72	limit 70 to ed=20130816-20140210	(36)

1 **Table 46: Clinical search terms (Embase)**

Line number	Search term	Number retrieved
	Strategy used: --- 1 irritable colon/ (15666) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (11866) 3 (Irritable* adj4 colon*).tw. (601) 4 IBS.tw. (8300) 5 exp gastrointestinal motility/ (27134) 6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (554236) 7 flatulence/ (8164) 8 (Flatu* or bloat*).tw. (7724) 9 feces incontinence/ (13650) 10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (35717) 11 FI.tw. (12816) 12 Encopres*.tw. (733) 13 diarrhea/ (151059) 14 (Diarrhoea* or diarrhea*).tw. (98357) 15 constipation/ (55549) 16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw.	1

	(24457) 17 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (1510) 18 dyspepsia/ (24993) 19 (Dyspeps* or Indigest*).tw. (13749) 20 or/1-19 (818587) 21 exp hypnosis/ (13248) 22 Hypno*.tw. (22458) 23 exp psychotherapy/ (182031) 24 Psychotherap*.tw. (45193) 25 ((Psychodynamic* or interpersonal*) adj4 (therap* or treat* or techni* or manag* or train*)).tw. (4010) 26 relaxation training/ (8459) 27 (Relax* adj4 (therap* or treat* or techni* or manag* or train*)).tw. (7813) 28 mental stress/ (60225) 29 (Stress* adj4 (therap* or treat* or techni* or manag* or train*)).tw. (29551) 30 or/21-29 (298624) 31 20 and 30 (8845) 32 Nonhuman/ not Human/ (3381252) 33 31 not 32 (8490) 34 Systematic Review/ (70069) 35 Meta Analysis/ (80432) 36 Review/ (2043522) 37 Review.pt. (2039408) 38 (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw. (81339) 39 (review$ or overview$).ti. (342048) 40 (systematic$ adj4 (review$ or overview$)).tw. (73335) 41 ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw. (4821) 42 ((studies or trial$) adj1 (review$ or overview$)).tw. (9486) 43 (integrat$ adj2 (research or review$ or literature)).tw. (4667) 44 (pool$ adj1 (analy$ or data)).tw. (13316) 45 (handsearch$ or (hand adj2 search$)).tw. (6622) 46 (manual$ adj2 search$).tw. (3860) 47 or/34-46 (2360028) 48 nonhuman/ not human/ (3381252) 49 47 not 48 (2239437) 50 exp Clinical Trials/ (92875) 51 Randomization/ (64837) 52 Placebo/ (235150) 53 Double Blind Procedure/ (120415) 54 Single Blind Procedure/ (18996) 55 Crossover Procedure/ (39883) 56 ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw. (867302) 57 (random$ adj2 allocat$).tw. (25549) 58 placebo$.tw. (201652) 59 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (160694) 60 (crossover$ or (cross adj over$)).tw. (69925) 61 or/50-60 (1235505)	

	62 nonhuman/ not human/ (3381252) 63 61 not 62 (1188050) 64 49 or 63 (3170326) 65 33 and 64 (4436) 66 limit 65 to english language (3998) 67 limit 66 to em=200700-201332 (2049) 68 limit 67 to embase (1927) 69 limit 68 to (conference abstract or conference paper) (135) 70 68 not 69 (1792) 71 limit 70 to em=201332-201406 (5)	

1 **Table 47: Clinical search terms (PsyINFO)**

Line number	Search term	Number retrieved
	Search Strategy: --- 1 Irritable Bowel Syndrome/ (551) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (686) 3 (Irritable* adj4 colon*).tw. (1) 4 IBS.tw. (507) 5 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (5566) 6 (Flatu* or bloat*).tw. (122) 7 Fecal Incontinence/ (163) 8 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (3071) 9 FI.tw. (533) 10 Encopres*.tw. (163) 11 Diarrhea/ (151) 12 (Diarrhoea* or diarrhea*).tw. (889) 13 Constipation/ (161) 14 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (801) 15 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (53) 16 Dyspepsia/ (55) 17 (Dyspeps* or Indigest*).tw. (232) 18 or/1-17 (10833) 19 exp Hypnosis/ (1857) 20 Hypno*.tw. (4648) 21 exp Psychotherapy/ (75245) 22 Psychotherap*.tw. (38375) 23 ((Psychodynamic* or interpersonal*) adj4 (therap* or treat* or techni* or manag* or train*)).tw. (4120) 24 Relaxation Therapy/ (339) 25 (Relax* adj4 (therap* or treat* or techni* or manag* or train*)).tw. (1439) 26 Psychological Stress/ (2874) 27 (Stress* adj4 (therap* or treat* or techni* or manag* or train*)).tw. (7063) 28 or/19-27 (99122)	23

	29 18 and 28 (627) 30 limit 29 to (english language and yr="2007 -Current") (331) 31 limit 29 to (english language and yr="2013 -2014") (39)	

1 **Table 48: Clinical search terms (HTA, DARE, CDRS, DARE)**

Line number	Search term	Number retrieved
	Search Strategy: --- #1 MeSH descriptor: [Irritable Bowel Syndrome] this term only 406 #2 (Irritable* near/4 bowel* near/4 syndrome*):ti,ab,kw 1099 #3 (Irritable* near/4 colon*):ti,ab,kw 293 #4 IBS:ti,ab,kw 597 #5 MeSH descriptor: [Gastrointestinal Motility] explode all trees 2410 #6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) near/4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)):ti,ab,kw 34702 #7 MeSH descriptor: [Flatulence] this term only 213 #8 (Flatu* or bloat*):ti,ab,kw 1610 #9 MeSH descriptor: [Fecal Incontinence] this term only 391 #10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) near/4 (incontinen* or urge* or leak* or soil* or seep* or impact*)):ti,ab,kw 2228 #11 FI:ti,ab,kw 375 #12 Encopres*:ti,ab,kw 52 #13 MeSH descriptor: [Diarrhea] this term only 2061 #14 (Diarrhoea* or diarrhea*):ti,ab,kw 9936 #15 MeSH descriptor: [Constipation] this term only 844 #16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*):ti,ab,kw 3622 #17 MeSH descriptor: [Colonic Diseases, Functional] this term only 311 #18 (Function* near/4 (colon* or bowel*) near/4 (disease* or disorder*)):ti,ab,kw 400 #19 MeSH descriptor: [Dyspepsia] this term only 889 #20 (Dyspeps* or Indigest*):ti,ab,kw 2551 #21 {or #1-#20} 47420 #22 MeSH descriptor: [Hypnosis] explode all trees 566 #23 Hypno*:ti,ab,kw 4983 #24 MeSH descriptor: [Psychotherapy] explode all trees 14254 #25 Psychotherap*:ti,ab,kw 6365 #26 ((Psychodynamic* or interpersonal*) near/4 (therap* or treat* or techni* or manag* or train*)):ti,ab,kw 785 #27 MeSH descriptor: [Relaxation Therapy] this term only 1129 #28 (Relax* near/4 (therap* or treat* or techni* or manag* or train*)):ti,ab,kw 2625 #29 MeSH descriptor: [Stress, Psychological] this term only 3191 #30 (Stress* near/4 (therap* or treat* or techni* or manag* or train*)):ti,ab,kw 4212 #31 {or #22-#30} 27162	40

	#32 #21 and #31 from 2013 to 2014 50	

Table 49: Clinical search terms (Pubmed)

Line number	Search term	Number retrieved
	Search Strategy: --- Search Add to builder Query Items found #10 Add Search (#7) AND ("2013/08/01"[Date - Entrez] : "3000"[Date - Entrez]) 17 #8 Add Search (#7 and publisher [sb]) 0 #7 Add Search (#1 and #6) 570 #6 Add Search (#2 or #5) 325275 #5 Add Search (#3 and #4) 262572 #4 Add Search (therap* or treat* or techni* or manag* or train*[Title/Abstract]) 7340101 #3 Add Search (Psychodynamic* or interpersonal* or Relax* or Stress*[Title/Abstract]) 696106 #2 Add Search (Hypno* or Psychotherap*[Title/Abstract]) 69343 #1 Add Search (Irritable* bowel* syndrome* or Irritable* colon* or IBS[Title/Abstract]) 7298	

D.4.2 Health economic search summary

Table 50: Health economics search summary

Databases	Date searched	No. retrieved

Databases	Date searched	No. retrieved
MEDLINE (Ovid)	06/03/14	333
MEDLINE In-Process (Ovid)	06/03/14	8
EMBASE (Ovid)	06/03/14	1018
NHS Economic Evaluation Database - NHS EED (Wiley)	06/03/14	8
Health Economic Evaluations Database – HEED (Wiley)	06/03/14	7
PubMed	06/03/14	2

1 **Table 51: Health economic search terms (Medline and Medline in Process)**

Search term
Search Strategy: --- 1 Irritable Bowel Syndrome/ (4064) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (7236) 3 (Irritable* adj4 colon*).tw. (510) 4 IBS.tw. (4441) 5 exp Gastrointestinal Motility/ (32495) 6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (406671) 7 Flatulence/ (1179) 8 (Flatu* or bloat*).tw. (4753) 9 Fecal Incontinence/ (7722) 10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (22296) 11 FI.tw. (4830) 12 Encopres*.tw. (547) 13 Diarrhea/ (38031) 14 (Diarrhoea* or diarrhea*).tw. (71789) 15 Constipation/ (10523) 16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (14650) 17 Colonic Diseases, Functional/ (3658) 18 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (980) 19 Dyspepsia/ (7184) 20 (Dyspeps* or Indigest*).tw. (9315) 21 or/1-20 (532575) 22 exp Hypnosis/ (10562) 23 Hypno*.tw. (17118) 24 exp psychotherapy/ (147413) 25 Psychotherap*.tw. (29403) 26 ((Psychodynamic* or interpersonal*) adj4 (therap* or treat* or techni* or manag* or train*)).tw. (2660) 27 Relaxation Therapy/ (5653) 28 (Relax* adj4 (therap* or treat* or techni* or manag* or train*)).tw. (5618) 29 Stress, Psychological/ (84306) 30 (Stress* adj4 (therap* or treat* or techni* or manag* or train*)).tw. (20845) 31 or/22-30 (261916) 32 21 and 31 (5163) 33 Economics/ (26508) 34 exp "Costs and Cost Analysis"/ (178069)

Search term
35 Economics, Dental/ (1853)
36 exp Economics, Hospital/ (19221)
37 exp Economics, Medical/ (13508)
38 Economics, Nursing/ (3887)
39 Economics, Pharmaceutical/ (2507)
40 Budgets/ (9617)
41 exp Models, Economic/ (9913)
42 Markov Chains/ (9437)
43 Monte Carlo Method/ (19364)
44 Decision Trees/ (8650)
45 econom$.tw. (150098)
46 cba.tw. (8624)
47 cea.tw. (15744)
48 cua.tw. (779)
49 markov$.tw. (10981)
50 (monte adj carlo).tw. (19965)
51 (decision adj3 (tree$ or analys$)).tw. (7950)
52 (cost or costs or costing$ or costly or costed).tw. (293286)
53 (price$ or pricing$).tw. (22220)
54 budget$.tw. (16720)
55 expenditure$.tw. (33620)
56 (value adj3 (money or monetary)).tw. (1287)
57 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3319)
58 or/33-57 (630780)
59 "Quality of Life"/ (113933)
60 quality of life.tw. (130420)
61 "Value of Life"/ (5381)
62 Quality-Adjusted Life Years/ (6754)
63 quality adjusted life.tw. (5583)
64 (qaly$ or qald$ or qale$ or qtime$).tw. (4634)
65 disability adjusted life.tw. (1089)
66 daly$.tw. (1088)
67 Health Status Indicators/ (19623)
68 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (14442)
69 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (954)
70 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2383)
71 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (20)
72 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (323)
73 (euroqol or euro qol or eq5d or eq 5d).tw. (3455)
74 (qol or hql or hqol or hrqol).tw. (22792)
75 (hye or hyes).tw. (53)
76 health$ year$ equivalent$.tw. (38)
77 utilit$.tw. (105910)
78 (hui or hui1 or hui2 or hui3).tw. (811)
79 disutili$.tw. (188)
80 rosser.tw. (71)
81 quality of wellbeing.tw. (5)

Search term
82 quality of well-being.tw. (316)
83 qwb.tw. (159)
84 willingness to pay.tw. (2025)
85 standard gamble$.tw. (634)
86 time trade off.tw. (689)
87 time tradeoff.tw. (198)
88 tto.tw. (543)
89 or/59-88 (303013)
90 58 or 89 (892441)
91 32 and 90 (740)
92 Animals/ not Humans/ (3807921)
93 91 not 92 (723)
94 limit 93 to ed=20070601-20140306 (367)
95 limit 94 to english language (333)

1 **Table 52: Health economic search terms (EMBASE)**

Search term
Search Strategy:
----
1 irritable colon/ (15719)
2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (11913)
3 (Irritable* adj4 colon*).tw. (604)
4 IBS.tw. (8332)
5 exp gastrointestinal motility/ (27185)
6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (556859)
7 flatulence/ (8214)
8 (Flatu* or bloat*).tw. (7775)
9 feces incontinence/ (13731)
10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (36027)
11 FI.tw. (12965)
12 Encopres*.tw. (734)
13 diarrhea/ (151868)
14 (Diarrhoea* or diarrhea*).tw. (98930)
15 constipation/ (55832)
16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (24607)
17 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (1516)
18 dyspepsia/ (25080)
19 (Dyspeps* or Indigest*).tw. (13796)
20 or/1-19 (822645)
21 exp hypnosis/ (13272)
22 Hypno*.tw. (22527)
23 exp psychotherapy/ (182514)
24 Psychotherap*.tw. (45295)
25 ((Psychodynamic* or interpersonal*) adj4 (therap* or treat* or techni* or manag* or train*)).tw. (4027)
26 relaxation training/ (8480)
27 (Relax* adj4 (therap* or treat* or techni* or manag* or train*)).tw. (7841)
28 mental stress/ (60431)

Search term
29 (Stress* adj4 (therap* or treat* or techni* or manag* or train*)).tw. (29691)
30 or/21-29 (299538)
31 20 and 30 (8873)
32 exp Health Economics/ (618525)
33 exp "Health Care Cost"/ (202322)
34 exp Pharmacoeconomics/ (173338)
35 Monte Carlo Method/ (21775)
36 Decision Tree/ (6029)
37 econom$.tw. (208490)
38 cba.tw. (9620)
39 cea.tw. (21866)
40 cua.tw. (908)
41 markov$.tw. (15866)
42 (monte adj carlo).tw. (27447)
43 (decision adj3 (tree$ or analys$)).tw. (11603)
44 (cost or costs or costing$ or costly or costed).tw. (423443)
45 (price$ or pricing$).tw. (32451)
46 budget$.tw. (23596)
47 expenditure$.tw. (45197)
48 (value adj3 (money or monetary)).tw. (1927)
49 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (6246)
50 or/32-49 (1113042)
51 "Quality of Life"/ (248870)
52 Quality Adjusted Life Year/ (12158)
53 Quality of Life Index/ (1569)
54 Short Form 36/ (11409)
55 Health Status/ (85076)
56 quality of life.tw. (214253)
57 quality adjusted life.tw. (8778)
58 (qaly$ or qald$ or qale$ or qtime$).tw. (8673)
59 disability adjusted life.tw. (1569)
60 daly$.tw. (1665)
61 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (23235)
62 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1457)
63 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (4177)
64 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (36)
65 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (323)
66 (euroqol or euro qol or eq5d or eq 5d).tw. (6777)
67 (qol or hql or hqol or hrqol).tw. (42243)
68 (hye or hyes).tw. (91)
69 health$ year$ equivalent$.tw. (43)
70 utilit$.tw. (153308)
71 (hui or hui1 or hui2 or hui3).tw. (1261)
72 disutili$.tw. (360)
73 rosser.tw. (90)
74 quality of wellbeing.tw. (19)
75 quality of well-being.tw. (378)

Search term
76 qwb.tw. (195)
77 willingness to pay.tw. (3331)
78 standard gamble$.tw. (791)
79 time trade off.tw. (1011)
80 time tradeoff.tw. (228)
81 tto.tw. (888)
82 or/51-81 (532598)
83 50 or 82 (1559824)
84 31 and 83 (2222)
85 Nonhuman/ not Human/ (3391370)
86 84 not 85 (2217)
87 limit 86 to em=200700-201409 (1331)
88 limit 87 to embase (1185)
89 limit 88 to (conference abstract or conference paper) (167)
90 88 not 89 (1018)

1 **Table 53: Health economic search terms (NHS EED)**

Search term
Search Strategy:

#1 MeSH descriptor: [Irritable Bowel Syndrome] this term only 406
#2 (Irritable* near/4 bowel* near/4 syndrome*):ti,ab,kw 1100
#3 (Irritable* near/4 colon*):ti,ab,kw 293
#4 IBS:ti,ab,kw 597
#5 MeSH descriptor: [Gastrointestinal Motility] explode all trees 2410
#6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) near/4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)):ti,ab,kw 34704
#7 MeSH descriptor: [Flatulence] this term only 213
#8 (Flatu* or bloat*):ti,ab,kw 1611
#9 MeSH descriptor: [Fecal Incontinence] this term only 391
#10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) near/4 (incontinen* or urge* or leak* or soil* or seep* or impact*)):ti,ab,kw 2232
#11 FI:ti,ab,kw 375
#12 Encopres*:ti,ab,kw 52
#13 MeSH descriptor: [Diarrhea] this term only 2061
#14 (Diarrhoea* or diarrhea*):ti,ab,kw 9939
#15 MeSH descriptor: [Constipation] this term only 844
#16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*):ti,ab,kw 3622
#17 MeSH descriptor: [Colonic Diseases, Functional] this term only 311
#18 (Function* near/4 (colon* or bowel*) near/4 (disease* or disorder*)):ti,ab,kw 401
#19 MeSH descriptor: [Dyspepsia] this term only 889
#20 (Dyspeps* or Indigest*):ti,ab,kw 2551
#21 {or #1-#20} 47430
#22 MeSH descriptor: [Hypnosis] explode all trees 566
#23 Hypno*:ti,ab,kw 4983
#24 MeSH descriptor: [Psychotherapy] explode all trees 14255
#25 Psychotherap*:ti,ab,kw 6366
#26 ((Psychodynamic* or interpersonal*) near/4 (therap* or treat* or techni* or manag* or train*)):ti,ab,kw 785
#27 MeSH descriptor: [Relaxation Therapy] this term only 1129

Search term		
#28	(Relax* near/4 (therap* or treat* or techni* or manag* or train*)):ti,ab,kw	2624
#29	MeSH descriptor: [Stress, Psychological] this term only	3192
#30	(Stress* near/4 (therap* or treat* or techni* or manag* or train*)):ti,ab,kw	4213
#31	{or #22-#30}	27164
#32	#21 and #31 from 2007 to 2014	8

Table 54: Health economic search terms (HEED)

Search term
Search Strategy: --- All data: 'IBS' or Irritable* bowel* syndrome* or Irritable* colon* or IBS AND All data: Psychotherap* or psychodynamic* or interpersonal* or relax* or stress* or hypno*

Table 55: Health economic search terms (PubMed)

Search term

Search Strategy:

Search	Add to builder	Query	Items found
#4	Add	Search (#3) AND ("2014/03/01"[Date - Entrez] : "3000"[Date - Entrez])	2
#3	Add	Search (#1 and #2)	962
#2	Add	Search (Psychotherap* or psychodynamic* or interpersonal* or relax* or stress* or hypno*))	661871
#1	Add	Search (Irritable* bowel* syndrome* or Irritable* colon* or IBS)	7793

D.5 Review question 5b (CCBT and Mindfulness)

D.5.1 Clinical search summary

Table 56: Clinical search summary (further update search)

Database	Date searched	Number retrieved
CDSR (Wiley)	08/05/2014	203
Database of Abstracts of Reviews of Effects – DARE (Wiley)	08/05/2014	31
HTA database (Wiley)	08/05/2014	6
CENTRAL (Wiley)	08/05/2014	897
MEDLINE (Ovid)	08/05/2014	968/566
MEDLINE In-Process (Ovid)	08/05/2014	110
EMBASE (Ovid)	08/05/2014	993/804

Database	Date searched	Number retrieved
PsycINFO (Ovid)	08/05/2014	233
PubMed	08/05/2014	24

Table 57: Clinical search terms (Medline and Medline in process)

Line number	Search term	Number retrieved
	Search Strategy: --- 1 Irritable Bowel Syndrome/ (4184) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (7381) 3 (Irritable* adj4 colon*).tw. (513) 4 IBS.tw. (4544) 5 exp Gastrointestinal Motility/ (32695) 6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (411338) 7 Flatulence/ (1189) 8 (Flatu* or bloat*).tw. (4839) 9 Fecal Incontinence/ (7796) 10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (22757) 11 FI.tw. (4917) 12 Encopres*.tw. (557) 13 Diarrhea/ (38370) 14 (Diarrhoea* or diarrhea*).tw. (72683) 15 Constipation/ (10610) 16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (14833) 17 Colonic Diseases, Functional/ (3660) 18 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (994) 19 Dyspepsia/ (7219) 20 (Dyspeps* or Indigest*).tw. (9392) 21 or/1-20 (538737) 22 exp Psychotherapy/ (149736) 23 (Psychotherap* or logotherap*).tw. (29802) 24 ((Psychological* or Psychodynamic* or Interpersonal*) adj4 (therap* or technic* or treat* or manag* or train* or counsel*)).tw. (12182) 25 Psychoanalysis/ (8002) 26 Psychoanaly*.tw. (11645) 27 (cogniti* adj4 (behavio* or therap* or techni* or treat* or manag* or train* or counsel* or restructur* or challenge* or psychotherap*)).tw. (35556) 28 ((behavio* or condition*) adj4 (therap* or technic* or treat* or manag* or train* or counsel* or psychotherap* or modificat*)).tw. (101856) 29 (CBT or CCBT).tw. (4425) 30 (Hypno* or mesmerism*).tw. (17337) 31 ((Accept* or commit*) adj4 (therap* or technic* or treat* or	776

	manag* or train* or counsel*)).tw. (21919) 32 ((Person* or client*) adj4 (therap* or technic* or treat* or manag* or train* or counsel*)).tw. (32147) 33 ((Gestalt* or existential* or realit* or solution-focus* or solution* focus*) adj4 (therap* or technic* or treat* or manag* or train* or counsel*)).tw. (2279) 34 Psychosynthe*.tw. (19) 35 Mindfulness/ (102) 36 Mindfulness*.tw. (1452) 37 (Low* adj4 intensit* adj4 (therap* or technic* or treat* or manag* or train* or counsel* or psychological*)).tw. (1482) 38 or/22-37 (333572) 39 21 and 38 (7922) 40 Randomized Controlled Trial.pt. (372317) 41 Controlled Clinical Trial.pt. (88255) 42 Clinical Trial.pt. (486871) 43 exp Clinical Trials as Topic/ (279613) 44 Placebos/ (32527) 45 Random Allocation/ (80352) 46 Double-Blind Method/ (125473) 47 Single-Blind Method/ (18989) 48 Cross-Over Studies/ (34018) 49 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (719381) 50 (random$ adj3 allocat$).tw. (20202) 51 placebo$.tw. (150339) 52 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (122914) 53 (crossover$ or (cross adj over$)).tw. (55962) 54 or/40-53 (1355260) 55 39 and 54 (1790) 56 Animals/ not Humans/ (3843498) 57 55 not 56 (1738) 58 limit 57 to english language (1572)	

1 **Table 58: Clinical search terms (Embase)**

Line number	Search term	Number retrieved
	Search Strategy: --- 1 irritable colon/ (15401) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (11577) 3 (Irritable* adj4 colon*).tw. (566) 4 IBS.tw. (8215) 5 exp gastrointestinal motility/ (25745) 6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (536316) 7 flatulence/ (8302) 8 (Flatu* or bloat*).tw. (7670) 9 feces incontinence/ (13507) 10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or	804

soil* or seep* or impact*)).tw. (35669)
11 FI.tw. (12911)
12 Encopres*.tw. (706)
13 diarrhea/ (151590)
14 (Diarrhoea* or diarrhea*).tw. (95465)
15 constipation/ (56119)
16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (24168)
17 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (1462)
18 dyspepsia/ (24754)
19 (Dyspeps* or Indigest*).tw. (13307)
20 or/1-19 (797736)
21 exp *psychotherapy/ (87751)
22 (Psychotherap* or logotherap*).tw. (43687)
23 ((Psychological* or Psychodynamic* or Interpersonal*) adj2 (therap* or technic* or treat* or manag* or train* or counsel*)).tw. (11021)
24 exp psychoanalysis/ (33776)
25 Psychoanaly*.tw. (16862)
26 (cogniti* adj2 (behavio* or therap* or techni* or treat* or manag* or train* or counsel* or restructur* or challenge* or psychotherap*)).tw. (42283)
27 ((behavio* or condition*) adj2 (therap* or technic* or treat* or manag* or train* or counsel* or psychotherap* or modificat*)).tw. (68692)
28 (CBT or CCBT).tw. (7339)
29 (Hypno* or mesmerism*).tw. (21686)
30 ((Accept* or commit*) adj2 (therap* or technic* or treat* or manag* or train* or counsel*)).tw. (14863)
31 ((Person* or client*) adj2 (therap* or technic* or treat* or manag* or train* or counsel*)).tw. (23583)
32 ((Gestalt* or existential* or realit* or solution-focus* or solution* focus*) adj4 (therap* or technic* or treat* or manag* or train* or counsel*)).tw. (3443)
33 Psychosynthe*.tw. (23)
34 mindfulness/ (368)
35 Mindfulness*.tw. (2537)
36 (Low* adj4 intensit* adj4 (therap* or technic* or treat* or manag* or train* or counsel* or psychological*)).tw. (1935)
37 or/21-36 (276860)
38 20 and 37 (8047)
39 exp Clinical Trials/ (101133)
40 Randomization/ (61764)
41 Placebo/ (237956)
42 Double Blind Procedure/ (112848)
43 Single Blind Procedure/ (18159)
44 Crossover Procedure/ (38658)
45 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (968251)
46 (random$ adj3 allocat$).tw. (25600)
47 placebo$.tw. (194991)
48 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (155023)
49 (crossover$ or (cross adj over$)).tw. (67695)

	50 or/39-49 (1301331) 51 nonhuman/ not human/ (3419593) 52 50 not 51 (1245226) 53 38 and 52 (2295) 54 Nonhuman/ not Human/ (3419593) 55 53 not 54 (2295) 56 limit 55 to english language (2188) 57 limit 56 to embase (2095) 58 limit 57 to (conference abstract or conference paper) (288) 59 57 not 58 (1807)	

1 **Table 59: Clinical search terms (PsyINFO)**

Line number	Search term	Number retrieved
	Search Strategy: --- 1 Irritable Bowel Syndrome/ (797) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (1102) 3 (Irritable* adj4 colon*).tw. (32) 4 IBS.tw. (764) 5 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (10379) 6 (Flatu* or bloat*).tw. (203) 7 Fecal Incontinence/ (548) 8 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (4526) 9 FI.tw. (2158) 10 Encopres*.tw. (585) 11 Diarrhea/ (242) 12 (Diarrhoea* or diarrhea*).tw. (1407) 13 Constipation/ (267) 14 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (1313) 15 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (90) 16 Dyspepsia/ (112) 17 (Dyspeps* or Indigest*).tw. (469) 18 or/1-17 (20149) 19 exp Psychotherapy/ (174492) 20 (Psychotherap* or logotherap*).tw. (100015) 21 ((Psychological* or Psychodynamic* or Interpersonal*) adj4 (therap* or technic* or treat* or manag* or train* or counsel*)).tw. (27869) 22 Psychoanalysis/ (43747) 23 Psychoanaly*.tw. (81389) 24 (cogniti* adj4 (behavio* or therap* or techni* or treat* or manag* or train* or counsel* or restructur* or challenge* or psychotherap*)).tw. (69496) 25 ((behavio* or condition*) adj4 (therap* or technic* or treat* or manag* or train* or counsel* or psychotherap* or modificat*)).tw. (96053)	233

	26 (CBT or CCBT).tw. (7676) 27 (Hypno* or mesmerism*).tw. (21146) 28 ((Accept* or commit*) adj4 (therap* or technic* or treat* or manag* or train* or counsel*)).tw. (9758) 29 ((Person* or client*) adj4 (therap* or technic* or treat* or manag* or train* or counsel*)).tw. (55345) 30 ((Gestalt* or existential* or realit* or solution-focus* or solution* focus*) adj4 (therap* or technic* or treat* or manag* or train* or counsel*)).tw. (6445) 31 Psychosynthe*.tw. (162) 32 Mindfulness/ (3169) 33 Mindfulness*.tw. (4622) 34 (Low* adj4 intensit* adj4 (therap* or technic* or treat* or manag* or train* or counsel* or psychological*)).tw. (296) 35 or/19-34 (410959) 36 18 and 35 (2494) 37 limit 36 to english language (2194) 38 exp Clinical Trials/ (7531) 39 exp Placebo/ (3758) 40 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (104092) 41 (random$ adj3 allocat$).tw. (2336) 42 placebo$.tw. (30931) 43 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (19570) 44 (crossover$ or (cross adj over$)).tw. (7014) 45 or/38-44 (128390) 46 37 and 45 (240)	

1 **Table 60: Clinical search terms (DARE, HTA, Central, CDRS)**

Line number	Search term	Number retrieved
	Search Strategy: --- #1 MeSH descriptor: [Irritable Bowel Syndrome] this term only 470 #2 (Irritable* near/4 bowel* near/4 syndrome*):ti,ab,kw 1157 #3 (Irritable* near/4 colon*):ti,ab,kw 244 #4 IBS:ti,ab,kw 642 #5 MeSH descriptor: [Gastrointestinal Motility] explode all trees 2494 #6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) near/4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)):ti,ab,kw 34733 #7 MeSH descriptor: [Flatulence] this term only 227 #8 (Flatu* or bloat*):ti,ab,kw 1653 #9 MeSH descriptor: [Fecal Incontinence] this term only 421 #10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) near/4 (incontinen* or urge* or leak* or soil* or seep* or impact*)):ti,ab,kw 2441 #11 FI:ti,ab,kw 399 #12 Encopres*:ti,ab,kw 52 #13 MeSH descriptor: [Diarrhea] this term only 2141	1117

	#14 (Diarrhoea* or diarrhea*):ti,ab,kw 9914 #15 MeSH descriptor: [Constipation] this term only 937 #16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*):ti,ab,kw 3580 #17 MeSH descriptor: [Colonic Diseases, Functional] this term only 316 #18 (Function* near/4 (colon* or bowel*) near/4 (disease* or disorder*)):ti,ab,kw 408 #19 MeSH descriptor: [Dyspepsia] this term only 908 #20 (Dyspeps* or Indigest*):ti,ab,kw 2505 #21 {or #1-#20} 47781 #22 MeSH descriptor: [Psychotherapy] explode all trees 15559 #23 (Psychotherap* or logotherap*):ti,ab,kw 6714 #24 ((Psychological* or Psychodynamic* or Interpersonal*) near/4 (therap* or technic* or treat* or manag* or train* or counsel*)):ti,ab,kw 4688 #25 MeSH descriptor: [Psychoanalysis] this term only 15 #26 Psychoanaly*:ti,ab,kw 270 #27 (cogniti* near/4 (behavio* or therap* or techni* or treat* or manag* or train* or counsel* or restructur* or challenge* or psychotherap*)):ti,ab,kw 12356 #28 ((behavio* or condition*) near/4 (therap* or technic* or treat* or manag* or train* or counsel* or psychotherap* or modificat*)):ti,ab,kw 19543 #29 (CBT or CCBT):ti,ab,kw 2006 #30 (Hypno* or mesmerism*):ti,ab,kw 5060 #31 ((Accept* or commit*) near/4 (therap* or technic* or treat* or manag* or train* or counsel*)):ti,ab,kw 2540 #32 ((Person* or client*) near/4 (therap* or technic* or treat* or manag* or train* or counsel*)):ti,ab,kw 4381 #33 ((Gestalt* or existential* or realit* or solution-focus* or solution* focus*) near/4 (therap* or technic* or treat* or manag* or train* or counsel*)):ti,ab,kw 461 #34 Psychosynthe*:ti,ab,kw 2 #35 MeSH descriptor: [Mindfulness] this term only 6 #36 Mindfulness*:ti,ab,kw 627 #37 (Low* near/4 intensit* near/4 (therap* or technic* or treat* or manag* or train* or counsel* or psychological*)):ti,ab,kw 497 #38 {or #22-#37} 44890 #39 #21 and #38 1546	

1 **Table 61: Clinical search terms (Pubmed)**

Line number	Search term	Number retrieved
	Search Strategy: --- Search Query Items found #28 Search (#25 or #27) 25 #27 Search (#23 and #26) 25 #26	24

Search publisher [sb] 451444

#25
Search (#23 and #24) 1

#24
Search ("2014/05/05"[Date - Entrez] : "3000"[Date - Entrez]) 12565

#23
Search (#1 and #22) 1289

#22
Search (#2 or #5 or #6 or #9 or #12 or #13 or #14 or #16 or #17 or #21) 1077751

#21
Search (#18 and #20) 27608

#20
Search (therap* or technic* or treat* or manag* or train* or counsel* or psychological*[Title/Abstract]) 6391988

#18
Search Low* intensit*[Title/Abstract] 77862

#17
Search (Psychosynthe* or Mindfulness*.[Title/Abstract]) 1899

#16
Search (#15 and #4) 32864

#15
Search (Accept* or commit* or Person* or client* or Gestalt* or existential* or realit* or solution-focus* or solution* focus*[Title/Abstract]) 69289

#14
Search (Hypno* or mesmerism*[Title/Abstract]) 38608

#13
Search (CBT or CCBT[Title/Abstract]) 5291

#12
Search (#10 and #11) 783836

#11
Search (therap* or technic* or treat* or manag* or train* or counsel* or psychotherap* or modificat*[Title/Abstract]) 6543443

#10
Search (behavio* or condition*[Title/Abstract]) 2365842

#9
Search (#7 and #8) 129981

	#8 Search (behavio* or therap* or techni* or treat* or manag* or train* or counsel* or restructur* or challenge* or psychotherap*[Title/Abstract]) 8454734 #7 Search cogniti*[Title/Abstract] 215393 #6 Search Psychoanaly*[Title/Abstract] 12053 #5 Search (#3 and #4) 127222 #4 Search (therap* or technic* or treat* or manag* or train* or counsel*[Title/Abstract]) 6299164 #3 Search (Psychological* or Psychodynamic* or Interpersonal*[Title/Abstract]) 376771 #2 Search (Psychotherap* or logotherap*[Title/Abstract]) 80005 #1 Search (Irritable* bowel* syndrome* or Irritable* colon* or IBS[Title/Abstract]) 7448	

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D.5.2 Health economics search summary

3 **Table 62: Health economics search summary**

Databases	Date searched	No. retrieved
MEDLINE (Ovid)	14/08/14	699
MEDLINE In-Process (Ovid)	14/08/14	86
EMBASE (Ovid)	14/08/14	962
NHS Economic Evaluation Database - NHS EED (Wiley)	14/08/14	10
Health Economic Evaluations Database – HEED (Wiley)	14/08/14	7
PubMed	14/08/14	0

4 **Table 63: Health economic search terms (Medline and Medline in Process)**

Search term
Search Strategy: --- 1 Irritable Bowel Syndrome/ (4451) 2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (7695) 3 (Irritable* adj4 colon*).tw. (521) 4 IBS.tw. (4794) 5 exp Gastrointestinal Motility/ (33357)

Search term
6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (421681)
7 Flatulence/ (1211)
8 (Flatu* or bloat*).tw. (5001)
9 Fecal Incontinence/ (7976)
10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (23619)
11 FI.tw. (5068)
12 Encopres*.tw. (566)
13 Diarrhea/ (39013)
14 (Diarrhoea* or diarrhea*).tw. (74320)
15 Constipation/ (10912)
16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (15280)
17 Colonic Diseases, Functional/ (3681)
18 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (1032)
19 Dyspepsia/ (7354)
20 (Dyspeps* or Indigest*).tw. (9606)
21 or/1-20 (552007)
22 exp Psychotherapy/ (152486)
23 (Psychotherap* or logotherap*).tw. (30290)
24 ((Psychological* or Psychodynamic* or Interpersonal*) adj4 (therap* or technic* or treat* or manag* or train* or counsel*)).tw. (12557)
25 Psychoanalysis/ (8050)
26 Psychoanaly*.tw. (11712)
27 (cogniti* adj4 (behavio* or therap* or techni* or treat* or manag* or train* or counsel* or restructur* or challenge* or psychotherap*)).tw. (37025)
28 ((behavio* or condition*) adj4 (therap* or technic* or treat* or manag* or train* or counsel* or psychotherap* or modificat*)).tw. (104811)
29 (CBT or CCBT).tw. (4674)
30 (Hypno* or mesmerism*).tw. (17584)
31 ((Accept* or commit*) adj4 (therap* or technic* or treat* or manag* or train* or counsel*)).tw. (22464)
32 ((Person* or client*) adj4 (therap* or technic* or treat* or manag* or train* or counsel*)).tw. (33172)
33 ((Gestalt* or existential* or realit* or solution-focus* or solution* focus*) adj4 (therap* or technic* or treat* or manag* or train* or counsel*)).tw. (2346)
34 Psychosynthe*.tw. (19)
35 Mindfulness/ (178)
36 Mindfulness*.tw. (1576)
37 (Low* adj4 intensit* adj4 (therap* or technic* or treat* or manag* or train* or counsel* or psychological*)).tw. (1542)
38 or/22-37 (341471)
39 21 and 38 (8154)
40 Economics/ (27091)
41 exp "Costs and Cost Analysis"/ (183882)
42 Economics, Dental/ (1862)
43 exp Economics, Hospital/ (19754)
44 exp Economics, Medical/ (13642)
45 Economics, Nursing/ (3984)
46 Economics, Pharmaceutical/ (2566)
47 Budgets/ (9803)
48 exp Models, Economic/ (10369)

Search term
49 Markov Chains/ (10039)
50 Monte Carlo Method/ (20281)
51 Decision Trees/ (8892)
52 econom$.tw. (157149)
53 cba.tw. (8748)
54 cea.tw. (16214)
55 cua.tw. (801)
56 markov$.tw. (11694)
57 (monte adj carlo).tw. (20914)
58 (decision adj3 (tree$ or analys$)).tw. (8348)
59 (cost or costs or costing$ or costly or costed).tw. (307250)
60 (price$ or pricing$).tw. (23172)
61 budget$.tw. (17278)
62 expenditure$.tw. (35534)
63 (value adj3 (money or monetary)).tw. (1375)
64 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3426)
65 or/40-64 (657292)
66 "Quality of Life"/ (120911)
67 quality of life.tw. (139050)
68 "Value of Life"/ (5926)
69 Quality-Adjusted Life Years/ (7228)
70 quality adjusted life.tw. (6081)
71 (qaly$ or qald$ or qale$ or qtime$).tw. (5011)
72 disability adjusted life.tw. (1183)
73 daly$.tw. (1171)
74 Health Status Indicators/ (20320)
75 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (15473)
76 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (992)
77 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2652)
78 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (22)
79 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (333)
80 (euroqol or euro qol or eq5d or eq 5d).tw. (3860)
81 (qol or hql or hqol or hrqol).tw. (24697)
82 (hye or hyes).tw. (54)
83 health$ year$ equivalent$.tw. (39)
84 utilit$.tw. (112160)
85 (hui or hui1 or hui2 or hui3).tw. (867)
86 disutili$.tw. (213)
87 rosser.tw. (71)
88 quality of wellbeing.tw. (7)
89 quality of well-being.tw. (335)
90 qwb.tw. (171)
91 willingness to pay.tw. (2189)
92 standard gamble$.tw. (656)
93 time trade off.tw. (738)
94 time tradeoff.tw. (202)
95 tto.tw. (588)

Search term
96 or/66-95 (321266)
97 65 or 96 (934691)
98 39 and 97 (1223)
99 Animals/ not Humans/ (3902135)
100 98 not 99 (1204)
101 limit 100 to english language (1057)
102 limit 101 to yr="2004 -Current" (699)

Table 64: Health economic search terms (EMBASE)

Search term
Search Strategy:
1 irritable colon/ (15950)
2 (Irritable* adj4 bowel* adj4 syndrome*).tw. (12041)
3 (Irritable* adj4 colon*).tw. (569)
4 IBS.tw. (8659)
5 exp gastrointestinal motility/ (26083)
6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) adj4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)).tw. (549639)
7 flatulence/ (8530)
8 (Flatu* or bloat*).tw. (8019)
9 feces incontinence/ (13851)
10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) adj4 (incontinen* or urge* or leak* or soil* or seep* or impact*)).tw. (37093)
11 FI.tw. (13292)
12 Encopres*.tw. (710)
13 diarrhea/ (155172)
14 (Diarrhoea* or diarrhea*).tw. (97966)
15 constipation/ (57665)
16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*).tw. (25010)
17 (Function* adj4 (colon* or bowel*) adj4 (disease* or disorder*)).tw. (1514)
18 dyspepsia/ (25253)
19 (Dyspeps* or Indigest*).tw. (13648)
20 or/1-19 (817122)
21 exp *psychotherapy/ (89035)
22 (Psychotherap* or logotherap*).tw. (44258)
23 ((Psychological* or Psychodynamic* or Interpersonal*) adj2 (therap* or technic* or treat* or manag* or train* or counsel*)).tw. (11317)
24 exp psychoanalysis/ (33927)
25 Psychoanaly*.tw. (16974)
26 (cogniti* adj2 (behavio* or therap* or techni* or treat* or manag* or train* or counsel* or restructur* or challenge* or psychotherap*)).tw. (43965)
27 ((behavio* or condition*) adj2 (therap* or technic* or treat* or manag* or train* or counsel* or psychotherap* or modificat*)).tw. (70729)
28 (CBT or CCBT).tw. (7763)
29 (Hypno* or mesmerism*).tw. (22096)
30 ((Accept* or commit*) adj2 (therap* or technic* or treat* or manag* or train* or counsel*)).tw. (15297)
31 ((Person* or client*) adj2 (therap* or technic* or treat* or manag* or train* or counsel*)).tw. (24509)
32 ((Gestalt* or existential* or realit* or solution-focus* or solution* focus*) adj4 (therap* or

Search term
technic* or treat* or manag* or train* or counsel*)).tw. (3554)
33 Psychosynthe*.tw. (24)
34 mindfulness/ (607)
35 Mindfulness*.tw. (2769)
36 (Low* adj4 intensit* adj4 (therap* or technic* or treat* or manag* or train* or counsel* or psychological*)).tw. (2010)
37 or/21-36 (283183)
38 20 and 37 (8310)
39 exp Health Economics/ (617662)
40 exp "Health Care Cost"/ (205448)
41 exp Pharmacoeconomics/ (167451)
42 Monte Carlo Method/ (21757)
43 Decision Tree/ (5923)
44 econom$.tw. (208777)
45 cba.tw. (9093)
46 cea.tw. (21848)
47 cua.tw. (900)
48 markov$.tw. (15978)
49 (monte adj carlo).tw. (27295)
50 (decision adj3 (tree$ or analys$)).tw. (11729)
51 (cost or costs or costing$ or costly or costed).tw. (426544)
52 (price$ or pricing$).tw. (32733)
53 budget$.tw. (23805)
54 expenditure$.tw. (45109)
55 (value adj3 (money or monetary)).tw. (1948)
56 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (6296)
57 or/39-56 (1110879)
58 "Quality of Life"/ (256553)
59 Quality Adjusted Life Year/ (12378)
60 Quality of Life Index/ (1717)
61 Short Form 36/ (12415)
62 Health Status/ (85102)
63 quality of life.tw. (219080)
64 quality adjusted life.tw. (8890)
65 (qaly$ or qald$ or qale$ or qtime$).tw. (8981)
66 disability adjusted life.tw. (1569)
67 daly$.tw. (1664)
68 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (23564)
69 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1427)
70 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (4371)
71 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (36)
72 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (331)
73 (euroqol or euro qol or eq5d or eq 5d).tw. (7209)
74 (qol or hql or hqol or hrqol).tw. (44273)
75 (hye or hyes).tw. (94)
76 health$ year$ equivalent$.tw. (38)
77 utilit$.tw. (155234)

Search term
78 (hui or hui1 or hui2 or hui3).tw. (1312)
79 disutili$.tw. (381)
80 rosser.tw. (89)
81 quality of wellbeing.tw. (19)
82 quality of well-being.tw. (375)
83 qwb.tw. (196)
84 willingness to pay.tw. (3467)
85 standard gamble$.tw. (794)
86 time trade off.tw. (1001)
87 time tradeoff.tw. (221)
88 tto.tw. (899)
89 or/58-88 (540448)
90 57 or 89 (1564526)
91 38 and 90 (1883)
92 Nonhuman/ not Human/ (3464318)
93 91 not 92 (1874)
94 limit 93 to english language (1725)
95 limit 94 to embase (1594)
96 limit 95 to (conference abstract or conference paper) (353)
97 95 not 96 (1241)
98 limit 97 to yr="2004 -Current" (962)

1 **Table 65: Health economic search terms (NHS EED)**

Search term
Search Strategy:

#1 MeSH descriptor: [Irritable Bowel Syndrome] this term only 477
#2 (Irritable* near/4 bowel* near/4 syndrome*):ti,ab,kw 1171
#3 (Irritable* near/4 colon*):ti,ab,kw 260
#4 IBS:ti,ab,kw 655
#5 MeSH descriptor: [Gastrointestinal Motility] explode all trees 2498
#6 ((Intestin* or gastrointestin* or gastro* or gastric* or colon* or bowel*) near/4 (motilit* or sensitiv* or function* or irritable* or irritat* or gas* or spastic* or unstable* or instabilit* or spasm* or empt*)):ti,ab,kw 35230
#7 MeSH descriptor: [Flatulence] this term only 227
#8 (Flatu* or bloat*):ti,ab,kw 1713
#9 MeSH descriptor: [Fecal Incontinence] this term only 421
#10 ((Faec* or fec* or anal* or anus* or alvi* or stool* or bowel* or double or defecat* or defaecat*) near/4 (incontinen* or urge* or leak* or soil* or seep* or impact*)):ti,ab,kw 2473
#11 FI:ti,ab,kw 411
#12 Encopres*:ti,ab,kw 53
#13 MeSH descriptor: [Diarrhea] this term only 2151
#14 (Diarrhoea* or diarrhea*):ti,ab,kw 10230
#15 MeSH descriptor: [Constipation] this term only 941
#16 (Constipat* or costiveness* or dyschezia* or colonic* inertia*):ti,ab,kw 3729
#17 MeSH descriptor: [Colonic Diseases, Functional] this term only 316
#18 (Function* near/4 (colon* or bowel*) near/4 (disease* or disorder*)):ti,ab,kw 407
#19 MeSH descriptor: [Dyspepsia] this term only 908
#20 (Dyspeps* or Indigest*):ti,ab,kw 2557
#21 {or #1-#20} 48604
#22 MeSH descriptor: [Psychotherapy] explode all trees 15658

Search term
#23 (Psychotherap* or logotherap*):ti,ab,kw 6792
#24 ((Psychological* or Psychodynamic* or Interpersonal*) near/4 (therap* or technic* or treat* or manag* or train* or counsel*)):ti,ab,kw 4764
#25 MeSH descriptor: [Psychoanalysis] this term only 15
#26 Psychoanaly*:ti,ab,kw 273
#27 (cogniti* near/4 (behavio* or therap* or techni* or treat* or manag* or train* or counsel* or restructur* or challenge* or psychotherap*)):ti,ab,kw 12592
#28 ((behavio* or condition*) near/4 (therap* or technic* or treat* or manag* or train* or counsel* or psychotherap* or modificat*)):ti,ab,kw 19814
#29 (CBT or CCBT):ti,ab,kw 2053
#30 (Hypno* or mesmerism*):ti,ab,kw 5094
#31 ((Accept* or commit*) near/4 (therap* or technic* or treat* or manag* or train* or counsel*)):ti,ab,kw 2581
#32 ((Person* or client*) near/4 (therap* or technic* or treat* or manag* or train* or counsel*)):ti,ab,kw 4454
#33 ((Gestalt* or existential* or realit* or solution-focus* or solution* focus*) near/4 (therap* or technic* or treat* or manag* or train* or counsel*)):ti,ab,kw 478
#34 Psychosynthe*:ti,ab,kw 2
#35 MeSH descriptor: [Mindfulness] this term only 10
#36 Mindfulness*:ti,ab,kw 652
#37 (Low* near/4 intensit* near/4 (therap* or technic* or treat* or manag* or train* or counsel* or psychological*)):ti,ab,kw 507
#38 {or #22-#37} 45523
#39 #21 and #38 10

1 **Table 66: Health economic search terms (HEED)**

Search term
Search Strategy:

All data: 'IBS' or Irritable* bowel* syndrome* or Irritable* colon* or IBS AND
All data: Psychotherap* or psychodynamic* or mindfulnes* or cognitive behaviour therapy or cognitive behavior therapy or CBT or CCBT

2 **Table 67: Health economic search terms (PubMed)**

Search term		
Search Strategy:		
#25	Search (#23 and #24)	0
#24	Search ("2014/08/11"[Date - Entrez] : "3000"[Date - Entrez])	12565
#23	Search (#1 and #22)	1289
#22	Search (#2 or #5 or #6 or #9 or #12 or #13 or #14 or #16 or #17 or #21)	1077751
#21	Search (#18 and #20)	27608
#20	Search (therap* or technic* or treat* or manag* or train* or counsel* or psychological*[Title/Abstract])	6391988
#18	Search Low* intensit*[Title/Abstract]	77862
#17	Search (Psychosynthe* or Mindfulness*.[Title/Abstract])	1899

Search term		
#16	Search (#15 and #4)	32864
#15	Search (Accept* or commit* or Person* or client* or Gestalt* or existential* or realit* or solution-focus* or solution* focus*[Title/Abstract])	69289
#14	Search (Hypno* or mesmerism*[Title/Abstract])	38608
#13	Search (CBT or CCBT[Title/Abstract])	5291
#12	Search (#10 and #11)	783836
#11	Search (therap* or technic* or treat* or manag* or train* or counsel* or psychotherap* or modificat*[Title/Abstract])	6543443
#10	Search (behavio* or condition*[Title/Abstract])	2365842
#9	Search (#7 and #8)	129981
#8	Search (behavio* or therap* or techni* or treat* or manag* or train* or counsel* or restructur* or challenge* or psychotherap*[Title/Abstract])	8454734
#7	Search cogniti*[Title/Abstract]	215393
#6	Search Psychoanaly*[Title/Abstract]	12053
#5	Search (#3 and #4)	127222
#4	Search (therap* or technic* or treat* or manag* or train* or counsel*[Title/Abstract])	6299164
#3	Search (Psychological* or Psychodynamic* or Interpersonal*[Title/Abstract])	376771
#2	Search (Psychotherap* or logotherap*[Title/Abstract])	80005
#1	Search (Irritable* bowel* syndrome* or Irritable* colon* or IBS[Title/Abstract])	7448

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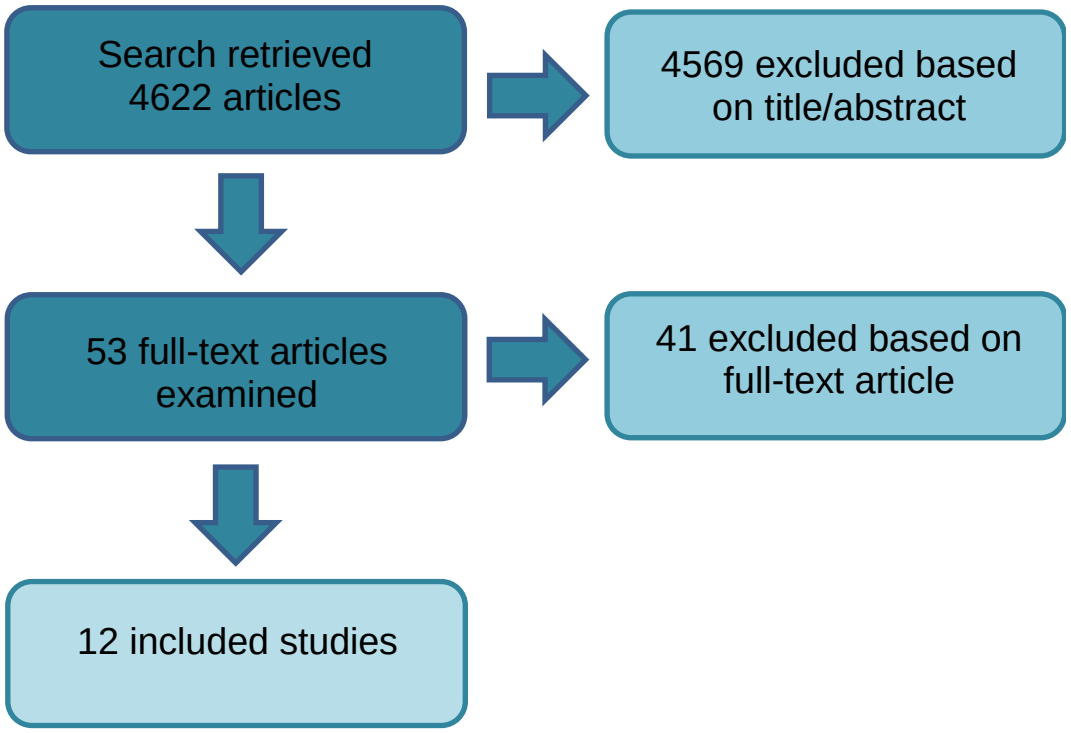
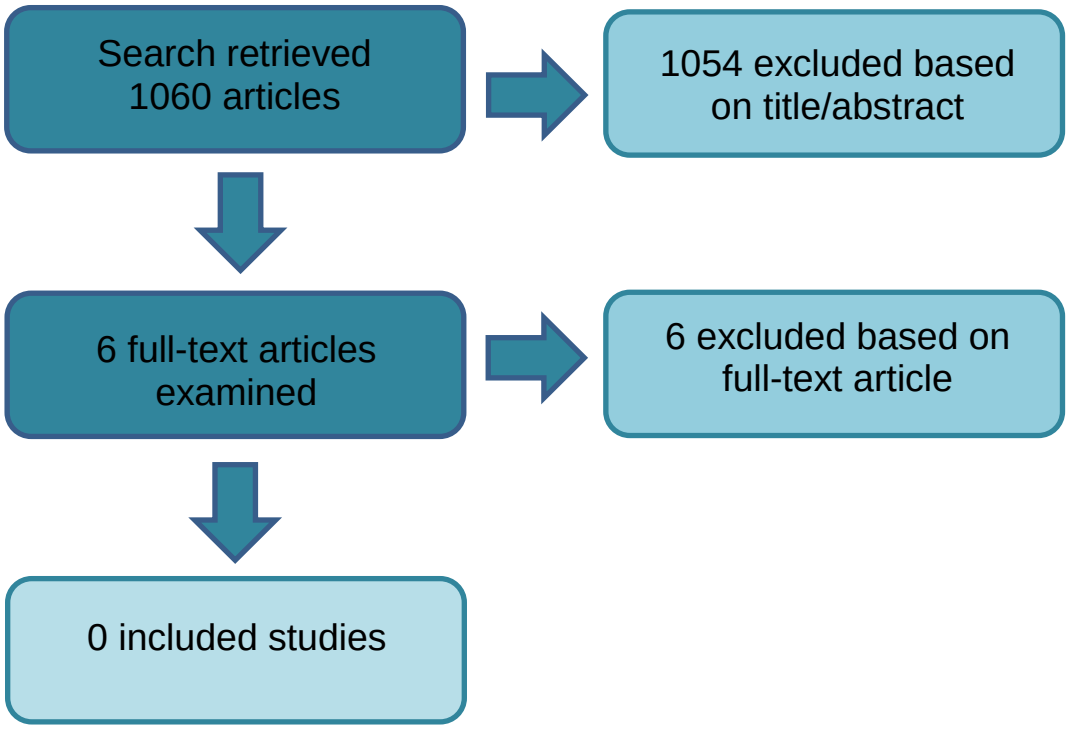
Appendix E: Review flowcharts

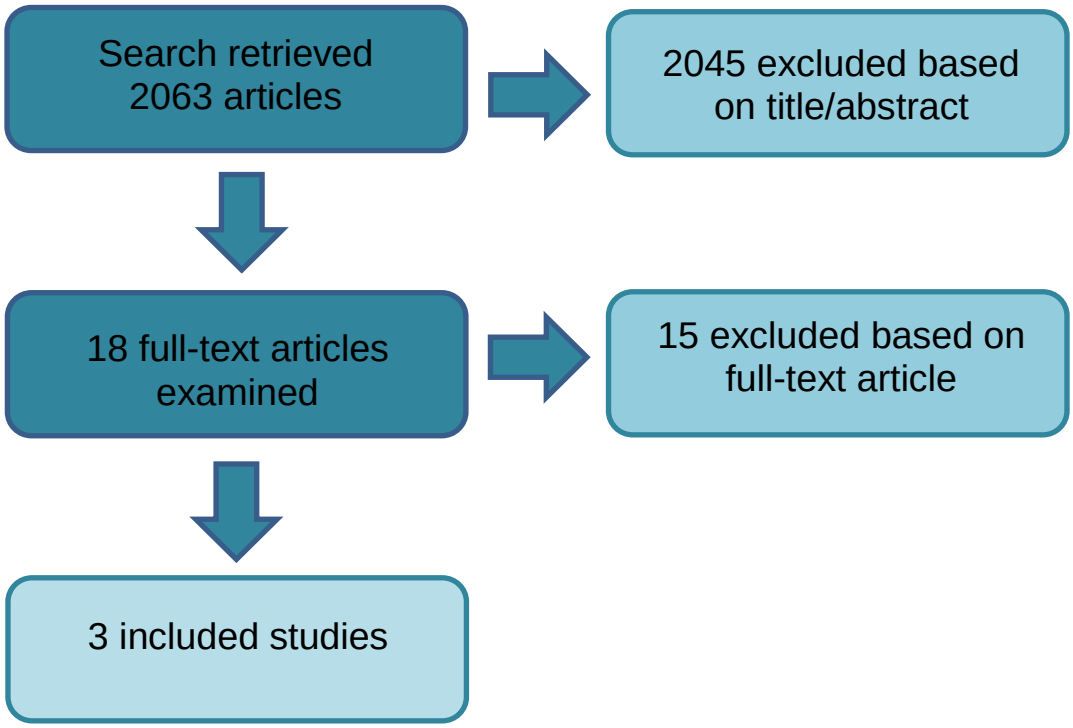
E.1 Review question 1 – Clinical (antidepressants)



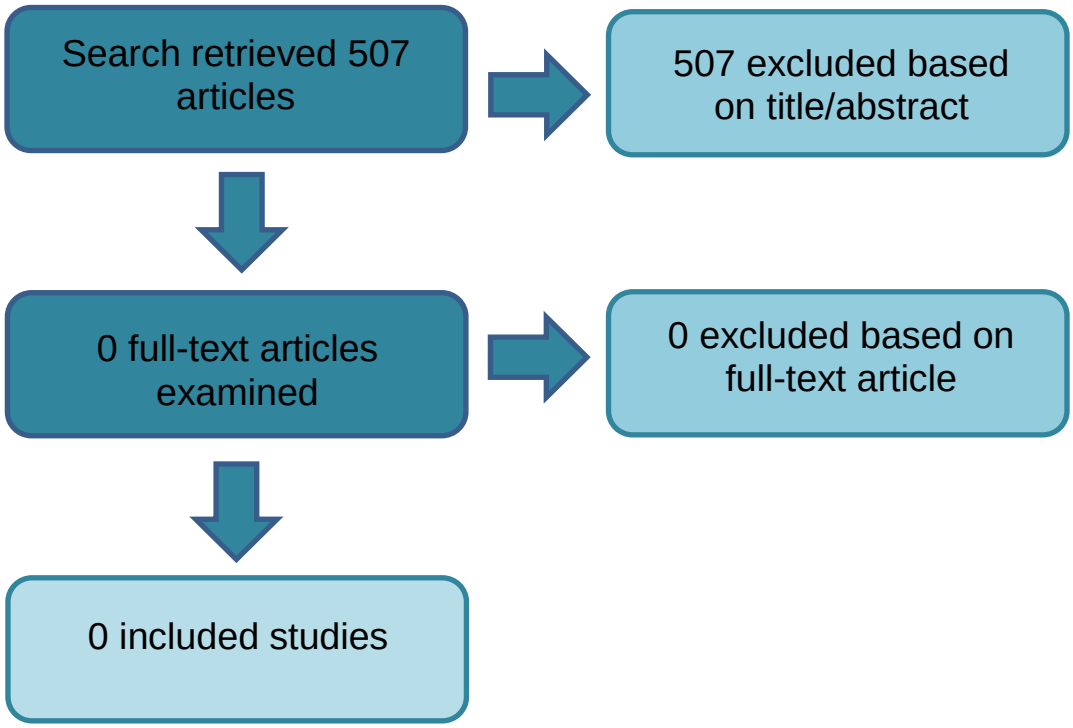
E.21 Review question 1 – Health Economics (antidepressants)



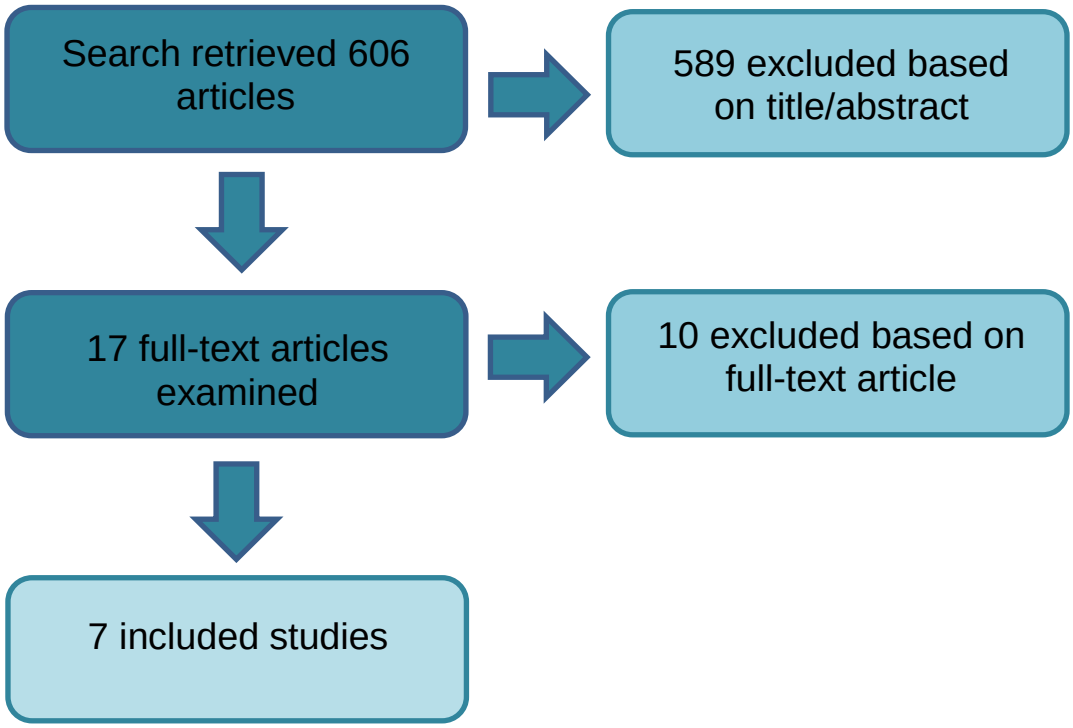
E.31 Review question 2 – Clinical (low FODMAP diet)



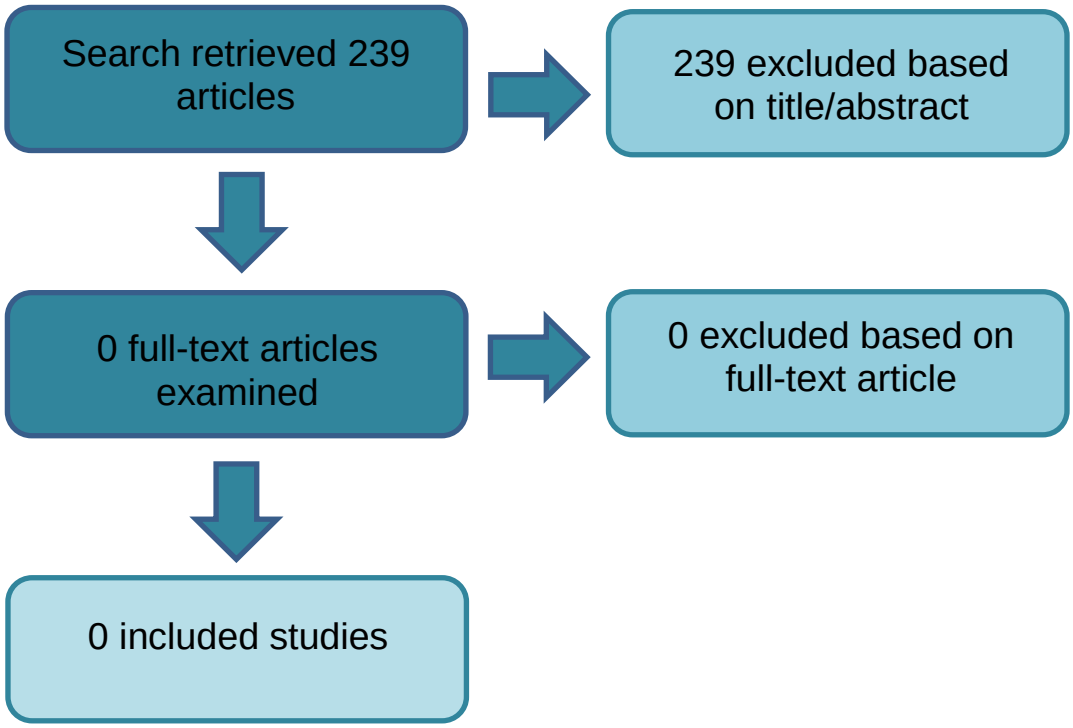
E.41 Review question 2 – Health Ecomonic (low FODMAP diet)



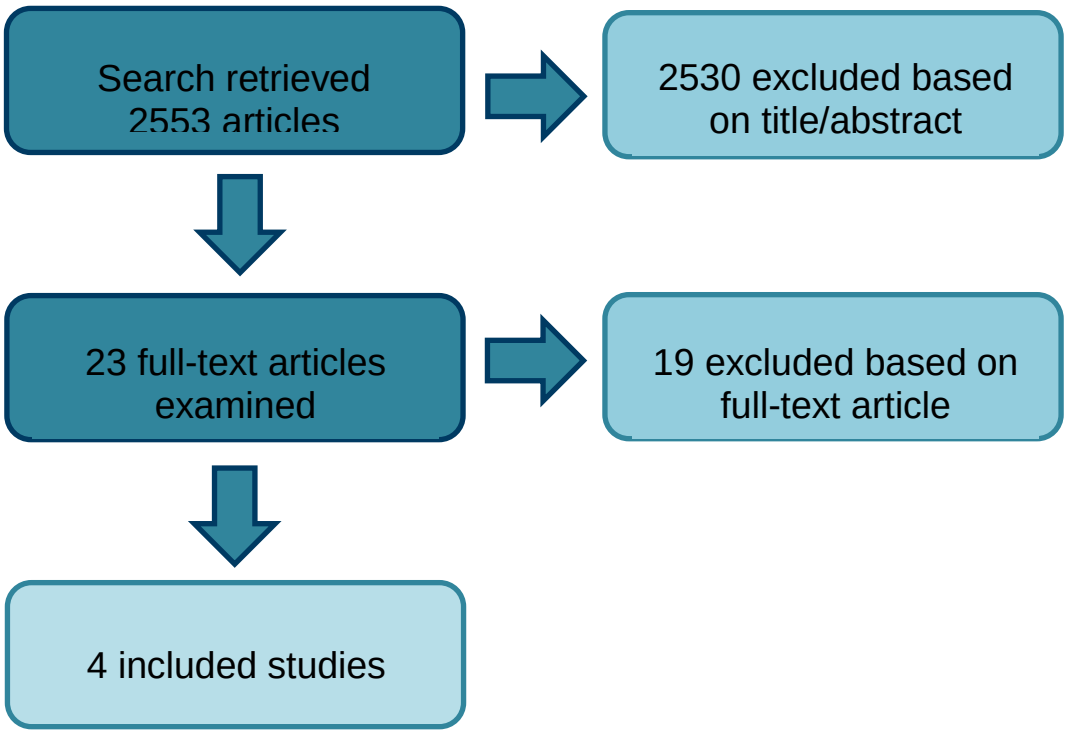
E.5 Review question 3 & 4 – Clinical (lubiprostone and linclotide)



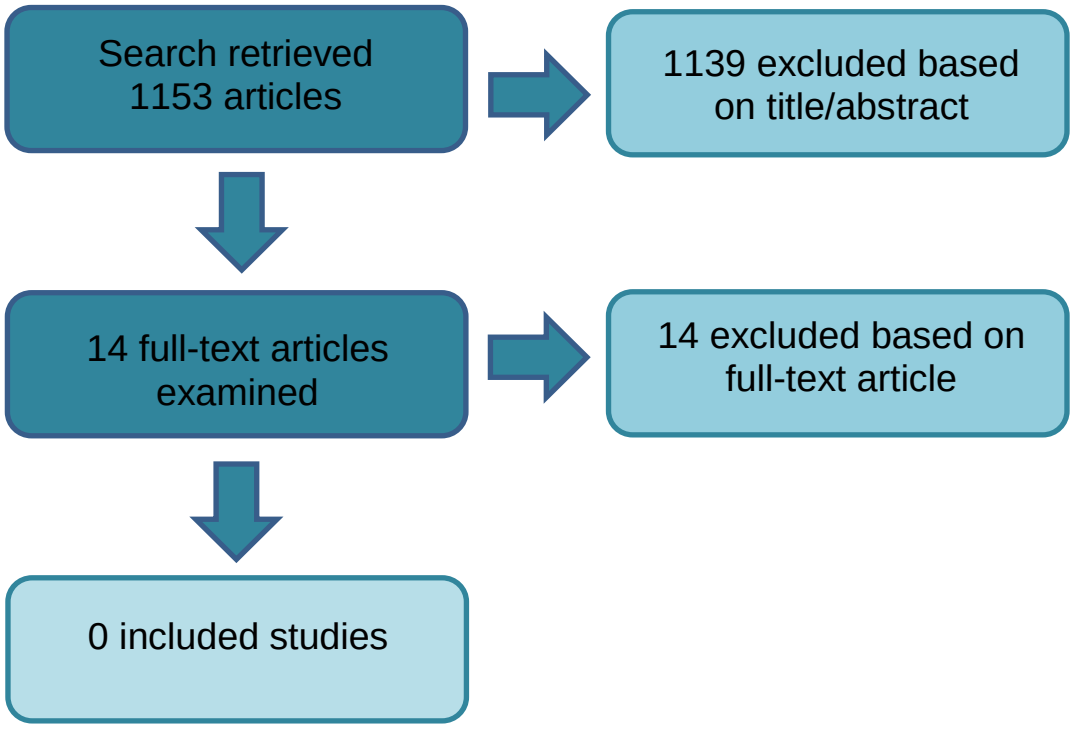
E.6 Review question 3 & 4 – Health Economics (lubiprostone and linclotide)



E.7 Review question 5a – Clinical (relaxation therapy)



E.81 Review question 5a – Health Economic (relaxation therapy)



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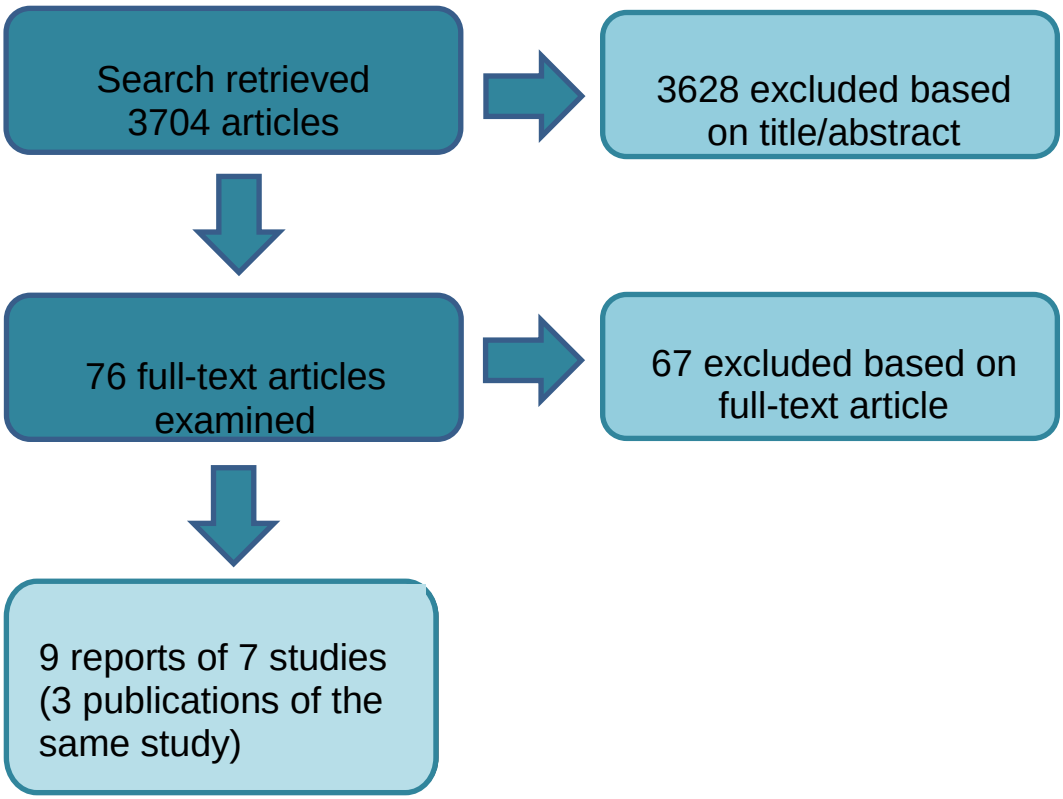
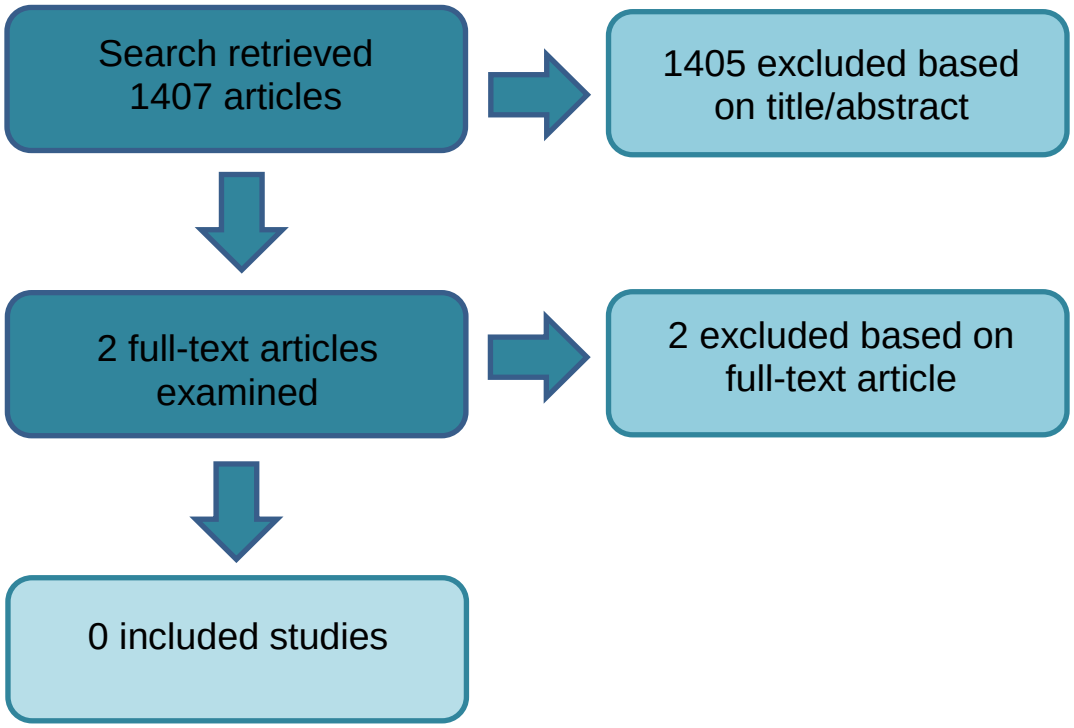
E.9 Review question 5b - Clinical (CCBT and Mindfulness therapy)



E.10 Review question 5b - Health Economics (CCBT and Mindfulness therapy)



1 Appendix F: Excluded studies

F.12 Review question 1 (antidepressants)

Reference	Reason for exclusion
Anon (2007) Systematic review on the management of irritable bowel syndrome in the European Union. *European Journal of Gastroenterology & Hepatology* 19:suppl-37	Not a systematic review
Aursnes I, Gjertsen MK (2008) Common adverse events associated with an SSRI: meta-analysis of early paroxetine data. *Pharmacoepidemiology and Drug Safety*. 17:707-713	Meta-analysis did not match protocol: Adverse effects of SSRIs, not used for IBS
Bahar RJ, Collins BS et al. (2008) Double-blind placebo-controlled trial of amitriptyline for the treatment of irritable bowel syndrome in adolescents. *Journal of Pediatrics*. 152:685-689	Population does not match that specified in protocol (Adolescents)
Bassett JT, Cash BD (2008) A review of irritable bowel syndrome and an update on therapeutic approaches. *Expert Opinion on Pharmacology*. 9:1129-1143	Not a systematic review
Boerner D, Eberhardt R, Metz K, and Schick E (1988) Wirksamkeit ind vertraeglichkeit eines antidepressivums beim colon irritablie, *Therapiewoche,* 38:201-8.	Study not published in English, foreign language publication only.
Brandt LJ, Chey WD et al. (2008) An evidence-based position statement on the management of irritable bowel syndrome. *American Journal of Gastroenterology*. 104:supplS1-S35	Guidelines
Brennan BP, Fogarty KV et al. (2009) Duloxetine in the treatment of irritable bowel syndrome: an open-label pilot study. *Human Psychopharmacology*. 24:423-428	Study not an RCT; excluded due to other high quality RCT evidence being available for this question
Chao G, Zhang S (2013) A meta-analysis of the therapeutic effects of amitriptyline for treating irritable bowel syndrome. *Internal Medicine*. 52:419-424	Higher quality systematic review available: all relevant studies included in this review are included in Cochrane review or excluded from review question
Ford AC, Talley NJ et al. (2009) Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. *Gut*. 58:367-378	Higher quality systematic review available: all relevant studies included in this review are included in Cochrane review or excluded from review

Reference	Reason for exclusion
	question
Ford AC, Guyatt GH et al. (2010) Errors in the conduct of systematic reviews of pharmacological interventions for irritable bowel syndrome. *American Journal of Gastroenterology.* 150:280-288	Systematic review/ meta-analysis did not match protocol : a systematic review of methods
Ford AC, Talley NJ (2012) Irritable bowel syndrome. *BMJ (Online)*. 345:7873	Not a systematic review
Ford AC, Moayyedi P (2010) Meta-analysis: factors affecting placebo response in the irritable bowel syndrome. *Alimentary Pharmacology and Therapeutics*. 32:144-158	Systematic review/ meta-analysis did not match protocol :placebo response rates in IBS trials
Fortea J, Prior M (2013) Irritable bowel syndrome with constipation: a European-focused systematic literature review of disease burden. *Journal of Medical Economics*. 16:329-341	Not a systematic review
Ghadir MR, Habibinejad H et al. (2011) Doxepin is more effective than nortriptyline and placebo for the treatment of diarrhoea-predominant irritable bowel syndrome: a randomised triple-blind placebo-controlled trial. *Tehran University Medical Journal*. 6:352-358	Study not published in English, foreign language publication only.
Gilkin RJ (2005) The spectrum of irritable bowel syndrome: a clinical review. *Clinical Therapeutics*. 27:1696-1709	Not a systematic review
Iskandar HN, Cassell B et al. (2014) Tricyclic antidepressants for management of residual symptoms in inflammatory bowel disease. *J Clin Gastroenterol*.	Intervention and comparison does not match that specified in protocol: Comparison of IBD and IBS
Lai R-M, Cao L-Y et al. (2012) Efficacy and safety of selective serotonin reuptake inhibitor antidepressants in patients with irritable bowel syndrome: a systematic review. *World Chinese Journal of Digestology*.	Study not published in English, foreign language publication only.
Lundberg GD (2008) Evidence that amitriptyline may be effective in treating diarrhoea-predominant irritable bowel syndrome. *Medscape Journal of Medicine*. 10:132	Incorrect publication type: Video file
Marks DM, Han C et al. (2008) History of depressive and anxiety disorders and paroxetine response in patients with irritable bowel syndrome: post hoc analysis from a placebo-controlled study. *Primary Care Companion to the Journal of Clinical Psychiatry*. 10:368-375	Population does not match that specified in protocol : Response to therapy in those with a history of anxiety/depression and those without
Masand PS, Pae CU et al. (2009) A double-blind, randomised, placebo-controlled trial of paroxetine controlled-release in irritable bowel syndrome. *Psychosomatics*. 50:78-86	Study already included in Cochrane review, which is included in this review.

Reference	Reason for exclusion
Mayer EA (2008) Clinical practice. Irritable bowel syndrome. *NEJM*. 358:1692-1699	Not a systematic review
Mozaffari S, Nikfar S et al. (2013) Metabolic and toxicological considerations for the latest drugs used to treat irritable bowel syndrome. *Expert Opinion on Drug Metabolism and Toxicology*. 9:403-421	Not a systematic review
Myren J, Lovland B, Larssen SE, and Larsen S (1984) Psychopharmacologic drugs in the treatment of the irritable bowel syndrome. A double blind study of the effect of trimipramine, *Annales De Gastroenterologie Et D'Hepatologie.,*(3):117-23.	Intervention does not match that specified in protocol: comparison of trimipramine doses
Olden KW (2012) Targeted therapies for diarrhoea-predominant irritable bowel syndrome. *Clinical & Experimental Gastroenterology*. 5:69-100	Not a systematic review
Pae C-U, Lee S-J et al. (2013) Atypical antipsychotics as a possible treatment for irritable bowel syndrome. *Expert Opinion on Investigational Drugs*. 5:565-572	Not a systematic review
Pae CU, Masand PS et al. (2007) Irritable bowel syndrome in psychiatric perspectives: a comprehensive review. *International Journal of Clinical Practice*. 10:1708-1718	Not a systematic review
Pare P, Bridges R et al. (2007) Recommendations on chronic constipation (including constipation associated with irritable bowel syndrome) treatment. *Canadian Journal of Gastroenterology*. 2007:suppl :3B-22B	Guidelines: Canadian recommendations
Poitras P, Gougeon A et al. (2008) Extra digestive manifestations of irritable bowel syndrome: intolerance to drugs? *Digestive Diseases and Sciences*. 53:2168-2176	Intervention and comparison does not match that specified in protocol: Intolerance to drugs in IBS
Rahimi R, Nikfar S et al. (2009) Efficacy of tricyclic antidepressants in irritable bowel syndrome: a meta-analysis. *World Journal of Gastroenterology*. 15:1548-1553	Higher quality systematic review or Cochrane review available: all relevant studies included in Cochrane review or excluded from review
Rahimi R, Nikfar S et al. (2008) Selective serotonin reuptake inhibitors for the management of irritable bowel syndrome: a meta-analysis of randomized controlled trials. *Archives of Medical Sciences*. 4:71-76	Higher quality systematic review or Cochrane review available: all relevant studies included in Cochrane review or excluded from review
Saad RJ, Chey WD (2008) Recent developments in the therapy of irritable bowel syndrome. *Expert Opinion on Investigational Drugs*. 17:117-130	Not a systematic review
Sainsbury A, Ford AC (2011) Review: treatment of irritable bowel syndrome: beyond fiber and antispasmodic agents. *Therapeutic*	Not a systematic review

Reference	Reason for exclusion
Advances in Gastroenterology. 4:115-127	
Schmulson M, Chang L (2011) Review article: the treatment of functional abdominal bloating and distension. *Alimentary Pharmacology and Therapeutics*. 33:1071-1086	Not a systematic review
Shah E, Kim S et al. (2012) Evaluation of harm in the pharmacotherapy of irritable bowel syndrome. *American Journal of Medicine*. 125:381-393	Higher quality systematic review or Cochrane review available: all relevant studies included in Cochrane review or excluded from review
Shekhar C, Whorwell PJ (2009) Emerging drugs for irritable bowel syndrome. *Expert Opinion on Emerging Drugs*. 14:673-685	Not a systematic review
Smoot LC (2004) GERD, IBS, and IBD: often misunderstood gastrointestinal disorders. *Drug Topics*. 148:64	Incorrect publication type: News article
Sohn W, Lee OY et al. (2012) Tianeptine vs amitriptyline for the treatment of irritable bowel syndrome with diarrhoea: a multicentre, open-label, non-inferiority, randomized controlled study. *Neurogastroenterology & Motility*. 24:860-e398	Intervention does not match that specified in protocol: Drug not in BNF
Solati DK, Adibi P et al. (2010) Effects of relaxation and citalopram on severity and frequency of the symptoms of irritable bowel syndrome with diarrhoea predominance. *Pakistan Journal of Medical Sciences*. 26:88-91	Intervention does not match that specified in protocol: Relaxation study
Spiller R, Aziz Q et al. Guidelines on the irritable bowel syndrome: mechanisms and practical management. *Gut*. 56:1770-1798	Guidelines
Spinelli A (2007) Irritable bowel syndrome. *Clinical Drug Investigation*. 27:15-33	Not a systematic review
Storr MM, Andrews CN (2008) Medical management of irritable bowel syndrome in 2008: current and future directions. *Canadian Journal of Gastroenterology*. 8:673-675	Incorrect publication type: Expert opinion
Szkotak J, Shek A (2012) An evidence-based review of treatment options for irritable bowel syndrome. *Formulary* 47. 9:319	Not a systematic review
Tack J, Broekaert D et al. (2006) A controlled crossover study of the selective serotonin reuptake inhibitor citalopram in irritable bowel syndrome. *Gut*. 55:1095-1103	Study already included in Cochrane review, which is included in this review.
Talley NJ, Kellow JE et al. (2008) Antidepressant therapy (imipramine and citalopram) for irritable bowel syndrome: a double-blind randomized, placebo-controlled trial. *Digestive Diseases & Sciences*. 53:108-115	Study already included in Cochrane review, which is included in this review.
Talley NJ (2008) Newer antidepressants in irritable bowel syndrome: what is the evidence? *Archives in Medical Sciences*. 4:77-78	Incorrect publication type: Commentary
Trindade E, Menon D et al. (1998) Adverse effects associated with	Higher quality systematic

Reference	Reason for exclusion
selective serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis. *CMAJ*. 159:1245-1252	review or Cochrane review available
Trinkley KE, Nahata MC (2011) Treatment of irritable bowel syndrome. *Journal of Clinical Pharmacy & Therapeutics*. 36:275-282	Not a systematic review
Vahedi H, Merat S et al. (2005) The effect of fluoxetine in patients with pain and constipation-predominant irritable bowel syndrome: a double-blind randomized-controlled study. *Aliment Pharmacol Ther*. 22:381-385	Study already included in Cochrane review, which is included in this review.
Vahedi H, Merat S et al. (2008) Clinical trial: the effect of amitriptyline in patients with diarrhoea-predominant irritable bowel syndrome. *Alimentary Pharmacology & Therapeutics*. 27:678-684	Study already included in Cochrane review, which is included in this review.
van Kerkhoven LAS, Laheij RJF et al. (2007) The role of selective serotonin reuptake inhibitor citalopram in irritable bowel syndrome. *Gut*. 5:733	Incorrect publication type: Letter
van Nieuwenhoven MA, Kilkens TO (2012) The effect of acute serotonergic modulation on rectal motor function in diarrhoea-predominant irritable bowel syndrome and healthy controls. *European Journal of Gastroenterology & Hepatology.* 24:1259-1265	Intervention does not match that specified in protocol: Not antidepressants
Wang X-Y, Feng Y-G et al. (2011) Efficacy and safety of low-dose tricyclic antidepressants in patients with irritable bowel syndrome: a meta-analysis. *World Chinese Journal of Digestology*. 19:3458-3463	Study not published in English, foreign language publication only.
Studies included in CG61 (not in 2007 Cochrane review)	
Creed F, Fernandes L et al. (2003) The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome. *Gastroenterology*. 124:303-17	Comparison does not match that specified in protocol: comparison group received usual care, not stated whether they received other pharmacological treatments in addition to usual care. (previously included in CG61)
Kuiken SD, Tytgat GN et al. (2003) The selective serotonin reuptake inhibitor fluoxetine does not change rectal sensitivity and symptoms in patients with irritable bowel syndrome: a double blind, randomized, placebo-controlled study. *Clinical Gastroentrology and Hepatology*. 1:21.9-228	Study already included in Cochrane review, which is included in this review.
Steinhart MJ, Wong PY et al. (1982) Therapeutic usefulness of amitriptyline in spastic colon syndrome. *International Journal of Psychiatry in Medicine*. 11:45-47	Outcomes not reported in a manner that allows extraction: No scale used for symptom score
Tabas G, Beaves M et al. (2004) Paroxetine to treat irritable bowel syndrome not responding to high-fibre diet: a double-blind, placebo-controlled trial. *American Journal of Gastroenterology*. 99:914-20	Study already included in Cochrane review, which is included in this review.
Tanum L, Malt UF (1996) A new pharmacologic treatment of functional	Population does not

Reference	Reason for exclusion
gastrointestinal disorder. A double-blind placebo-controlled study with mianserin. *Scandinavian Journal of Gastroenterology*. 31:318-25	match that specified in protocol: Only 60% of participants had IBS
Shrivastava RK and Siegel H (1984) The role of tricyclics and benzodiazepine compounds in the treatment of irritable gut syndrome and peptic ulcer disease. *Psychopharmacology Bulletin*. 20:616-21	Population does not match that specified in protocol: Included children, participants with peptic ulcer and IBS
Tripathi BM, Misra NP et al. (1983) Evaluation of tricyclic compound (Trimipramine) vis-à-vis placebo in irritable bowel syndrome. *Journal of the Association of Physicians of India*. 31:201-3	Population does not match that specified in protocol: Included children, participants with peptic ulcer and IBS

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F.22 Review question 1 (antidepressants), economic studies

Reference	Reason for exclusion
Ljotsson B (2011) Acceptability, effectiveness, and cost-effectiveness of internet-based exposure treatment for irritable bowel syndrome in a clinical sample: a randomized controlled trial. BMC Gastroenterology 11:110	Irrelevant intervention for this question (not antidepressants)
Creed F, Fernandes L, Guthrie E et al. (2003) The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome. Gastroenterology 124: 303-17.	Included in 2008 guideline
Fedorak RN, Vanner SJ, Paterson WG et al. (2012) Canadian Digestive Health Foundation Public Impact Series 3: Irritable bowel syndrome in Canada. Incidence, prevalence, and direct and indirect economic impact. Canadian Journal of Gastroenterology.26 (5) (pp 252-256), 2012.Date of Publication: May 2012. 252-6.	Burden of disease analysis
Fortea J, Prior M (2013) Irritable bowel syndrome with constipation: A European-focused systematic literature review of disease burden. Journal of Medical Economics.16 (3) (pp 329-341), 2013.Date of Publication: 2013. 329-41.	Burden of disease analysis
Hillila MT, Frkkila NJ, Farkkil MA (2010) Societal costs for irritable bowel syndrome a population based study. Scandinavian Journal of Gastroenterology.45 (5) (pp 582-591), 2010.Date of Publication: May 2010. 582-91.	Burden of disease analysis
Mapel DW (2013) Functional disorders of the gastrointestinal tract: Cost effectiveness review. Best Practice and Research: Clinical Gastroenterology.27 (6) (pp 913-931), 2013.Date of Publication: December 2013. 913-31.	Commentary only on a wide range of gastrointestinal disorders. i.e. Not an economic evaluation.

F.33 Review question 2 (low FODMAP diet)

Reference	Reason for exclusion
Barrett JS, Gibson PR (2010) Development and validation of a comprehensive semi-quantitative food frequency questionnaire that includes FODMAP intake and glycaemic index. *J Am Diet Assoc*. 110:1469-1476	Incorrect publication type: Questionnaire validation
Barrett JS, Gearry RB et al. (2010) Dietary poorly absorbed, short-chain carbohydrates increase delivery of water and fermentable substrates to the proximal colon. *Aliment Pharmacol Ther*. 31:874-882	Population does not match that specified in protocol: Participants had ileostomies

Reference	Reason for exclusion
Barrett JS (2013) Extending our knowledge of fermentable, short-chain carbohydrates for managing gastrointestinal symptoms. *Nutrition in Clinical Practice*. 28:261-268	Not a systematic review
Barrett JS, Gibson PR (2012) Fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) and nonallergic food intolerance: FODMAPs or food chemicals? *Therap Adv Gastroenterol*. 5:261-268	Not a systematic review
de Roest RH, Dobbs BR et al. The low FODMAP diet improves gastrointestinal symptoms in patients with irritable bowel syndrome: a prospective study. *Int J Clin Pract*. 67:895-903	Study not an RCT; excluded due to other high quality RCT evidence being available for this question
Fedewa A, Rao SS (2014) Dietary fructose intolerance, fructan intolerance and FODMAPs. *Curr Gastroenterol* Rep. 16:370	Not a systematic review
Gibson PR, Shepherd SJ (2010) Evidence-based dietary management of functional gastrointestinal symptoms: the FODMAP approach. *Journal of Gastroenterology & Hepatology*. 25:252-258	Not a systematic review
Marcason W (2012) What is the FODMAP diet? J Acad Nutr Diet. 112:1696	Incorrect publication type: Description of the diet
Muir JG, Gibson PR (2013) The low FODMAP diet for treatment of irritable bowel syndrome and other gastrointestinal disorders. *Gastroenterol Hepatol.*	Incorrect publication type: Expert opinion
Olesen M, Gummand-Hoyer E (2000) Efficacy, safety, and tolerability of fructooligosaccharides in the treatment of irritable bowel syndrome. *American Journal of Clinical Nutrition*. 72:1570-1575	Intervention does not match that specified in protocol: Not low FODMAP, fructooligosaccharide compared with placebo
Ong DK, Mitchell SB et al. (2010) Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome. *Journal of Gastroenterology & Hepatology*. 25:1366-1373	Only 2 days of dietary intervention which was judged to be insufficient. See protocol footnote.
Rangnekar AS, Chey WD (2009) The FODMAP diet for irritable bowel syndrome: food fad or roadmap to a new treatment paradigm? *Gastroenterology*. 36:37-46	Incorrect publication type: Study summary
Reggie TJ, Nanda R et al. (2012) A FODMAP diet update: craze or credible? *Practical Gastroenterology*. 2012:37-46	Not a systematic review
Shepherd SJ, Parker FC et al. (2008) Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomised placebo controlled evidence. *Clin Gastroenterol Hepatol*. 6:765-771	Intervention does not match that specified in protocol: Baseline of responders to low FODMAP, not low FODMAP compared with other diets
Staudacher HM, Irving PM et al. (2014) Mechanisms and efficacy of dietary FODMAP restriction in IBS. *Nat Rev Gastroenterol Hepatol*.	Not a systematic review

F.41 Review question 3 (linaclotide)

Reference	Reason for exclusion
Andresen V, Camilleri M et al. (2007) Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. Gastroenterology 133(3) p 761-768	Insufficient sample size (n=12 per arm) and follow up period (5 days) which

Reference	Reason for exclusion
	was judged to be insufficient .
Atluri DK, Chandar AK, Bharucha AE, Falck-Ytter Y. (2014) Effect of linaclotide in irritable bowel syndrome with constipation (IBS-C): a systematic review and meta-analysis. Neurogastroenterology and Motility. 26 p 499-509.	Meta-analysis did not report study detail of interest in sufficient detail, therefore individual papers included in review. .
Casey T (2013) Linaclotide improves abdominal and bowel symptoms. Annals of Long-Term Care. 21(8) p20)	Not a systematic review: not original research
Rao SS, Quigley EM et al. (2014) Effect of linaclotide on severe abdominal symptoms in patients with irritable bowel syndrome with constipation. Clinical Gastroeneterology and Hepatology. 12:616-623.	Duplication of study already included: Sub-population of earlier study. No additional outcomes.
Thomas RH and Allmond K. (2013) Linaclotide (Linzess) for irritable bowel syndrome with constipation and for chronic idiopathic constipation. Pharmacy and Therapeutics 38 (3) p154-160.	Incorrect publication type: Drug Forecast/ review
Wensel TM and Luthin DR. (2011) Linaclotide: a novel approach to the treatment of irritable bowel syndrome. Annals of Pharmacotherapy 45(12) p1535-1543.	Not a systematic review
Videlock EJ, Cheng V et al. (2013) Effects of linaclotide in patients with irritable bowel syndrome with constipation or chronic constipation: a meta-analysis. Clinical Gastroenterology and Hepatology. 11(9) p1084-1092.	Meta-analysis did not report study detail and outcomes of interest in sufficient detail, therefore individual papers included in review.

F.51 Review question 4 (lubiprostone)

Reference	Reason for exclusion
Anon (2005) Lubiprostone: RU 0211, SPI 0211. [Review] [9 refs]. Drugs in R & D 6: 245-8.	Not a systematic review: Not a primary study.
Chey WD, Drossman DA, Johanson JF et al. (2012) Safety and patient outcomes with lubiprostone for up to 52 weeks in patients with irritable bowel syndrome with constipation. Aliment.Pharmacol.Ther 35: 587-99.	Study not an RCT; excluded due to other high quality RCT evidence being available for this question: Open labelled study. No comparison with placebo.
Fukudo S, Hongo M, Kaneko H et al. (2011) Efficacy and safety of oral lubiprostone in constipated patients with or without irritable bowel syndrome: a randomized, placebo-controlled and dose-finding study. Neurogastroenterology & Motility 23: 544-e205.	Sample size of study too small: Numbers in IBS-C subgroup too small to enable accurate interpretation of results.

F.62 Review question 5a (relaxation therapy)

Reference	Reason for exclusion
Acosta RD, Cash BD. Existing and emerging therapies for irritable bowel syndrome. *Expert Opinion on Emerging Drugs 16 (2) (pp 389-402), 2011 Date of Publication: June 2011* 2011;(2):389-402	Not a systematic review

Reference	Reason for exclusion
Bassett JT, Cash BD. A review of irritable bowel syndrome and an update on therapeutic approaches. *Expert Opinion on Pharmacotherapy 9 (7) (pp 1129-1143), 2008 Date of Publication: May 2008* 2008;(7):1129-1143	Not a systematic review
Blanchard EB, Greene BA, Scharff L, Schwarz-McMorris S. Relaxation Training as a Treatment for Irritable Bowel Syndrome. Biofeedback and Self- Regulation 18[3], 125-132. 1993.	Study reported as an RCT but breaks randomisation, therefore not considered an RCT and excluded from review. Study was included in CG61.
Boye B, Lundin KE, Jantschek G, Leganger S, Mokleby K, Tangen T et al. INSPIRE study: does stress management improve the course of inflammatory bowel disease and disease-specific quality of life in distressed patients with ulcerative colitis or Crohn's disease? A randomized controlled trial. *Inflammatory Bowel Diseases* 2011; 17(9):1863-1873	Intervention does not match that specified in protocol: Relaxation as part of a psychotherapy programme, unable to assess the relaxation element
De WN, Zijdenbosch I, Van Der Heijden G, Quartero O, Rubin G. Psychological treatments for the management of irritable bowel syndrome. *Cochrane Database of Systematic Reviews* 2007;(2)	Systematic review did not match protocol: Cochrane review, not all interventions are relaxation
Dehkordy, S.,Adibi, P &Gharamaleky, S Effects of relaxation and citalopram in severity and frequency of the symptoms of irritable bowel syndrome with diarrhea predominance. *Pakistani Journal of Medical science* 2010; 26(1); 88-91.	Study not an RCT: Insufficient detail to indicate that this is a randomised controlled trial. Excluded due to other high quality RCT evidence being available for this question
Dobbin A, Dobbin J, Ross SC, Graham C, Ford MJ. Randomised controlled trial of brief intervention with biofeedback and hypnotherapy in patients with refractory irritable bowel syndrome. *Journal of the Royal College of Physicians of Edinburgh 43 (1) (pp 15-23), 2013 Date of Publication: 2013* 2013;(1):15-23	Intervention does not match that specified in protocol: biofeedback and hypnotherapy
Dorn SD. Systematic review: self-management support interventions for irritable bowel syndrome. [Review]. *Alimentary Pharmacology & Therapeutics* 2010; 32(4):513-521	Systematic review did not match protocol: did not include papers with relaxation alone, always as part of a multi-modal approach
Drossman D, Morris CB, Hu Y, Toner BB, Diamant N, Whitehead WE et al. Characterization of health related quality of life (HRQOL) for patients with functional bowel disorder (FBD) and its response to treatment. *American Journal of Gastroenterology* 2007; 102(7):1442-1453	Incorrect publication type: Study testing the value of IBS QoL questionnaires
Enck P, Junne F, Klosterhalfen S, Zipfel S, Martens U. Therapy options in irritable bowel syndrome. [Review]. *European Journal of Gastroenterology & Hepatology* 2010; 22(12):1402-1411	Meta-analysis did not match protocol: Meta-analysis of many different treatments for IBS.
Ford AC, Talley NJ, Schoenfeld PS, Quigley EM, Moayyedi P. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. [Review] [71 refs]. *Gut* 2009; 58(3):367-378	Systematic review/ meta-analysis did not report study detail in sufficient detail, relevant individual

Reference	Reason for exclusion
	papers from publication included in review
Ford AC, Talley NJ. Irritable bowel syndrome. *BMJ (Online) 345 (7873) , 2012 Article Number: e5836 Date of Publication: 08 Sep 2012* 2012;(Online)	Not a systematic review; overview of current treatment options for IBS.
Halland M, Talley NJ. New treatments for IBS. *Nature Reviews Gastroenterology and Hepatology 10 (1) (pp 13-23), 2013 Date of Publication: January 2013* 2013;(1):13-23. Ref ID: 1819	Not a systematic review
Kearney DJ, Brown-Chang J. Complementary and alternative medicine for IBS in adults: mind-body interventions. [Review] [101 refs]. *Nature Clinical Practice Gastroenterology & Hepatology* 2008; 5(11):624-636	Not a systematic review; relaxation as part of a multi-modal approach.
Keefer L, Blanchard EB. The effects of relaxation response meditation on the symptoms of irritable bowel syndrome: results of a controlled treatment study. Behaviour Research & Therapy 39, 801-811. 2001.	Extremely serious risk of bias in study design: Randomisation very unclear; states matched pairs randomised, n<10, very high risk of bias. Included in CG61
Sinagra E, Romano C, Cottone M. Psychopharmacological treatment and psychological interventions in irritable bowel syndrome. *Gastroenterology Research and Practice* 2012; , 2012. Article Number: 486067. Date of Publication: 2012	Not a systematic review
Van der Veek PP, van Rood YR, Masclee AA. Clinical trial: short- and long-term benefit of relaxation training for irritable bowel syndrome. *Alimentary Pharmacology & Therapeutics* 2007; 26(6):943-952	Reported as an RCT but breaks randomisation, therefore not considered an RCT and excluded from review: If people from intervention group dropped out, the participants were allowed to cross over from control to intervention group during study period to replace the dropouts. Lack of detail about when and how many occurences of this.
Yoon SL, Grundmann O, Koepp L, Farrell L. Management of irritable bowel syndrome (IBS) in adults: conventional and complementary/alternative approaches. [Review]. *Alternative Medicine Review* 2011; 16(2):134-151	Not a systematic review
Zernicke KA, Campbell TS, Blustein PK, Fung TS, Johnson JA, Bacon SL et al. Mindfulness-based stress reduction for the treatment of irritable bowel syndrome symptoms: A randomized wait-list controlled trial. [References]. *International Journal of Behavioral Medicine* 2013; 20(3):385-396	Intervention does not match that specified in protocol: mindfulness

F.7 Review question 5a (relaxation therapies), economic studies

Reference	Reason for exclusion
Ahl A, Mikocka-Walus A, Gordon A et al. (2013) Are self-administered or minimal therapist contact psychotherapies an effective treatment for irritable bowel syndrome (IBS): A systematic review. Journal of Psychosomatic Research.75 (2) (pp 113-120), 2013.Date of Publication: August 2013. 113-20.	Not an economic evaluation
Andersson E, Ljotsson B, Smit F et al. (2011) Cost-effectiveness of internet-based cognitive behavior therapy for irritable bowel syndrome: results from a randomized controlled trial. BMC Public Health 11: 215.	Irrelevant intervention for this question (not relaxation therapy)
Camilleri M (2000) Economic burden of irritable bowel syndrome: proposed strategies to control expenditures. PharmacoEconomics 17(4):331-338	Burden of disease analysis
Creed F (2003) The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome. Gastroenterology 124(2):303-317	Included in previous guideline
Gilkin J (2005) The spectrum of irritable bowel syndrome: A clinical review. Clinical Therapeutics.27 (11) (pp 1696-1709), 2005.Date of Publication: November 2005. 1696-709.	Burden of disease analysis
Hedman E, Ljotsson B, Lindefors N (2012) Cognitive behavior therapy via the Internet: a systematic review of applications, clinical efficacy and cost-effectiveness. [Review]. Expert Review of Pharmacoeconomics & Outcomes Research 12: 745-64.	Irrelevant intervention (not relaxation therapy)
Kennedy TM, Chalder T, McCrone P et al. (2006) Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: Randomised controlled trial. Health Technology Assessment.10 (19) (pp iii-48), 2006.Date of Publication: June 2006. iii-48.	Irrelevant intervention (not relaxation therapy)
Lee V, Guthrie E, Robinson A et al. (2008) Functional bowel disorders in primary care: Factors associated with health-related quality of life and doctor consultation. Journal of Psychosomatic Research.64 (2) (pp 129-138), 2008.Date of Publication: February 2008. 129-38.	Not an economic evaluation
Ljotsson B, Andersson G, Andersson E et al. (2011) Acceptability, effectiveness, and cost-effectiveness of internet-based exposure treatment for irritable bowel syndrome in a clinical sample: a randomized controlled trial. BMC Gastroenterology 11: 110.	Irrelevant intervention for this question (not relaxation therapy)
McCrone P, Knapp M, Kennedy T et al. (2008) Cost-effectiveness of cognitive behaviour therapy in addition to mebeverine for irritable bowel syndrome. European Journal of Gastroenterology & Hepatology 20: 255-63.	Irrelevant intervention (not relaxation therapy)
Muller-Lissner SA (2002) Irritable bowel syndrome in Germany. A cost of illness study. European Journal of Gastroenterology and Hepatology 14:1325-1329	Burden of disease analysis
van der Veek PP, van Rood YR, Masclee AA (2007) Clinical trial: short- and long-term benefit of relaxation training for irritable bowel syndrome. Alimentary Pharmacology & Therapeutics 26: 943-52.	Not an economic evaluation
Van Tilburg MAL, Palsson OS, Levy RL et al. (2008) Complementary and alternative medicine use and cost in functional bowel disorders: A six month prospective study in a large HMO. BMC Complementary and Alternative Medicine.8 , 2008.Article Number: 46.Date of Publication: 24 Jul 2008.	Burden of disease analysis
Zijdenbos IL, de Wit NJ, van der Heijden GJ et al. (2009) Psychological treatments for the management of irritable bowel	No economic outcomes

Reference	Reason for exclusion
syndrome. [Review] [111 refs]. Cochrane Database of Systematic Reviews : CD006442.	

F.81 Review question 5b (CCBT and Mindfulness therapy)

Reference	Reason for exclusion
Ahl A, Mikocka-Walus A, Gordon A et al. (2013) Are self-administered or minimal therapist contact psychotherapies an effective treatment for irritable bowel syndrome (IBS): a systematic review. [Review]. Journal of Psychosomatic Research 75: 113-20.	Systematic review did not report study detail in sufficient detail, therefore individual papers included in review: used as cross checking.
Barabasz A, Barabasz M (2006) Effects of tailored and manualized hypnotic inductions for complicated irritable bowel syndrome patients. International Journal of Clinical & Experimental Hypnosis 54: 100-12.	Intervention does not match that specified in protocol: Hypnotherapy
Berrill JW, Sadlier M, Hood K et al. (2014) Mindfulness-based therapy for inflammatory bowel disease patients with functional abdominal symptoms or high perceived stress levels. J Crohns Colitis	Population does not match that specified in protocol: IBD population, not IBS.
Blanchard EB, Lackner JM, Sanders K et al. (2007) A controlled evaluation of group cognitive therapy in the treatment of irritable bowel syndrome. Behaviour Research & Therapy 45: 633-48.	Intervention does not match that specified in protocol: CBT only (not CCBT)
Blanchard EB, Lackner JM, Sanders K et al. (2007) A controlled evaluation of group cognitive therapy in the treatment of irritable bowel syndrome. [References]. Behaviour Research and Therapy 45: 633-48.	Intervention does not match that specified in protocol: CBT only (not CCBT)
Brotto LA (2012) Mindfulness training reduces the severity of irritable bowel syndrome in women: Results of a randomized controlled trial. Journal of Sexual Medicine 9: 967-8.	Incorrect publication type: review of the Gaylord (2011) paper.
Cash BD (2009) Review: Antidepressants and psychological therapies improve symptoms of irritable bowel syndrome. Evidence-Based Medicine.14 (4) (pp 119), 2009.Date of Publication: August 2009.	Incorrect publication type: Abstract only.
Craske MG, Wolitzky-Taylor KB, Labus J et al. (2011) A cognitive-behavioral treatment for irritable bowel syndrome using interoceptive exposure to visceral sensations. Behaviour Research & Therapy 49: 413-21.	Intervention does not match that specified in protocol: CBT only (not CCBT)
Creed F, Fernandes L, Guthrie E et al. (2003) The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome. Gastroenterology 124: 303-17.	Intervention does not match that specified in protocol: Psychotherapy and already included in the original guideline 2007.
Creed F, Tomenson B, Guthrie E et al. (2008) The relationship between somatisation and outcome in patients with severe irritable bowel syndrome. Journal of Psychosomatic Research 64: 613-20.	Incorrect publication type: not about treatment efficacy or effectiveness.
Deechakawan W, Cain KC, Jarrett ME et al. (2013) Effect of self-management intervention on cortisol and daily stress levels in irritable bowel syndrome. Biological Research for Nursing 15: 26-36.	Intervention does not match that specified in protocol.
Deechakawan WI (2011) Effect of a comprehensive self-management intervention on urine cortisol/catecholamine levels and daily stress/emotional symptoms in adults with Irritable Bowel Syndrome. Dissertation Abstracts International: Section B: The Sciences and Engineering 72: 2030.	Intervention does not match that specified in protocol.
Dobbin A, Dobbin J, Ross SC et al. (2013) Randomised controlled trial of brief intervention with biofeedback and hypnotherapy in patients with refractory irritable bowel syndrome. Journal of the Royal College of Physicians of Edinburgh 43: 15-23.	Intervention does not match that specified in protocol: Hypnotherapy and biofeedback

Reference	Reason for exclusion
Dorn SD (2010) Systematic review: self-management support interventions for irritable bowel syndrome. [Review]. Alimentary Pharmacology & Therapeutics 32: 513-21.	Systematic review did not match protocol: Included other interventions that were not covered by the update remit – used as cross checking.
Drossman DA, Toner BB, Whitehead WE et al. (2003) Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders. Gastroenterology 125: 19-31.	Intervention does not match that specified in protocol: CBT only (not CCBT), included in the original guideline 2007.
Everitt H, Moss-Morris R, Sibelli A et al. (2013) Management of irritable bowel syndrome in primary care: The results of an exploratory randomised controlled trial of mebeverine, methylcellulose, placebo and a self-management website. BMC Gastroenterology.13 (1), 2013.Article Number: 68.Date of Publication: 21 Apr 2013.	Outcomes not reported in a manner that allows extraction: A 3x3 design with various combinations of different drugs and CCBT, the data was analysed in combination – unable to extract data from each arm under each intervention.
Everitt HA, Moss-Morris RE, Sibelli A et al. (2010) Management of irritable bowel syndrome in primary care: feasibility randomised controlled trial of mebeverine, methylcellulose, placebo and a patient self-management cognitive behavioural therapy website. (MIBS trial). BMC Gastroenterology 10: 136.	Incorrect publication type: Research protocol only.
Fernandez C, Amigo I (2006) Efficacy of training in stress and contingency management in cases of irritable bowel syndrome. Stress and Health.22 (5) (pp 285-295), 2006.Date of Publication: December 2006.	Intervention does not match that specified in protocol. Included in different section of the the original guideline 2007.
Fernandez C, Perez M, Amigo I et al. (1998) Stress and contingency management in the treatment of irritable bowel syndrome. Stress Medicine 14: 31-42.	Intervention does not match that specified in protocol. Included in different section of the the original guideline 2007.
Fjorback LO, Arendt M, Ornbol E et al. (2013) Mindfulness therapy for somatization disorder and functional somatic syndromes: randomized trial with one-year follow-up. Journal of Psychosomatic Research 74: 31-40.	Population does not match that specified in protocol: Not IBS population.
Flik CE, van Rood YR, Laan W et al. (2011) A randomised controlled trial on hypnotherapy for irritable bowel syndrome: design and methodological challenges (the IMAGINE study). BMC Gastroenterology 11: 137.	Intervention does not match that specified in protocol: Hypnotherapy
Forbes A, MacAuley S, Chiotakakou-Faliakou E (2000) Hypnotherapy and therapeutic audiotape: effective in previously unsuccessfully treated irritable bowel syndrome? International Journal of Colorectal Disease 15: 328-34.	Intervention does not match that specified in protocol. Included in different section of the the original guideline 2007.
Ford AC, Talley NJ, Schoenfeld PS et al. (2009) Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. [Review] [71 refs]. Gut 58: 367-78.	Systematic review did not match protocol: Included other interventions that were not covered by the update remit – used as

Reference	Reason for exclusion
	cross checking.
Ford AC, Talley NJ, Schoenfeld PS et al. (2009) Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis (Structured abstract). Gut 58: 367-78.	Duplication of study already included
Gaylord S, Palsson OS, Garland E et al. (2011) Therapeutic impact of mindfulness meditation on Irritable Bowel Syndrome (IBS): Results of a randomized controlled trial [conference abstract]. Gastroenterology [abstracts from Digestive Disease Week, DDW 2011 Chicago, IL United States.May 7-10] 140	Incorrect publication type: Abstract only.
Gaylord SA, Whitehead WE, Coble RS et al. (2009) Mindfulness for irritable bowel syndrome: protocol development for a controlled clinical trial. BMC Complementary & Alternative Medicine 9: 24.	Incorrect publication type: Research protocol only.
Gerson CD, Gerson J, Gerson MJ (2013) Group hypnotherapy for irritable bowel syndrome with long-term follow-up. International Journal of Clinical & Experimental Hypnosis 61: 38-54.	Intervention does not match that specified in protocol: Hypnotherapy
Gholamrezaei A, Ardestani SK, Emami MH (2006) Where does hypnotherapy stand in the management of irritable bowel syndrome? A systematic review. [Review] [48 refs]. Journal of Alternative & Complementary Medicine 12: 517-27.	Intervention does not match that specified in protocol: Hypnotherapy
Grundmann O, Yoon SL (2013) Mind-body therapies for functional bowel disorders-A review of recent clinical trials. European Journal of Integrative Medicine.5 (4) (pp 296-307), 2013.Date of Publication: August 2013.	Population does not match that specified in protocol: Population of functional bowel disorders, unable to extract subgroup data for IBS population.
Haghayegh SA, Kalantari M, Molavi H et al. (2011) The efficacy of cognitive-behavior group therapy on health-related quality of life, health anxiety and depression in patients with diarrhea-predominant irritable bowel syndrome. Pakistan journal of medical sciences 27: 749-53.	Intervention does not match that specified in protocol: CBT only (not CCBT)
Jarrett ME, Cain KC, Burr RL et al. (2009) Comprehensive self-management for irritable bowel syndrome: randomized trial of in-person vs. combined in-person and telephone sessions. American Journal of Gastroenterology 104: 3004-14.	Intervention does not match that specified in protocol:
Kafi M, Afshar H, Moghtadaei K et al. (2014) Effectiveness of mindfulness-based cognitive-therapy on psychological signs women with irritable bowel syndrome. Koomesh 15: 255-64.	Study not published in English, foreign language publication only.
Kennedy T, Jones R, Darnley S et al. (2005) Cognitive behaviour therapy in addition to antispasmodic treatment for irritable bowel syndrome in primary care: randomised controlled trial. BMJ 331: 435.	Intervention does not match that specified in protocol: CBT only (not CCBT) Included in different section of the the original guideline 2007.
Labus J, Gupta A, Gill HK et al. (2013) Randomised clinical trial: symptoms of the irritable bowel syndrome are improved by a psycho-education group intervention. Alimentary Pharmacology & Therapeutics 37: 304-15.	Intervention does not match that specified in protocol: Psychoeducation
Lackner JM, Jaccard J, Krasner SS et al. (2007) How does cognitive behavior therapy for irritable bowel syndrome work? A mediational analysis of a randomized clinical trial. Gastroenterology 133: 433-44.	Study type does not match that specified in protocol: Not a comparative study.
Lackner JM, Jaccard J, Krasner SS et al. (2008) Self-administered cognitive behavior therapy for moderate to severe irritable bowel syndrome: clinical efficacy, tolerability, feasibility. Clinical	Intervention does not match that specified in protocol: CBT only (not CCBT)

Reference	Reason for exclusion
Gastroenterology & Hepatology 6: 899-906.	
Lackner JM, Gudleski GD, Keefer L et al. (2010) Rapid response to cognitive behavior therapy predicts treatment outcome in patients with irritable bowel syndrome. Clinical Gastroenterology & Hepatology 8: 426-32.	Intervention does not match that specified in protocol: CBT only (not CCBT)
Lackner JM, Keefer L, Jaccard J et al. (2012) The Irritable Bowel Syndrome Outcome Study (IBSOS): rationale and design of a randomized, placebo-controlled trial with 12 month follow up of self- versus clinician-administered CBT for moderate to severe irritable bowel syndrome. Contemporary Clinical Trials 33: 1293-310.	Incorrect publication type: Research protocol only
Lee HH, Choi YY, Choi M-G (2014) The efficacy of hypnotherapy in the treatment of irritable bowel syndrome: A systematic review and meta-analysis. Journal of Neurogastroenterology and Motility.20 (2) (pp 152-162), 2014.Date of Publication: 2014.	Intervention does not match that specified in protocol: Hypnotherapy
Lindfors P, Unge P, Arvidsson P et al. (2012) Effects of gut-directed hypnotherapy on IBS in different clinical settings-results from two randomized, controlled trials. American Journal of Gastroenterology 107: 276-85.	Intervention does not match that specified in protocol: Hypnotherapy covered by the update remit.
Lindfors P, Ljotsson B, Bjornsson E et al. (2013) Patient satisfaction after gut-directed hypnotherapy in irritable bowel syndrome. Neurogastroenterology & Motility 25: 169-e86.	Study type does not match that specified in protocol: Qualitative study,
Ljotsson B, Andreewitch S, Hedman E et al. (2010) Exposure and mindfulness based therapy for irritable bowel syndrome--an open pilot study. Journal of Behavior Therapy & Experimental Psychiatry 41: 185-90.	Study type does not match that specified in protocol: before and after study.
Ljotsson B, Hesser H, Andersson E et al. (2013) Mechanisms of change in an exposure-based treatment for irritable bowel syndrome. Journal of Consulting & Clinical Psychology 81: 1113-26.	Study type does not match that specified in protocol: Not RCT, not a comparative study of effectiveness.
Ljotsson B, Lindfors P, Lackner JM et al. (2013) Prediction of symptomatic improvement after exposure-based treatment for irritable bowel syndrome. BMC Gastroenterology.13 (1) , 2013.Article Number: 160.Date of Publication: 19 Nov 2013.	Study type does not match that specified in protocol: Not a comparative study.
Ljotsson B, Hedman E, Lindfors P et al. (2014) Long-term follow-up of internet-delivered exposure and mindfulness based treatment for irritable bowel syndrome. Behaviour Research and Therapy 49: 58-61.	Duplication of Ljotsson (2011) paper.
Ljotsson B, Andreewitch S, Hedman E et al. (2010) Exposure and mindfulness based therapy for irritable bowel syndrome-An open pilot study. [References]. Journal of Behavior Therapy and Experimental Psychiatry 41: 185-90.	Study type does not match that specified in protocol: Not RCT, before and after study.
Ljotsson B, Falk L, Vesterlund AW et al. (2010) Internet-delivered exposure and mindfulness based therapy for irritable bowel syndrome - A randomized controlled trial. [References]. Behaviour Research and Therapy 48: 531-9.	Duplication of Ljotsson (2010) paper.
Ljtsson B, Falk L, Hedman E et al. (2011) Internet-delivered cognitive behavior therapy for irritable bowel syndrome - A randomized controlled trial [conference abstract]. Gastroenterology [abstracts from Digestive Disease Week, DDW 2011 Chicago, IL United States.May 7-10] 140	Incorrect publication type Abstract only.
Lowen MB, Mayer EA, Sjoberg M et al. (2013) Effect of hypnotherapy and educational intervention on brain response to visceral stimulus in the irritable bowel syndrome. Alimentary Pharmacology & Therapeutics 37: 1184-97.	Intervention does not match that specified in protocol: Hypnotherapy
Mahvi-Shirazi M, Fathi-Ashtiani A, Rasoolzade-Tabatabaei S-K et al.	Intervention does not match

Reference	Reason for exclusion
(2012) Irritable bowel syndrome treatment: Cognitive behavioral therapy versus medical treatment. Archives of Medical Science 8: 123-9.	that specified in protocol: CBT only (not CCBT)
McCrone P, Knapp M, Kennedy T et al. (2008) Cost-effectiveness of cognitive behaviour therapy in addition to mebeverine for irritable bowel syndrome. European Journal of Gastroenterology & Hepatology 20: 255-63.	Intervention does not match that specified in protocol: CBT only (not CCBT)
Moser G, Dejaco C, Fuhrer M et al. (2012) Gut-focused group hypnosis for treatment of irritable bowel syndrome - A randomised controlled trial. Journal of psychosomatic research [abstracts of the 15th annual meeting of the european association for consultation-liaison psychiatry and psychosomatics, EACLPP and 29th european conference on psychosomatic research, ecpr.2012 jun 27-30; aarhus denmark 72: 494-5.	Intervention does not match that specified in protocol: Hypnotherapy
Moser G, Tragner S, Gajowniczek EE et al. (2013) Long-term success of GUT-directed group hypnosis for patients with refractory irritable bowel syndrome: a randomized controlled trial. American Journal of Gastroenterology 108: 602-9.	Intervention does not match that specified in protocol: Hypnotherapy
Moss-Morris R, McAlpine L, Didsbury LP et al. (2010) A randomized controlled trial of a cognitive behavioural therapy-based self-management intervention for irritable bowel syndrome in primary care. Psychological Medicine 40: 85-94.	Intervention does not match that specified in protocol:
Reme SE, Kennedy T, Jones R et al. (2010) Predictors of treatment outcome after cognitive behavior therapy and antispasmodic treatment for patients with irritable bowel syndrome in primary care.[Erratum appears in J Psychosom Res. 2010 Nov;69(5):523]. Journal of Psychosomatic Research 68: 385-8.	Study type does not match that specified in protocol: Not a comparative study.
Reme SE, Stahl D, Kennedy T et al. (2011) Mediators of change in cognitive behaviour therapy and mebeverine for irritable bowel syndrome. Psychological Medicine 41: 2669-79.	Study type does not match that specified in protocol: Not a comparative study.
Reme SE, Kennedy T, Jones R et al. (2010) "Predictors of treatment outcome after cognitive behavior therapy and antispasmodic treatment for patients with irritable bowel syndrome in primary care": Erratum. Journal of Psychosomatic Research 69: 523.	Incorrect publication type: Erratum of Reme (2010)
Roberts L, Wilson S, Singh S et al. (2006) Gut-directed hypnotherapy for irritable bowel syndrome: piloting a primary care-based randomised controlled trial. British Journal of General Practice 56: 115-21.	Intervention does not match that specified in protocol: Hypnotherapy
Schoultz M, Atherton IM, Hubbard G et al. (2013) The use of mindfulness-based cognitive therapy for improving quality of life for inflammatory bowel disease patients: study protocol for a pilot randomised controlled trial with embedded process evaluation. Trials [Electronic Resource] 14: 431.	Population does not match that specified in protocol: IBD patients, not IBS patients.
Tonkin-Crine S, Bishop FL, Ellis M et al. (2013) Exploring patients' views of a cognitive behavioral therapy-based website for the self-management of irritable bowel syndrome symptoms. Journal of Medical Internet Research 15: e190.	Study type does not match that specified in protocol: Not RCT, qualitative study on patients' views.
Webb AN, Kukuruzovic RH, Catto-Smith AG et al. (2007) Hypnotherapy for treatment of irritable bowel syndrome. [Review] [49 refs]. Cochrane Database of Systematic Reviews : CD005110.	Intervention does not match that specified in protocol: Hypnotherapy
Weinland SR, Morris CB, Dalton C et al. (2010) Cognitive factors affect treatment response to medical and psychological treatments in functional bowel disorders. American Journal of Gastroenterology 105: 1397-406.	Not relevant.
Whitehead WE (2006) Hypnosis for irritable bowel syndrome: The empirical evidence of therapeutic effects. [References]. International	Intervention does not match that specified in protocol:

Reference	Reason for exclusion
Journal of Clinical and Experimental Hypnosis 54: 7-20.	Hypnotherapy
Wilson S, Maddison T, Roberts L et al. (2006) Systematic review: the effectiveness of hypnotherapy in the management of irritable bowel syndrome. [Review] [50 refs]. Alimentary Pharmacology & Therapeutics 24: 769-80.	Intervention does not match that specified in protocol: Hypnotherapy
Zijdenbos IL, de Wit NJ, van der Heijden GJ et al. (2009) Psychological treatments for the management of irritable bowel syndrome. [Review] [111 refs]. Cochrane Database of Systematic Reviews : CD006442.	Systematic review/ meta-analysis did not match protocol: Included other interventions that were not covered by the update remit
Zomorodi S, Abdi S, Tabatabaee SKR (2014) Comparison of long-term effects of cognitive-behavioral therapy versus mindfulness-based therapy on reduction of symptoms among patients suffering from irritable bowel syndrome. Gastroenterology and Hepatology from Bed to Bench.7 (2) (pp 118-124), 2014.Date of Publication: 2014.	Population does not match that specified in protocol: population used healthy population.

F.9 Review question 5b (CCBT and mindfulness therapy), economic studies

Reference	Reason for exclusion
Andersson E, Ljotsson B, Smit F et al. (2011) Cost-effectiveness of internet-based cognitive behavior therapy for irritable bowel syndrome: results from a randomized controlled trial. BMC Public Health 11: 215.	Not sufficiently applicable to this guideline: setting for trial and costs is Sweden; perspective is societal; health effects not expressed as QALYs
Ljotsson B, Andersson G, Andersson E et al. (2011) Acceptability, effectiveness, and cost-effectiveness of internet-based exposure treatment for irritable bowel syndrome in a clinical sample: a randomized controlled trial. BMC Gastroenterology 11: 110.	Not sufficiently applicable to this guideline: setting for trial and costs is Sweden; perspective is societal; health effects not expressed as QALYs

1 Appendix G: Evidence tables

G.1 2 Review question 1 (antidepressants)

Bibliographic reference	Ruepert L, Quartero AO et al (2011) Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. Cochrane Review
Study type	Cochrane review to evaluate the efficacy of bulking agents, antispasmodics, and antidepressants for the treatment of irritable bowel syndrome
Study quality	Quality assessment criteria included; method of randomisation, concealment of allocation, blinding of partients and outcomes measurers, description of lost to follow-up Allocation; - Studies that reported the methods for randomisation and rated as low risk; Kuiken (2003), Tabas (2004), Talley (2008), Vahedi (2005), Vahedi (2008), Vij (1991) - Studies rated as unclear; Masand (2009) Mryen (1982), Rajagopalan (1998), Tack (2006) Blinding; - Studies that were rated as low risk; Kuiken (2003), Myren (1982), Rajagopalan (1998), Tabas (2004), Tack (2006), Talley (2008), Vahedi (2005), Vahedi (2008), Vij (1991) - Studies rated as unclear; Masand (2009) Incomplete outcome data; - Studies that were rated as low risk; Kuiken (2003), Masand (2009), Myren (1982), Tabas (2004), Tack (2006), Vahedi (2005), Vahedi (2008), Vij (1991) - Studies rated as unclear; Rajagopalan (1998), Talley (2008) Selective reporting; - Studies that were rated as low risk; Kuiken (2003), Masand (2009), Myren (1982), Rajagopalan (1998), Tabas (2004), Tack (2006), Talley (2008), Vahedi (2005), Vahedi (2008), Vij (1991)
Number of patients	
Patient characteristics	Searches of MEDLINE, EMBASE, The Cochrane library, CINAHL, PsychoInfo, 1966-2009, update search 2011 Inclusion:

Bibliographic reference	Ruepert L, Quartero AO et al (2011) Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. Cochrane Review
	- RCTs comparing antidepressants with a placebo in those with irritable bowel aged over 12 years - Primary outcome had to include improvement of abdominal pain, global assessment or symptom score - IBS diagnosed either using predefined diagnostic criteria (Rome or Manning) or on clinical grounds - Studies of functional bowel disorders without separate IBS data included if the proportion of IBS patients was ≥75%
Intervention	Antidepressants (tricyclic and SSRIs)
Comparison	Placebo
Length of follow up	
Location	
Outcomes measures and effect size	Results for bulking agents and antispasmodics not reported in this ET Antidepressants, 419 studies identified, 15 included; - Bahar (2008), excluded from this review, study in adolescents - Bergman (1991), excluded, not in English - Boerner (1988), in CG61,excluded, not in English - Drossman (2003), excluded from this drug not in the BNF (desipramine) - Heefner (1978), excluded in CG61, excluded from this review, drug not in the BNF (desipramine) - Kuiken (2003), in CG61, included - Masand (2009), identified for inclusion through the search for this update - Myren (1982), in CG61, included - Rajagopalana (1998), in CG61, included - Tabas (2004), in CG61, included - Tack (2006), excluded in CG61 in the diagnostic section, have included - Talley (2008), included - Vahedi (2005), excluded in CG61 in the diagnostic section, have included - Vahedi (2008), included - Vij (1991), in CG61, included 10 studies included in this review; - Kuiken (2003), Masand (2009), Myren (1982), Rajagopalan (1998), Tabas (2004), Tack (2006), Talley (2008), Vahedi (2005), Vahedi (2008), Vij (1991)

Bibliographic reference	**Ruepert L, Quartero AO et al (2011) Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. Cochrane Review**

Reference	Study type	Participants	Intervention	Outcomes reported
Kuiken (2003)	RCT (double-blind)	N=40 (SSRI vs placebo)	Fluoxetine 20mg (od) for 6weeks	Abdominal pain, global assessment
Masand (2009)	RCT (double-blind)	N=72 (SSRI vs placebo)	Paroxetine 12.5-50mg for 12weeks	Global assessment, IBS-symptoms
Myren (1982)	RCT (double-blind)	N=61 (TCA vs placebo)	Trimipramine 50mg (dd) for 4weeks	Global assessment
Rajagopalan (1998)	RCT (double-blind)	N=22 (TCA vs placebo)	Amitriptyline 75mg (od) for 12weeks	Abdominal pain
Tabas (2004)	RCT (double-blind)	N=90 (SSRI vs placebo)	Paroxetine 10 or 20mg (od) for 12weeks	Abdominal pain, global assessment
Tack (2006)	Crossover (double-blind)	N=23 (SSRI vs placebo)	Citalopram 20-40mg for 6weeks	Abdominal pain, global assessment
Talley (2008)	RCT (double-blind)	N=51 (SSRI, TCA vs placebo)	Imipramine 50mg (dd) for 12weeks Citalopram 40mg (dd) for 12weeks	Abdominal pain, global assessment
Vahedi (2005)	RCT (double-blind)	N=44 (SSRI vs placebo)	Fluoxetine 20mg (od) for 12weeks	Abdominal pain
Vahedi (2008)	RCT (double-blind)	N=50 (TCA vs placebo)	Amitriptyline 10mg for 2months	Abdominal pain, IBS-symptom score
Vij (1991)	RCT (double-blind)	N=50 (TCA vs placebo)	Doxepin 75mg (od) for 6weeks	Abdominal pain, global assessment

Source of funding	
Comments	All studies blinded for reviewers in respect of authors, date of publication, journal or database of publication.

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Bibliographic reference	**Abdul-Baki et al (2009) A randomized controlled trial of imipramine in patients with irritable bowel syndrome. World J Gastroenterol**

Bibliographic reference	Abdul-Baki et al (2009) A randomized controlled trial of imipramine in patients with irritable bowel syndrome. World J Gastroenterol
Study type	Double-blind RCT, randomisation by a computer-generated random number table (1.2 to 1 stratification in favour of imipramine), randomisation key locked until study completion Study drugs/placebo given in opaque envelopes Aim; to evaluate the efficacy and safety of imipramine hydrochloride in patients with IBS who have failed to respond satisfactorily to antispasmodics
Study quality	
Number of patients	N=107 (N=59 imipramine, N=48 placebo)
Patient characteristics	Recruited from adverts in clinics and pharmacies or referral from primary care or speciality clinics (December 2004 to May 2006) Inclusion: - Fulfilment of Rome II criteria - History of unsatisfactory response to ≥1 of the available prescription antispasmodics Exclusion: - <18yrs, allergy to imipramine - History of symptoms of GI bleeding, severe constipation - Pregnancy, history of cardiac arrhythmias - Use of any drug that could influence bowel function within previous month - Lactose intolerance, use of antidepressants or signs and symptoms of clinical depression or any evidence of advanced organic or psychiatric disease that may impact compliance or adherence to the study protocol All completed a pre-treatment SF-36 Both groups comparable with regard to age, sex and symptoms; mean age imipramine (42.6±12.4yrs), placebo (45.3±13.8yrs)
Intervention	Imipramine 25mg, daily before bed for 12weeks At day 14 patient with unsatisfactory global improvement could double their daily dose – decision taken by patients based on their tolerance to side effects (once change made had to be continued)
Comparison	Placebo
Length of follow up	4weeks (16weeks in total)
Location	Lebanon

Bibliographic reference	Abdul-Baki et al (2009) A randomized controlled trial of imipramine in patients with irritable bowel syndrome. World J Gastroenterol

Outcomes measures and effect size

Feeling of global symptom relief as reported by subjects (contacted on weeks 4, 8, and 12 of treatment, and week 16 off-treatment) to the questions; “Have your symptoms improved satisfactorily since starting the study drug?”

At week 12 SF-36 questionnaire

Compliance checked by pill count

Doubling dose;

- N=16 (27.1%) imipramine and N=19 (39.6%) placebo doubled dose at day 14 (p=0.188)
- No association between increased dose in imipramine and global symptom improvement, side effects or adverse events

Drop-outs by week 16;

	Imipramine (N=59)	Placebo (N=48)	P value
Total	28 (47.5%)	23 (47.9%)	NS
Premature withdrawal	8 (13.6%)	14 (29.2%)	<0.05
Lost to follow-up	3 (5.1%)	3 (6.3%)	NS
Protocol violation	3 (5.1%)	0	NS
Side effects	14 (23.7%)	6 (12.5%)	0.094
	Side effects reported; sleep disturbance, urologic symptoms, palpitations, anxiety, dry mouth, dizziness, flushing and sweating, constipation		

Results

Global symptom relief;

	Imipramine ITT analysis	Placebo ITT analysis	P value ITT analysis	Imipramine PP analysis	Placebo PP analysis	P value PP analysis
Week 4	59.3%	43.8%	NS	90.3%	68.0%	<0.05
Week 8	50.8%	37.5%	NS	87.1%	64.0%	<0.05
Week 12	42.4%	25.0%	0.06	80.6%	48.0%	<0.05
Week 16	30.5% (18/59)	14.6% (7/48)	NS	58.1%	28.0%	<0.05

<table>
<tr><th>Bibliographic reference</th><th>Abdul-Baki et al (2009) A randomized controlled trial of imipramine in patients with irritable bowel syndrome. World J Gastroenterol</th></tr>
<tr><td></td><td>Relief of baseline symptoms at 12weeks (per protocol);
- 80.6% (imipramine) vs 48.0% (placebo), p=0.01

Change in QoL (SF-36) at week 12 (per protocol);
- Baseline mean SF-36; imipramine (96.1±25.0), placebo (102.2±17.0), p=0.307
- Week 12; imipramine (113.7±19.4), placebo (108.6±15.9), p=0.3
- Mean percent difference; imipramine 11.8%±13.2%, placebo 4.3%±9.0%, p=0.02

Adverse effects:
N=14/28 (23.7%) with imipramine dropped out due to side effects, N=6 (12.5%) with placebo, p=0.094
<table>
<tr><td>Reasons for drop-out (imipramine)</td><td>N=14</td></tr>
<tr><td>Sleep disturbance</td><td>3 (21%)</td></tr>
<tr><td>Urologic symptoms</td><td>2 (14%)</td></tr>
<tr><td>Palpitations</td><td>2 (14%)</td></tr>
<tr><td>Anxiety</td><td>1 (7%)</td></tr>
<tr><td>Dry mouth</td><td>1 (7%)</td></tr>
<tr><td>Dizziness</td><td>3 (21%)</td></tr>
<tr><td>Flushing & sweating</td><td>1 (7%)</td></tr>
<tr><td>Constipation</td><td>1 (7%)</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>Sample size calculation based on the assumption of 60% response to imipramine vs a 30% response to placebo, estimated sample size 56 patient/arm. Did not meet this in recruitment, from those randomised calculated the power to be 88.4%.
Analysis of primary end-point (global symptom relief) used ITT
SF-36 scores, per protocol analysis</td></tr>
</table>

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Bibliographic reference	Ladabaum et al (2010) Citalopram is not effective therapy for non-depressed patient with irritable bowel syndrome. Clin Gastroenterol Hepatol
Study type	Double-blind RCT (Investigational drug pharmacy generated 3 block-randomisation lists stratified by IBS-subtype) To examine the effect of the SSRI citalopram on symptoms and quality of life in non-depressed patients with IBS
Study quality	

Bibliographic reference	Ladabaum et al (2010) Citalopram is not effective therapy for non-depressed patient with irritable bowel syndrome. Clin Gastroenterol Hepatol
Number of patients	N=54 (N=27 citalopram, N=27 placebo)
Patient characteristics	Recruited from primary, secondary and tertiary care settings, including general medicine and gastroenterology clinics and community practices through fliers, letters to providers, on-site recruitment and invitation letters Inclusion: - 18-75yrs, fulfilment of Rome II criteria - Not depressed, without conditions to explain abdominal pain and altered defecation, normal sigmoidoscopy or colonscopy within 5yrs of enrolment, normal blood count and thyroid function, those with diarrhoea had to have negative stool studies for ova and parasites and normal colon biopsies - Average pain/discomfort of ≥3 during the screening week Exclusion: - diagnosis of depression, taking anti-depressant medication, pregnancy - Taking IBS medications including alosetron, tegaserod, antispasmodics, or anticholinergics, or chronic pain medications including opiates within 4weeks of entry - Prior colon or rectal surgery, major organ disease including diabetes Fibre or loperamide use as needed was allowed Demographic characteristics did not differ substantially between the groups
Intervention	Citalopram 20mg (1 capsule/day) for 4weeks, then 40mg for 4weeks
Comparison	Placebo – identical capsules
Length of follow up	No additional follow-up
Location	USA
Outcomes measures and effect size	Symptoms; Primary measure – self-reported weekly “adequate relief” of IBS symptoms. Overall response defined as achieving “adequate relief” on ≥3 of the last 6weeks Quality of life; Primary measure – change in IBS-QOL score from baseline to study end Rectal sensitivity by barostat (results not reported in this ET)

Bibliographic reference	Ladabaum et al (2010) Citalopram is not effective therapy for non-depressed patient with irritable bowel syndrome. Clin Gastroenterol Hepatol

Secondary outcomes;

Changes in overall IBS symptom score, pain/discomfort score, number and consistency of daily bowel movements, urgency score, number of days/week with adequate relief, satisfaction with these parameters

IBS subtypes;

	Total	Citalopram	Placebo
Constipation	21 (39%)	10 (37%)	11 (41%)
Diarrhoea	23 (43%)	12 (44%)	11 (41%)
Alternating	10 (19%)	5 (19%)	5 (19%)

Drop-outs (all withdrew due to side effects);

N=7/20 (26%) citalopram, 2/25 (7%) placebo

Results

Symptoms;

Overall response rate;

N=12/27 (44%) citalopram, N=15/27 (56%) placebo, p=0.59

Not superior for citalopram vs placebo for any of the IBS subgroups

Adequate relief;

No statistically significant differences between the groups during any week (for both ITT or PP analysis)

Logistic regression model of adequate relief as a function of study week (assuming citalopram effect builds linearly over time starting at week 3), OR for citalopram vs placebo 0.80(95%CI, 0.614 to 1.035)

Symptom and satisfaction scores;

	Week 4 Mean (SD)			Week 8 Mean (SD)		
	Citalopram (N=22)	Placebo (N=25)	P value	Citalopram (N=20)	Placebo (N=25)	P value
Overall IBS symptoms	4.0 (2.2)	4.4 (2.4)	0.48	3.5 (2.5)	4.4 (3.0)	0.24
Satisfaction with IBS symptoms	5.4 (2.7)	4.6 (3.0)	0.42	5.9 (3.4)	5.4 (3.4)	0.71

Bibliographic reference	Ladabaum et al (2010) Citalopram is not effective therapy for non-depressed patient with irritable bowel syndrome. Clin Gastroenterol Hepatol

Days with adequate relief/week	3.6 (2.1)	3.4 (2.1)	0.76	4.0 (2.3)	4.0 (2.3)	0.88
Abdominal pain	4.2 (2.6)	4.4 (2.5)	0.80	3.7 (2.6)	4.3 (3.0)	0.39
Urgency	3.7 (2.6)	3.3 (2.6)	0.60	3.6 (2.5)	3.2 (2.7)	0.56
No. bowel movements/week	2.2 (1.1)	2.2 (3.2)	0.09	2.3 (1.4)	1.9 (1.6)	0.29
Stool consistency	6.5 (2.0)	6.0 (1.9)	0.38	6.2 (2.0)	6.1 (1.8)	0.79

Quality of life;

IBS-QOL overall score and subscores;

	Week 0 Mean (SD)			Week 8 Mean (SD)		
	Citalopram (N=27)	Placebo (N=27)	P value	Citalopram (N=20)	Placebo (N=25)	P value
Overall	71 (6)	67 (23)	0.85	74 (18)	74 (24)	0.85
Body image	71 (20)	70 (21)	0.82	75 (18)	79 (22)	0.26
Dysphoria	69 (21)	65 (27)	0.73	73 (24)	72 (29)	0.64
Food avoidance	61 (23)	56 (29)	0.62	60 (30)	66 (27)	0.38
Health worry	68 (21)	58 (29)	0.24	74 (21)	68 (27)	0.58
Interference with activity	67 (20)	67 (25)	0.83	68 (22)	76 (27)	0.16
Relationships	77 (17)	72 (32)	0.78	83 (18)	78 (26)	0.89
Social reaction	79 (17)	73 (26)	0.77	83 (21)	79 (26)	0.73
Sexual	77 (32)	74 (32)	0.71	83 (28)	77 (31)	0.62

Adverse effect;

N=9 (17%) withdrew due to adverse effects (N=7 (26%) intervention, N=2 (7%) placebo), NS difference between the groups

Source of funding	NIH Grant M01-RR00079 (including clinical associate physician award to first author), NIH/NCRR UCSF-CTSI grant number UL 1 RR024131, AGA/Solway Award for clinical research in irritable bowel syndrome/motility
Comments	Using previous standardised reported mean improvements in pain with antidepressants estimated that to detect an effect size of 0.9SD in global symptoms with a 2-sided α0.05, 54 subjects were needed Used ITT, those who withdrew were considered as non-responders

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<table>
<tr><th>Bibliographic reference</th><th>Ruepert L, Quartero AO et al (2011) Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. Cochrane Review</th></tr>
<tr><td>Quality of life outcomes measures – studies included in Cochrane 2011</td><td>No quality of life outcomes;
- Kuiken (2003), Masand (2009), Myren (1982), Rajagopalan (1998), Tack (2006), Vahedi (2005), Vahedi (2008), Vij (1991)

Quality of life outcomes;
- Tabas (2004), Talley (2008)

Tabas (2004):
High fibre diet with paroxetine (10 or 20mg) compared with high fibre diet with placebo (baseline IBS QOL compared with scores at week 14)
<table>
<tr><td>IBS QOL scores, % of improvement</td><td>Paroxetine (N=38)</td><td>Placebo (N=43)</td><td>P value</td></tr>
<tr><td>Food avoidance score</td><td>25.4</td><td>13.7</td><td>0.03</td></tr>
<tr><td>Work function score</td><td>25.4</td><td>12.0</td><td>0.08</td></tr>
<tr><td>Social function score</td><td>22.5</td><td></td><td>0.76</td></tr>
<tr><td>Desire to continue medication when clinical trial ends, no. (%)</td><td>21 (84%)</td><td>11 (36.7%)</td><td><0.001</td></tr>
</table>
Talley (2008):
Imipramine, citalopram compared with placebo (baseline to week 12)
<table>
<tr><td>Change scores in variable</td><td>Citalopram (N=17)</td><td>Imipramine (N=18)</td><td>Placebo (N=16)</td><td>P value</td></tr>
<tr><td>SF-36, physical component</td><td>3.5 (6.1)</td><td>7.3 (7.3)</td><td>6.5(4.6)</td><td>0.40</td></tr>
<tr><td>SF-36 mental component</td><td>0.0 (4.1)</td><td>4.8 (4.5)</td><td>-1.9 (7.2)</td><td>0.07</td></tr>
</table>
</td></tr>
</table>

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<table>
<tr><th>Bibliographic reference</th><th>Ruepert L, Quartero AO et al (2011) Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. Cochrane Review</th></tr>
<tr><td>Adverse effects reporting – studies included in Cochrane 2011</td><td>No adverse effects outcomes reported;
- Myren (1982), Rajagopalan (1998), Tabas (2004), Tack (2006)

Adverse effects reported;</td></tr>
</table>

Bibliographic reference	Ruepert L, Quartero AO et al (2011) Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. Cochrane Review

- Kuiken (2003), Masand (2009), Talley (2008), Vahedi (2005), Vahedi (2008), Vij (1991)

Kuiken (2003):

Fluoxetine 20mg compared with placebo

N=6 intolerable adverse effects, dropped out (N=2 intervention, N=4 placebo)

Adverse effects (most frequently dizziness and drowsiness, less frequently diarrhoea, constipation, headaches, nausea, itching) similar between groups (N=10 intervention, N=8 placebo)

Masand (2009):

Paroxetine (12.5-50mg) compared with placebo

NS differences between the groups in treatment-emergent adverse events

Adverse events occurring in ≥5% of subjects during the study period, number (%)		
	Paroxetine (N=36)	Placebo (N=36)
Drowsiness	13 (36.1%)	9 (25.0%)
Dry mouth	10 (27.7%)	6 (16.6%)
Female genital disorders (paroxetine N=31, placebo N=32)	8 (25.8%)	4 (12.5%)
Erectile dysfunction (paroxetine N=5, placebo N=4)	1 (20.0)	0
Nightmare/vivid dreams	6 (16.6%)	5 (13.8%)
Poor sleep	6 (16.6%)	5 (13.8%)
Fatigue	6 (16.6%)	5 (13.8%)
Increased appetite	5 (13.8%)	3 (8.3%)
Constipation	3 (8.3%)	3 (8.3%)
Headache	3 (8.3%)	7 (19.4%)
Anxiety	3 (8.3%)	2 (5.5%)
Weight gain	3 (8.3%)	1 (2.8%)
Sweating	2 (5.5%)	3 (8.3%)
Nausea	2 (5.5%)	3 (8.3%)

Vahedi (2005):

Bibliographic reference	Ruepert L, Quartero AO et al (2011) Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. Cochrane Review

Fluoxetine 20mg compared with placebo
NS difference between the groups in adverse events
No adverse event was sever enough to lead to discontinuation of medications

Adverse event	Fluoxetine (N=22)	Placebo (N=22)
Nausea	4	3
Anorexia	5	1
Diarrhoea	3	1
Nervousness	3	2
Tremor	4	2
Anxiety	3	1
Insomnia	2	3
Headache	5	4
Abdominal cramp	4	2
Oesophagitis	2	0

Vahedi (2008):
Amitriptyline 10mg compared with placebo
NS difference between the groups in adverse events

Adverse event No. (%)	Amitriptyline (N=25)	Placebo (N=25)
Sleepiness	4 (16%)	3 (12%)
Tachycardia	3 (12%)	3 (12%)
Constipation	0	2 (8%)
Blurred vision	0	2 (8%)
Dry mouth	3 (12%)	3 (12%)

Vij (1991):
Doxepin 75mg compared with placebo
N=6/25 (24%) on doxepin experienced drowsiness;

Bibliographic reference	Ruepert L, Quartero AO et al (2011) Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. Cochrane Review
	- N=4 mild, N=2 excessive and withdrew from study

1

G.2 2 Review question 2 (low FODMAP diet)

Bibliographic reference	Halmos et al (2014) A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. Gastroenterology
Study type	RCT, crossover (randomised according to computer generated order), participants blinded to the diet, almost all food was provided Study aim; to compare GI symptoms over 3weeks of a low FODMAP diet with a moderate FODMAP intake on a typical Australian diet in patients with IBS who had not previously received advice from a dietician
Study quality	
Number of patients	N=45 initially, N=38 in analysis (N=30 IBS, N=8 healthy controls)
Patient characteristics	Recruited via advertisements in breath testing centres, community newspapers, and through word of mouth Inclusion: - IBS according to Rome III criteria and health controls - Must not previously have visited a dietician for dietary management of IBS or be currently taking other therapies for IBS - Those with IBS assessed by a gastroenterologist to ensure inclusion and exclusion criteria were met Exclusion: - Exclusion of coeliac disease by duodenal biopsy and/or negative coeliac serologic testing while consuming a gluten-rich diet - Previous abdominal surgery, comorbid conditions such as diabetes NS differences between the IBS groups and the healthy controls in age, sex, BMI, fructose malasorbers, baseline dietary intake Of the N=30 IBS; N=10 IBS-D, N=13 IBS-C, N=5 IBS-M, N=2 IBS-U Baseline GI symptoms in IBS group, 36.0mm (95%CI, 29.5 to 42.5mm) – similar to previous published data

Bibliographic reference	Halmos et al (2014) A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. Gastroenterology
Intervention	Diet low in FODMAP for 21 days – aimed to keep oligosaccharide, fructose in excess of glucose and polyol content of <0.5g Washout of at least 21 days (had usual diet in this period) then crossed over, second interventional diet not commenced until symptoms had returned to the same level as during the baseline period Almost all food (3 main meals and 3 snacks) was provided. Participants instructed to eat to their appetite, additional food lists provided if participants wanted more. (if they ate a meal out or wanted to include other foods they contacted the study investigator for guidance). All food consumed recorded in food diaries From days 17-21 of both interventions – all faeces collected On day 19 – hourly breath samples from 12.00 to 18.00, content of hydrogen analysed
Comparison	Diet containing FODMAP content of a typical Australian diet for 21 days – aimed to mimic the FODMAP content previously established by a validated food company questionnaire to be a typically daily content of 4.4g oligosaccharides and 2.6g polyols
Length of follow up	21 day study (21day washout) then crossover to other diet
Location	Australia
Outcomes measures and effect size	Participants further sub-classified as diarrhoea-predominant (IBS-D), constipation-predominant (IBS-C), both diarrhoea and constipation (IBS-M), and those with neither diarrhoea or constipation (IBS-U) GI symptoms measured daily during baseline week and interventional diet periods using a 100-mm analogue scale (0 indicated no symptoms, 100 was worst symptoms ever experienced). VAS score used to measure; overall GI symptoms, abdominal pain, bloating, passage of wind, dissatisfaction with stool consistency Faecal assessment; single independent observer noted faecal frequency, weight, and rated using the King's Stool Chart End point was the difference in overall GI symptoms averaged over the last 14 days of each of the interventional dietary periods measured by the 100-mm VAS Secondary end points included; difference in symptoms of abdominal pain, bloating, passage of wind, dissatisfaction with stool consistency over the last 14 days of interventional periods Only participants who attempted both the diets were included in the analysis

Bibliographic reference	Halmos et al (2014) A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. Gastroenterology

N=7/45 (3 IBS, 4 healthy controls) dropped out before the second diet

N=38, N=30 IBS, N=8 healthy controls

Results:
Overall GI symptoms, compared with baseline (36.0mm (95%CI, 29.5 to 42.5mm)

- Low FODMAP – 22.8mm (95%CI, 16.7 to 28.8mm), p<0.001
- Typical diet – 44.9mm (95%CI, 36.6 to 53.1mm), p<0.001

Bloating, abdominal pain and dissatisfaction with stool consistency:

	Bloating (VAS 0-100mm)	**Abdominal pain (VAS 0-100mm)**	**Dissatisfaction with stool consistency (VAS 0-100mm)**	**Composite scores (VAS 0-300mm)**
IBS, N=30, typical diet	45.1 (35.1 to 55.0), p<0.001	43.8 (35.0 to 52.5), p<0.001	47.8 (37.6 to 57.9), p<0.001	137 (110 to 163), p<0.001
IBS, N=30, low FODMAP	24.2 (17.1 to 31.2)	22.5 (16.3 to 28.6)	25.9 (18.9 to 32.9)	73.1 (54.0 to 92.1)
Healthy controls, N=8, typical diet	11.8 (5.9 to 17.8), p=0.742	9.6 (5.1 to 14.4), p=0.742	17.7 (7.5 to 27.9), p=0.547	38.7 (19.4 to 57.9), p=0.304
Healthy controls, N=8, low FODMAP	10.4 (5.4 to 15.4)	9.1 (4.6 to 13.7)	10.1 (4.9 to 15.2)	29.6 (14.9 to 44.4)

Source of funding	The National Health and Medical Research Council of Australia, the Eva and Les Erdi Foundation, scholarship from the Faculty of Medicine, Nursing and Health Sciences
Comments	Power calculations based on consensus opinion as previously published data were not suitable. Assumed that the minimum detectable difference in the primary end point was 20mm, that the variance for the difference was 25mm for an 80% power and p of 0.05, with this 27 patients would be required. No power calculations done for healthy participants

1

Bibliographic reference	Staudacher et al (2012) Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. The Journal of Nutrition
Study type	RCT (randomisation by a computer-based random number generator, undertaken by researcher not involved in patient recruitment) Study aim; to investigate the effects of fermentable carbohydrate restriction on luminal microbiota, short-chain fatty acids

Bibliographic reference	Staudacher et al (2012) Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. The Journal of Nutrition
	and GI symptoms in patients with IBS
Study quality	
Number of patients	N=41
Patient characteristics	Recruited via medical notes review, recruited from GI outpatient clinics at Guy's and St. Thomas's NHS Foundation Trust Inclusion: - 18-65yrs, IBS defined by Rome III criteria - Bloating and/or diarrhoea Exclusion: - If their major IBS symptom was constipation or if their bloating or diarrhoea did not fulfil the severity criteria - Pregnancy or lactation, use of probiotics or prebiotics, lactulose, or bowel preparation in the 4weeks prior to study - Change in IBS medication in the 4weeks prior to the study, or during the study 7-day screening period; completed symptom diary based on the GI Symptom Rating Scale (validated in IBS), stool frequency and consistency using the Bristol Stool Chart, completed a food diary All participants advised to avoid probiotics and prebiotics for the duration of the study All advise to both groups given by the same dietician In response to the global symptom question, NS difference at baseline in those reporting adequate control between the groups
Intervention	N=19, for 4weeks Advised to restrict foods high in fructans, galactooligiosaccharides, polyols, lactose and excess fructose
Comparison	N=22 Advised to continue with their habitual diet
Length of follow up	
Location	UK
Outcomes measures and effect size	Outcomes on fluorescent in situ hydribization, faecal microbiota (primary outcome), short-chain fatty acids and pH (secondary outcomes) not reported in this evidence table. N=6/41 dropped out;

Bibliographic reference	Staudacher et al (2012) Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. The Journal of Nutrition

- 4 withdrew (2 started antibiotics, 1 lost to follow-up, 1 poor symptom control)
- 2 withdrawn due to protocol violations

In the final week of the 4weeks completed a 7-day symptom, stool, and food diary and repeated baseline investigations

Results:
Symptom response (secondary outcome)

Adequate symptom control;

- N=13/19 (68%) intervention, N=5/22 (23%) control, p=0.005 (ITT analysis)

Incidence (mean (95%CI) days/wk experienced symptom) and severity score (per protocol analysis);

	Incidence Control	Incidence Intervention	P value	Severity Control	Severity Intervention	P value
Bloating	5.7 (4.9 to 6.4)	3.8 (3.0 to 4.6)	0.002	1.4 (1.2 to 1.6)	0.9 (0.6 to 1.1)	0.002
Abdominal pain	4.8 (4.1 to 5.5)	3.6 (2.8 to 4.4)	0.02	1.1 (0.9 to 1.4)	0.8 (0.5 to 1.1)	0.07
Flatulence	5.6 (4.6 to 6.5)	4.3 (3.3 to 5.3)	0.07	1.2 (1.0 to 1.5)	0.8 (0.5 to 1.1)	0.018
Borborygmi	2.8 (1.9 to 3.7)	2.0 (1.0 to 3.0)	0.22	0.7 (0.4 to 0.9)	0.4 (0.2 to 0.6)	0.11
Urgency	3.7 (2.7 to 4.7)	2.6 (1.5 to 3.7)	0.15	0.8 (0.6 to 1.1)	0.6 (0.3 to 0.8)	0.13
Diarrhoea	2.2 (1.3 to 3.1)	1.4 (0.4 to 2.4)	0.24	0.4 (0.2 to 0.6)	0.3 (0.1 to 0.5)	0.34
Constipation	1.0 (0.5 to 1.5)	0.8 (0.3 to 1.3)	0.56	0.2 (0.1 to 0.2)	0.1 (0.1 to 0.2)	0.69
Incomplete evacuation	3.1 (2.1 to 4.1)	2.1 (1.0 to 3.2)	0.16	0.7 (0.4 to 0.9)	0.4 (0.2 to 0.7)	0.16
Heartburn	0.5 (0.0 to 1.1)	0.7 (0.0 to 1.3)	0.70	0.1 (0.0 to 0.2)	0.1 (0.0 to 0.2)	0.98
Nausea	1.8 (0.9 to 2.7)	1.5 (0.5 to 2.5)	0.67	0.4 (0.2 to 0.6)	0.3 (0.1 to 0.5)	0.64
Tiredness	2.0 (1.1 to 3.9)	1.3 (0.6 to 2.6)	0.35	0.9 (0.7 to 1.1)	0.5 (0.3 to 0.7)	0.015
Overall	1.6 (1.3 to 1.9)	0.9 (0.8 to 1.1)	0.001	1.7 (1.4 to 1.9)	1.1 (0.8 to 1.3)	0.002

Stool frequency (per protocol analysis);

Output	Control	Intervention	P value

Bibliographic reference	Staudacher et al (2012) Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. The Journal of Nutrition
	<table><tr><td>Stool frequency mean no./wk</td><td>13.5 (11.9 to 15.1)</td><td>10.2 (8.5 to 11.9)</td><td>0.008</td></tr><tr><td>Stool consistency (Bristol stool chart, BSC)</td><td>4.7 (4.2 to 5.1)</td><td>4.5 (4.0 to 5.0)</td><td>0.56</td></tr><tr><td>% with normal consistency (BSC)</td><td>6.6 (1.6 to 14.9)</td><td>23.6 (11.9 to 39.1)</td><td>0.02</td></tr></table> Adverse events (not considered to be related to the trial or intervention); - N=2 intervention (bronchitis, pharyngitis) - N=2 control (exacerbation of asthma, pharyngitis)
Source of funding	Not reported
Comments	Sample size calculation based on primary endpoint ITT analysis

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Bibliographic reference	Staudacher et al (2011) Comparison of symptom response following advice for a diet low in fermentable carbohydrates (FODMAPs) versus standard dietary advice in patients with irritable bowel syndrome. Journal of Human Nutrition and Dietetics
Study type	Controlled trial (not randomised) Study aim; to compare in an IBS outpatient service, the clinical effectiveness of the low FODMAP diet with the standard NICE guidelines for dietary therapy for IBS
Study quality	
Number of patients	N=82 (N=43 FODMAP, N=39 standard diet)
Patient characteristics	Consecutive adults with IBS who returned for follow-up dietetic outpatient visits for dietary management of their symptoms Inclusion: - IBS using NICE criteria (abdominal pain or discomfort or bloating or change in bowel habit for at least 6mths)(Rome III stated to not have been used because they are generally used as a research tool rather than in the clinical setting) - First diagnosed with IBS by primary care physician or gastroenterologist, then referred for dietary advice, then seen by a dietician within the previous 2-6mths for management of symptoms NS differences between the groups with regard to age and gender or in the prevalence of each symptom before dietary intervention bloating (70%), diarrhoea (60%), abdominal pain (55%), constipation (40%)
Intervention	Low FODMAP group (seen after implementation of the low FODMAP service); - Advised on reducing dietary FODMAP intake

<table>
<tr><th>Bibliographic reference</th><th>Staudacher et al (2011) Comparison of symptom response following advice for a diet low in fermentable carbohydrates (FODMAPs) versus standard dietary advice in patients with irritable bowel syndrome. Journal of Human Nutrition and Dietetics</th></tr>
<tr><td></td><td>- Clinical judgement and hydrogen breath test results, where available, dictated whether fructose and/or lactose restriction had occurred
- Written information provided at initial consultation via colour booklet</td></tr>
<tr><td>Comparison</td><td>Standard group (those seen before June 2009, before implementation of the low FODMAP service);
- Standard dietary advice based on the general NICE guidelines
- Predominantly general dietary advice (74%)
- Other specific advice provided; reducing lactose (12%), increasing/decreasing fibre (8%), exclusion diet (5%)(avoidance of one or two trigger foods e.g. wheat, milk)
- Written information provided at initial consultation via two-page written resource</td></tr>
<tr><td>Length of follow up</td><td>Unclear</td></tr>
<tr><td>Location</td><td>UK</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Rated symptoms using IBS Global Improvement Scale on;
- changes for bloating, abdominal pain/discomfort, flatulence/wind, diarrhoea, constipation, nausea and energy level

Further four statements related to satisfaction with symptom response and dietary advice;
- ‘overall I am satisfied with the improvement in my symptoms’
- ‘I found the diet easy to follow’
- ‘I found the written information easy to understand’
- ‘I would be interested in further changing my diet to improve my symptoms’

All data recorded anonymously

Results:
Symptom response;

<table>
<tr><th></th><th>Group</th><th>Improved p value</th><th>P value</th><th>No change or worse</th><th>Slightly improved</th><th>Moderately improved</th><th>Substantially improved</th><th>P value</th></tr>
<tr><td rowspan="2">Bloating</td><td>Standard</td><td>17/35(49)</td><td rowspan="2">0.002</td><td>18/35(51)</td><td>3/35(9)</td><td>6/35(17)</td><td>8/35(23)</td><td rowspan="2">0.026</td></tr>
<tr><td>FODMAP</td><td>32/39 (82)</td><td>7/39(18)</td><td>5/39(13)</td><td>11/39(28)</td><td>16/39(41)</td></tr>
<tr><td>Abdominal</td><td>Standard</td><td>20/33(61)</td><td>0.023</td><td>13/33(40)</td><td>7/33(21)</td><td>4/33(12)</td><td>9/33(27)</td><td>0.014</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Staudacher et al (2011) Comparison of symptom response following advice for a diet low in fermentable carbohydrates (FODMAPs) versus standard dietary advice in patients with irritable bowel syndrome. Journal of Human Nutrition and Dietetics

pain/discomfort	FODMAP	29/34(85)		5/34(15)	3/34(9)	13/34(38)	13/34(38)	
Flatulence/ wind	Standard	14/28(50)	0.001	14/28(50)	7/28(25)	4/28(14)	3/28(11)	0.01
	FODMAP	33/38(87)		5/38(13)	15/38(40)	7/38(18)	11/38(29)	
Diarrhoea	Standard	18/29(62)	0.052	11/29(38)	7/29(24)	2/29(7)	9/29(31)	0.017
	FODMAP	30/36(83)		6/36(17)	3/36(8)	10/36(28)	17/36(47)	
Constipation	Standard	10/22(45)	0.161	12/22(55)	6/22(27)	0/22(0)	4/22(18)	0.007
	FODMAP	10/21(67)		7/21(33)	1/21(5)	7/21(33)	6/21(29)	
Nausea	Standard	4/14(29)	0.04	10/14(71)	1/14(7)	2/14(15)	1/14(7)	0.155
	FODMAP	10/15(67)		5/15(33)	4/15(27)	2/15(13)	1/15(27)	
Energy levels	Standard	11/30(37)	0.042	19/30(63)	4/30(13)	5/30(17)	2/30(7)	0.235
	FODMAP	20/32(63)		12/32(37)	6/32(19)	10/32(31)	4/32(13)	
Composite score	Standard	19/39(49)	<0.001	20/39(51)	8/39(21)	7/39(18)	4/39(10)	0.002
	FODMAP	37/43(86)		6/43(14)	9/43(21)	16/43(37)	12/43(28)	

Satisfaction with symptom response;
Satisfaction;
- Low FODMAP 32/42 (76%), standard group 20/37 (54%), p=0.038

Ease of understanding of written information;
- Low FODMAP 100%, standard group 94%, p=0.116

Ease of following the diet;
- Low FODMAP 70%, standard group 85%, p=0.112

Interested in implementing further change to their diet to improve symptoms;
- Low FODMAP 25%, standard group 5%, p=0.014

Subgroup of low FODMAP asked about compliance, N=36/43 (84%);
- Followed diet strictly (N=23/36, 64%); ≥50% of the time (N=11/36, 30%)

Time taken for symptom resolution (N=10), 3.5 (median 2, range 2 to 8)weeks

Source of funding	Guy's and St Thomas' Charity Grant

Bibliographic reference	Staudacher et al (2011) Comparison of symptom response following advice for a diet low in fermentable carbohydrates (FODMAPs) versus standard dietary advice in patients with irritable bowel syndrome. Journal of Human Nutrition and Dietetics
Comments	Power calculations based on consensus opinion as previously published data were not suitable. Assumed that the minimum detectable difference in the primary end point was 20mm, that the variance for the difference was 25mm for an 80% power and p of 0.05, with this 27 patients would be required. No power calculations done for healthy participants

G.31 Review question 3 (linaclotide)

Bibliographic reference	Chey WD, Lembo, AJ, Lavins BJ et al (2012) Linaclotide for Irritable Bowel Syndrome With Constipation: A 26 week, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate Efficacy and Safety. American Journal of Gastroenterology; 107, 1702-1712.
Study type	RCT (Double-blind, parallel-group, placebo controlled randomised phase III trial)
Study Aim	Assess safety and efficacy of linaclotide 290µg vs. placebo for IBS-C over 12 and 26 weeks.
Number of patients	804 (ITT population), 805 (safety population)
Patient characteristics	**Inclusion:** Rome II criteria for IBS-C. 18+. Eligibility for randomisation: average score of ≥3 for daily abdominal pain at its worst (11 point rating scale, 0=no abdo pain, 10=severe abdominal pain) and an average of <3 CSBMs (SBM accompanied by patient self-reporting of a feeling of complete evacuation) per week and ≤5 SBMs/week during the baseline period ((12 weeks) not necessarily consecutive, in the 12 months before the screening visit). **Exclusion:** >25% of BMs loose or watery during 12 weeks before trial History of laxative abuse Pelvic floor dysfunction History of surgery to bowel Bariatric surgery Appendectomy/cholecystectomy within 2 months or other abdominal surgeries within 6 months History of diverticulitis or chronic condition that could be associated with abdominal pain Taking drugs that could cause constipation (TCAs allowed as long as on stable dose with no plan to change during study period) Colonoscopy requirements based on American Gastroenterology Association Guidelines. **Baseline characteristics**

Bibliographic reference	**Chey WD, Lembo, AJ, Lavins BJ et al (2012) Linaclotide for Irritable Bowel Syndrome With Constipation: A 26 week, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate Efficacy and Safety. American Journal of Gastroenterology; 107, 1702-1712.**
	IBS-C. Mean age 44yrs, Female 90%, White 78%. There was a significantly higher proportion of men in the placebo group than the linaclotide group (12.7 vs 8.2% p=0.037). **Attrition** Mean compliance with study drug dosing was 97.2% and 96.8% respectively 655 pts (81.5%) completed 12 weeks and 599 pts (74.4%) completed 26 weeks of study drug. For discontinuation by study arm, see below.
Intervention	Linaclotide 290µg orally OD, 30 mins before breakfast
Comparison	Placebo
Length of follow up	12 and 26 weeks
Location	102 Clinical centres in USA
Outcomes measures and effect size	**Clinical Outcomes** Symptoms recorded using participant voice response system on a daily basis for all outcomes below, except constipation severity (assessed weekly). Pain measured using 11 point numerical rating scale. CSBM = Complete spontaneous bowel movement (frequency)

	12 Weeks		RR (95% CI) (calculated by reviewer)	26 Weeks		RR (95% CI) (calculated b reviewer)
Outcome	**Placebo n=403 (%)**	**Linaclotide n=401 (%)**		**Placebo n=403 (%)**	**Linaclotide n=401 (%)**	
FDA Pain Responder (≥30% improvement 50% of weeks)	139 (34.5)	196(48.9)	1.42 [1.20, 1.68]	126 (31.3)	197 (49.1)	1.57 [1.32,1.8
FDA responder for stool frequency (≥3 CSBMs/week plus increase of ≥1 CSBM/week, 50% of weeks)	91 (22.6)	191 (47.6)	2.11 [1.71, 2.60]	75 (18.6)	175 (43.6)	2.34 [1.85, 2.
FDA Combined responder pain and stool frequency (50% of weeks)	56 (13.9)	135 (33.7)	2.42 [1.83, 3.20]	53 (13.2)	130 (32.4)	2.47 [1.85, 3.
FDA Pain Responder (≥30% improvement 75% of weeks)	79 (19.6)	156 (38.9)	1.98 [1.57, 2.50]	70 (17.4)	148 (36.9)	2.12 [1.66, 2.
FDA Combined responder Pain and stool frequency 75% of	12 (3.0)	51 (12.7)	4.27 [2.31, 7.89]	10 (2.5)	48 (12.0)	4.82 [2.48, 9.

Bibliographic reference	**Chey WD, Lembo, AJ, Lavins BJ et al (2012) Linaclotide for Irritable Bowel Syndrome With Constipation: A 26 week, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate Efficacy and Safety. American Journal of Gastroenterology; 107, 1702-1712.**

weeks						
Constipation Responder (improvement in stool consistency ≥1 point on BSFS)	159 (39.5)	244 (60.8)	1.54 [1.34, 1.78]	139 (34.5)	221 (55.1)	1.60 [1.36, 1.88]
Bloating Responder (improvement for min 50% wks)	96 (23.8)	172 (42.9)	1.80 [1.46, 2.22]	101 (25.1)	170 (42.4)	1.69 [1.38, 2.07]

Constipation Severity (5 point scale)	**Placebo**	**Linaclotide**
Baseline MEAN (SD)	3.8 (0.7)	3.8 (0.7)
12 weeks (no SD)	3.2	2.6
Least squares mean change from baseline (ANCOVA)*	-0.6	-1.2
26 weeks (no SD)	3.2	2.6
Least squares mean change from baseline (ANCOVA)*	-0.6	-1.2
*Difference -0.6, p<0.0001		

Discontinuation, adverse events (AE) and serious adverse events (SAE)

Discontinuation

	Placebo n=403 (%)	**Linaclotide n=402 (%)**	**Total n=805 (%)**	**RR (95% CI) Calculated by reviewer**
Total discontinued*(26 weeks)* Data not reported at 12 weeks.	98 (24.3)	108 (26.9)	206 (25.7)	1.13 [0.90, 1.43]
Total completed	*305 (75.7)*	*284 (73.1)*	*599 (74.3)*	-

Reason for Discontinuation (Safety population, 26 weeks)

Bibliographic reference	Chey WD, Lembo, AJ, Lavins BJ et al (2012) Linaclotide for Irritable Bowel Syndrome With Constipation: A 26 week, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate Efficacy and Safety. American Journal of Gastroenterology; 107, 1702-1712.

	Placebo n=403 (%)	Linaclotide n=402 (%)	Total n=805 (%)	RR (95% CI) (Calculated by reviewer)
Adverse event	10 (2.5)	41 (10.2)	51 (6.3)	4.1 [2.08, 8.09]
Adverse Event = diarrhoea	1 (0.2)	18 (4.5)	19 (4.7))	18.0 [2.42, 134.5]
Withdrew consent	26 (6.5)	24 (6.0)	50 (6.2)	0.93 [0.54, 1.58]
Insufficient therapeutic response	33 (8.2)	15 (3.7)	48 (6.0)	0.45 [0.25, 0.83]
Lost to follow-up	13	18	31 (3.9)	Not calculated
Other	5	2	7 (0.9)	Not calculated
Protocol violation	11	8	19 (2.4)	Not calculated

Treatment Emergent Adverse Events (Safety population, 26 weeks) reported in ≥2% of linaclotide treated patients and at incidence greater than placebo treated patients.

	Placebo n=403 (%)	Linaclotide n=402 (%)	RR (95% CI) (calculated by reviewer)
Participants with at least one TEAE	228 (56.6)	263 (65.4)[a]	1.16 [1.03, 1.29]
Diarrhoea	10 (2.5)	79 (19.7)[b]	7.92 [4.16, 15.1]
Abdominal Pain	16 (4.0)	18 (4.5)	1.12 [0.58, 2.18]
Flatulence	9 (2.2)	15 (3.7)	1.67 [0.74, 3.78]
Abdominal distension	6 (1.5)	9 (2.2)	1.50 [0.54, 4.19]
URTI	22 (5.5)	22 (5.5)	Not calculated
Viral gastroenteritis	9 (2.2)	15 (3.7)	Not calculated
Headache	11 (2.7)	13 (3.2)	Not calculated

[a] p value reported <0.05 (Fisher's exact)
[b] p value reported 0.0001 (Fisher's exact)

Serious Adverse Events

	Placebo n=403 (%)	Linaclotide n=402 (%)	RR (95% CI) (Calculated by reviewer)

Bibliographic reference	**Chey WD, Lembo, AJ, Lavins BJ et al (2012) Linaclotide for Irritable Bowel Syndrome With Constipation: A 26 week, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate Efficacy and Safety. American Journal of Gastroenterology; 107, 1702-1712.**
	SAE* | 7 (1.7) | 4 (1.0) | 0.57 [0.17, 1.93] *(Cuff syndrome, appendicitis, cystopexy and Hodgkin's disease. None deemed by site investigator to be related to linaclotide)
Source of funding	Forest Research Institute and Ironwood Pharmaceuticals
Comments	

- Constipation rescue medication (5mg bisacodyl or 10mg suppositories) was permitted and recorded but there is no reporting of frequency of use by study arm.
- There is no mention of use of fibre supplementation, dietary fibre modification, exercise or fluid intake by study arm.
- There is no report of the frequency of assessment or recording for adverse events, raising concern around possible recall bias.

Other non-protocol outcomes reported: Abdominal fullness, severity of straining, treatment satisfaction.

1

Bibliographic reference	**Rao S, Lembo MD, Shiff SJ, Kurtz CB, Currie MG, MacDougall JE, Jia XD, Shao JZ, Fitch DA, Baird MJ, Schneier HA, Johnston JM (2012) A 12-Week, Randomized, Controlled Trial With a 4-week Randomized Withdrawal Period to Evaluate the Efficacy and Safety of Linaclotide in Irritable Bowel Syndrome With Constipation. American Journal Gastroenterology; 107:1714-1724.**
Study type	RCT (double-blind, parallel group, placebo controlled phase 3 trial)
Aim	To determine the efficacy and safety of linaclotide in patients with IBS-C
Number of patients	800 (ITT) (placebo 395, linaclotide 405) 802 (Safety Population)
Patient characteristics	**Inclusion:** Rome II criteria for IBS-C. 18+. Eligibility for randomisation: average score of ≥3 for daily abdominal pain at its worst (11 point rating scale, 0=no abdo pain, 10=severe abdominal pain) and an average of <3 CSBMs (SBM accompanied by patient self-reporting of a feeling of complete evacuation) per week and ≤5 SBMs/week during the baseline period ((12 weeks) not necessarily consecutive, in the 12 months before the screening visit). **Exclusion:** >25% of BMs loose or watery during 12 weeks before trial

<table>
<tr><th>Bibliographic reference</th><td>Rao S, Lembo MD, Shiff SJ, Kurtz CB, Currie MG, MacDougall JE, Jia XD, Shao JZ, Fitch DA, Baird MJ, Schneier HA, Johnston JM (2012) A 12-Week, Randomized, Controlled Trial With a 4-week Randomized Withdrawal Period to Evaluate the Efficacy and Safety of Linaclotide in Irritable Bowel Syndrome With Constipation. American Journal Gastroenterology; 107:1714-1724.</td></tr>
<tr><td></td><td>History of laxative or enema abuse
History of cathartic colon or ischaemic colitis
Pelvic floor dysfunction
History of surgery to bowel
Bariatric surgery
Appendectomy/cholecystectomy within 2 months or other abdominal surgeries within 6 months
History of diverticulitis or chronic condition that could be associated with abdominal pain or discomfort
Family history of a familial form of colorectal cancer
Taking drugs that could cause constipation (TCAs allowed as long as on stable dose with no plan to change during study)
Colonoscopy requirements based on American Gastroenterology Association Guidelines.
Adequate contraception in women of childbearing age
Patients were asked to avoid making any lifestyle changes such as starting a new diet or exercise regimen

Baseline Characteristics
<table>
<tr><th></th><th>Total 800 ITT</th><th>Placebo n=395</th><th>Linaclotide n=405</th></tr>
<tr><td>Mean age (Y)</td><td>43.5</td><td>43.7(18-84)</td><td>43.3(19-81)</td></tr>
<tr><td>Gender F</td><td>724 (90.5)</td><td>357(90.4)</td><td>367(90.6)</td></tr>
</table>
Attrition
See discontinuation below</td></tr>
<tr><td>Intervention</td><td>Linaclotide 290µg OD (timing not specified)</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Length of follow up</td><td>12 Weeks (+21 day screening period and 14-21 day baseline period).</td></tr>
<tr><td>Location</td><td>111 outpatient clinical research centres USA, 7 centres in Canada. Email correspondence confirmed there was no duplication of study participants between the very similar study reported above (Chey et al. 2012).</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Clinical Outcomes
Daily symptoms recorded using voice response system on all outcomes below, except constipation severity (weekly assessment). Pain measured using 11 point numerical rating scale.
CSBM = Complete spontaneous bowel movement (frequency)</td></tr>
</table>

Bibliographic reference	**Rao S, Lembo MD, Shiff SJ, Kurtz CB, Currie MG, MacDougall JE, Jia XD, Shao JZ, Fitch DA, Baird MJ, Schneier HA, Johnston JM (2012) A 12-Week, Randomized, Controlled Trial With a 4-week Randomized Withdrawal Period to Evaluate the Efficacy and Safety of Linaclotide in Irritable Bowel Syndrome With Constipation. American Journal Gastroenterology; 107:1714-1724.**

	Week 12		
Outcome	**Placebo n=395 (%)**	**Linaclotide n=405 (%)**	**RR (95% CI) Calculated by reviewer**
FDA Pain Responder (≥30% improvement 50% of weeks)	148 (37.5)	203 (50.1)	RR 1.38 [1.14, 1.57]
FDA responder for stool frequency (≥3 CSBMs/Wk plus increase of ≥1 CSBM/week for 50% of weeks)	117 (29.6)	197 (48.6)	RR 1.64 [1.37, 1.97]
FDA Combined responder pain and stool frequency (50% of weeks)	83 (21.0)	136 (33.6)	RR 1.60 [1.26, 2.02]
FDA pain responder (≥30% improvement 75% of weeks)	107 (27.1)	139 (34.3)	RR 1.26 [1.03, 1.56]
FDA Combined responder pain and stool frequency (75% of weeks)	20 (5.1)	49 (12.1)	RR 2.39 [1.44, 3.94]
Constipation Responder (improvement in stool consistency ≥1 point on BSFS)	168 (42.5)	241 (59.5)	RR 1.40 [1.22, 1.61]
Bloating Responder (improvement 50% wks)	118 (29.9)	176 (43.5)	RR 1.45 [1.20, 1.75]

Constipation Severity (5 point scale)	**Placebo**	**Linaclotide**
Baseline MEAN (SD)	3.7 (0.6)	3.8 (0.6)
12 weeks (no SD)	3.1	2.6
Least squares mean change from baseline (ANCOVA)	-0.6	-1.2
Difference -0.6 P <0.0001		

Discontinuation and Adverse Events (AE)

Discontinuation (All reasons)

	Placebo n=397 (%)	**Linaclotide n=406**	**Total**	**RR (95% CI)**

Bibliographic reference	**Rao S, Lembo MD, Shiff SJ, Kurtz CB, Currie MG, MacDougall JE, Jia XD, Shao JZ, Fitch DA, Baird MJ, Schneier HA, Johnston JM (2012) A 12-Week, Randomized, Controlled Trial With a 4-week Randomized Withdrawal Period to Evaluate the Efficacy and Safety of Linaclotide in Irritable Bowel Syndrome With Constipation. American Journal Gastroenterology; 107:1714-1724.**

		(%)	n=803 (%)	Calculated by reviewer
Total discontinued	62 (15.6)	94 (23.2)	156 (19.4)	1.48 [1.11, 1.98]
Total completed (12 weeks)	*335*	*312*	*647*	-

Reason for Discontinuation

	Placebo n=397 n (%)	Linaclotide n=406 n (%)	Total n=803 n (%)	RR (95% CI) Calculated by reviewer
Adverse Event	10 (2.5)	32 (7.9)	42 (5.2)	3.13 [1.56, 6.28]
Adverse Event = diarrhoea	1 (0.3)	23 (5.7)	24 (3.0)	22.49 [3.05, 165.74]
Withdrew consent	25 (6.3)	25 (6.2)	50 (6.2)	0.98 [0.57, 1.67]
Insufficient response	4 (1.0)	5 (1.2)	9 (1.1)	1.22 [0.33, 4.52]
Lost to follow-up	10	17	27	Not calculated
Protocol violation	9	10	19	Not calculated
Other	4	5	9	Not calculated

Treatement Emergent Adverse Events (TEAE) reported in ≥2% of linaclotide treated patients and at incidence greater than placebo treated patients.

Adverse Event	Placebo n=396 (%)	Linaclotide n=406 (%)	P value (Fisher's Exact)	RR (95% CI) Calculated by reviewer
At least 1 TEAE	210 (53.0)	228 (56.2)	0.3949	1.06 [0.93, 1.20]
Diarrhoea	14(3.5)	79 (19.5)	<0.0001	5.50 [3.17, 9.55]
Abdominal Pain	10 (2.5)	22(5.4)	0.0462	2.15 [1.03, 4.47]
Flatulence	6(1.5)	20(4.9)	0.0084	3.25 [1.32, 8.01]
Abdominal distension	3(0.8)	9(2.2)	0.1434	2.93 [0.80, 4.39]
Headache	14(3.5)	20(4.9)	0.3825	Not calculated

SAEs, 2 patients in each group (0.5%). Of the 2 patients in the treatment group, 1 participant had asthma, and 1 had peri-

Bibliographic reference	**Rao S, Lembo MD, Shiff SJ, Kurtz CB, Currie MG, MacDougall JE, Jia XD, Shao JZ, Fitch DA, Baird MJ, Schneier HA, Johnston JM (2012) A 12-Week, Randomized, Controlled Trial With a 4-week Randomized Withdrawal Period to Evaluate the Efficacy and Safety of Linaclotide in Irritable Bowel Syndrome With Constipation. American Journal Gastroenterology; 107:1714-1724.**
	cardial effusion and pericarditits leading to withdrawal from the study. RR (95% CI), calculated by reviewer; 0.98 [0.14, 6.89].
Source of funding	Forest Research Institute and Ironwood Pharmaceuticals
Comments	• Rescue medication was permitted and recorded in daily voice recording but data is not presented on frequency of use (or evaluation of any differences in frequency) by study arm. This is a concern as the intervention and the rescue medication are both treating constipation. • Patients on stable regimen of fibre, bulk laxatives, stool softeners or probiotics were allowed to continue provided they maintained a stable dosage throughout. There is no mention of compliance. Ongoing use of other classes of laxatives, without evidence of frequency of use by study arm, is a major concern since the intervention is also a laxative. • Patients were asked to avoid making any lifestyle changes such as starting a new diet or exercise regimen but there was no mention of compliance by study arm. • AE data were reported at each clinic visit using retrospective questioning. This raises concern about recall bias. • There was commonality with authorship, participant numbers and recruitment periods and potential commonality with clinical sites between this study, and the above study (Chey et al 2012), thus the corresponding author was contacted via email for clarification. The response received indicated separate clinical sites and only 2 patients had been enrolled in both trials (at different sites) in violation of the protocol, but we were advised this was addressed in US and EU marketing authorisation filings and that sensitivity analyses showed no alteration of the safety and efficacy conclusions of either trial.
Other non-protocol outcomes reported: Straining, abdominal fullness	

1

Bibliographic reference	**Johnston JM, Kurtz CB, MacDougall JE, Lavins BJ, Currie MG, Fitch DA, O'Dea C, Baird M, Lembo AJ (2010) Linaclotide Improves Abdominal Pain and Bowel Habits in a Phase IIb Study of Patients with Irritable Bowel Syndrome with Constipation; 139:1877-1886.**
Study type	RCT (randomised, double-blind, parallel-group, placebo controlled, phase IIb study)
Aim	To assess the efficacy, safety and dose response of linaclotide
Number of patients	420 (efficacy) 419 ITT population.

Bibliographic reference	**Johnston JM, Kurtz CB, MacDougall JE, Lavins BJ, Currie MG, Fitch DA, O'Dea C, Baird M, Lembo AJ (2010) Linaclotide Improves Abdominal Pain and Bowel Habits in a Phase IIb Study of Patients with Irritable Bowel Syndrome with Constipation; 139:1877-1886.**
Patient characteristics	**Inclusion:** 18+ Rome II criteria <3 SBMs per week and ≥1 of the following for at least 12 wks in the preceding 12 months: 4) Straining during ≥25% of bowel movements 5) Lumpy or hard stools during ≥25% of bowel movements 6) Sensation of incomplete evacuation during ≥25% of bowel movements, plus Mean score of ≥2 for abdo (non-menstrual) pain or discomfort on 5 point scale 1=none, 5=v.severe) and Mean of <3 CSBMs and ≤6 SBMs per week. Discontinuation of ineligible medication (e.g. anticholinergic agents, opiods) **Exclusion:** Loose or watery stools in the absence of laxatives for >25% bowel movements 12 weeks preceding the study >1 loose, mushy stool without laxatives in previous 24hrs. History of pelvic floor dysfunction Need to use manual manoeuvres to achieve a BM Surgery of colon (any time) or abdominal surgery within 60 days of entry Laxative abuse Neurological, metabolic disorders or other significant disease Pre-treatment lab/ECG findings determined by investigator to impair participation. Use of prohibited medications (e.g. prokinetics, narcotics) Any surgery within 30 days Pregnant or breast feeding. Use of an investigational drug within 30 days. Patients >50 without colonoscopy screening. Any patients with alarm symptoms must have had a negative colonoscopy Patients were asked to avoid making any lifestyle changes such as starting a new diet or exercise regimen **Baseline Characteristics** N=420 (safety), 419 ITT population. Three other dose arms (see intervention below) were evaluated in this study, however results for 290µg linaclotide only are reported below. This is because two larger RCTs (see above Chey et al 2012 and Rao et al 2012) have evaluated this dose

<table>
<tr><th>Bibliographic reference</th><th>Johnston JM, Kurtz CB, MacDougall JE, Lavins BJ, Currie MG, Fitch DA, O'Dea C, Baird M, Lembo AJ (2010) Linaclotide Improves Abdominal Pain and Bowel Habits in a Phase IIb Study of Patients with Irritable Bowel Syndrome with Constipation; 139:1877-1886.</th></tr>
<tr><td></td><td>
<table>
<tr><th></th><th>All (n=419) ITT</th><th>Placebo (n=85)</th><th>290µg linaclotide (n=84)</th></tr>
<tr><td>Age y. mean (range)</td><td>44.4 (18-72)</td><td>44.3 (21-65)</td><td>46.0 (21-72)</td></tr>
<tr><td>Sex (female) n (%)</td><td>386 (92)</td><td>78 (92)</td><td>77 (92)</td></tr>
</table>

Attrition
83 (19.8%) patients did not complete the study. 25 (6.0%) due to AEs, 4 (1.0%) non-compliance, 34 (8.1%) withdrew consent (reason not stated in paper), 1 (0.2%) at investigator's request and 19 (4.5%) were lost to follow up. These data are not reported by study arm. See discontinuation and adverse events below.
</td></tr>
<tr><td>Intervention</td><td>Linaclotide once daily BEFORE first meal
75µg n=82
150µg(145µg) n=82
300µg(290µg) n=84
600µg n=89</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Length of follow up</td><td>12 weeks (+ up to 28 day screening period and 14 day baseline period and 2 week post-treatment period)</td></tr>
<tr><td>Location</td><td>92 clinical centres in USA/Canada</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Clinical Outcomes
Interactive voice response system used for participants to report IBS and bowel symptoms daily. Degree of relief and constipation severity was recorded weekly. QOL was recorded at baseline and completion.

Results - 290µg arm reported only

QOL (IBS QOL scale = 34 items each rated on 5 point Likert scale, low score = worse QOL)
<table>
<tr><th></th><th>Placebo (n=85)</th><th>Linaclotide 290µg (n=84)</th></tr>
<tr><td>Baseline (mean) (SD)</td><td>53.6 (22.1)</td><td>58.4 (19.0)</td></tr>
<tr><td>12 weeks</td><td>68.1</td><td>72.4</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Johnston JM, Kurtz CB, MacDougall JE, Lavins BJ, Currie MG, Fitch DA, O'Dea C, Baird M, Lembo AJ (2010) Linaclotide Improves Abdominal Pain and Bowel Habits in a Phase IIb Study of Patients with Irritable Bowel Syndrome with Constipation; 139:1877-1886.

Mean change (improvement) ANCOVA*	14.5	14

*No p value reported

QOL (IBS QOL scale) (>14 points stated in the study to be clinically meaningful)

	Placebo (n=85)	**Linaclotide 290µg (n=84)**	**RR (95% CI) calculated by reviewer**
>14 point change	31 (36.5)	31 (36.9)	1.01 (0.68, 1.50)

Interference with your life (subscale of IBS-Severity Scale /100)

	Placebo (n=85)	**Linaclotide 290µg (n=84)**	**P Value**
Baseline (mean) (SD)	Not reported*	Not reported*	
12 weeks	49.5	36.6	<0.01 unadjusted
Mean Change	Unable to calculate	Unable to calculate	

*IBS SS in entirety was reported at baseline, but not by subscales

IBS degree of relief responders (Equivalent to EMA recommended outcome)
(7 point scale 1=completely relieved, 7 = as bad as I can imagine) symptoms 'considerably' or 'completely' relieved (scores 1 or 2) for ≥6/12wks, or 'somewhat', 'considerably' or 'completely' relieved (scores 1,2 or 3) for all 12 wks).

	Placebo (n=85)	**Linaclotide 290µg (n=84)**	**RR (95% CI)**
Responder	25 (29.4)	49 (58.3)	1.98 (1.36, 2.89)

Constipation Severity (5 point scale, 1 = none, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe)

	Placebo (n=85)	**Linaclotide 290µg (n=84)**

Bibliographic reference	**Johnston JM, Kurtz CB, MacDougall JE, Lavins BJ, Currie MG, Fitch DA, O'Dea C, Baird M, Lembo AJ (2010) Linaclotide Improves Abdominal Pain and Bowel Habits in a Phase IIb Study of Patients with Irritable Bowel Syndrome with Constipation; 139:1877-1886.**

Baseline (mean) (SD)	3.7 (0.7)	3.5 (0.7)
12 weeks (mean) No SD	2.95	2.15
Mean difference (improvement)*	0.75	1.35

*No p-value reported

Rescue medication use – 1.0-2.5% of days over the 12 weeks. Reported no significant change in rescue medication use during the post-treatment period compared with the pre-treatment or treatment periods.

Discontinuation and Adverse Events

Discontinuation was not reported by study arm (See attrition above).
Of the 25 patients who discontinued due to adverse events, diarrhoea was the reason in 0 of 2 (placebo) and 1 of 3 in the 290µg dose arm.

AE experienced by ≥3% of ALL linaclotide patients

	Placebo n=85 (%)	**290µg n=85 (%)**	**RR (95% CI) Calculated by reviewer**	**All doses (n=335) ITT (%**
Diarrhoea	1(1.2)	14(16.5)	14 [1.88, 1.04]	49(14.6)
Abdominal pain	3(3.5)	4(4.7)	1.33 [0.31, 5.78]	18(5.4)
Nausea	5(5.9)	1(1.2)	0.2 [0.02, 1.68]	13(3.9)
UTI	2(2.4)	5(5.9)	2.5 [0.50, 12.5]	14(14.2)
Nasopharyngitis	5(5.9)	1(1.2)	Not calculated	11(3.3)
Headache	6(7.1)	3(3.7)	Not calculated	11(3.3)
URTI	3(3.5)	4(4.7)	Not calculated	11(3.3)

1 participant in the 290 µg arm had a SAE. Hospitalisation for faecal impacting leading to temporary withholding of study medication. The participant recovered and completed the study.

Source of funding	Ironwood Pharmaceuticals
Comments	

Bibliographic reference	Johnston JM, Kurtz CB, MacDougall JE, Lavins BJ, Currie MG, Fitch DA, O'Dea C, Baird M, Lembo AJ (2010) Linaclotide Improves Abdominal Pain and Bowel Habits in a Phase IIb Study of Patients with Irritable Bowel Syndrome with Constipation; 139:1877-1886.

- Rescue medication was permitted and recorded in daily voice recording but data is not presented on frequency of use (or evaluation of any differences in frequency) by study arm. This is a concern as the intervention and the rescue medication are both treating constipation.
- Participants were prohibited from taking OTC or prescription medications for IBS or constipation (except in rescue cases) but there is no mention of compliance by study arm.
- Participants were permitted to continue stable fibre therapy and antidepressants and were asked to avoid making any lifestyle changes such as starting a new diet or exercise regimen. There was no mention of compliance by study arm.

Other non-protocol outcomes reported: straining, overall satisfaction with study medication's ability to relieve IBS, likelihood that the participant would continue taking study medication.

1

Bibliographic reference	Quigley EMM, Tack J, Chey WD, Rao SS, Fortea J, Falques M, Diaz C, Shiff SJ, Currie MG & Johnston JM (2013) Randomised clinical trials: linaclotide phase 3 studies in IBS-C – a prespecified further analysis based on European Medicines Agency-specified endpoints; Ailmentary Pharmacology & Therapeutics; 37: 49-61.
Study type	A pre-specified further analysis (of 2 previously published RCTs) based on European Medicines Agency-specified endpoints. Both studies summarised individually above, Chey et al 2012 and Rao et al 2012
Aim	To evaluate the efficacy and safety of linaclotide in IBS-C based on EMA recommended endpoints
Number of patients	803 (Trial 1, Rao et al 2012) 805 (Trial 2, Chey et al 2012). See individual evidence tables above.
Patient characteristics	See tables 1 and 2 above
Intervention	See tables 1 and 2 above
Comparison	See tables 1 and 2 above
Length of follow up	See tables 1 and 2 above
Location	See tables 1 and 2 above
Outcomes measures and effect size	**Clinical Outcomes** Daily symptoms recorded using voice response system. Constipation severity and symptom relief recorded weekly. QOL recorded at baseline and completion. **IBS QOL Scale** (34 questions (divided into 8 subscale scores) each with 5 point scale. Higher score = worse QOL) - ITT

Bibliographic reference	Quigley EMM, Tack J, Chey WD, Rao SS, Fortea J, Falques M, Diaz C, Shiff SJ, Currie MG & Johnston JM (2013) Randomised clinical trials: linaclotide phase 3 studies in IBS-C – a prespecified further analysis based on European Medicines Agency-specified endpoints; Ailmentary Pharmacology & Therapeutics; 37: 49-61.

	Rao 2012			Chey 2012 (Week 12)		
	Placebo (n=395)	**Linaclotide (n=405)**	**Least Sq mean difference**	**Placebo (n=403)**	**Linaclotide (n=401)**	**Least Sq mean difference**
Mean change from baseline* (improvement)	15.2	18.4	3.3 (1.0, 5.5) p=0.004	11.1	16.6	5.5 (3.4, 7.6) p<0.0001

*No baseline values were reported.

No data for Week 26 (Chey et al. 2012) provided.

EMA 12-week abdominal pain/discomfort responders (Pain rated on 11 point NRS. Responder = those with an improvement of ≥30% for at least 6/12 weeks)

	Rao 2012			Chey 2012		
	Placebo (n=395)	**Linaclotide (n=405)**	**RR (95% CI) Calculated by reviewer**	**Placebo (n=403)**	**Linaclotide (n=401)**	**RR (95% CI) Calculated by reviewer**
Responder N, (%)	165 (41.8)	222 (54.8)	1.31 [1.13, 1.52]	155 (38.5)	217 (54.1)	1.41 [1.21, 1.64]

EMA 26-week abdominal pain/discomfort responders (as above but for 13/26 weeks)

	Chey 2012		
	Placebo (n=403)	**Linaclotide (n=401)**	**RR (95% CI)**
Responder N, (%)	145 (36.0)	215 (53.6)	1.49 (1.27, 1.75)

P value <0.0001 CMH test.

<table>
<tr><th>Bibliographic reference</th><td colspan="7">Quigley EMM, Tack J, Chey WD, Rao SS, Fortea J, Falques M, Diaz C, Shiff SJ, Currie MG & Johnston JM (2013) Randomised clinical trials: linaclotide phase 3 studies in IBS-C – a prespecified further analysis based on European Medicines Agency-specified endpoints; Ailmentary Pharmacology & Therapeutics; 37: 49-61.</td></tr>
<tr><td></td><td colspan="7">
EMA 12 week degree of relief responders
((7 point symptom scale 1=completely relieved, 7 = as bad as I can imagine) symptoms ‘considerably’ or ‘completely’ relieved (equivalent to scores of 1 or 2) for ≥6/12wks, or
‘somewhat’, ‘considerably’ or ‘completely’ relieved (scores of 1,2 or 3) for all 12 wks were classified as a responder.
<table>
<tr><td></td><td colspan="3">Rao 2012</td><td colspan="3">Chey 2012</td></tr>
<tr><td></td><td>Placebo (n=395)</td><td>Linaclotide (n=405)</td><td>RR (95% CI)</td><td>Placebo (n=403)</td><td>Linaclotide (n=401)</td><td>RR (95% CI)</td></tr>
<tr><td>Responder N(%)</td><td>73 (18.5)</td><td>150 (37)</td><td>2.00 [1.57, 2.56]</td><td>67 (16.6)</td><td>158 (39.4)</td><td>2.37 [1.85, 3.04]</td></tr>
</table>
EMA 26-week degree of relief responders (as above but for at least 13/26 weeks)
<table>
<tr><td></td><td colspan="3">Chey 2012</td></tr>
<tr><td></td><td>Placebo (n=403)</td><td>Linaclotide (n=401)</td><td>RR (95% CI) Calculated by reviewer</td></tr>
<tr><td>Responder N, (%)</td><td>68 (16.9)</td><td>149 (37.2)</td><td>2.20 [1.71, 2.83]</td></tr>
</table>
P value <0.0001 CMH test.

Safety and Adverse Events
See tables 1 and 2 above
</td></tr>
<tr><td>Source of funding</td><td colspan="7">Ironwood Pharmaceuticals and Forest Laboratories funded individual trials.</td></tr>
<tr><td>Comments</td><td colspan="7">See tables 1 and 2 above. This study did not report any additional non-protocol outcomes.</td></tr>
</table>

G.41 Review question 4 (lubiprostone)

Bibliographic reference	**Whitehead WE, Palsson OS, Gangarosa L, Turner M, Tucker J. (2011) Lubiprostone does not influence visceral pain thresholds in patients with Irritable Bowel Syndrome. Neurogastroenterology Motility; 23(10): 944-e400.**
Study type	RCT (double-blind) cross-over design
Aim	To evaluate whether lubiprostone influences visceral pain thresholds in patients with IBS-C.
Number of patients	62
Patient characteristics	**Inclusion:** Physician diagnosis of IBS and Rome III criteria for IBS-C. Age 18+ **Exclusion:** Use of laxatives or prokinetics within 2 weeks prior to or during the study Use of IBS-specific compounds, opiates, anticholinergics or any drug with constipation as a potential side effect Use of analgesics for 48 hours prior to the study Hypothyroidism History of bowel resection except appendectomy or cholecystectomy Psychotic disorder Major depression, substance abuse (other than tobacco), or other psychiatric condition Renal disease Inflammatory or ischemic disease of the rectum Evidence that the subject was an unreliable research participant Pregnant women (or planning pregnancy) due to radiation exposure Individuals working with radiation or previous participation in studies involving radiation in past 12 months. **Baseline Characteristics:** (not reported by arm) Mean age (SD) 41.95 (13.56), 85.5% Female. Average IBS Severity Score at baseline was 296 (95% CI 274,317). Percentages per score category were: Mild (score<175) - 8.1% Moderate (175-300) - 46.7% Severe (>300) - 45.2% **Attrition:** 71 participants were recruited, 62 completed the study. There was no reporting of reasons for discontinuation by study arm and no reporting of discontinuation by treatment period.
Intervention	Lubiprostone 48µg (delivered in two capsules – 1 capsule BD)

Comparison	Placebo
Length of follow up	14 day treatment period, 14 day washout then 14 day placebo, or the reverse.
Location	North Carolina, USA.
Outcomes measures and effect size	**Clinical Symptoms** - Daily symptom recording diary and the retrospective calculation of IBS-SS - see below table. Protocol outcomes highlighted in bold in below table.

Effects of lubiprostone 48 µg day−1 on transit time, stool consistency and symptoms

	N=	Baseline	Treatment Period 1		Treatment Period 2		Drug × period interaction (*P*)
			Active	Placebo	Active	Placebo	
Sitzmark transit study							
Total Sitzmarks on Day 6	62	-	49.25 + 5.13	60.77 + 5.30	54.54 + 5.01	42.84 + 4.86	0.981
Right hemicolon on Day 6	62	-	20.91 + 2.39	23.63 + 2.46	22.57 + 2.75	17.59 + 2.66	0.614
Stool consistency							
Average Bristol Score (0–10)	60	3.20 + 0.15	4.27 + 0.17	3.41 + 0.18	4.21 + 0.17	3.46 + 0.16	0.000
Days with hard/lumpy stools or no stools (%)	**60**	**59.4 + 3.9**	**32.4 + 3.8[D]**	**50.9 + 3.9**	**42.7 + 3.5**	**43.5 + 3.4**	**0.011**
SD (Calculated by reviewer)		**30.2**	**-**	**-**	**27.1**	**26.3**	**-**
Difference from baseline and between arms (calculated by reviewer)		**-**	**-**	**-**	**-16.7**	**-15.9**	**Not analysed further**
Daily symptom ratings							
Pain (0–10 scale)	**60**	**4.08 + 0.31**	**4.21 + 0.33[P]**	**3.52 + 0.35**	**3.28 + 0.29**	**3.23 + 0.28**	**0.136**
SD (Calculated by reviewer)		**2.4**	**-**	**-**	**2.2**	**2.2**	**-**
Difference from baseline and between arms (calculated by reviewer)		**-**	**-**	**-**	**-0.8**	**-0.85**	**Mean difference (95% CI) 0.05 (-0.74, 0.81)**
Bloating (0–10 scale)	**60**	**4.89 + 0.30**	**4.71 + 0.35**	**4.29 + 0.36**	**3.93 + 0.36**	**3.89 + 0.35**	**0.424**

SD (Calculated by reviewer)		**-**	**-**	**-**	**2.8**	**2.7**	**-**
Difference from baseline and between arms (calculated by reviewer)		**-**			**-0.96**	**-1**	**Mean difference 0.04 [-0.94, 1.02]**
Bowel habit dissatisfaction	60	6.12 + 0.30	5.47 + 0.36	5.06 + 0.35	4.46 + 0.35	4.43 + 0.33	0.504
Life interference (0–10 scale)	**60**	**3.59 + 0.31**	**3.59 + 0.34[P]**	**3.02 + 0.35**	**3.03 + 0.26**	**2.80 + 0.25**	**0.036**
SD (Calculated by reviewer)		**-**	**-**	**-**	**2.0**	**1.9**	**-**
Difference from baseline and between arms (calculated by reviewer)		**-**	**-**	**-**	**-0.56**	**-0.79**	**Mean Difference (95% CI) 0.23 [-0.48, 0.94]**
IBS-SS questionnaire							
IBS-SS score (0–500)	**62**	**295.65 + 10.79 [95% CI 274-317]**	**266.26 + 14.66**	**262.99 + 15.14**	**240.90 + 15.86**	**233.22 + 15.36**	**0.643**
SD (Calculated by reviewer)		**-**	**-**	**-**	**123**	**119**	**-**
Difference from baseline Calculated by reviewer		**-**	**29.4**	**32.66**	**54.8**	**62.43**	**Mean Difference (95% CI) 7.68 [-34.89, 50.25]**

- Values in table are mean + S.E. [P]significant difference from Period 1 to Period 2 ($P < 0.05$).
- [D]significant difference between lubiprostone and placebo ($P < 0.05$).

Safety and Adverse Events There was no mention of safety, AEs or serious AEs.

Source of funding	Takeda Pharmaceuticals
Comments	• There were no differences between groups for adherence to the drug regimen. • Subjects were paid $500 to complete the study. • Potential confounders not mentioned include fluid intake, exercise levels and fibre intake (diet or supplements). • Specific drug classes (laxatives and prokinetics) were prohibited and use of these and opiates, anti-cholinergics or any drug likely to cause constipation as a side effect, formed part of the exclusion criteria. However, there was no mention of compliance by study arm. • The Bristol Score is reported inconsistently (Table 1 as scale of 0-10, page 4 it is reported correctly as a 7 point scale of 1-

	7 with one being hardest stools). This is a potential error, but is of minimal impact as Bristol stool score has not been evaluated as a specific protocol outcome. • Missing data on pain values for 11 vs. 14 participants (drug vs. placebo arms) but this relates to pain thresholds and this outcome was not evaluated. • The study was powered to detect a difference in pain thresholds. Due to missing data on pain thresholds, this outcome became underpowered. and was not adequately powered for the protocol outcomes.
	Other non-protocol outcomes reported: Visceral pain thresholds (n=42) (Visceral pain sensitivity assessed by intraluminal (colon/rectum) balloon test (Barostat) using response rating criteria (i.e. six point rating scale, 0-5 for pain at different inflation pressures)). Pressures recorded when pain ratings of 3 (moderate) were given. Measured at end of both intervention periods and data pooled. 17.36mmHg (lubiprostone) vs. 17.83mmHg (placebo). No CIs given. NS. Transit time (n=62) (Sitzmark test, using radio-opaque capsules, x-ray and calculation of distance/transit through GI tract). Measured at end of both intervention periods and data pooled. 51.27hrs (lubiprostone) vs. 51.81hrs (placebo). No CIs given. Sensitivity (ability to distinguish between different pressure intensities), bowel habit dissatisfaction, urgency to defecate thresholds.

Bibliographic reference	**Drossman DA, Chey WD, Johanson JF, Fass R, Scott C, Panas R & Ueno R (2009) Clinical trial: lubiprostone in patients with constipation associated irritable bowel syndrome – results of two randomized, placebo-controlled studies. Alimentary Pharmacology & Therapeutics 29, 329-341.**
Study type	Results of two RCTs not previously published elsewhere (Phase-3 trials).
Aim	To assess the efficacy and safety in lubiprostone in IBS-C
Number of patients	Combined n= 1171 Study A n=590 (ITT placebo n=193, lubiprostone n=390) Study B n=581 (ITT placebo n=192, lubiprostone n=379)
Patient characteristics	**Inclusion:** (Both studies) Rome II diagnosis of IBS-C. Age 18+. Compliance with daily diary completion ≥70% during the 4 week baseline period. Min 2 of the following 4. <3 SBMs / week 5. At least 25% SBMs accompanied by at least moderate straining

6. At least 25% SBMs associated with stool consistency rating

Exclusion:
(Both studies)
Unable or unwilling to use an acceptable method of birth control
Pregnant or breastfeeding
Those with potential for non-compliance
Previous GI or abdominal surgery (except common causes)
Organic disorder of the large or small bowel
Mechanical obstruction
Unexplained significant weight loss or rectal bleeding
Diagnosis of any medical condition associated with constipation (other than IBS)
Conditions that might interfere with study conduct
Other significant medical conditions (renal impairment, cancer, abnormal laboratory tests, recent abuse of alcohol or durgs)
Use of any medication indicated for treatment of IBS within preceding 4 weeks
Use of investigational medications within preceding 4 weeks.

Baseline Characteristics: (Combined from both studies)

	Placebo n=385	**Lubiprostone n=769**	**Total**	**P-Value**
Age, Mean (min, max) (SD)	47.7 (18.0-85.0) (12.94)	46.1 (19.0-83.0) (12.84)	46.6 (18.0-85.0) (12.89)	0.049
Gender (Female)	359 (93.2%)	698 (90.8%)	1057 (91.6%)	0.152

There were no significant differences for the remaining baseline characteristics (see outcome reporting below).

Attrition:
Completion rates Study 1 - 73.9%, Study 2 – 78.1% (mean of both arms).
See below for discontinuation summary.

Intervention	Lubiprostone 16µg (8µg twice daily) with breakfast and dinner and with 8oz water
Comparison	Placebo (twice daily)
Length of follow up	12 week duration with monthly follow-up (plus 4 week screening/initiation period)
Location	Multiple centres, USA
Outcomes measures and	Participants entered daily (and weekly) responses onto an electronic diary.

effect size

Combined ITT and LOCF analysis (both studies) n = 1154.

Question asked "How would you rate your relief of IBS symptoms over the past week compared to how you felt before you entered the study?" (7 point scale. 1=significantly worse, 2=moderately worse, 3=a little bit worse, 4=unchanged, 5=a little bit relieved, 6=moderately relieved, 7=significantly relieved).

[(a)] Classifications of responders

Weekly – moderate or significantly relieved for that week (secondary study endpoint).

Monthly – moderately relieved or better in 4 out of 4 weeks OR significantly relieved in 2 out of 4 weeks. Could not discontinue treatment during 4 week period and % of days of rescue medication did not increase from baseline (Secondary study endpoint)

Overall – Monthly responders for at least 2 of the 3 months of the study (primary study endpoint).

Results at month 3 / Week 12 only are reported (unless stated otherwise)

	Placebo n=385 (%)	**Lubiprostone n=769 (%)**	**P value** No CIs given	**RR 95% CI calculated by reviewer**
Overall responder [a]	39 (10.1)	138 (17.9)	0.001	1.77 [1.27, 2.47]
Monthly responder [a]	56 (14.5)	169 (22.0)	0.003	1.51 [1.15, 1.99]
Weekly responder [a]	25 (ruler)	31.5 (ruler)	≤0.030	Not calculated due to crude extraction method

Symptom ratings

Symptom ratings at months 1, 2 and 3 were mentioned. Here, month 3 data only is reported.

Mean scores for each rated symptom were not reported at follow-up at any time point.

Mean change (from baseline) values for abdominal discomfort/pain were the only values reported by study arm.

Mean change for the remaining symptoms was presented graphically according to overall responder status (with corresponding p-values and no CIs). Data could thus not be accurately extracted. In addition, reporting data by responder status introduces reporting bias. Responder status was calculated from rated symptom relief thus responders should have higher mean change than non-responders for each symptom.

Combined (both studies) ITT LOCF analysis in all but QOL outcomes	***Baseline (mean, SD)***		***Month 3 (mean change)***		
	Placebo	**Lubiprostone**	**Placebo**	**Lubiprostone**	**P value**

	n=385	N=769			
Abdominal discomfort/pain (5 point likert scale)*	2.08 (0.667)	2.07 (0.658)	1.72 reviewer calculated (-0.36)	1.62 reviewer calculated (-0.45)	0.028
Bloating (5 point likert scale)*	2.26 (0.694)	2.26 (0.684)	Not reported appropriately	Not reported appropriately	NS
Weekly SBM frequency	3.84 (3.571)	2.22 (3.320)	Not reported	Not reported	NS
Stool consistency**	2.75 (0.690)	2.76 (0.658)	Not reported appropriately	Not reported appropriately	≤0.022
Constipation severity*	2.25 (0.645)	2.22 (0.661)	Not reported appropriately	Not reported appropriately	≤0.05
QOL (overall)	Not reported	Not reported	Not reported	Not reported	NS
QOL sub analysis 'body image' and 'health worry'	Not reported	Not reported	Not reported	Not reported	≤0.025

*0 (absent), 1 (mild), 2 (moderate), 3 (severe), 4 (very severe)

**0 (very loose [watery]), 1 (loose), 2 (normal), 3 (hard), 4 (very hard [little balls])

SBM = spontaneous bowel movement

Discontinuation and Adverse Events

Study A

Discontinuation reason	**Placebo N=194 *(%)***	**Lubiprostone N=387 *(%)***	**RR (95% CI) calculated by reviewer**
Adverse Event	9 (4.6)	20 (5.1)	1.11 [0.52, 2.40]
Lack of efficacy	8 (4.1)	10 (2.5)	0.63 [0.25, 1.56]
Lost to follow-up	4 (2.1)	8 (2.0)	1.00 [0.31, 3.29]
Withdrew consent	28 (14.4)	39 (9.8)	0.70 [0.44, 1.10]
Noncompliance	3 (1.5)	13 (3.3)	2.17 [0.63, 7.53]
Other	3 (1.5)	9 (2.3)	1.50 [0.41, 5.49]
Total discontinuation	**56 (28.4)**	**99 (25.0)**	**0.89 [0.67, 1.17]**

Study B

Discontinuation reason	**Placebo N=194 *(%)***	**Lubiprostone N=387 *(%)***	**RR (95% CI) calculated by reviewer**
Adverse Event	15 (7.7)	18 (4.7)	0.60 [0.31, 1.17]
Lack of efficacy	8 (4.1)	18 (4.7)	1.13 [0.50, 2.55]
Lost to follow-up	6 (3.1)	6 (1.6)	0.50 [0.16, 1.53]
Withdrew consent	10 (5.2)	25 (6.5)	1.25 [0.61, 2.56]
Noncompliance	3 (1.5)	8 (2.1)	1.34 [0.36, 4.98]
Other	1 (0.5)	9 (2.3)	4.51 [0.58, 35.35]
Total discontinuation	**43 (22)**	**84 (22)**	**0.98 [0.71, 1.35]**

Adverse Events combined (both studies)

All patients received at least one dose of study medication

	Placebo (n=387) *N (%)*	**Lubiprostone (n=779) *N (%)***	**RR (95% CI) calculated by reviewer**
Treatment related AE	81 (21)	171 (22)	1.05 [0.83, 1.32]
At least one adverse event	197 (51)	390 (50)	0.98 [0.87, 1.11]
Nausea	15 (4)	62 (8)	2.05 [1.18, 3.56]
Diarrhoea	15 (4)	47 (6)	1.52 [0.86, 2.69]
Abdominal distension	8 (2)	16 (2)	0.99 [0.43, 2.30]

Serious Adverse Events

	Placebo (n=387) *N (%)*	**Lubiprostone (n=779) *N (%)***	**RR (95% CI) calculated by reviewer**
SAEs	4 (1)	8 (1)	0.99 [0.30, 3.28]
Treatment related SAE	0	1 (0.1)	1.49 [0.06, 36.55]

1 patient died but the investigator reported not thought to be related to lubiprostone (cardiac arrest on background of multiple co-morbidities). 1 patient had non-cardiac related chest pain deemed possibly related to lubiprostone. Detail not given for remaining 6 SAEs.

Source of funding	Sucampo Pharmaceuticals
Comments	• Use of rescue medication (suppository, then fleet enema + additional if both failed) was allowed in absence of a SBM for >3 days. There is no report on use/frequency of rescue medication between the study arms. This is a major confounder. • The dose of the intervention drug was reduced by the investigators to OD if nausea, diarrhoea or other AEs persisted for >2 days. There is no reporting of the number and duration of dose reduction by study arm. • The question for the primary endpoint (responder status) is a leading question, implying "relief" and asks participants to record weekly relief in the past week vs how they felt before the study. This could introduce recall bias. There is no mention of validation of this scale. • Participants were allowed to take daily fibre supplements but were recommended to keep "stable fibre therapy throughout". There was no report of compliance with this, or reporting of dietary fibre intake, fluid or exercise by study arms. • For the secondary endpoints (except abdominal discomfort/pain and QOL), results were reported and analysed between "responders" and "non-responders" with reference to statistically significant differences only. No mean scores or mean improvement ratings were given by treatment arm. • There was no mention of potential confounders such as fluid intake, activity levels, or dietary fibre (+fibre supplementation) (all which can affect constipation) by study arm. • This study was conducted by same research group as an earlier study (Johanson, Drossman et al 2008) – see below table. No dates are given for recruitment period/duration. • While we were told medications used during the study period were recorded, frequency and type used are not presented by study arm. Use of analgesia for example, could confound the ratings for pain. Non Protocol Outcomes also reported: subjective evaluation of efficacy of treatment, degree of straining, responder statuses by month (prior to end), correlation of responder status with clinical endpoints.

1

Bibliographic reference	**Johanson JF, Drossman DA, Panas R, Wahle A & Ueno R (2008) Clinical Trial: Phase 2 study of lubiprostone for irritable bowel syndrome with constipation. Alimentary Pharmacology and Therapeutics 27, 685-696.**
Study type	RCT Phase 2 study ITT and LOCF analysis
Aim	To assess the efficacy and safety of three lubiprostone doses for IBS-C
Number of patients	195
Patient characteristics	**Inclusion:** 18-80 years old Not pregnant, not lactating.

Bibliographic reference	Johanson JF, Drossman DA, Panas R, Wahle A & Ueno R (2008) Clinical Trial: Phase 2 study of lubiprostone for irritable bowel syndrome with constipation. Alimentary Pharmacology and Therapeutics 27, 685-696.

Rome II diagnostic criteria for IBS
Rome II modular questionnaire criteria for IBS-C
Sigmoidoscopy or colonoscopy within 5 years to rule out other causes/diseases.
In 4 week initiation period
Avoidance of disallowed medications (not specified)
Satisfactorily complete electronic diary
Min 2 of the following
7. <3 SBMs / week
8. At least 25% SBMs accompanied by at least moderate straining
9. At least 25% SBMs associated with stool consistency rating

Exclusion:
Previous GI or abdominal surgery (except common causes unrelated to IBS)
Organic disorder of large or small bowel
Mechanical obstruction
Unexplained significant weight loss or rectal bleeding
Diagnosis of any other medical condition associated with constipation
Renal impairment, clinically significant cancer abnormal lab tests, recent abuse of alcohol or drugs
Use of any medication indicated for IBS during 4 weeks preceding study.

Baseline Characteristics:

	Placebo	**16µg**	**32µg**	**48µg**
Mean age (SD)	44/6 (11.1)	46.5 (10.1)	48.3(11.9)	43.9 (11.6)
Gender M/F	4/44	4/47	3/46	7/38

NS differences between the 4 treatment arms for any of the baseline characteristics
Overall percentage male 9% female 91%

Attrition:
194 participants included in the safety analysis, 193 were included in the efficacy analysis.
Lubiprostone was associated with higher rates of withdrawal that seemed to be dose related (see table below).
Exposure to the drug/placebo was affected due to participant withdrawal.
Mean (SD) exposure days:

Bibliographic reference	**Johanson JF, Drossman DA, Panas R, Wahle A & Ueno R (2008) Clinical Trial: Phase 2 study of lubiprostone for irritable bowel syndrome with constipation. Alimentary Pharmacology and Therapeutics 27, 685-696.**
	Placebo – 76(19), 16µg – 73(26), 32µg – 66(29), 48µg – 67(29) (Maximum days 84).
Intervention	Lubiprostone **16**µg daily (8µg BD) OR **32**µg (16µg BD) OR **48**µg (24µg BD) with breakfast and dinner and 8oz H^20
Comparison	Placebo
Length of follow up	12 week duration with monthly follow-up (plus 4 week initiation/screening period)
Location	19 centres, USA.
Outcomes measures and effect size	The results (mean change from baseline, for the primary and secondary endpoints 1-4 were not provided other than in graphical form) thus data was ***crudely extracted by the reviewer (using a ruler on bar charts/graphs).*** The first month of treatment is cited as the primary endpoint in this three month study, but graphical results were reported at months 1, 2 and 3. 95% CIs were provided graphically only and thus are not extracted as crude estimations would be inaccurate. P values tended to be given if they were <0.05. Where a 5 point symptom scale was used this was 0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe unless otherwise stated. Attention should be paid to the graphically presented ratings which show mean change from baseline. <1 point change on the rating scale raises questions about clinical significance. See GRADE profiles. **Primary end point of study** ***Abdominal discomfort/pain*** score (during first month of treatment) (mean change by month)

Treatment arm	**Month 1** **N = not specified**	**Month 2** **N= not specified**	**Month 3** **N = not specified**
Placebo	-0.19	-0.21	-0.33
16µg	-0.45	-0.51 (p=0.039)	-0.54
32µg	-0.4	-0.52 (p=0.033)	-0.58
48µg	-0.47 (p=0.023)	-0.53 (p=0.028	-0.51
Overall test for trend	P=0.0431	P=0.0336	P=0.2601

Bibliographic reference	Johanson JF, Drossman DA, Panas R, Wahle A & Ueno R (2008) Clinical Trial: Phase 2 study of lubiprostone for irritable bowel syndrome with constipation. Alimentary Pharmacology and Therapeutics 27, 685-696.

Secondary end points

1) ***Abdominal bloating*** *(5 point scale) mean change by month*

Treatment arm	**Month 1 N = not specified**	**Month 2 N= not specified**	**Month 3 N = not specified**
Placebo	-0.18	-0.25	-0.33
16µg	-0.41	-0.5	-0.55
32µg	-0.32	-0.5	-0.54
48µg	-0.43 (p=0.011)	-0.53 (p=0.033)	-0.52
Overall test for trend	P=0.0298	P=0.0398	NS (value not reported)

2) ***Constipation severity*** *(5 point scale) mean change by month*

Treatment arm	**Baseline**	**Month 1 N = not specified**	**Month 2 N= not specified**	**Month 3 N = non specified**	**Month 3 sco (back calcula by reviewer)**
Placebo	2.1 (0.57)	-0.2	-0.38	-0.3	1.8
16µg	2.2 (0.63)	-0.48 (P=0.033)	-0.5	-0.57	1.63
32µg	2.3(0.58)	-0.59 (p=0.004)	-0.65 (p=0.012)	-0.66 (p=0.030)	1.64
48µg	2.1 (0.58)	-0.78 (p<0.0001)	-0.78 (p=0.0005)	-0.72 (p=0.007)	1.38
Mean of all drug doses (reviewer calculated)	2.2	Not calculated	Not calculated	-0.64	1.55
Overall test for trend	Not reported	P<0.0001	P=0.0003	P=0.0056	Not reported

3) ***SBM frequency*** *(weekly rate) mean change by month*

Treatment arm	**Baseline**	**Month 1 N = not specified**	**Month 2 N= not specified**	**Month 3 N = non specified**	**Month 3 frequency (b calculated by reviewer)**
Placebo	4.3 (3.2)	0.7	0.75	0.5	4.8
16µg	3.7 (2.83)	1.8	1.7 (p=0.009)	1.75	5.45
32µg	3.8 (2.81)	2.1 (p=0.046)	1.8 (p=0.026)	1.5 (p=0.040)	5.3

Bibliographic reference	Johanson JF, Drossman DA, Panas R, Wahle A & Ueno R (2008) Clinical Trial: Phase 2 study of lubiprostone for irritable bowel syndrome with constipation. Alimentary Pharmacology and Therapeutics 27, 685-696.

48µg	3.2 (2.24)	3.3 (p=0.0002)	2.6 (p=0.050)	2.4 (p=0.033)	5.6
Mean frequency of all drug doses (reviewer calculated)	3.6	Not calculated	Not calculated	1.91	5.45
Overall test for trend	Not reported	P=0.0004	P=0.0204	P=0.0296	Not reported

SBM = Spontaneous bowel movements

4) ***Stool consistency*** *(5 point scale, 0=very loose, 1=loose, 2=normal, 3=hard, 4=v.hard) mean change by month*

Treatment arm	**Month 1 N = not specified**	**Month 2 N= not specified**	**Month 3 N = non specified**
Placebo	-0.1	-0.2	-0.2
16µg	-0.57 (p=0.004)	-0.58	-0.52
32µg	-0.61 (p=0.003)	-0.59	-0.54
48µg	-0.95 (p<0.0001)	-0.9 ((p=0.0001)	-0.88 (p<0.0001)
Overall test for trend	P<0.0001	P<0.0001	P<0.0001

5) QOL *(IBS-QOL, 34 Questions each with 5 point scale. Max score 170, higher score = worse QOL)*

IBS-QOL Scale	**Placebo**	**48µg Lubiprostone**	**All Lubiprostone doses (mean) Reviewer calculated**
Baseline, mean (SD)	61.8 (17.2)	59.8 (21.7)	58.5
Week 12 Score	Not reported	Not reported	Not reported
Mean change (p value)	Reported as NS only	Reported as NS only	Not estimable

Reporting of sub analyses showed significant improvement for the domain ‘health worry’ at weeks 4 and 12 only, in the 48µg lubiprostone arm vs. placebo.

IBS-QOL Health Worry only (3 questions out of 34)	**Placebo**	**48µg Lubiprostone**
Baseline	45.3	44.1
Week 12	58.5	66.1
Mean Change (calculated)	13.2	22.0

Bibliographic reference	Johanson JF, Drossman DA, Panas R, Wahle A & Ueno R (2008) Clinical Trial: Phase 2 study of lubiprostone for irritable bowel syndrome with constipation. Alimentary Pharmacology and Therapeutics 27, 685-696.

	P=0.021

Discontinuation, Safety and AEs

	Placebo N=48 (%)	16µg Lubiprostone N=52 (%)	32µg N=49 (%)	48µg N=46 (%)	Total all dose arms n=147	RR (95% CI) All drug arms vs placebo calculated by reviewer	RR (95% CI) 48µg arm vs placebo calculated by reviewer
Total Discontinuation	7 (14.5)	10 (19.2)	16 (32.7)	15 (33.3)	41 (27.9)	1.91 [0.91, 3.98]	2.24 [1.00, 4.
Adverse event	1 (2.1)	3 (5.8)	8 (16.3)	6 (13.3)	17 (11.6)	5.55 [0.76, 40.6]	6.26 [0.78, 50
Lack of efficacy	6 (12.5)	3 (5.8)	4 (8.1)	4 (8.8)	11 (7.5)	0.60 [0.23, 1.53]	0.70 [0.21, 2.
Lost to follow up	0	0	1 (2.0)	1 (2.2)	2 (1.4)	1.66 [0.08, 33.89]	3.13 [0.13, 74
Non-compliance	0	0	0	1(2.2)	1 (0.7)	0.99 [0.04, 23.99]	3.13 [0.13, 74
Withdrew consent	0	4 (7.7)	3 (6.1)	2 (4.4)	9 (6.1)	6.29 [0.37, 106.11]	5.21 [0.26, 105.74]
Other	0	0	0	1 (2.2)	1 (0.7)	0.99 [0.04, 23.99]	3.13 [0.13, 74

64% reported at least one AE. The most common AEs were gastrointestinal - nausea, diarrhoea, abdo distension and pain and were significantly higher in lubiprostone vs placebo arms (P=0.020).

3 serious AEs were reported (perforated appendix, cholecystitis, ectopic pregnancy, all resolved).

	Placebo N=48 (%)	16µg Lubiprostone N=52 (%)	32µg N=49 (%)	48µg N=46 (%)	Total all Dose Arms N=147	RR (95% CI) All drug arms vs placebo calculated by reviewer	RR (95% CI) 48µg arm vs placebo calculated by reviewer
Patients with at least 1 AE	28(58)	35(67)	30(61)	32(71)	97 (66)	1.13 [0.87, 1.48]	1.19 [0.88, 1.62]
Patients with at least 1 SAE	0	0	1(2)	2(4)	3	2.32 [0.12, 44.08]	5.21 [0.26, 105.74]

Bibliographic reference	Johanson JF, Drossman DA, Panas R, Wahle A & Ueno R (2008) Clinical Trial: Phase 2 study of lubiprostone for irritable bowel syndrome with constipation. Alimentary Pharmacology and Therapeutics 27, 685-696.

Abdominal distention	5(10)	1(2)	5(10)	5(11)	11	0.72 [0.26, 1.96]	1.04 [0.32, 3.37]
Diarrhoea	2(4)	7(14)	6(12)	12(27)	25	4.08 [1.00, 16.6]	6.26 [1.48, 26.46]
Nausea	6(13)	10(19)	9(18)	14(31)	33	1.79 [0.80, 4.02]	2.43 [1.02, 5.79]
Abdominal pain	3(6)	4(8)	3(6)	2(4)	9	0.98 [0.28, 3.47]	0.70 [0.12, 3.97]

Source of funding	Sucampo Pharmaceuticals
Comments	• This was a pre-study of Johanson et al 2009 (same research group). Unclear if any overlap with sampling although 2009 study states that data was not previously published. Recruitment dates are not specified • Participants were allowed to take daily fibre supplements but were recommended to keep “stable fibre therapy throughout”. There was no report of compliance with this, use fibre supplements or dietary fibre intake between study arms. • There was no mention of potential confounders such as fluid intake or activity levels by study arm. • Use of rescue medication (suppository, then Fleet enema + additional if both failed) was allowed in absence of a SBM for >3 days. There is no report on use/frequency of rescue medication between the study arms. • While we were told participants were required to discontinue disallowed medications, these were not defined, there was no mention of monitoring or compliance with this nor was there any reporting of their use by study arm. Use of analgesia for example, could confound the ratings for pain.
	Non Protocol Outcomes also reported: straining, efficacy of treatment (patients subjective evaluation)

G.5 Review question 5a (relaxation therapy)

Bibliographic reference	Boyce P, Talley NJ, Koloski N et al. (2003) A Randomized Controlled Trial of Cognitive Behavioural Therapy, Relaxation Training, and Routine Clinical Care for the Irritable Bowel Syndrome. 98: 2209-18.
Study type	Design: RCT Randomisation: sealed opaque envelopes prepared containing cards with treatment conditions. Randomly allocated participant identification numbers using random number generator before the study. On entry to study participant allocated next ID number and envelope was opened by secretary
Aim	Aim: to compare CBT, relaxation training and routine clinical care for IBS

Bibliographic reference	**Boyce P, Talley NJ, Koloski N et al. (2003) A Randomized Controlled Trial of Cognitive Behavioural Therapy, Relaxation Training, and Routine Clinical Care for the Irritable Bowel Syndrome. 98: 2209-18.**
Patient characteristics	Recruited through advertisement (n=51) and outpatient clinics (n=54). *Inclusion* • >18 years of age • Patients diagnosed using Rome 1 criteria • Have no structural bowel pathology that would account for their symptoms • To be able to speak sufficient English to be able to understand the therapy *Exclusion* • Major current medical or psychotic illness • History of alcoholism • Current psychological treatment and current use of antidepressants or antipsychotic medications • Current use of medications that could affect bowel function (e.g. antispasmodics) Vast majority of people in the study were not taking medication at the time of randomisation. Baseline characteristics comparable between groups. However, SF36 scores were generally lower in the relaxation training group compared to clinical care in all domains apart from vitality and mental health (see outcome measures for baseline data).
Number of Patients	N=105
Intervention	Relaxation training Patients received routine clinical care and weekly 30 minute face-to-face instructional sessions for 8 weeks in a range of relaxation strategies. (progressive muscle relaxation, release only, cue-controlled , applied relaxation). Subjects also completed homework sheets between sessions to measure their levels of tensions before and after they practised their relaxation.
Comparison	Routine clinical care Three 15-30 minute sessions with a gastroeneterologist (i.e. after randomisation there were 2 more sessions). Provided patients either routine medical management of their IBS, in which they could discuss symptoms, receive standard dietary advice regarding fibre intake. Included a dietary information booklet an 20g high fibre diet with bulking agent psyllium husk (3.4g daily – standard dose)
Length of follow up	52 week follow up, 8 weeks intervention. Data collected at randomisation, 4 weeks after baseline, 8 weeks after baseline and at 26 weeks and 52 weeks of follow-up.
Location	Department of Psychological Medicine, University of Sydney, NSW, Australia

Bibliographic reference	**Boyce P, Talley NJ, Koloski N et al. (2003) A Randomized Controlled Trial of Cognitive Behavioural Therapy, Relaxation Training, and Routine Clinical Care for the Irritable Bowel Syndrome. 98: 2209-18.**

Outcomes measures and effect size

Bowel Symptom Severity scale (mean, SD), per protocol analysis

	Frequency		**Distress**		**Interference**	
Time point	**RT**	**RCC**	**RT**	**RCC**	**RT**	**RCC**
Baseline	20.6 (4.4)	21.0 (4.6)	17.7 (5.6)	16.3 (4.5)	16.5 (5.9)	14.5 (5.3)
4 weeks	18.1 (4.2)	19 (4.4)	14.2 (4.0)	17.9 (4.7)	12.5 (3.9)	13.8 (5.2)
8 weeks	18.0 (5.0)	18.0 (5.0)	14.4 (4.2)	13.4 (4.4)	13.1 (5.7)	12.6 (4.9)
26 weeks	16.1 (4.3)	18.8 (4.8)	13.1 (3.8)	13.4 (4.4)	12.5 (4.3)	11.8 (4.3)
52 weeks	16.2 (3.7)	17.0 (4.6)	13.2 (4.8)	12.5 (3.4)	12.0 (5.0)	11.4 (4.0)
Mean change from baseline*	-4.4	-4.0	-4.5	-3.8	-4.5	-3.1

*Calculated by analyst for purposes of calculating imprecision, unable to calculate SD. Only baseline to 52 weeks change calculated as most appropriate follow up time to assess change in QoL due to chronic nature of IBS. Maximum score of 48 (calculated by analyst).

ITT analysis: significant changes in scores over time (frequency subscale $F=20.1$, $p<0.01$, impairment $F=33.1$, $p<0.001$, distress $F=29.6$, $p<0.01$), but not between the three treatment groups.

SF36 (mean, SD), per protocol analysis

Time point	**Physical functioning**		**Role – physical**		**Pain**		**General health**	
	RT	**RCC**	**RT**	**RCC**	**RT**	**RCC**	**RT**	**RCC**
Baseline	79.4 (17.7)	86.5 (16.7)	45.7 (37.6)	62.9 (37.6)	53.0 (21.4)	59.3 (18.4)	59.7 (20.1)	65.4 (17.9)

Bibliographic reference	**Boyce P, Talley NJ, Koloski N et al. (2003) A Randomized Controlled Trial of Cognitive Behavioural Therapy, Relaxation Training, and Routine Clinical Care for the Irritable Bowel Syndrome. 98: 2209-18.**

4 weeks	87.2 (16.3)	88.2 (15.5)	80.4 (27.1)	67.5 (37.6)	68.7 (19.2)	66.1 (21.2)	58.7 (18.2)	65.5 (19.1)
8 weeks	90.0 (11.4)	88.6 (15.2)	72.2 (30.8)	59.4 (44.0)	63.7 (22.2)	67.9 (21.0)	61.7 (17.7)	64.5 (21.2)
Mean change from baseline to 8 weeks*	+10.6	-2.1	+26.5	-3.5	+10.7	+8.2	+2.0	-0.9
26 weeks	92.9 (7.7)	87.7 (18.1)	72.1 (38.4)	61.5 (42.3)	64.8 (20.4)	70.3 (17.3)	68.1 (20.4)	63.2 (22.6)
52 weeks	91.9 (14.7)	88.8 (18.0)	75.0 (38.1)	64.5 (41.9	64.2 (21.0)	68.0 (24.1)	65.9 (23.4)	66.0 (21.7)
Mean change from baseline*	+12.5	+2.3	+30.7	+1.6	+11.2	+8.7	+6.2	+0.6

*Calculated by analyst for purposes of calculating imprecision, unable to calculate SD. Only baseline to 52 weeks change calculated as most appropriate follow up time to assess change in QoL due to chronic nature of IBS. Maximum score = 100

Time point	**Vitality**		**Social functioning**		**Role- emotional**		**Mental health**	
	RT	**RCC**	**RT**	**RCC**	**RT**	**RCC**	**RT**	**RCC**
Baseline	48.0 (20.7)	50 (20.6)	66.1 (23.6)	72.8 (21.6)	58.1 (39.9)	70.7 (35.1)	64.1 (17.5)	64.7 (18.9)
4 weeks	63.7 (18.3)	50.8 (21.5)	84.2 (15.6)	77.5 (24.4)	78.2 (31.1)	78.9 (32.1)	74.6 (9.5)	69.4 (19.3)
8 weeks	59.7 (17.3)	57.8 (21.7)	83.1 (19.2)	87.5 (15.2)	81.5 (28.5)	73.6 (34.0)	71.4 (11.8)	73.6 (19.0)
Mean change from baseline	+11.7	+7.8	+17.0	+14.7	+23.4	+2.9	+7.3	+8.9

Bibliographic reference	**Boyce P, Talley NJ, Koloski N et al. (2003) A Randomized Controlled Trial of Cognitive Behavioural Therapy, Relaxation Training, and Routine Clinical Care for the Irritable Bowel Syndrome. 98: 2209-18.**

to 8 weeks*								
26 weeks	60.6 (17.7)	54.4 (23.6)	81.9 (25.1)	85.9 (20.8)	66.7 (36.2)	80.6 (35.3)	70.0 (16.1)	70.8 (15.9)
52 weeks	61.5 (19.4)	59.2 (24.2)	76.9 (22.7)	80.3 (22.2)	66.7 (43.0)	75.0 (41.7)	71.4 (13.0)	77.1 (20.8)
Mean change from baseline to 52 weeks*	+13.5	+9.2	+10.8	+7.2	+8.6	+4.3	+7.3	+12.4

*Calculated by analyst for purposes of calculating imprecision, unable to calculate SD. Only baseline to 52 weeks change calculated as most appropriate follow up time to assess change in QoL due to chronic nature of IBS

ITT analysis: significant improvement in physical functioning (F=5.55, p<0.001), physical role (F= 4.25, p <0.01), pain (f=6.12, p<0.001), vitality (F=7.77, p<0.001), general health (F=4.03, p<0.01) and social functioning (F=6.47, p<0.001). There were no differences for mental health (F=3.23, p<0.05) or emotional role (F=1.87, p=ns).

Automatic Thoughts Questionnaire (ATQ), Locus of Control Behaviour (LCB) & Hospital Anxiety and Depression Scale (HADS) (Mean, SD), per protocol analysis

Time point	**Automatic thoughts**		**Locus of control**		**HAD: anxiety**		**HAD: depression**		**HAD: Total**	
	RT	**RCC**	**RT**	**RCC**	**RT**	**RCC**	**RT**	**RCC**	**RT**	**RCC**
Baseline	46.21 (17.64)	43.64 (13.04)	29.78 (9.75)	29.09 (9.37)	8.6 (3.5)	8.5 (3.6)	5.4 (3.8)	5.6 (3.8)	14.0 (6.4)	14.1 (6.1)
4 weeks	41.39 (10.13)	43.38 (15.46)	23.28 (10.74)	27.55 (11.70)	6.7 (2.9)	7.0 (3.3)	3.5 (3.2)	5.6 (3.5)	10.2 (5.2)	12.6 (6.0)
8 weeks	42.83	40.97	26.49	26.82	7.0	6.9	4.2	4.1	11.	11.0

Bibliographic reference	**Boyce P, Talley NJ, Koloski N et al. (2003) A Randomized Controlled Trial of Cognitive Behavioural Therapy, Relaxation Training, and Routine Clinical Care for the Irritable Bowel Syndrome. 98: 2209-18.**

	(16.35)	(12.70)	(10.98)	(11.25)	(3.2)	(4.4)	(3.4)	(3.4)	2 (5.9)	(6.5)
26 weeks	37.82 (6.27)	39.96 (9.65)	27.76 (7.28)	30.04 (10.46)	6.2 (2.5)	7.3 (3.6)	3.4 (2.8)	4.8 (3.4)	9.6 (4.6)	12.0 (5.5)
52 weeks	40.31 (7.47)	40.48 (19.56)	24.23 (8.93)	27.90 (12.01)	7.1 (2.6)	6.5 (4.0)	3.6 (3.2)	4.4 (4.5)	10.7 (5.4)	11.0 (7.6)
Mean change from baseline*	-5.90	-3.16	-5.55	-1.19	-1.5	-2.0	-1.8	-1.2	-3.3	-3.1

*Calculated by analyst for purposes of calculating imprecision, unable to calculate SD. Only baseline to 52 weeks change calculated as most appropriate follow up time to assess change in QoL due to chronic nature of IBS. Range of scores for ATQ= 30-150, LCB total score 0-85, HAD total score of 42 (21 each for anxiety and depression).

ITT analysis (with last observation carried forward): changes over time on the HAD ($F=10.59$, $p<0.001$), automatic thoughts questionnaire ($F=3.59$, $p<0.001$) and the locus of control of behaviour scale ($F=6.93$,$p<0.001$).

Source of funding	Research grant from National Health and medical research council of Australia
Comments	2 week washout before randomisation into trial arms – no further information about concurrent drug treatment. Gastroenterologists were blinded to treatment status. Per protocol and ITT (last observation carried forward) analysis undertaken, data only presented for per protocol analysis. Only F and p values given for ITT analysis. 62% attrition for relaxation training group between baseline and 52 week follow up, 38% attrition for routine clinical care group

1

Bibliographic reference	**Forbes et al (2000) Hypnotherapy and therapeutic audiotape: effective in previously unsuccessfully treated irritable bowel syndrome. Int J Colorectal Dis**
Study type	Study design: RCT Randomisation based on computer generated numbers in blocks of 10, stratified according to predominant feature of patient's syndrome
Aim	Aim: To compare effectiveness of audiotape therapy compared to hypnotherapy.
Patient characteristics	*Inclusion criteria:* • Positive diagnosis of IBS, presence of at least 3 of manning criteria, with abdominal pain or discomfort as one of these • Describe symptoms of sufficient frequency to also satisfy Rome criteria • Symptomatic for at least 6 months, failed to respond adequately to conventional use of fibre, antispasmodics and dietary manipulation • Patients who failed trials of antidepressant medication or a variety of "alternative" therapies, either self- administered or prescribed by non-medical practitioners Patients allowed to continue with pre-existing therapy *Exclusion criteria:* • Current organic disease • Investigation within preceding 12 months Baseline characteristics Baseline characteristics were generally well balanced between groups. There was a tendency towards higher self- rating of health in the audiotape arm of the study (for both SF36 and HAD scores), though the authors state the differences are not significant – see data in table below (median, range):

Bibliographic reference	**Forbes et al (2000) Hypnotherapy and therapeutic audiotape: effective in previously unsuccessfully treated irritable bowel syndrome. Int J Colorectal Dis**

QoL measure	Audiotape (n=25)	Hypnotherapy (n=27)
SF36- Physical function	95 (40-100)	72 (10-100)
SF36-Physcial role	75 (0-100)	37 (0-100)
SF36-Emotional role	100 (0-100)	100 (0-100)
SF36-Social function	67 (25-100)	62 (0-87)
SF36-Pain	47 (0-84)	41 (0-84)
SF36-Mental state	72 (28-100)	62 (32-92)
SF36- Vitality	50 (15-100)	40 (10-85)
SF36- Perception of health	35 (10-95)	37 (5-92)
SF36-Health change	50 (0-75)	50 (0-100)
HAD - anxiety	6 (0-20)	9.5 (3-21)

those who failed to respond to the allocated therapy at 3 months were given the option to switch to the alternative limb of the study, these were included in a post- hoc analysis, the results are not reported here

Bibliographic reference	Forbes et al (2000) Hypnotherapy and therapeutic audiotape: effective in previously unsuccessfully treated irritable bowel syndrome. Int J Colorectal Dis
Number of Patients	N=52 (37 women)
Intervention	Audiotape (n=27) Lasts approximately 30 minutes. Contains background information about IBS, suggested routes to reducing life stresses and structured relaxation. Tape was recorded by the same person administering hypnotherapy. There are pauses for contemplation, but no background music or other sounds. Patients were given a copy of the tape and advised to listen to it daily. Patients met with clinician at week 6 and 12. Consultations at these time points aimed to replicate the type of interchange expected in a conventional GI outpatient clinic.
Comparison	Hypnotherapy (n=25) Regime is specifically gut directed. Briefly, a trance is induced by fixation, success is judged by eye closure and altered breathing pattern. This is followed by deepening strategies, such as general relaxation of the principle muscle groups. Gut direction takes note of the predominant symptoms and uses pertinent analogy (such as altered flow of a river in controlling diarrhoea or constipation. Patients received 6 sessions at 2 week intervals, each appointment was booked for 30 minutes and the patient was hypnotised for about 15 minutes. An audiotape of the session (usually the 3rd) was made for between appointment use at home.
Length of follow up	6 and 12 weeks
Location	St Mark's Hospital, Harrow, UK
Outcomes measures and effect size	Primary outcome; change in the overall symptom score (the score was designed for this study, based on 8 areas (e.g. severity of pain, abdominal bloating, fatigue and tiredness), each area scored by the patient, score ranges from 0- 30 (higher score, worse symptoms). A diary was filled in every two weeks. The symptom scores were based on the mean of the first two diaries (baseline) and the last 2 diaries (end of study).

Bibliographic reference	**Forbes et al (2000) Hypnotherapy and therapeutic audiotape: effective in previously unsuccessfully treated irritable bowel syndrome. Int J Colorectal Dis**

Secondary outcome; patients overall satisfaction with progress, changes in concomitant medication and/ or other therapeutic modalities

Results:

Overall symptom score (median)

	Audiotape (n=unclear)		Hypnotherapy (n=unclear)	
	Baseline	Follow up	Baseline	Follow up
ITT (n=52)	14*	13	14*	11
Patients completing diaries (n= 45)	13	13	14	8.5
Available case (n=25)	11	11	14.5	7.5

*values calculated, not specifically stated in paper
Score based on 8 areas (e.g. severity of pain, abdominal bloating, fatigue and tiredness), each area scored by the patient, score ranges from 0- 30 (higher score, worse symptoms)

General Health Questionnaire (median, range) , Likert scale

	Audiotape (n=13)			Hypnotherapy (n=12)		
	Baseline	Follow up	Mean change from baseline*	Baseline	Follow up	Mean change from baseline*

Bibliographic reference	**Forbes et al (2000) Hypnotherapy and therapeutic audiotape: effective in previously unsuccessfully treated irritable bowel syndrome. Int J Colorectal Dis**

Somatisation	7 (4-11)	5.5 (1-10)	-1.5	9.5 (2-18)	4.5 (2-13)	-5.0
Anxiety/ insomnia	4.5 (0-10)	6 (0-13)	+1.5	7 (2-16)	6 (1-18)	-1.0
Social dysfunction	7 (6-10)	7(6-12)	0.0	10.5 (5-16)	6.5 (1-17)	-4.0
Depression	0 (0-9)	1 (0-7)	+1.0	2.5 (0-16)	2.5 (0-18)	0
Sum	19.5 (12-29)	22 (11-35)	-2.5	26.5 (11-63)	22.5 (5-64)	-4.0
Psychiatric “case-ness” ***** (scored on Likert 1-4)	N=9	NS		N=10	NS	

*mean change calculated by analyst for purposes of interpreting imprecision. SD could not be calculated for these values. Total score out of 36

Hospital Anxiety and Depression Scale (Median, range) total score out of 42 (21 each for anxiety & depression)

	Audiotape (n=13)			Hypnotherapy (n=12)		
	Baseline	Follow up	Mean change from baseline*	Baseline	Follow up	Mean change from baseline*
Anxiety	5 (0-13)	8 (0-15)	+3.0	11.5 (3-21)	10.5 (2-15)	-1.0

Bibliographic reference	**Forbes et al (2000) Hypnotherapy and therapeutic audiotape: effective in previously unsuccessfully treated irritable bowel syndrome. Int J Colorectal Dis**

Depression	4 (0-7)	4 (0-15)	0.0	5.5 (0-13)	4 (0-13)	-1.5
Possible psychiatric disorder	N=3	NR		N=4	NR	
Probable psychiatric disorder	N=5	NR		N=8	NR	

*mean change calculated by analyst for purposes of interpreting imprecision. SD could not be calculated for these values. Total score out of 42 (21 each for anxiety & depression).

SF-36 (median, range) total score out of 100

	Hypnotherapy (n=12)			Audiotape (n=13)		
	Baseline	Follow up	Mean change from baseline*	Baseline	Follow up	Mean change from baseline*
Physical function	67 (35-100)	75 (35-100)	+8.0	95 (60-100)	87 (70-100)	-8
Physical role	25 (0-100)	50 (0-100)	+25	75 (0-100)	25 (0-100)	-50
Emotional role	67 (0-100)	67 (0-100)	0	100 (0-100)	100 (0-100)	0
Social function	50 (12-87)	44 (12-100)	-6	75 (50-100)	75 (37-100)	0

Bibliographic reference	**Forbes et al (2000) Hypnotherapy and therapeutic audiotape: effective in previously unsuccessfully treated irritable bowel syndrome. Int J Colorectal Dis**

Pain	41 (0-84)	46 (0-100)	+5	51 (0-84)	56 (12-84)	+5
Mental state	52 (32-84)	52 (36-84)	0	72 (44-84)	62 (40-88)	-10
Vitality	27 (10-85)	30 (5-75)	+3	50 (20-100)	50 (15-95)	0
Perception of health	37 (5-92)	53 (5-87)	+16	65 (10-95)	52 (20-100)	-13
Health change	50 (0-100)	67 (0-100)	+17	50 (0-75)	50 (25-100)	0

*mean change calculated by analyst for purposes of interpreting imprecision. SD could not be calculated for these values. Total score out of 100

Medical consumption:

Both groups could take medication concurrently.

	Audiotape (n= unclear)		Hypnotherapy (n= unclear)	
Antispasmodics	7	6*	4	
Antidepressants	5	5*	4	
Loperamide/ codeine phosphate		2 discontinued		1 discontinued
Anxiolytics		1 discontinued		

Bibliographic reference	**Forbes et al (2000) Hypnotherapy and therapeutic audiotape: effective in previously unsuccessfully treated irritable bowel syndrome. Int J Colorectal Dis**

	Opioid analgesics		1 discontinued		1 discontinued
	Laxatives		1 discontinued		
	Pro motility agents				2 discontinued

*calculated from information given in paper, values not specifically stated within study.

Source of funding	Not reported
Comments	Study states that analysis is Intention to treat, however 52 people entered the study and full data and results available for 25 Loss to follow-up : at 12 weeks review, full set of symptom diaries available for 45 patients(7 dropouts), but only 25 patients complied with full protocol of questionnaires (n=27 dropouts) Formal power calculations not used, would require >300 participants in each group. One assessor for each patient blinded to trial allocation and when scoring the symptom diaries and questionnaires. Overall symptom score not validated outcome measurement.

1

Bibliographic reference	**Lahman et al (2010) Functional relaxation as complementary therapy in irritable bowel syndrome: a randomized, controlled trial. Journal of Alternative and Complementary Medicine**
Study type	Study design: RCT, Randomisation was carried out in confidence by a study nurse, allocation concealment using a randomisation list created

Bibliographic reference	**Lahman et al (2010) Functional relaxation as complementary therapy in irritable bowel syndrome: a randomized, controlled trial. Journal of Alternative and Complementary Medicine**
	before the study. Interviewers were blind to the treatment group
Aim	Aim: to compare the brief relaxation technique of functional relaxation with enhanced medical care (treatment as usual plus two counselling interviews
Patient characteristics	Patients recruited at a German university medical outpatient centre for gastroenterology within a 6-month period *Inclusion criteria:* • Diagnosis of IBS according to Rome-II criteria established by a consultant gastroenterologist within the previous 2yrs *Exclusion criteria:* • <18yrs or >70yrs • Severe psychiatric or somatic disease • GI allergy • Any current medication for IBS • Previous experience in body-psychotherapy or psychotherapy within the last 3months before inclusion in the trial • Current mental illness excluded within a clinical face-to-face interview Baseline characteristics showed no differences in age, gender, occupation, duration of condition (intervention group 12.9yrs (SD 9.8) and comparator group 14.8yrs (SD 11.2), diarrhoea or constipation predominant, pain, or psychotherapy within last 3years
Number of Patients	N=80
Intervention	Functional relaxation (n=40); - 5weeks, x 2/ week, 60 minute sessions

Bibliographic reference	**Lahman et al (2010) Functional relaxation as complementary therapy in irritable bowel syndrome: a randomized, controlled trial. Journal of Alternative and Complementary Medicine**
	- Small groups of n=3 - Carried out by a psychotherapist certified in functional relaxation - All therapy session were videotaped and adherence rated by an independent researcher also certified in functional relaxation - Adapted to special features of patients with IBS
Comparison	Enhanced medical care (n=40); - Treatment as usual plus 2 counselling interviews – the goal of these was to promote personal care skills and shared decision making - Delivered by a consultant GI physician
Length of follow up	3 months , outcomes also reported at 5 weeks Loss to follow-up n=16 due to incomplete or missing questionnaires (interviewers were blind to treatment group and were instructed only to assess the degree of impairment and not to ask for the patients' experience of the intervention)
Location	Germany
Outcomes measures and effect size	Primary outcome; impairment-severity score – assessed by trained and clinically experienced interviewers. Assesses the severity of psychological impairment in 3 areas with specific scores; bodily (bod), psychic (psy) and social (soc) impairment. On a 5-point Likert scale

Bibliographic reference	**Lahman et al (2010) Functional relaxation as complementary therapy in irritable bowel syndrome: a randomized, controlled trial. Journal of Alternative and Complementary Medicine**

The benchmark dividing those with clinical conditions from healthy individuals is a cumulative value of all 3 scores of ≥5 (inter-rater reliability ranges from 0.85 to 0.92)

Participants also asked to assess their subjective overall impairment by IBS symptoms as well as their subjective impairment due to abdominal pain and tenderness, diarrhoea and/or constipation and bloating on a scale rating from 10 (marginally impaired) to 50 (highly impaired)

- No further details were given on the instrument used for this assessment, not stated whether validated.

Results:

Impairment severity score (mean, SD)

	Bodily impairment		Psychic impairment		Social impairment	
Group	FR (N=40)	EMC (N=40)	FR (N=40)	EMC (N=40)	FR (N=40)	EMC (N=40)
baseline	2.20 (0.94)	2.14 (0.72)	2.06 (0.72)	1.97 (0.70)	0.94 (0.87)	1.22 (0.87)
5 weeks	1.59 (0.73)	2.03 (0.70)	1.48 (0.59)	1.77 (0.75)	0.90 (0.88)	1.11 (0.97)
3 months	1.69 (0.95)	2.08 (0.79)	1.64 (0.72)	1.88 (0.89)	1.01 (0.91)	1.14 (0.91)
Mean change	-0.51	-0.04	-0.42	-0.09	+0.07	-0.08

Bibliographic reference	Lahman et al (2010) Functional relaxation as complementary therapy in irritable bowel syndrome: a randomized, controlled trial. Journal of Alternative and Complementary Medicine

from baseline *						

*mean change calculated by analyst for purposes of interpreting imprecision. SD could not be calculated for these values.
Total score out of 12

Subjective overall impairment by IBS symptoms: (assumed to be mean, SD, not explicitly stated in paper)

Rating	Time	Functional relaxation (n=40)	Enhanced medical care (n=40)	ANCOVA; $F_{(1;77)}$, p value
Overall IBS symptoms	Pre	31.8 (6.3)	31.0 (6.4)	
	Post	23.5 (6.7)	29.8 (5.3)	35.0; <0.001
	Follow-up	26.2 (6.8)	30.6 (6.1)	13.1; 0.001
	Mean change from baseline*	-5.6	-0.04	
Abdominal pain and tenderness	Pre	33.0 (9.8)	31.4 (10.3)	
	Post	27.0 (8.9)	29.7 (9.6)	3.6; 0.063
	Follow-up	25.7 (9.9)	27.3 (10.5)	1.0; 0.325
	Mean change from	-7.3	-4.1	

Bibliographic reference	Lahman et al (2010) Functional relaxation as complementary therapy in irritable bowel syndrome: a randomized, controlled trial. Journal of Alternative and Complementary Medicine

	baseline*			
Diarrhoea and/or constipation	Pre	33.4 (8.8)	32.4 (7.2)	
	Post	27.3 (7.2)	31.0 (6.0)	12.2; 0.001
	Follow-up	29.1 (7.5)	29.2 (7.8)	0.042; 0.838
	Mean change from baseline*	-4.3	-2.2	
Bloating	Pre	35.4 (7.7)	34.9 (8.2)	
	Post	27.0 (7.6)	32.0 (8.5)	11.0; 0.001
	Follow-up	28.1 (7.6)	33.2 (7.5)	13.2; <0.001
	Mean change from baseline*	-7.3	-1.7	

*mean change calculated by analyst for purposes of interpreting imprecision. SD could not be calculated for these values. Total score range of 10-50 (total of 40).

Source of funding	Study was not funded externally
Comments	Power calculation based on Impairment Score as primary outcome measure, assumed effect size 0.65 (two-tailed, power 80%, error probability 0.05), detection of an effect at 0.65 required a sample size of at least 39 per group To fulfil the principle of ITT all missing values of the interviewer and patient ratings were replaced by SPSS missing values

Bibliographic reference	**Lahman et al (2010) Functional relaxation as complementary therapy in irritable bowel syndrome: a randomized, controlled trial. Journal of Alternative and Complementary Medicine**
	procedure using a linear regression model People taking specific IBS medication were excluded from the study. Functional relaxation is a somatopsychotherapeutic intervention technique used for the treatment of psychosomatic disorders. The therapeutic effects are delivered through the assumed mechanism of positive stimulation of the autonomic nervous system as well as facilitation of proprioceptive awareness

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Bibliographic reference	**Shinozaki et al (2010) Effect of autogenic training on general improvements in patients with irritable bowel syndrome: a randomised controlled trial. Appl Psychophysiol Biofeedback**
Study type	Study design: RCT, No details on randomisation, states “enrolled at random”, allocation concealment not reported
Aim	Aim: to test the hypothesis that autogenic training would improve GI symptoms, negative emotion and health related quality of life in patient with IBS
Patient characteristics	IBS patients visiting the Department of Psychosomatic Medicine. Tohoku University Hospital; Dec 2001 to July 2005 *Inclusion criteria:* • Diagnosis of IBS according to Rome-II criteria • At 8 weeks following prescribed treatments at diagnosis (see below) those with no adequate relief enrolled in the study Baseline characteristics showed no differences in age, sex, IBS subtype, SIBSQ, SDS and STAI. The SF-36 social functioning in the intervention group was significantly lower than the control group No exclusion details provided.
Number of Patients	n=21

Bibliographic reference	**Shinozaki et al (2010) Effect of autogenic training on general improvements in patients with irritable bowel syndrome: a randomised controlled trial. Appl Psychophysiol Biofeedback**
Intervention	Autogenic training (n=11); - Individually for 8 sessions in 8weeks - Interval between sessions was 2-4 weeks (depending on patient's social situation) - 30-40 minutes of full exercise - During the interval between sessions home-exercise was recommended – patients were given a set of explanatory leaflets and an audiotape - Standard exercise; my right (left) arm (leg) is heavy; my right (left) arm (leg) is warm; my heart beat is calm and regular; it breathes me; my solar plexus is warm; my forehead is cool and clear; cancellation
Comparison	Control session (n=10): - Aimed at discussing diet therapy - Session time and frequency same as the autogenic training sessions - Contents for control session textbook; what is IBS; treatment of IBS; nutrients and dietary fibres; diet therapy for IBS; diet therapy for diarrhoea-predominant IBS; diet therapy for constipation-predominant IBS; diet therapy for alternating IBS; summary
Length of follow up	8 weeks, outcomes assessed at the last session
Location	Japan
Outcomes measures and effect size	Primary outcomes; answer to one oral question asked during medical visit - Adequate relief considered clinically useful to assess improvement of abdominal pain and/or discomfort

Bibliographic reference	Shinozaki et al (2010) Effect of autogenic training on general improvements in patients with irritable bowel syndrome: a randomised controlled trial. Appl Psychophysiol Biofeedback
	- Question – 'Did you have adequate relief of IBS related abdominal pain or discomfort?' - Scored dichotomously – yes or no - Not stated whether validated outcome Secondary endpoints; 4 validated questionnaires - Self-reported IBS questionnaire (SIBSQ); validated disease-specific questionnaire, based on Rome-II criteria, consists of 14 GI symptoms-related questions (on a 7-point Likert scale), the sum of the scores gives a total SIBSQ score. Also 7 additional questions that are used to obtain more detailed characterisation of IBS symptoms. A higher score indicate worse symptoms. - State-trait anxiety inventory (STAI); well-validated 40 item self-reported questionnaire, 20 items to measure state anxiety and 20 items for trait anxiety - Self-rating depression scale (SDS); validated scale, 20 questions score on a 4-point Likert scale - SF-36 **Results:** **Adequate relief;** At the last session, proportion of adequate relief autogenic training, n=9/11 (81.3%) compared with control group, n=3/10 (30.0%), (chi square = 5.74, p<0.05). Rate ratio between the groups 2.73 (95%CI 1.02 to 7.32). Significant differences between the groups also found at the 4th (p<0.05) and 7th (p<0.001) sessions **Self-reported IBS questionnaire** (**SIBSQ);** assessed on a 7 point scale, higher score= worse. All values are mean (SD) Subscores showed no differences between the autogenic training group and the control group. Analysis of the SIBSQ total scores showed no significant difference between the two groups

Bibliographic reference	**Shinozaki et al (2010) Effect of autogenic training on general improvements in patients with irritable bowel syndrome: a randomised controlled trial. Appl Psychophysiol Biofeedback**

Autogenic Training (n=11)				Control (n=10)			
Baseline	End of treatment	Mean change from baseline*	P value	Baseline	End of treatment	Mean change from baseline*	P value
52.1 (11.6)	48.9 (6.1)	-3.2	0.473	55.9 (13.9)	36.3 (23.4)	-19.6	0.008

*calculated by analyst for purposes of assessing imprecision. SD not calculated, total score = 98

Self-rating depression scale (SDS); All values are mean (SD)

Showed no differences between the autogenic training and the control group

	Autogenic Training (n=11)			Control (n=10)			
Baseline	End of treatment	Mean change from baseline*	P value	Baseline	End of treatment	Mean change from baseline*	P value
46.4 (5.9)	44.6 (7.4)	-1.8	0.315	45.9 (5.9)	45.8 (9.4)	-0.01	0.553

*calculated by analyst for purposes of assessing imprecision. SD not calculated. Total score range = 10- 80 (70)

Bibliographic reference	**Shinozaki et al (2010) Effect of autogenic training on general improvements in patients with irritable bowel syndrome: a randomised controlled trial. Appl Psychophysiol Biofeedback**

State-trait anxiety inventory (**STAI);** All values are mean (SD)

Showed no differences between the autogenic training and the control group

	Autogenic Training (n=11)				Control (n=10)			
	Baseline	End of treatment	Mean change from baseline *	P value	Baseline	End of treatment	Mean change from baseline*	P value
State anxiety	50.0 (9.1)	47.2 (7.9)	-2.8	0.755	54.6 (11.0)	51.4 (10.5)	-3.2	0.173
Trait anxiety	56.0 (8.1)	54.5 (9.4)	-1.5	0.102	56.8 (11.4)	52.8 (14.5)	-4.0	0.097

*calculated by analyst for purposes of assessing imprecision. SD not calculated. Total score range = 20- 80 (60)

SF-36;

No significant group effect, period effect or group x period interaction in subscores was detected

With the autogenic training group there were significant changes in bodily pain (baseline 36.8±7.8, end of treatment 45.6±11.7, p=0.012) and social functioning (baseline 27.0±12.0, end of treatment 41.1±19.6, p=0.021)

SF36	Autogenic Training	Control

Bibliographic reference	**Shinozaki et al (2010) Effect of autogenic training on general improvements in patients with irritable bowel syndrome: a randomised controlled trial. Appl Psychophysiol Biofeedback**

domain								
	Baseline	End of treatment	Mean change from baseline*	P value	Baseline	End of treatment	Mean change from baseline*	P value
PF	47.7 (14.3)	51.2 (8.3)	+3.5	0.600	48.9 (7.8)	46.4 (13.7)	-2.5	0.655
RP	26.9 (18.9)	35.6 (20.4)	+8.7	0.310	23.7 (19.2)	33.8 (24.6)	+10.1	0.293
BP	36.8 (7.8)	45.6 (11.7)	+8.8	0.012	38.5 (9.6)	41.3 (10.7)	+2.8	0.735
GH	30.9 (10.6)	34.7 (9.4)	+4.8	0.069	32.8(10.4)	33.8 (17.4)	+1.0	0.484
VT	35.4 (8.3)	37.1 (6.6)	+1.7	0.463	36.6 (6.3)	34.5 (10.7)	-2.1	0.097
SF	27.0 (12.0)	41.1 (19.6)	+14.1	0.021	43.4 (9.0)	42.6 (15.7)	-0.8	0.866
RE	34.2 (14.5)	46.4 (15.5)	+12.2	0.051	33.9 (16.0)	41.2 (18.2)	+7.3	0.575
MH	36.6 (9.0)	42.0 (4.9)	+5.4	0.239	35.9 (8.5)	35.6 (13.5)	-0.3	0.889

*calculated by analyst for purposes of assessing imprecision. SD not calculated. Total score range = 100

All values are mean (SD). PF physical functioning, BP bodily pain, GH general health, VT vitality, SF social functioning, RE role emotional, MH mental health,

Source of funding	Grants from the Ministry of Education, Culture, Sports, Science and Technology, Japan and the Ministry of Health, Welfare and Labor, Japan

Bibliographic reference	**Shinozaki et al (2010) Effect of autogenic training on general improvements in patients with irritable bowel syndrome: a randomised controlled trial. Appl Psychophysiol Biofeedback**
Comments	Sample size (α=0.05), based on clinical experience hypothesised that improvement rate would be 85% with autogenic training and 25% in control. With this assumption the sample size was estimated as 10 Patients were not informed which group they were in, however they were not completely blinded as they understood the contents of the treatments. No further information about assessor/ investigator blinding reported. Attrition not reported, not clear whether ITT analysis.

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G.62 Review question 5b (CCBT and Mindfulness therapy)

Bibliographic reference	**Ljotsson (2010)** **Internet-delivered exposure and mindfulness based therapy for irritable bowel syndrome e A randomized controlled trial.** **ID: 2511** **Andersson (2011)** **Cost-effectiveness of internet-based cognitive behaviour therapy for irritable bowel syndrome: results from a randomized controlled trial** **ID: 252** **Ljotsson (2011)c** **Long-term follow-up of internet-delivered exposure and mindfulness based treatment for irritable bowel syndrome** **ID: 295**
Study type	RCT *Note: The Andersson (2011) study is the further publication of the Ljotsson (2010) study with additional outcomes and cost-effectiveness analysis.* *Note: The Ljotsson (2011)c study is the long-term follow-up study of the Ljotsson (2010) study.*
Aim	The aim of this study was to investigate if cognitive behaviour therapy (CBT) based on exposure and mindfulness exercises

Bibliographic reference	**Ljotsson (2010)** **Internet-delivered exposure and mindfulness based therapy for irritable bowel syndrome e A randomized controlled trial.** **ID: 2511** **Andersson (2011)** **Cost-effectiveness of internet-based cognitive behaviour therapy for irritable bowel syndrome: results from a randomized controlled trial** **ID: 252** **Ljotsson (2011)c** **Long-term follow-up of internet-delivered exposure and mindfulness based treatment for irritable bowel syndrome** **ID: 295**
	delivered via the Internet would be effective in treating participants with irritable bowel syndrome (IBS). Abbreviation for Intervention: CCBT-Mindfulness/Exposure
Patient characteristics	85 self-referred IBS-patients *Inclusion:* Patients self-declared to have had a previous diagnosis of IBS given by a physician and if they presently fulfilled the Rome III criteria for IBS *Exclusion:* • patients with symptoms that would that in a live care setting would have rendered a somatic investigation to rule out organic disease. • symptom debut after age 50. • blood in stool without satisfactory medical explanation (such as known haemorrhoids). • diarrhoea predominant IBS with no colonoscopy performed. • rapid weight loss that could not be linked to change in diet. • night symptoms that persistently caused sleeplessness. • less than 2 years of IBS-symptoms (regardless of when diagnosis had been given). • any presence of current or previous inflammatory bowel disease. • lactose or gluten intolerance where proper adjustments in diet had not been made. • with suicidal ideation and severe depressive symptoms. • with substance dependence, psychosis, manic episode, or anorexia. *Baseline characteristics:*

Bibliographic reference	**Ljotsson (2010)** **Internet-delivered exposure and mindfulness based therapy for irritable bowel syndrome e A randomized controlled trial.** **ID: 2511** **Andersson (2011)** **Cost-effectiveness of internet-based cognitive behaviour therapy for irritable bowel syndrome: results from a randomized controlled trial** **ID: 252** **Ljotsson (2011)c** **Long-term follow-up of internet-delivered exposure and mindfulness based treatment for irritable bowel syndrome** **ID: 295**
	Gender (Male/Female): Intervention group = 7/35; Waitlist (online discussion forum) = 6/37 Age (mean years, SD): Intervention group = 36.4 (10.1); Waitlist (online discussion forum) = 32.8 (8.6) Years since diagnosis (mean years): Intervention group = 7.2; Waitlist (online discussion forum) = 5.5
Number of Patients	85 self-referred IBS-patients through contacting a Swedish online discussion forum for people with IBS, a major newspaper wrote an article about the study, and outpatients at a clinic located in Stockholm specialized at treating IBS. *Total number of patients:* CCBT-Mindfulness/Exposure = 42; Waitlist (online discussion forum) = 43 *Those completed the post-assessment:* CCBT-Mindfulness/Exposure = 38; Waitlist (online discussion forum) = 43 *Those completed the 12-month follow-up assessment:* CCBT-Mindfulness/Exposure = 35; Waitlist (online discussion forum) = 40
Intervention	**CCBT-Mindfulness/Exposure (10-week CBT-protocol)** A text based self-help manual (presented on printer-friendly web pages) divided into five steps: • A rationale for the treatment and instructions on mindfulness. • Three steps of presentation of a psychological model of IBS and continued mindfulness exercises. • Exposure exercises and instruction on how to use mindfulness during exposure. Participants were given access to the five steps sequentially. • They were required to report their homework exercises for each step before they could access the next step. They were

Bibliographic reference	**Ljotsson (2010)** **Internet-delivered exposure and mindfulness based therapy for irritable bowel syndrome e A randomized controlled trial.** **ID: 2511** **Andersson (2011)** **Cost-effectiveness of internet-based cognitive behaviour therapy for irritable bowel syndrome: results from a randomized controlled trial** **ID: 252** **Ljotsson (2011)c** **Long-term follow-up of internet-delivered exposure and mindfulness based treatment for irritable bowel syndrome** **ID: 295**
	instructed to spend about one week per step and reach step five by mid-treatment. • Step five consisted of instructions for exposure exercises and the participants stayed on this step and continued doing exposure exercises for the remainder of the treatment. • During treatment, participants also had access online closed discussion forum where they could discuss the treatment with each other. *Therapist contact:* • Participants had contact with a graduate psychology student, trained in CBT, through an online asynchronous message system (at least one message per week about their work with the treatment and received feedback on their message within 24-48 hours). • The total time spent by the student therapists per participant over the 10 weeks of treatment: Mean (min, SD) = 165 min (85 min); Range = 8min to 315 min
Comparison	**Waitlist (online discussion forum) (W-ODF)** • An online discussion forum (separate from the one used by the treatment intervention) where suggestions about general discussions regarding IBS were given each week. • Participants were also allowed to initiate contact with a student therapist if they wished to receive general support, but were offered no CBT-based advice on how to handle IBS-symptoms or psychological distress.
Length of follow up	10-week treatment period with 3-month follow-up online assessment
Location	Between May 5th 2008 and July 1st 2008 in Sweden

Bibliographic reference	**Ljotsson (2010)** **Internet-delivered exposure and mindfulness based therapy for irritable bowel syndrome e A randomized controlled trial.** **ID: 2511** **Andersson (2011)** **Cost-effectiveness of internet-based cognitive behaviour therapy for irritable bowel syndrome: results from a randomized controlled trial** **ID: 252** **Ljotsson (2011)c** **Long-term follow-up of internet-delivered exposure and mindfulness based treatment for irritable bowel syndrome** **ID: 295**
Outcomes measures and effect size	LOCF was conducted for the analyses. **IBS-QoL (total score: 0 to 100, with 0 = minimum QoL)** [30% improvement = at least 30 point increase from baseline]

CCBT-M/E (N=42)			**W-ODF (N=43)**			
Baseline (mean, SD)	Post-treatment (mean, SD)	Mean change from baseline	Baseline (mean, SD)	Post-treatment (mean, SD)	Mean change from baseline	Cohen's d (95%CI)
52.2 (19.9)	72.8 (19.9)	+20.6	53.8 (18.9)	52.9 (21.3)	-0.9	0.93 (0.47 to 1.36)
CCBT-M/E (N=35)			**W-ODF (N=40)**			
Baseline (mean, SD)	12-mth follow-up (mean, SD)	Mean change from baseline	Baseline (mean, SD)	12-mth follow-up (mean, SD)	Mean change from baseline	Cohen's d (95%CI)
52.2 (19.9)	70.3 (21.5)	+18.1	53.8 (18.9)	73.2 (21.8)	+19.4	No between groups reported

GSRS-IBS (Gastrointestinal Symptom Rating Scale for IBS) (total score: 13 to 91, with 13 = no discomfort at all)
Responder (clinically significant improvement was defined as a 50% reduction of GSRS-IBS score)
Post-treatment:
CCBT-M/E = 15/42; W-ODF = 1/43; RR = 15.36 (95%CI: 2.12 to 111.13)

GSRS-IBS (Gastrointestinal Symptom Rating Scale for IBS) (total score: 13 to 91, with 13 = no discomfort at all)
[30% improvement = at least 23.4 points decrease from baseline]

CCBT-M/E (N=42)			**W-ODF (N=43)**			
Baseline	Post-treatment	Mean change	Baseline	Post-treatment	Mean change	Cohen's d

Bibliographic reference

Ljotsson (2010)
Internet-delivered exposure and mindfulness based therapy for irritable bowel syndrome e A randomized controlled trial.
ID: 2511
Andersson (2011)
Cost-effectiveness of internet-based cognitive behaviour therapy for irritable bowel syndrome: results from a randomized controlled trial
ID: 252
Ljotsson (2011)c
Long-term follow-up of internet-delivered exposure and mindfulness based treatment for irritable bowel syndrome
ID: 295

(mean, SD)	(mean, SD)	from baseline	(mean, SD)	(mean, SD)	from baseline	(95%CI)
48.5 (8.8)	32.4 (12.1)	-16.1	49.6 (11.8)	47.3 (12.6)	-2.3	1.21 (0.73 to 1.66)
CCBT-M/E (N=35)			**W-ODF (N=40)**			
Baseline (mean, SD)	12-mth follow-up (mean, SD)	Mean change from baseline	Baseline (mean, SD)	12-mth follow-up (mean, SD)	Mean change from baseline	Cohen's d (95%CI)
48.5 (8.8)	39.5 (14.4)	-9.0	49.6 (11.8)	35.0 (13.6)	-14.6	No between groups reported

The GI symptom diary (mean daily rating) (5-point scale: 0 = not a problem; 4 = debilitating)
[30% improvement = at least 1.5 points decrease from baseline]

	CCBT-M/E (N=42)			**W-ODF (N=43)**			
Symptom	Baseline (mean, SD)	Post-treatment (mean, SD)	Mean change from baseline	Baseline (mean, SD)	Post-treatment (mean, SD)	Mean change from baseline	Cohen's d (95%CI)
Total pain	2.6 (1.7)	1.4 (1.5)	-1.2	2.4 (1.5)	2.4 (1.6)	0.0	0.64 (0.17 to 1.10)
Constipation	0.5 (0.4)	0.3 (0.4)	-0.2	0.7 (0.6)	0.7 (0.6)	0.0	0.76 (0.26 to 1.27)
Diarrhoea	0.7 (0.6)	0.4 (0.5)	-0.3	0.6 (0.6)	0.6 (0.7)	0.0	0.32 (0.15 to 0.79)
Bloating	1.6 (0.9)	0.9 (0.9)	-0.7	1.7 (0.8)	1.7 (0.8)	0.0	0.94 (0.46 to 1.41)
Nausea	0.8 (0.9)	0.5 (0.9)	-0.3	0.6 (0.5)	0.6 (0.6)	0.0	0.13 (0.34 to 0.60)
Flatulence	1.4 (0.9)	0.9 (0.7)	-0.5	1.4 (0.7)	1.4 (0.8)	0.0	0.6 (0.19 to 1.12)
Belching	0.6 (0.6)	0.4 (0.5)	-0.2	0.5 (0.6)	0.5 (0.5)	0.0	0.20 (0.34 to 0.74)
Primary symptoms*	5.3 (2.8)	3.0 (2.7)	-2.3	5.1 (2.5)	5.2 (2.6)	+0.1	0.83 (0.36 to 1.29)

*Primary symptoms = (abdominal pain and tenderness, diarrhoea and constipation

Bibliographic reference	**Ljotsson (2010)** **Internet-delivered exposure and mindfulness based therapy for irritable bowel syndrome e A randomized controlled trial.** **ID: 2511** **Andersson (2011)** **Cost-effectiveness of internet-based cognitive behaviour therapy for irritable bowel syndrome: results from a randomized controlled trial** **ID: 252** **Ljotsson (2011)c** **Long-term follow-up of internet-delivered exposure and mindfulness based treatment for irritable bowel syndrome** **ID: 295**
Source of funding	The Stockholm County Council, the Centre for Psychiatry Research, and the Söderströmska-Königska Foundation.
Comments	ITT principles were used in the analysis; allocation concealment was complied. Potential selection bias as participants was self-referred. Though blinding of participants was not achievable, as all outcomes were self-reported subjective measurement, the impact of potential placebo-effect needs further consideration. Reasons for withdrawal in the CCBT-Mindfulness/Exposure arm not reported. The 3-month follow-up data only available for the intervention group (within-subjects comparisons).

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Bibliographic reference	**Ljotsson (2011)** **Internet-Delivered Exposure-Based Treatment vs. Stress Management for Irritable Bowel Syndrome: A Randomized Trial** **ID: 226**
Study type	RCT
Aim	To compare an internet-delivered cognitive behavioural treatment (exposure-mindfulness based) with internet-delivered stress management (ISM) for IBS to assess whether the effects of ICBT are specific. Abbreviation for Interventions: CCBT-Mindfulness/Exposure; ISM
Patient characteristics	195 self-referred IBS-patients *Inclusion:* Patients self-declared to have had a previous diagnosis of IBS given by a physician and if they presently fulfilled the Rome III criteria for IBS

Bibliographic reference	**Ljotsson (2011)** **Internet-Delivered Exposure-Based Treatment vs. Stress Management for Irritable Bowel Syndrome: A Randomized Trial** **ID: 226**
	Exclusion: • patients with symptoms that would that in a live care setting would have rendered a somatic investigation to rule out organic disease. • symptom debut after age 50. • blood in stool without satisfactory medical explanation (such as known haemorrhoids). • diarrhoea predominant IBS with no colonoscopy performed. • rapid weight loss that could not be linked to change in diet. • night symptoms that persistently caused sleeplessness. • less than 2 years of IBS-symptoms (regardless of when diagnosis had been given). • any presence of current or previous inflammatory bowel disease. • lactose or gluten intolerance where proper adjustments in diet had not been made. • with suicidal ideation and severe depressive symptoms. • with substance dependence, psychosis, manic episode, or anorexia. *Baseline characteristics:* Gender (Female): CCBT-Mindfulness/Exposure = 77.6%; ISM = 80.4% Age (mean years, SD): CCBT-Mindfulness/Exposure = 38.3 (11.9); ISM = 37.4 (10.3) Years since diagnosis (mean years, SD): CCBT-Mindfulness/Exposure = 14.8 (12.7); ISM = 15.1 (9.7)
Number of Patients	195 self-referred IBS-patients. Information about the study was spread through several channels. Several websites (e.g., online newspaper articles, an online discussion forum about IBS, a web portal for internet-based treatments) linked to the research group's website, where information about this upcoming study had been posted since June 2008 in Sweden. *Total number of patients:* CCBT-Mindfulness/Exposure = 98; ISM = 97 *Those completed the post-assessment:* CCBT-Mindfulness/Exposure = 97; ISM = 94 *Those completed the 6-month follow-up assessment:* CCBT-Mindfulness/Exposure = 87; ISM = 82

Bibliographic reference	**Ljotsson (2011)** **Internet-Delivered Exposure-Based Treatment vs. Stress Management for Irritable Bowel Syndrome: A Randomized Trial** **ID: 226**
	*Reasons for withdrawal not reported.
Intervention	**CCBT-Mindfulness/Exposure (10-week CBT-protocol)** A text based self-help manual (presented on printer-friendly web pages) divided into five steps: • A rationale for the treatment and instructions on mindfulness. • Three steps of presentation of a psychological model of IBS and continued mindfulness exercises. • Exposure exercises and instruction on how to use mindfulness during exposure. Participants were given access to the five steps sequentially. • They were required to report their homework exercises for each step before they could access the next step. They were instructed to spend about one week per step and reach step five by mid-treatment. • Step five consisted of instructions for exposure exercises and the participants stayed on this step and continued doing exposure exercises for the remainder of the treatment. • During treatment, participants also had access online closed discussion forum where they could discuss the treatment with each other. *Therapist contact:* • Participants had contact with a graduate psychology student, trained in CBT, through an online asynchronous message system (at least one message per week about their work with the treatment and received feedback on their message within 2 to 3 days). • The total time spent by the student therapists per participant per week: Mean (min, SD) = 10.1 min (7.5 min) *The therapists were randomly assigned participants from both conditions in equal numbers to control for any therapist-specific effects.*
Comparison	**Internet-delivered stress management (ISM)** • With elements that are common to all psychological interventions • Based on the common notion that IBS symptoms are exacerbated by daily stressors and better coping with these

<table>
<tr><th>Bibliographic reference</th><th>Ljotsson (2011)
Internet-Delivered Exposure-Based Treatment vs. Stress Management for Irritable Bowel Syndrome: A Randomized Trial
ID: 226</th></tr>
<tr><td></td><td>stressors should alleviate the burden of symptoms.
• The protocol was obtained from IBS self-help books that contain stress and symptom management instructions, an educative booklet about IBS and a tinnitus self-help book with relaxation instructions.
• The treatment interventions were (i) progressive applied relaxation, used to put the body in a state of immediate relaxation in response to IBS symptoms and psychological distress; (ii) diet strategies; (iii) problem-solving strategies used to divide daily hassles into smaller and solvable problems; and (iv) advice on how to increase the quality of sleep using common sleep hygiene strategies.

<u>Therapist contact:</u>
• Participants had contact with a graduate psychology student, trained in CBT, through an online asynchronous message system (at least one message per week about their work with the treatment and received feedback on their message within 2 to 3 days).
• The total time spent by the student therapists per participant per week: Mean (min, SD) = 7.8 min (6.2 min)</td></tr>
<tr><td>Length of follow up</td><td>10-week treatment period with 6-month follow-up online assessment</td></tr>
<tr><td>Location</td><td>Between 8 February and 16 April 2010 in Sweden.</td></tr>
<tr><td>Outcomes measures and effect size</td><td>IBS-QoL (total score: 0 to 100, with 0 = minimum QoL)
[30% improvement = at least 30 point increase from baseline]
<table>
<tr><td></td><td>Baseline (mean, SD)</td><td>Post treatment (mean, SD)</td><td>Mean change from baseline</td><td>6-month follow-up (mean, SD)</td><td>Mean change from baseline</td></tr>
<tr><td>CCBT-M/E</td><td>N=98
57.1 (19.1)</td><td>N=97
75.7 (17.7)</td><td>+18.6</td><td>N=87
74.9 (20.8)</td><td>+17.8</td></tr>
<tr><td>ISM</td><td>N=97
55.5 (18.9)</td><td>N=94
65.7 (21.1)</td><td>+10.2</td><td>N=82
68.7 (19.0)</td><td>+13.2</td></tr>
</table>
GSRS-IBS (Gastrointestinal Symptom Rating Scale for IBS) (total score: 13 to 91, with 13 = no discomfort at all)
[30% improvement = at least 23.4 points decrease from baseline]
<table>
<tr><td></td><td>Baseline</td><td>Post</td><td>Mean change</td><td>6-month</td><td>Mean change</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Ljotsson (2011)** **Internet-Delivered Exposure-Based Treatment vs. Stress Management for Irritable Bowel Syndrome: A Randomized Trial** **ID: 226**

	(mean, SD)	treatment (mean, SD)	from baseline	follow-up (mean, SD)	from baseline
CCBT-M/E	N=98 47.5 (10.5)	N=96 36.3 (12.7)	-11.2	N=87 33.4 (13.4)	-14.1
ISM	N=97 47.3 (9.4)	N=90 41.1 (12.4)	-6.2	N=82 39.3 (13.3)	-8.0

Adequate relief (responder) *[Question: "In the past week, have you had adequate relief from IBS pain or discomfort?"]*

	CCBT-M/E	ISM	RR (95%CI)
Post-treatment	68/98	56/97	1.20 (0.97 to 1.49)
6-month follow-up	64/98	43/97	1.47 (1.13 to 1.92)

XX

Source of funding	The Stockholm County Council, the Centre for Psychiatry Research, the Söderströmska-Königska Foundation, and the Bror Gadelius Foundation.
Comments	Allocation concealment was complied. Potential selection bias as participants was self-referred. Though blinding of participants was not achievable, as all outcomes were self-reported subjective measurement, the impact of potential placebo-effect needs further consideration. Reasons for withdrawal in the trial not reported.

1

Bibliographic reference	**Ljotsson (2011)b** **Acceptability, effectiveness, and cost-effectiveness of internet-based exposure treatment for irritable bowel syndrome in a clinical sample: a randomized controlled trial.** **ID: 209**
Study type	RCT
Aim	The aim of this study to investigate the acceptability, effectiveness, and cost-effectiveness of ICBT for IBS using a consecutively recruited sample from a gastroenterological clinic.
Patient characteristics	61 IBS-patients

Bibliographic reference	**Ljotsson (2011)b** **Acceptability, effectiveness, and cost-effectiveness of internet-based exposure treatment for irritable bowel syndrome in a clinical sample: a randomized controlled trial.** **ID: 209**
	Inclusion: Participants were eligible for the study if they: • had their first visit at the recruiting clinic (through referral or self-referral) and were diagnosed during the recruitment period • had IBS symptoms as their primary reason for consultation • fulfilled Rome III-criteria for IBS • were between 18 and 65 years old • had no presence of current or previous inflammatory bowel disease • lived in Stockholm County *Exclusion:* • reported first time of IBS symptoms after 50 years of age and were judged to require continued monitoring at the clinic, • suffered from such severe diarrhoea that IBS-symptom modifying drugs with psychotropic effects, such as tricyclic antidepressants or selective serotonin reuptake inhibitors, were judged to be the treatment of choice • could not read or write Swedish • did not have access to the internet • were judged to be highly unsuitable for ICBT for somatic or psychological reasons as assessed by the gastroenterologist • were not willing to participate in the study *Baseline characteristics:* All included patients were given standardized information about IBS and basic dietary and lifestyle advice on how to manage their IBS. If appropriate they were also prescribed medication and/or given information about over-the-counter drugs. To ensure that this basic IBS management would have had its effect before patients begun their participation in the study, the pre-treatment assessment was conducted at least one month after inclusion. Gender (Female): Intervention group = 77%; Waitlist (online discussion forum) = 71% Age (mean years, SD): Intervention group = 33.5 (11.2); Waitlist (online discussion forum) = 36.3 (11.3) Years since diagnosis (mean years, SD): Intervention group = 11.7 (12.7); Waitlist (online discussion forum) = 11.3 (11.1) IBS sub-type (%):

Bibliographic reference	**Ljotsson (2011)b** **Acceptability, effectiveness, and cost-effectiveness of internet-based exposure treatment for irritable bowel syndrome in a clinical sample: a randomized controlled trial.** **ID: 209**
	IBS-C: Intervention group = 20%; Waitlist (online discussion forum) = 23% IBS-D: Intervention group = 27%; Waitlist (online discussion forum) = 32% IBS-Mixed: Intervention group = 53%; Waitlist (online discussion forum) = 45%
Number of Patients	61 patients were consecutively recruited at a single gastroenterological clinic located in Stockholm, Sweden. Patients came to the clinic by referral or by self-referral. *Total number of patients:* CCBT-Mindfulness/Exposure = 30; Waitlist (online discussion forum) = 31 *Those completed the post-assessment:* CCBT-Mindfulness/Exposure = 23; Waitlist (online discussion forum) = 27
Intervention	**CCBT-Mindfulness/Exposure (10-week CBT-protocol)** A text based self-help manual (presented on printer-friendly web pages) divided into five steps: • A rationale for the treatment and instructions on mindfulness. • Three steps of presentation of a psychological model of IBS and continued mindfulness exercises. • Exposure exercises and instruction on how to use mindfulness during exposure. Participants were given access to the five steps sequentially. • They were required to report their homework exercises for each step before they could access the next step. They were instructed to spend about one week per step and reach step five by mid-treatment. • Step five consisted of instructions for exposure exercises and the participants stayed on this step and continued doing exposure exercises for the remainder of the treatment. • During treatment, participants also had access online closed discussion forum where they could discuss the treatment with each other. *Therapist contact:* • Participants had contact with clinical psychologists, trained in CBT, through an online asynchronous message system (at least one message per week about their work with the treatment and received feedback on their message within 24-

<table>
<tr><th>Bibliographic reference</th><th>Ljotsson (2011)b
Acceptability, effectiveness, and cost-effectiveness of internet-based exposure treatment for irritable bowel syndrome in a clinical sample: a randomized controlled trial.
ID: 209</th></tr>
<tr><td></td><td>48 hours).
• The total time spent with a clinical psychologist per participant per week: Mean (min, SD) = 7.3 min (5.2 min); Range = 0 min to 24.5 min</td></tr>
<tr><td>Comparison</td><td>Waitlist (online discussion forum) (W-ODF)
• An online discussion forum (separate from the one used by the treatment intervention) where suggestions about general discussions regarding IBS were given each week.</td></tr>
<tr><td>Length of follow up</td><td>10-week treatment period with 12-month follow-up online assessment</td></tr>
<tr><td>Location</td><td>Between 19 November 2008 and 13 May 2009 in Sweden.</td></tr>
<tr><td>Outcomes measures and effect size</td><td>IBS-QoL (total score: 0 to 100, with 0 = minimum QoL)
[30% improvement = at least 30 point increase from baseline]
<table>
<tr><th colspan="3">CCBT-M/E
(baseline N=30; post-treatment N=23)</th><th colspan="3">W-ODF
(Baseline N=31; post-treatment N=27)</th><th></th></tr>
<tr><td>Baseline (mean, SD)</td><td>Post-treatment (mean, SD)</td><td>Mean change from baseline</td><td>Baseline (mean, SD)</td><td>Post-treatment (mean, SD)</td><td>Mean change from baseline</td><td>Cohen’s d (95%CI)</td></tr>
<tr><td>67.4 (20.9)</td><td>82.6 (13.4)</td><td>+15.2</td><td>76.1 (18.8)</td><td>67.4 (23.1)</td><td>-8.7</td><td>0.79 (0.20 to 1.35)</td></tr>
</table>
GSRS-IBS (Gastrointestinal Symptom Rating Scale for IBS) (total score: 13 to 91, with 13 = no discomfort at all)
[30% improvement = at least 23.4 points decrease from baseline]
<table>
<tr><th colspan="3">CCBT-M/E (N=42)</th><th colspan="3">W-ODF (N=43)</th><th></th></tr>
<tr><td>Baseline (mean, SD)</td><td>Post-treatment (mean, SD)</td><td>Mean change from baseline</td><td>Baseline (mean, SD)</td><td>Post-treatment (mean, SD)</td><td>Mean change from baseline</td><td>Cohen’s d (95%CI)</td></tr>
<tr><td>44.6 (11.1)</td><td>31.0 (10.2)</td><td>-13.6</td><td>39.8 (12.0)</td><td>40.9 (14.5)</td><td>+1.1</td><td>0.77 (0.19 to 1.34)</td></tr>
</table>
XX</td></tr>
<tr><td>Source of funding</td><td>The Stockholm County Council, the Centre for Psychiatry Research, and the Söderströmska-Königska Foundation.</td></tr>
</table>

Bibliographic reference	**Ljotsson (2011)b** **Acceptability, effectiveness, and cost-effectiveness of internet-based exposure treatment for irritable bowel syndrome in a clinical sample: a randomized controlled trial.** **ID: 209**
Comments	No allocation concealment. Potential selection bias as some participants were self-referred. Though blinding of participants was not achievable, as all outcomes were self-reported subjective measurement, the impact of potential placebo-effect needs further consideration. Reasons for withdrawal or lost to follow-up in the trial not reported.

1

Bibliographic reference	**Gaylord (2011)** **Mindfulness Training Reduces the Severity of Irritable Bowel Syndrome in Women: Results of a Randomized Controlled Trial.** **ID: 219**
Study type	RCT
Aim	The aim of this study was to determine the feasibility of developing a clinical trial comparing the efficacy of group training in mindfulness with an IBS support group (SG) in reducing IBS symptom severity.
Patient characteristics	75 women with IBS. *Inclusion:* • IBS diagnosis according to Rome II criteria and physician diagnosis • female • age 18 – 75 years • ability to understand English • willingness to document bowel symptoms and medication use regularly and complete the assessments • willingness to attend eight weekly sessions plus one additional half-day session of either mindfulness training or SG *Exclusion:* • diagnosis of mental illness with psychosis • a history of inpatient admission for psychiatric disorder within the past 2 years • a history or current diagnosis of inflammatory bowel disease or gastrointestinal malignancy • active liver or pancreatic disease; (v) uncontrolled lactose intolerance • coeliac disease

Bibliographic reference	**Gaylord (2011)** **Mindfulness Training Reduces the Severity of Irritable Bowel Syndrome in Women: Results of a Randomized Controlled Trial.** **ID: 219**
	• a history of abdominal trauma or surgery involving gastrointestinal resection • pregnancy *Baseline characteristics:* Women only study. All participants were informed that they should continue to receive usual care from their physicians and that no specific recommendations for changes in medications for IBS would be made by the research team. Age (mean years, SD): Mindfulness group = 44.72 (12.55); Support group = 40.89 (14.68) Baseline overall IBS severity (IBS-SS) score (mean, SD): Mindfulness group = 284.1 (84.3); Support group = 287.5 (109.9) Baseline ISB-QoL score (mean, SD): Mindfulness group = 64.8 (19.8); Support group = 67.4 (20.5) Baseline Mindfulness (FFMQ) score (mean, SD): Mindfulness group = 127.9 (22.3); Support group = 129.7 (23.3)
Number of Patients	75 Female patients with IBS under the care of a physician were recruited over a 3-year period from 2006 to 2009 through an existing registry of IBS patients interested in participating in research studies, as well as through physicians ' offices, local advertisements, and posted flyers. *Total number of patients:* MG = 36; SG = 39 *Those completed the 3-month post-outcome assessment:* MG = 34; SG = 32 Reasons for lost to follow-up not reported. Participants attended an average of 6.7 out of the 9 intervention sessions held for each group (6.3 sessions for SG and 7.1 for MG; P = 0.09).
Intervention	**Mindfulness group training (MG)** Mindfulness-based stress and pain management program (8 weekly 2-hour session, plus one half-day retreat) Taught by trained mindfulness instructors and based on the mindfulness-based stress reduction program developed at the University of Massachusetts. Training included instruction and homework assignments related to the body scan (i.e.,

<table>
<tr><th>Bibliographic reference</th><th>Gaylord (2011)
Mindfulness Training Reduces the Severity of Irritable Bowel Syndrome in Women: Results of a Randomized Controlled Trial.
ID: 219</th></tr>
<tr><td></td><td>focusing attention on different parts of the body sequentially to detect sensations such as muscle tension), sitting and walking meditation, and mindful yoga. Homework assigned each week throughout the course included daily mindfulness practices and readings from provided texts ‘Full Catastrophe Living’ and ‘IBS for Dummies’.

Participants continued with their usual medical care throughout the study, but no further information was provided.</td></tr>
<tr><td>Comparison</td><td>Support group (SG)
A social-support group intervention led by social workers to control for expectations of benefit and amount of group contact (8 weekly 2-hour session, plus one half-day retreat)

Weekly sessions facilitated by social-work group leaders, focused on specific pre-designated topics and involved open group discussions about participants’ experiences with, or reaction to, the topic. Weekly homework assignments included readings from the provided text - IBS for Dummies.

Participants continued with their usual medical care throughout the study, but no further information was provided.</td></tr>
<tr><td>Length of follow up</td><td>8 weeks treatment period with 10-week post-outcome assessment and then 3-month follow-up</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>IBS-QoL (total score: 0 to 100, with 0 = minimum QoL)
[30% improvement = at least 30 point increase from baseline]
<table>
<tr><th></th><th>MG (N=36)
(mean, SD)</th><th>SG (N=39)
(mean, SD)</th></tr>
<tr><td>Baseline</td><td>64.80 (19.80)</td><td>67.22 (20.73)</td></tr>
<tr><td>10-wk post treatment</td><td>74.99 (15.14)</td><td>70.92 (17.40)</td></tr>
<tr><td>Mean change from baseline</td><td>+10.19</td><td>+3.7</td></tr>
<tr><td>3-mth follow-up</td><td>76.73 (17.42)</td><td>71.05 (18.25)</td></tr>
<tr><td>Mean change from baseline</td><td>+11.93</td><td>+3.83</td></tr>
</table>
Time x group interaction: 10-week: p=0.075; 3-mth: p=0.027

IBS-SS (severity scale: maximum score = 500, with ≥50 points change considered as clinically important difference)
<u>Responder: at least 50-point reduction from baseline:</u>
At 10-week post-outcome assessment: MG = 25/36; SG = 18/39 (RR = 1.50 [95%CI: 1.00 to 2.25])</td></tr>
</table>

Bibliographic reference	**Gaylord (2011)** **Mindfulness Training Reduces the Severity of Irritable Bowel Syndrome in Women: Results of a Randomized Controlled Trial.** **ID: 219**

At 3-month follow-up: MG = 27/36; SG = 21/39 (RR = 1.39 [95%CI: 0.96 to 1.97])

IBS-SS (individual symptom scores)

Abdominal pain severity

	MG (N=36) (mean, SD)	**SG (N=39) (mean, SD)**
Baseline	54.54 (22.82)	53.35 (28.12)
10-wk post treatment	35.00 (28.24)	50.49 (28.85)
Mean change from baseline	-19.54	-2.86
3-mth follow-up	31.11 (25.69)	45.49 (28.33)
Mean change from baseline	-23.43	-7.86

Time x group interaction: 10-week: p=0.013; 3-mth: p=0.015

Bloating severity

	MG (N=36) (mean, SD)	**SG (N=39) (mean, SD)**
Baseline	55.03 (29.98)	52.91 (29.80)
10-wk post treatment	42.57 (28.86)	49.22 (29.39)
Mean change from baseline	-12.46	-3.69
3-mth follow-up	37.46 (29.18)	47.55 (30.26)
Mean change from baseline	-17.57	-5.36

Time x group interaction: 10-week: p=0.135; 3-mth: p=0.067

Dissatisfaction with bowel habit

	MG (N=36) (mean, SD)	**SG (N=39) (mean, SD)**
Baseline	68.17 (25.78)	72.59 (26.13)
10-wk post treatment	49.94 (27.48)	65.15 (30.24)

Bibliographic reference	**Gaylord (2011)** **Mindfulness Training Reduces the Severity of Irritable Bowel Syndrome in Women: Results of a Randomized Controlled Trial.** **ID: 219**
	<table><tr><td>Mean change from baseline</td><td>-18.23</td><td>-7.44</td></tr><tr><td>3-mth follow-up</td><td>45.69 (30.18)</td><td>62.56 (25.65)</td></tr><tr><td>Mean change from baseline</td><td>-22.48</td><td>-10.03</td></tr></table> Time x group interaction: 10-week: p=0.106; 3-mth: p=0.105 XX
Source of funding	National Institutes of Health, National Centre for Complementary and Alternative Medicine Grant, as well as the National Institutes of Health, National Institute of Diabetes, Digestive and Kidney Disease Grant.
Comments	ITT analysis was carried out by LOCF. A study on women only. Though blinding of participants was not achievable, as all outcomes were self-reported subjective measurement, the impact of potential placebo-effect needs further consideration. Reasons for withdrawal or lost to follow-up in the trial not reported.

1

Bibliographic reference	**Zernicke (2012)** **Mindfulness-Based Stress Reduction for the Treatment of Irritable Bowel Syndrome Symptoms: A Randomized Wait-list Controlled Trial** **ID: 1579**
Study type	RCT
Aim	To investigate the impact of Mindfulness-Based Stress Reduction (MBSR) programme on IBS symptoms.
Patient characteristics	90 people who received a diagnosis of IBS by a gastroenterologist in Calgary, Alberta, Canada. *Inclusion:* • age 18 years or older • English-speaking • had a diagnosis of IBS confirmed by a gastroenterologist using the standard Rome III criteria *Exclusion:*

Bibliographic reference	**Zernicke (2012)** **Mindfulness-Based Stress Reduction for the Treatment of Irritable Bowel Syndrome Symptoms: A Randomized Wait-list Controlled Trial** **ID: 1579**
	• a concurrent self-reported diagnosis of a DSM-IV axis I mood, anxiety, or psychotic disorder • current use of antipsychotics • past participation in an MBSR group *Baseline characteristics:* Gender (female/male): MBSR = 40/3; TAU = 41/6 Age (years, mean, SD): MBSR = 45 (12.4); TAU = 44 (12.6) Medication use was allowed but no information on baseline usage was reported. All participants were encouraged in both the treatment and control group to continue with their general medical care and IBS-specific care throughout the study (e.g. regularly scheduled appointments with gastroenterologist, to continue with any of their medications and treatments throughout the study).
Number of Patients	80 participants who received a diagnosis of IBS by a gastroenterologist in Calgary, Alberta, Canada were identified through medical chart review and recruited from multiple gastroenterologists' offices from summer 2007 to fall 2010 via invitation phone calls. *Total number of patients:* MBSR = 43; TAU = 47 *Those completed the post 8-week assessment:* MBSR = 24; TAU = 36 *Those completed the 6-month follow-up assessment:* MBSR = 20; TAU = 34 Reasons for withdrawal during 8-week treatment: *MBSR = 19* No reason given = 10; scheduling issues = 3; not interested = 2; others = 4 *TAU = 11* Too busy = 5; unavailable = 2; no reason given = 2; others = 2 Reasons for lost to follow-up at 6-month not reported.

Bibliographic reference	**Zernicke (2012)** **Mindfulness-Based Stress Reduction for the Treatment of Irritable Bowel Syndrome Symptoms: A Randomized Wait-list Controlled Trial** **ID: 1579**
Intervention	**Mindfulness-Based Stress Reduction (MBSR) (8 weekly group sessions)** The MBSR intervention was based on the program designed by Kabat-Zinn and colleagues at the Stress Reduction Clinic at the University of Massachusetts Medical Centre. All sessions were administered by a registered nurse who was also a certified yoga instructor and professionally trained. • This group intervention consisted of 8 weekly group sessions (90 min in duration), and a 3-hour morning workshop retreat between weeks 6 and 7. • At the start of the MBSR program, each patient was provided a 52-page booklet and two CDs to aid in home meditation and yoga practice. • Patients were taught meditation techniques and body awareness skills in a didactic classroom format and were encouraged to engage in home practice of meditation and yoga between class sessions. • General psychoeducation regarding stress and the stress response was taught. • The 3-hour retreat allows for an extended practice of a combination of mindfulness skills learned in the programme including yoga, sitting meditation, body scan, loving–kindness meditation, and walking meditation. Four cohorts were conducted, and within each class, there was a range of 11–19 patients.
Comparison	**Treatment as usual (TAU)** No other information provided by the study.
Length of follow up	8-week treatment period with 6 months follow-up
Location	Summer 2007 to fall 2010, Calgary, Canada.
Outcomes measures and effect size	The mean number of MBSR classes attended was 6 (out of 9), including the half-day silent retreat. The mean amount of home meditation and yoga practice, which did not include the weekly class practice or retreat, was 137 min/week. No significant differences were found between those who completed and those who did not complete the study in terms of the measured continuous or categorical demographic variables.

<table>
<tr><td>Bibliographic reference</td><td>Zernicke (2012)
Mindfulness-Based Stress Reduction for the Treatment of Irritable Bowel Syndrome Symptoms: A Randomized Wait-list Controlled Trial
ID: 1579</td></tr>
<tr><td></td><td>
IBS-SS (severity scale: maximum score = 500, with ≥50 points change considered as clinically important difference)
<u>Responder: at least 50-point reduction from baseline:</u>
At 8-week post-intervention assessment: MBSR = 10/43; TAU = 10/47 (RR = 1.09 [95%CI: 0.50 to 2.37])

IBS-SS mean total scores:
<table>
<tr><th></th><th>MBSR (N=43)
(mean, SD)</th><th>TAU (N=47)
(mean, SD)</th><th>Cohen’s d
(between group)</th></tr>
<tr><td>Baseline</td><td>248.6 (108.9)</td><td>249.0 (107.6)</td><td></td></tr>
<tr><td>8-wk post treatment</td><td>169.4 (125.9)</td><td>230.0 (117.9)</td><td>0.50</td></tr>
<tr><td>Mean change from baseline</td><td>-79.2</td><td>-19.0</td><td></td></tr>
<tr><td>6-mth follow-up</td><td>193.6 (128.5)</td><td>213.8 (119.3)</td><td>0.16</td></tr>
<tr><td>Mean change from baseline</td><td>-55.0</td><td>-35.2</td><td></td></tr>
</table>

IBS-QoL (total score: 0 to 100, with 0 = minimum QoL)
[30% improvement = at least 30 point increase from baseline]
<table>
<tr><th></th><th>MBSR (N=43)
(mean, SD)</th><th>TAU (N=47)
(mean, SD)</th><th>Cohen’s d
(between group)</th></tr>
<tr><td>Baseline</td><td>65.3 (23.6)</td><td>61.6 (23.3)</td><td></td></tr>
<tr><td>8-wk post treatment</td><td>75.0 (24.9)</td><td>63.1 (23.3)</td><td>0.49</td></tr>
<tr><td>Mean change from baseline</td><td>+9.7</td><td>+1.5</td><td></td></tr>
<tr><td>6-mth follow-up</td><td>74.3 (26.9)</td><td>66.5 (24.0)</td><td>0.31</td></tr>
<tr><td>Mean change from baseline</td><td>+9.0</td><td>+4.9</td><td></td></tr>
</table>
XX
</td></tr>
<tr><td>Source of funding</td><td>This research was supported by a Calgary Health Region/Centre for the Advancement of Health Research Grant.</td></tr>
<tr><td>Comments</td><td>No mention of allocation concealment.
Though blinding of participants was not achievable, as all outcomes were self-reported subjective measurement, the impact of potential placebo-effect needs further consideration.
No information on what consisted of the Treatment As Usual arm.</td></tr>
</table>

Bibliographic reference	**Zernicke (2012)** **Mindfulness-Based Stress Reduction for the Treatment of Irritable Bowel Syndrome Symptoms: A Randomized Wait-list Controlled Trial** **ID: 1579**
	Medication for IBS was allowed but no information was provided regarding usage between groups.

1

Bibliographic reference	**Hunt (2009)** **Brief cognitive-behavioural internet therapy for irritable bowel syndrome** **ID: 454**
Study type	RCT
Aim	To incorporate the results of recent research in illness-specific catastrophizing into the cognitive elements of the intervention.
Patient characteristics	54 IBS patients (44 women and 10 men). *Inclusion:* Participants who self-reported that they had been diagnosed with IBS by a medical professional, but were not currently diagnosed with any other GI disorder. *Exclusion:* No information reported. *Baseline characteristics:* Gender (female/male): CCBT-Exposure = 22/6; Waitlist = 22/4 Age (years, mean, SD): CCBT-Exposure = 39 (10); Waitlist = 38 (12)
Number of Patients	54 IBS patients (44 women and 10 men) were recruited by posting invitational messages on various IBS relevant websites (e.g. ibsgroup.org; helpforibs.com). *Total number of patients:* CCBT-Exposure = 28; Waitlist = 26 *Those completed the post 6-week assessment:* CCBT-Exposure = 13; Waitlist = 18 *Those completed the 3-month follow-up assessment (treatment group only):* CCBT-Exposure = 10

<table>
<tr><th>Bibliographic reference</th><th>Hunt (2009)
Brief cognitive-behavioural internet therapy for irritable bowel syndrome
ID: 454</th></tr>
<tr><td></td><td>Reasons for withdrawal and lost to follow-up at 3-month not reported.

No information on baseline use of medication for IBS or other types of treatments.</td></tr>
<tr><td>Intervention</td><td>CCBT-Exposure (5-week treatment)

The intervention consisted of five modules over 5 weeks:
Every week, participants in the treatment group were instructed to complete homework assignments, and to submit written materials to the study personnel via e-mail. The personnel responded within 48 hours providing individualized feedback and encouragement.
• First - education about the biological link between GI symptoms and stress and on relaxation training.
• Second - basic cognitive approach to stress management including the use of thought records.
• Third - IBS specific catastrophic thinking and encouraged people to identify their own catastrophic beliefs about their IBS symptoms and to apply the cognitive model to those fears.
• Fourth - introduced exposure therapy and encouraged participants to identify things they avoided and begin graduated exposure. This module also introduced the notion of ‘‘subtle avoidance’’ – safety behaviours such as carrying multiple medicines, scoping out bathrooms, and sitting only in the aisle seat.
• Fifth - focused on using behavioural experiments to test some of their beliefs about the social consequences of IBS</td></tr>
<tr><td>Comparison</td><td>Waitlist control

The wait-list control group completed weekly symptom checklists that were included to control for the basic self-monitoring effects. No other information provided.</td></tr>
<tr><td>Length of follow up</td><td>5-week treatment with 3-month follow-up (only incomplete 3-month data was reported).</td></tr>
<tr><td>Location</td><td>Philadelphia, USA.</td></tr>
<tr><td>Outcomes measures and effect size</td><td>IBS-QoL (only raw score provided, total score: 0 to 170, with 0 = minimum QoL)
[30% improvement = at least 51 point increase from baseline]
<table>
<tr><th></th><th>CCBT-E
(mean, SD)</th><th>Waitlist
(mean, SD)</th><th>Mean difference
(between group)</th></tr>
<tr><td>Baseline (N=28; N=26)</td><td>122 (27)</td><td>123 (26)</td><td></td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Hunt (2009)** **Brief cognitive-behavioural internet therapy for irritable bowel syndrome** **ID: 454**

6-wk post treatment (N=13; N=18)	84 (26)	111 (25)	
Mean change from baseline	-38	-12	

GSRS-IBS (Gastrointestinal Symptom Rating Scale for IBS) (total score: 13 to 91, with 13 = no discomfort at all)
[30% improvement = at least 23.4 points decrease from baseline]

	CCBT-E (mean, SD)	**Waitlist (mean, SD)**	**Mean difference (between group)**
Baseline (N=28; N=26)	57 (13)	61 (14)	
6-wk post treatment (N=13; N=18)	35 (12)	52 (14)	
Mean change from baseline	-22	-9	

XX

Source of funding	Not reported
Comments	No mention of allocation concealment. Participants were randomly assigned to condition based on order of enrolment. Though blinding of participants was not achievable, as all outcomes were self-reported subjective measurement, the impact of potential placebo-effect needs further consideration. No information on what consisted of the Waitlist arm. No baseline information on medication use.

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Bibliographic reference	**Ljotsson (2014)** **Provoking symptoms to relieve symptoms: A randomized controlled dismantling study of exposure therapy in irritable bowel syndrome.** **ID: 1535**
Study type	RCT
Aim	The aim of this study was to compare ICBT with the same protocol without systematic exposure (ICBT-WE) to assess if exposure had any incremental value.
Patient characteristics	311 self-referred IBS patients. *Inclusion:*

Bibliographic reference	**Ljotsson (2014)** **Provoking symptoms to relieve symptoms: A randomized controlled dismantling study of exposure therapy in irritable bowel syndrome.** **ID: 1535**
	Participants were eligible for the study if they declared to have had a previous diagnosis of IBS given by a physician, presently fulfilled the Rome III-criteria for IBS and were older than 18 years of age. *Exclusion:* • blood in stool without satisfactory medical explanation (such as known hemorrhoids) • diarrhoea-predominant IBS with no colonoscopy performed • rapid weight loss that could not be linked to change in diet • recent unexamined change in stool frequency or form if older than 50 years of age • any presence of current or previous inflammatory bowel disease • lactose or gluten intolerance where proper dietary adjustments had not been made • severe alcohol dependence, severe depressive symptoms, or suicidal ideation • insufficient language or computer skills to perform an online text-based treatment. *Baseline characteristics:* Gender (female): CCBT-M = 75.2%; CCBT-M/E = 77.3% Age (years, mean, SD): CCBT-M = 41.9 (14.9); CCBT-M/E = 43.0 (14.1) Duration of IBS symptoms (years, mean, SD): CCBT-M = 16.3 (12.9); CCBT-M/E = 15.5 (11.9) Years since diagnosis (mean, SD): CCBT-M = 8.8 (9.7); CCBT-M/E = 7.9 (9.1) Years since last consultation with physician about IBS: CCBT-M = 2.2 (2.7); CCBT-M/E = 2.2 (2.2) No information on baseline use of medication for IBS or other types of treatments.
Number of Patients	311 patients, recruited through self-referral and information about the study was spread through several channels, for example newspaper advertisements, an online discussion forum about IBS, and a web portal for internet-based treatment studies. *Total number of patients:* CCBT-M = 156; CCBT-M/E = 153 *Those completed the post 10-week assessment:* CCBT-M = 146; CCBT-M/E = 146 *Those completed the 6-month follow-up assessment:*

Bibliographic reference	**Ljotsson (2014)** **Provoking symptoms to relieve symptoms: A randomized controlled dismantling study of exposure therapy in irritable bowel syndrome.** **ID: 1535**
	CCBT-M = 135; CCBT-M/E = 134 Reasons for withdrawal were not reported based on treatment group. Overall: • Insufficient time for participation (N=16) • Improvement since treatment start (N=7) • Low faith in the treatment (N=7) • Not satisfied with the treatment format (N=7) • Wanted to or had started another treatment (N=6)
Intervention	**CCBT-M (10-week CBT protocol)** Procedure was same as CCBT-M/E below, but without the 'Exposure' step.
Comparison	**CCBT-M/E (10-week CBT protocol)** A text based self-help manual (presented on printer-friendly web pages) divided into five steps: • A rationale for the treatment and instructions on mindfulness. • Three steps of presentation of a psychological model of IBS and continued mindfulness exercises. • Exposure exercises and instruction on how to use mindfulness during exposure. Online therapist was used to guide the participants through the course of the treatment. 11 therapists conducted the treatments (5 advanced graduate psychology students; 6 clinical psychologists). Therapists were randomly assigned to participants from both conditions. During treatment, therapist contact was usually initiated by the participants who were encouraged to send at least one message per week about their work with the treatment to their therapist. Participants were given feedback within 2 to 3 days after they had written a message.
Length of follow up	10-week treatment with 6-month follow-up.
Location	Between 27 November 2011 and ended on 31 December 2011, Sweden.
Outcomes measures and effect size	No. of therapist message sent/received during treatment period (mean, SD): CCBT-M: sent = 9.5 (6.3); received = 9.1 (5.1) CCBT-M/E: sent = 10.7 (6.8); received = 10.0 (5.2)

Bibliographic reference	**Ljotsson (2014)** **Provoking symptoms to relieve symptoms: A randomized controlled dismantling study of exposure therapy in irritable bowel syndrome.** **ID: 1535**

The therapists spent a mean of 8.3 min (SD: 6.7) per participant and per week writing messages to the participants in the CCBT-M group and they spent 9.9 min (SD: 8.2) per week and per participant in the CCBT-M/E group.

IBS-QoL (only raw score provided, total score: 0 to 100, with 0 = minimum QoL)
[30% improvement = at least 30 point increase from baseline]

	CCBT-M (mean, SD)	CCBT-M/E (mean, SD)	Mean difference (between group, mixed-effects regression)
Baseline (N=156; N=153)	57.5 (20.7)	59.6 (20.3)	
10-wk post treatment (N=146; N=146)	73.6 (20.4)	79.2 (16.7)	5.2 (95%CI: 0.8 to 9.5)
Mean change from baseline	+16.1	+19.6	
6-mth follow-up (N=134; N=133)	76.5 (19.8)	81.4 (18.2)	5.1 (95%CI: 0.5 to 5.1)
Mean change from baseline	+19.0	+21.8	

GSRS-IBS (Gastrointestinal Symptom Rating Scale for IBS) (total score: 13 to 91, with 13 = no discomfort at all)
[30% improvement = at least 23.4 points decrease from baseline]

	CCBT-M (mean, SD)	CCBT-M/E (mean, SD)	Mean difference (between group, mixed-effects regression)
Baseline (N=156; N=153)	47.5 (11.0)	46.1 (10.2)	
10-wk post treatment (N=146; N=146)	38.2 (14.5)	31.8 (11.4)	5.3 (95%CI: 2.6 to 7.9)
Mean change from baseline	-9.3	-14.3	
6-mth follow-up (N=135; N=134)	37.3 (13.4)	32.2 (12.3)	5.4 (95%CI: 2.3 to 8.6)
Mean change from baseline	-10.2	-13.9	

Adverse events (No. of participants reported)
[Cluster of residual discomfort, worsening of symptoms, stress because of the study, depressed or anxious mood]
10-week post treatment: CCBT-M = 19/145; CCBT-M/E = 29/142; RR = 0.64 (95%CI: 0.38 to 1.09)
6-mth follow-up: CCBT-M = 9/127; CCBT-M/E = 3/131; RR = 3.09 (95%CI: 0.86 to 11.2)

Source of funding	Not reported

Bibliographic reference	**Ljotsson (2014)** **Provoking symptoms to relieve symptoms: A randomized controlled dismantling study of exposure therapy in irritable bowel syndrome.** **ID: 1535**
Comments	Participants were self-referred. Though blinding of participants was not achievable, as all outcomes were self-reported subjective measurement, the impact of potential placebo-effect needs further consideration. No baseline information on medication use.

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Appendix H: GRADE profiles

H.1 Review question 1 (antidepressants vs placebo)

Table 68: GRADE profile, successfully treated, abdominal pain

Number of studies	Design	Study length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
Antidepressants- TCA vs placebo								
2	RCTs	6-12weeks	Very serious [a]	Serious [c]	Very serious [d]	N=52 intervention N=52 placebo	RR 1.82 (95%CI 0.63 to 5.25)	Very low
Antidepressants - SSRI vs placebo								
4	RCTs	6-12weeks	Very serious [b]	Serious [c]	Very serious [e]	N= 96 intervention N= 101 placebo	RR2.29 (95%CI 0.79 to 6.68)	Very low

Studies included; TCAs, Vahedi (2008), Vij (1991); SSRIs, Kuiken (2003), Tabas (2004), Tack (2006), Vahedi (2005)

(a) Unclear if questionnaire/other tools validated and no additional follow-up (Kuiekn 2003, Tabas 2004, Tack 2006,)

(b) Unclear randomisation (Tack 2006) and unclear if questionnaire/other tools validated and no additional follow-up (Vahedi 2005 and 2008, Vij 1991)

(c) Study length 6-12weeks

(d) 95% confidence interval crosses the minimal important difference at 0.75 and 1.25, leading to very serious uncertainty. Downgraded 2 levels.

(e) 95% confidence interval crosses the minimal important difference at 1.25 and crosses line of no effect, leading to very serious uncertainty. Downgraded 2 levels

Table 69: GRADE profile, scores on abdominal pain

Number of studies	Design	Study length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
Antidepressants - TCAs vs placebo								
Rajagopalan 1998	RCT	8-12weeks	Very serious [a]	Serious [c]	No serious	N=11 intervention, N=11 placebo	Standardised mean difference 1.49 (95%CI 0.52 to 2.45)	Very low

Number of studies	Design	Study length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
Antidepressants - TCAs vs placebo								
Antidepressant - SSRIs vs placebo								
Tack 2006	RCT	8-12weeks	Very serious [b]	Serious [c]	No serious	N= 11 intervention N= 12 placebo	Standardised mean difference 4.60 (95%CI 2.93 to 6.28)	Very low

(a) *Unclear randomisation, unclear concealment (Rajagopalan 1998), unclear if questionnaire/other tools validated and no additional follow-up (Rajagopalan 1998) not low dose TCA, small number of study participants,*
(b) *Unclear if questionnaire/other tools validated and no additional follow-up (Tack 2006)*
(c) *Study length 8-12weeks*

Table 70: GRADE profile, successfully treated, global assessment

Number of studies	Design	Study length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
Antidepressants - TCAs vs placebo								
5	RCTs	4-12weeks	Very serious [a]	Serious [b]	Serious [c]	N=159 intervention, N=139 placebo	RR 1.43 (95%CI 1.15 to 1.79)	Very low
Antidepressants - SSRIs vs placebo								
5	RCTs	4-12weeks	Very serious [a]	Serious [b]	Very serious [d]	N=143 intervention, N=138 placebo	RR 1.51 (95%CI 0.87 to 2.61)	Very low

Studies included; TCAs, Abdul-Baki (2009), Myren (1982), Talley (2008), Vahedi (2008), Vij (1991); SSRIs, Kuiken (2003), Ladabaum (2010), Masand (2009), Tabas (2004), Talley (2008)
(a) *Unclear randomisation (Myren 1982, Masand 2009), small number of individual study participants (all included studies)*
(b) *Study length 4-12weeks*
(c) *95% confidence interval crosses the minimal important difference at 1.25, leading to serious uncertainty. Downgraded 1 level.*
(d) *95% confidence interval crosses the minimal important difference at 1.25 and crosses line of no effect, leading to very serious uncertainty. Downgraded 2 levels*

Table 71: GRADE profile, successfully treated, symptom score

Number of studies	Design	Study length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
Antidepressants - TCA vs placebo								
Vahedi 2008	RCTs	8-12weeks	Very serious [a]	Serious [c]	Very serious [d]	N=36 intervention, N=36 placebo	RR 1.36 (95%CI 0.81 to 2.27)	Very low
Antidepressants - SSRI vs placebo								
Masand 2009	RCTs	8-12weeks	Very serious [b]	Serious [c]	Serious[e]	N= 27 intervention N= 27 placebo	RR 2.43 (95%CI 1.21 to 4.89)	Very low

(a) *Unclear if questionnaire/other tools validated (Vahedi 2008, Masand 2009) small number of individual study participants (all included studies)*
(b) *Unclear randomisation, unclear allocation concealment (Masand 2009), unclear if questionnaire/other tools validated (Vahedi 2008, Masand 2009), no additional follow-up and small number of study participants (Masand 2009)*
(c) *Study length 8-12weeks*
(d) *95% confidence interval crosses the minimal important difference at 1.25 and crosses line of no effect, leading to very serious uncertainty. Downgraded 2 levels*
(e) *95% confidence interval crosses the minimal important difference at 1.25, leading to serious uncertainty. Downgraded 1 level*

Table 72: GRADE profile, symptom scores

Number of studies	Design	Study length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
Antidepressants - TCA vs placebo								
Vahedi 2008	RCTs	8-12weeks	Very serious [a]	Serious [c]	Very serious [d]	N=36 intervention, N=36 placebo	Standardised mean difference 0.05 (-0.41 to 2.27)	Very low
Antidepressants - SSRI vs placebo								
Masand 2009	RCTs	8-12weeks	Very serious [b]	Serious [c]	Serious[e]	N=25 intervention, N=25 placebo	Standardised mean difference 0.75 (0.17 to 1.32)	

(a) *Unclear if questionnaire/other tools validated (Vahedi 2008) small number of individual study participants (all included studies)*
(b) *Unclear randomisation, unclear allocation concealment (Masand 2009), unclear if questionnaire/other tools validated (Masand 2009), no additional follow-up (Masand 2009) small number of individual study participants (all included studies)*
(c) *Study length8-12weeks*

(d) *The 95% confidence interval crosses the MID of 0.5 and -0.5and crosses the line of no difference, leading to very serious imprecision in the effect size. Downgraded 2 levels.*
(e) *The 95% confidence interval crosses the MID of 0.5 (indicating moderate effect), leading to serious imprecision. Downgraded 1 level*

Table 73: GRADE profiles, quality of life 1 (SF-36)

Number of studies	Design	Study length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
SF-36- TCAs vs placebo								
Abdul-Baki 2009	RCT	12weeks	Serious [a]	None	Very serious [b]	N=31 intervention, N=25 placebo	Mean percent difference from baseline; imipramine 11.8%±13.2%, placebo 4.3%±9.0%, p=0.02	Very low

,
(a) *High drop-out rates, unclear if questionnaire/other tools validated*
(b) *Small sample size, quality of life outcomes per protocol analysis*

Table 74: GRADE profiles, quality of life 2 (SF-36)

Number of studies	Design	Study length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
SF-36TCAs and SSRIs vs placebo								
Talley 2008	RCT	12weeks	Serious [a]	None	Serious [b]	N17 citalopram, N=18 imipramine, N=16 placebo	Score change; physical component; citalopram 3.5(6.1), imipramine 7.3(7.3), placebo 6.5(4.6), p=0.40 Mental component; citalopram	Low

Number of studies	Design	Study length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
SF-36TCAs and SSRIs vs placebo								
							0(4.1), imipramine 4.8(4.5), placebo -1.9(7.2), p=0.07	

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(a) *No additional follow-up*
(b) *Small sample size*

Table 75: GRADE profiles, quality of life 3 (IBS-QOL scores)

Number of studies	Design	Study length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
IBS QOL scores *SSRIs* vs placebo,								
Ladabaum 2010	RCT	8weeks	Serious [a]	None	Serious [b]	N=20 intervention, N=25 placebo	Mean score (SD) citalopram 74 (18), placebo 74 (24), p=0.85	Low

(a) *Differences between groups in drop-out rates, unclear if questionnaire/other tools validated*
(b) *Small sample size*

Table 76: GRADE profiles, quality of life 4 (IBS-QOL scores)

Number of studies	Design	Study length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
IBS QOL *SSRIs*								
Tabas 2004	RCT	12weeks	Very serious [a]	None	Serious [b]	N=38 intervention, N=43 placebo	% of improvement; Food avoidance; paroxetine 25.4, placebo	Very low

Number of studies	Design	Study length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
IBS QOL *SSRIs*								
							13.7, p=0.03 Work function score; paroxetine 25.4, placebo 12.0, p=0.08 Social function score; paroxetine 25.4, placebo 13.7, p=0.76	

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(a) Unclear if questionnaire/other tools validated, no additional follow-up, poor adverse effects reporting
(b) Small sample size

H.2 Review question 2 (low FODMAP diet vs Standard diet)

Table 77: GRADE profile, Outcome: GI symptoms, overall response

Number of studies	Design	Study length	Risk of bias	Indirectness	Imprecision	No. of participants	Effect	Quality
FODMAP							**(95%CI)**	
Halmos 2014	RCT, crossover	21 days (each arm)	Very serious [a]	Serious [b]	Very serious [c]	N=30	VAS (from baseline); Low FODMAP 22.8mm (16.7 to 28.8), p<0.001 Typical diet 44.9mm (36.6 to 53.1), p<0.001	Very low
Staudacher 2012	RCT	4weeks	Serious [d]	Serious [e]	Serious [f]	N=41	Incidence (mean (95%CI) days/week); Low FODMAP 0.9(0.8 to 1.1), control 1.6 (1.3 to 1.9), p=0.001	Very low
Staudacher 2011	Controlled trial	Unclear	Very serious [g]	Serious [h,i]	Serious [f]	N=82	Improved; Low FODMAP 37/43(86%), standard diet 19/39(49%), p<0.001	Very low

(a) No allocation concealment, investigators not blinded to study group, no additional follow-up period following study completion (downgraded 2 levels)

(b) *FODMAP diet usually advised for 8weeks (downgraded 1 level)*
(c) *Unclear if VAS used had been validated, minimum detectable difference crossed by 95%CI in GI symptoms (primary outcome), small participant numbers (downgraded 2 levels)*
(d) *No additional follow-up period (downgraded 1 level)*
(e) *FODMAP diet usually advised for 8weeks (downgraded 1 level)*
(f) *Small participant numbers (downgraded 1 level)*
(g) *Non-randomised comparison, no blinding, differences in the dietary advice given in the comparison group, unclear follow-up period (downgraded 2 levels)*
(h) *Unclear length of study (downgraded 1 level)*
(i) *Convenience sample from dietetic clinic before and after implementation of low FODMAP service (downgraded 1 level)*

Table 78: GRADE profile, Outcome: bloating

Number of studies	Design	Study length	Risk of bias	Indirectness	Imprecision	No. of participants	Effect	Quality
FODMAP							**(95%CI)**	
Halmos 2014	RCT, crossover	21 days (each arm)	Very serious [a]	Serious [b]	Very serious [c]	N=30	VAS (from baseline); Low FODMAP 45.1mm (35.1 to 55.0), p<0.001 Typical diet 24.2mm (17.1 to 31.2)	Very low
Staudacher 2012	RCT	4weeks	Serious [d]	Serious [e]	Serious [f]	N=41	Incidence (mean (95%CI) days/week); Low FODMAP 3.8(3.0 to 4.6), control 5.7 (4.9 to 6.4), p=0.002	Very low
Staudacher 2011	Controlled trial	Unclear	Very serious [g]	Serious [h,i]	Serious [f]	N=82	Improved; Low FODMAP 32/39(82%), standard diet 17/35(49%), p=0.002	Very low

(a) *No allocation concealment, investigators not blinded to study group, no additional follow-up period following study completion (downgraded 2 levels)*
(b) *FODMAP diet usually advised for 8weeks (downgraded 1 level)*
(c) *Unclear if VAS used had been validated, secondary outcome (downgraded 2 levels)*
(d) *No additional follow-up period (downgraded 1 level)*
(e) *FODMAP diet usually advised for 8weeks (downgraded 1 level)*
(f) *Small participant numbers (downgraded 1 level)*
(g) *Non-randomised comparison, no blinding, differences in the dietary advice given in the comparison group, unclear follow-up period (downgraded 2 levels)*
(h) *Unclear length of study (downgraded 1 level)*
(i) *Convenience sample from dietetic clinic before and after implementation of low FODMAP service (downgraded 1 level)*

Table 79: GRADE profile, Outcome: abdominal pain

Number of studies	Design	Study length	Risk of bias	Indirectness	Imprecision	No. of participants	Effect	Quality
FODMAP							**(95%CI)**	
Halmos 2014	RCT, crossover	21 days (each arm)	Very serious [a]	Serious [b]	Very serious [c]	N=30	VAS (from baseline); Low FODMAP 43.8mm (35.0 to 52.5), p<0.001 Typical diet 22.5mm (16.3 to 28.6)	Very low
Staudacher 2012	RCT	4weeks	Serious [d]	Serious [e]	Serious [f]	N=41	Incidence (mean (95%CI) days/week); Low FODMAP 3.6(2.8 to 4.4), control 4.8 (4.1 to 5.5), p=0.02	Very low
Staudacher 2011	Controlled trial	Unclear	Very serious [g]	Serious [h,i]	Serious [f]	N=82	Improved; Low FODMAP 29/34(85%), standard diet 20/33(61%), p=0.023	Very low

(a) No allocation concealment, investigators not blinded to study group, no additional follow-up period following study completion (downgraded 2 levels)
(b) FODMAP diet usually advised for 8weeks (downgraded 1 level)
(c) Unclear if VAS used had been validated, secondary outcome (downgraded 2 levels)
(d) No additional follow-up period (downgraded 1 level)
(e) FODMAP diet usually advised for 8weeks (downgraded 1 level)
(f) Small participant numbers (downgraded 1 level)
(g) Non-randomised comparison, no blinding, differences in the dietary advice given in the comparison group, unclear follow-up period (downgraded 2 levels)
(h) Unclear length of study (downgraded 1 level)
(i) Convenience sample from dietetic clinic before and after implementation of low FODMAP service (downgraded 1 level)

Table 80: GRADE profile, Outcome: dissatisfaction with stool consistency

Number of studies	Design	Study length	Risk of bias	Indirectness	Imprecision	No. of participants	Effect	Quality
FODMAP							**(95%CI)**	
Halmos 2014	RCT, crossover	21 days (each arm)	Very serious [a]	Serious [b]	Very serious [c]	N=30	VAS (from baseline); Low FODMAP 47.8mm (37.6 to 57.9), p<0.001 Typical diet 25.9mm (18.9 to 32.9)	Very low

(a) No allocation concealment, investigators not blinded to study group, no additional follow-up period following study completion (downgraded 2 levels)
(b) FODMAP diet usually advised for 8weeks (downgraded 1 level)
(c) Unclear if VAS used had been validated, secondary outcome (downgraded 2 levels)

Table 81: GRADE profile, Outcome: flatuence/wind

Number of studies	Design	Study length	Risk of bias	Indirectness	Imprecision	No. of participants	Effect	Quality
FODMAP							**(95%CI)**	
Staudacher 2012	RCT	4weeks	Serious [d]	Serious [e]	Serious [f]	N=41	Incidence (mean (95%CI) days/week); Low FODMAP 4.3(3.3 to 5.3), control 5.6 (4.6 to 6.5), p=0.07	Very low
Staudacher 2011	Controlled trial	Unclear	Very serious [g]	Serious [h,i]	Serious [f]	N=82	Improved; Low FODMAP 33/38(87%), standard diet 14/28(50%), p=0.001	Very low

(a) *No additional follow-up period (downgraded 1 level)*
(b) *FODMAP diet usually advised for 8weeks (downgraded 1 level)*
(c) *Small participant numbers (downgraded 1 level)*
(d) *Non-randomised comparison, no blinding, differences in the dietary advice given in the comparison group, unclear follow-up period (downgraded 2 levels)*
(e) *Unclear length of study (downgraded 1 level)*
(f) *Convenience sample from dietetic clinic before and after implementation of low FODMAP service (downgraded 1 level)*

Table 82: GRADE profile, Outcome: diarrhoea

Number of studies	Design	Study length	Risk of bias	Indirectness	Imprecision	No. of participants	Effect	Quality
FODMAP							**(95%CI)**	
Staudacher 2012	RCT	4weeks	Serious [d]	Serious [e]	Serious [f]	N=41	Incidence (mean (95%CI) days/week); Low FODMAP 1.4(0.4 to 2.4), control 2.2 (1.3 to 3.1), p=0.24	Very low
Staudacher 2011	Controlled trial	Unclear	Very serious [g]	Serious [h,i]	Serious [f]	N=82	Improved; Low FODMAP 30/36(87%), standard diet 18/29(62%), p=0.052	Very low

(a) *No additional follow-up period (downgraded 1 level)*
(b) *FODMAP diet usually advised for 8weeks (downgraded 1 level)*
(c) *Small participant numbers (downgraded 1 level)*
(d) *Non-randomised comparison, no blinding, differences in the dietary advice given in the comparison group, unclear follow-up period (downgraded 2 levels)*
(e) *Unclear length of study (downgraded 1 level)*
(f) *Convenience sample from dietetic clinic before and after implementation of low FODMAP service (downgraded 1 level)*

Table 83: GRADE profile, Outcome: constipation

Number of studies	Design	Study length	Risk of bias	Indirectness	Imprecision	No. of participants	Effect	Quality
FODMAP							**(95%CI)**	
Staudacher 2012	RCT	4weeks	Serious [d]	Serious [e]	Serious [f]	N=41	Incidence (mean (95%CI) days/week); Low FODMAP 0.8(0.3 to 1.3), control 1.0 (0.5 to 1.5), p=0.56	Very low
Staudacher 2011	Controlled trial	Unclear	Very serious [g]	Serious [h,i]	Serious [f]	N=82	Improved; Low FODMAP 10/21(67%), standard diet 10/22(45%), p=0.161	Very low

(a) No additional follow-up period (downgraded 1 level)
(b) FODMAP diet usually advised for 8weeks (downgraded 1 level)
(c) Small participant numbers (downgraded 1 level)
(d) Non-randomised comparison, no blinding, differences in the dietary advice given in the comparison group, unclear follow-up period (downgraded 2 levels)
(e) Unclear length of study (downgraded 1 level)
(f) Convenience sample from dietetic clinic before and after implementation of low FODMAP service (downgraded 1 level)

H.3 Review question 3 (linaclotide)

Table 84: GRADE Profile, Outcome: Quality of Life (QOL)

Quality assessment						Number of patients		Effect		Quality
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**I = Linaclotide 290µg (%)**	**C = Placebo (%)**			
IBS-QOL Responder (>14 point improvement)								**Relative (95% CI)**	**Absolute (95% CI)**	
Johnston[a] 2010	RCT	Serious[b]	n/a	No serious	Very serious[c]	31/84 (26)	31/85 (26)	1.01 [0.68, 1.50]	0 more per 100 (12 fewer, 18 more)	Very low
IBS-QOL Scale (34 items each rated on 5 point Likert scale, low score = worse QOL)								**Mean difference (improvement) (95% CI)**		
Johnston[a]	RCT	Serious[b]	n/a	No serious	Very	84	85	I=14, C=14.5		Very low

Quality assessment						Number of patients		Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	I = Linaclotide 290µg (%)	C = Placebo (%)		
2010					serious[d]			No p value reported	
Quigley[e] 2012	RCT	Very serious[f]	n/a	No serious	No Serious	405	395	I=18.4, C=15.2 LS mean difference 3.3% (1.0, 5.5) p=0.004	Low
Quigley[g] 2012	RCT	Serious[h]	n/a	No serious	No Serious	401	403	I=16.6, C=11.1 LS mean difference 5.5% (3.4, 7.6) p<0.0001	Moderate

(a) Only the comparable dose arm (290µg) from this study is reported
(b) Per protocol analysis used for mean change endpoints but numbers per arm does not reflect drop-outs. Use of rescue medication (laxatives) was permitted but not reported by study arm. Fibre/diet/fluid/exercise/other relevant meds were not reported by study arm.
(c) Point estimate not reaching MID (GRADE default suggestion), 95% CIs incorporate both deterioration and improvement in QOL score
(d) No p value, SD / CIs reported.
(e) First of two studies reported in this further analysis of two RCTs (Rao et al 2012)
(f) Rescue medication (laxatives) and bulk laxatives and stool softeners were permitted throughout but not reported by study arm. Fibre/diet/fluid/exercise/other relevant meds were not reported by study arm.
(g) Second of two RCTs reported (Chey et al 2012)
(h) Rescue medication (laxatives) was permitted but not reported by study arm. Fibre/diet/fluid/exercise/other relevant meds were not reported by study arm.

Table 85: GRADE Profile, Outcome: symptoms

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	I = Linaclotide 290µg (%)	C = Placebo (%)			
2.1 FDA Pain responder (≥30% improvement in pain, for ≥half the study weeks)								**Relative (95% CI)**	**Absolute (95% CI)**	
2[a] (12 weeks)	RCT	Serious[b]	No Serious	No serious	Serious[c]	399/806 (50)	287/798 (36)	1.38 [1.23, 1.54]	14 more per 100 (8 more, 19 more)	Low
Chey 2012 (26 weeks)	RCT	Serious[b]	n/a	No serious	No Serious	197/401 (49)	126/403 (31)	1.57 [1.32, 1.87]	18 more per 100 (10 more, 27 more)	Moderate

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	I = Linaclotide 290µg (%)	C = Placebo (%)			
2.2 FDA Stool frequency responder (increase of ≥1 CSBM per week, for ≥half of study weeks)								**Relative (95% CI)**	**Absolute (95% CI)**	
2[a] (12 weeks)	RCT	Serious[b]	Serious[d]	No serious	No Serious	388/806 (48)	208/798 (26)	1.85 [1.45, 2.37]	22 more per 100 (12 more, 26 more)	Low
Chey 2012 (26 weeks)	RCT	Serious[b]	n/a	No serious	No Serious	175/401 (44)	75/403 (19)	2.34 (1.85, 2.96)	25 more per 100 (16 more, 36 more)	Moderate
2.3 FDA Combined responder for Pain and Stool Frequency for ≥half of study weeks)								**Relative (95% CI)**	**Absolute (95% CI)**	
2[a] (12 weeks)	RCT	Serious[b]	Serious[e]	No serious	No Serious	271/806 (34)	139/798 (17)	1.95 [1.30, 2.94]	17 more per 100 (5 more, 34 more)	Low
Chey 2012 (26 weeks)	RCT	Serious[b]	n/a	No serious	No serious	130/401 (32)	53/403 (13)	2.47 (1.85, 3.29)	19 more per 100 (11 more, 30 more)	Moderate
2.4 FDA Pain responder (≥30% improvement in pain, for ≥two thirds of study weeks)								**Relative (95% CI)**	**Absolute (95% CI)**	
2[a] (12 weeks)	RCT	Serious[b]	Serious[f]	No serious	Serious[g]	295/806 (37)	186/798 (23)	1.58 [1.02, 2.46]	14 more per 100 (0 more, 100 more)	Very low
Chey 2012 (26 weeks)	RCT	Serious[b]	n/a	No serious	No Serious	148/401 (37)	70/403 (17)	2.12 (1.66, 2.72)	19 more per 100 (11 more, 30 more)	Moderate
2.5 FDA Combined responder for Pain and Stool Frequency for ≥two thirds of study weeks)								**Relative (95% CI)**	**Absolute (95% CI)**	

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	I = Linaclotide 290µg (%)	C = Placebo (%)			
2[a] (12 weeks)	RCT	Serious[b]	No Serious	No serious	No Serious	100/806 (12)	32/798 (4)	3.09 [2.10, 4.51]	8 more per 100 (4 more, 14 more)	Moderate
Chey 2012 (26 weeks)	RCT	Serious[b]	n/a	No serious	No serious	10/401 (3)	48/403 (12)	4.82 (2.48, 9.40)	45 more per 100 (18 more, 100 more)	Moderate
2.6 EMA abdominal pain/discomfort responders (≥30% improvement with neither worsening from baseline, for ≥half of study weeks)								**Relative (95% CI)**	**Absolute (95% CI)**	
2[h]	RCT	Serious[b]	No Serious	No serious	Serious[i]	439/806 (54)	320/798 (40)	1.36 [1.22, 1.51]	14 more per 100 (9 more, 20 more)	Low
2.7 EMA Global Relief responders								**Relative (95% CI)**	**Absolute (95% CI)**	
3[j]	RCT	Very serious[b,k]	Serious[l]	No serious	No serious	312/890 (35)	165/883 (19)	1.87 [1.33, 2.63]	16 more per 100 (6 more, 30 more)	Very low

(a) Chey 2012 (at 12 weeks only), Rao 2012
(b) Use of rescue medication (laxatives) was permitted but not reported by study arm. Bulk laxatives and stool softeners were also permitted by one study (Rao et al 2012). Fibre/diet/fluid/exercise/other relevant meds were not reported by study arm.
(c) Lower end of 95% CI below the threshold for MID (GRADE default suggestion)
(d) Random effects analysis identifies significant heterogeneity - I2 68% Chi^2 3.17, P=0.08. Partial CI overlap
(e) Random effects analysis identifies significant heterogeneity - I2 80% Chi^2 5.02, P=0.03. CI overlap
(f) Random effects analysis identifies significant heterogeneity - I2 87%, Chi^2 7.88, P=0.005. CIs do not overlap
(g) 95%CIs cross threshold for MID (GRADE default suggestion)
(h) Rao and Chey via Quigley 2012
(i) 95%CIs cross threshold for MID (GRADE default suggestion)
(j) Rao and Chey via Quigley 2012, Johnston 2010
(k) Downgraded due to risk of recall bias, degree of relief was measured weekly, rating symptoms retrospectively vs. symptoms prior to trial inauguration (n=2 studies)
(l) Random effects analysis identifies significant heterogeneity - I^2 75%,Chi^2 =8.08, P=0.02. No overlap between 2/3 study CIs

Table 86: GRADE Profile, Outcome: stool score/general changes in bowel habit

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	I = Linaclotide 290µg (%)	C = Placebo (%)			
6.1 Consitpation Severity (% with decrease of ≥1 point on BSFS* for ≥half study weeks)								**Relative (95% CI)**	**Absolute (95% CI)**	
2[a] (12 weeks)	RCTs	Very serious[b,c]	No Serious	No serious	No serious	485/806 (60)	327/798 (41)	1.47 [1.33, 1.62]	19 more per 100 (14 more, 25 more)	Low
Chey 2012 (26 weeks)	RCT	Very serious[b,c]	N/A	No serious	No serious	221/401 (55)	139/403 (35)	1.60 (1.36, 1.88)	21 more per 100 (12 more, 30 more)	Low
6.2 Constipation severity (5 point scale) (12 weeks) Higher score = worse								**Mean difference**		
Chey 2012	RCT	Serious[b]	n/a	No serious	Very serious[d]	401	403	Least Sq mean change I = -1.2 C = -0.6 (no SD) p<0.0001		Very low
Rao 2012	RCT	Very serious[b]	n/a	No serious	Very serious[d]	405	395	Least Sq mean change I = -1.2 C = -0.6 (no SD) p<0.0001		Very low
Johnston 2010	RCT	Serious[b]	n/a	No serious	Very Serious[d]	84	85	I= 1.35 C= 0.75 (no SD, 95% CIs and no p-value reported)		Very low
6.2 Constipation severity (5 point scale) (26 weeks) Higher score = worse								**Mean difference**		
Chey 2012	RCT	Serious[b]	n/a	No serious	Very serious[d]	401	403	Least Sq mean change I = -1.2 C = -0.6 (no SD) p<0.0001		Very low

(a) Chey 2012, Rao 2012
(b) Use of rescue medication (laxatives) not reported by study arm has major potential for confounding on constipation severity. Bulk laxatives and stool softeners were also permitted by one study (Rao et al 2012). Fibre/diet/fluid/exercise/other relevant meds were not reported by study arm.
(c) 30% improvement (EMA recs for continuous outcomes) on 7 point BSFS = decrease of 2.1 points thus derivation of responder status using 1 point change for ≥half study weeks was not deemed to be clinically relevant.
(d) Does not meet MID (30% improvement (EMA recs for continuous outcomes) on 5 point scale =1.5 points), no 95% CIs.
*BSFS = Bristol Stool Form Scale

Table 87: GRADE Profile, Outcome: relapse or flatulence or bloating

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	I = Linaclotide 290µg (%)	C = Placebo (%)			
7.1 Bloating (% with improvement of ≥30% for ≥half of the study weeks)								**Relative (95% CI)**	**Absolute (95% CI)**	
2[a]	RCTs	Serious[b]	No Serious	No serious	No serious	348/806 (43)	214/798 (27)	1.61 [1.40, 1.85]	16 more per 100 (11 more, 23 more)	Moderate

(a) Chey 2012, Rao 2012
(b) Use of rescue medication (laxatives) not reported by study arm has potential for confounding on bloating. Bulk laxatives and stool softeners were also permitted by one study (Rao et al 2012). Fibre/diet/fluid/exercise/other relevant meds were not reported by study arm.

Discontinuation, Safety and Adverse Events

Table 88: GRADE profile - discontinuation (all reasons)

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	I = Linclotide 290µg (%)	C = Placebo (%)			
								Relative (95% CI)	**Absolute (95% CI)**	
2[a]	RCTs	Serious[b]	No Serious	No serious	Serious[c]	202/808 (25)	160/800 (20)	1.25 [1.04, 1.50]	5 more per 100 (3 more, 12 more)	Low

(a) Chey 2012, Rao 2012
(b) Use of rescue medication (laxatives) not reported by study arm has potential for confounding on perceived efficacy. Bulk laxatives and stool softeners were also permitted by one study (Rao et al 2012).
(c) CIs cross line of MID (GRADE default suggestion)

Table 89: GRADE profile - reason for discountinuation

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	I = Linaclotide 290µg (%)	C = Placebo (%)			
Adverse Event								**Relative (95% CI)**	**Absolute (95% CI)**	
2[a]	RCTs	Serious[b]	No Serious	No serious	No serious	73/808 (9)	20/800 (3)	3.62 [2.23, 5.87]	7 more per 100 (3 more, 12 more)	Moderate
Adverse Event = Diarrhoea								**Relative (95% CI)**	**Absolute (95% CI)**	
3[c]	RCTs	Serious[b]	No Serious	No Serious	No serious	55/893 (6)	3/885 (0.3)	18.19 [5.72, 57.88]	6 more per 100 (2 more, 19 more)	Moderate
Withdrew Consent								**Relative (95% CI)**	**Absolute (95% CI)**	
2[a]	RCTs	Serious[b]	No Serious	No Serious	Serious[d]	49/808 (6)	51/800 (6)	0.95 [0.65, 1.39]	0 fewer per 100 (2 fewer, 2 more)	Low
Insufficient Therapeutic Response								**Relative (95% CI)**	**Absolute (95% CI)**	
2[a]	RCTs	Serious[b]	No serious	No serious	No serious	20/808 (2)	37/800 (5)	0.54 [0.32, 0.92]	2 fewer per 100 (0 fewer, 3 fewer)	Moderate

(a) Chey 2012, Rao 2012
(b) Use of rescue medication (laxatives) not reported by study arm has potential for confounding on perceived efficacy. Bulk laxatives and stool softeners were also permitted by one study (Rao et al 2012).
(c) Chey 2012, Rao 2014, Johnston 2013
(d) CIs cross line of effect

Table 90: GRADE profile - adverse events

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	I = Linaclotide 290µg (%)	C = Placebo (%)			
At least one Adverse Event								**Relative (95% CI)**	**Absolute (95% CI)**	
2[a]	RCTs	Serious[b]	No Serious	No serious	Serious[c]	491/808 (60)	438/799 (55)	1.11 [1.02, 1.21]	6 more per 100 (1 more, 12 more)	Low
Diarrhoea								**Relative (95% CI)**	**Absolute (95% CI)**	
3[d]	RCTs	Serious[b]	No Serious	No serious	No serious	172/893 (19)	25/884 (3)	6.80 [4.52, 10.23]	16 more per 100 (10 more, 26 more)	Moderate
Abdominal Pain								**Relative (95% CI)**	**Absolute (95% CI)**	
3[d]	RCTs	Serious[b]	No Serious	No serious	Serious[e]	44/893 (5)	29/884 (3)	1.50 [0.95, 2.38]	2 more per 100 (0 fewer, 5 more)	Low
Flatulence								**Relative (95% CI)**	**Absolute (95% CI)**	
2[a]	RCT	Serious[b]	No Serious	No serious	No serious	35/808 (4)	15/799 (2)	2.31 (1.27, 4.20)	2 more per 100 (1 more, 6 more)	Moderate
Abdominal Distension								**Relative (95% CI)**	**Absolute (95% CI)**	
2[a]	RCT	Serious[b]	No Serious	No serious	Serious[e]	18/808 (2)	9/799 (1)	1.98 (0.90, 4.39)	1 more per 100 (0 fewer, 4 more)	Low

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	I = Linaclotide 290µg (%)	C = Placebo (%)			
Nausea								**Relative (95% CI)**	**Absolute (95% CI)**	
Johnston 2010	RCT	Serious[b]	n/a	No serious	Serious[e]	1/85 (1)	5/85 (6)	0.2 (0.02, 1.68)	5 fewer per 100 (6 fewer, 27 more)	Low
UTI								**Relative (95% CI)**	**Absolute (95% CI)**	
Johnston 2010	RCT	No Serious	n/a	No serious	Serious[e]	5/85 (6)	2/85 (2)	2.5 (0.50, 12.5)	4 more per 100 (1 fewer, 27 more)	Moderate

(a) Chey 2012, Rao 2012
(b) Use of rescue medication (laxatives) not reported by study arm has potential for confounding on adverse events. Bulk laxatives and stool softeners were also permitted by one study (Rao et al 2012). Fibre/diet/fluid/exercise/other relevant meds were not reported by study arm.
(c) Point estimate does not reach MID (GRADE default suggestion) with CIs also below threshold.
(d) Chey 2012, Rao 2012, Johnston 2010
(e) CIs cross line of effect

Table 91: GRADE profile - serious adverse events

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	I=Linaclotide 290µg	C = Placebo			
Serious Adverse Events[a]								**Relative (95% CI)**	**Absolute (95% CI)**	
3[b]	RCTs	No serious	No Serious	No serious	Serious[c]	7/893 (1)	9/884 (1)	0.79 [0.30, 2.04]	2 fewer per 1000 (7 fewer, 11 more)	Moderate

(a) Chey 2012, n=4 (intervention arm) cuff syndrome (1), appendicitis (1), cystopexy (1) and Hodgkin's disease (1). Rao 2012, n=2 (intervention arm) asthma (1) and pericardial effusion and pericarditits leading to withdrawal from the study (1). Johnston 2010, n=1 (intervention arm) faecal impaction requiring hospitalisation (1).
(b) Chey 2012, Rao 2012, Johnston 2010
(c) CIs cross line of effect

H.45 Review question 4 (lubiprostone)

Table 92: GRADE profile, Outcome: Quality of Life (QOL)

Quality assessment						Number of patients		Effect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	I = Lubiprostone	C = Placebo	Mean Difference	Quality
1.1 IBS QOL (34 Questions) Higher score = worse									
Drossman 2009[a]	RCT	Serious[b]	Cannot be assessed.	No serious	Very serious[c]	769	385	Reported as Non-Significant only (no p value)	Very Low
Johanson 2008	RCT (phase 2)	Serious[b]	N/A	No serious	Very Serious[c]	145	48	Reported as Non-Significant only (no p value)	Very Low
1.2 Life interference (11 point scale, sub scale of IBS-SS) Higher score = worse									
Whitehead 2011	RCT 14 day crossover (14 day washout)	Serious[d]	N/A	No serious	Serious[e]	60[f]	60[f]	0.23 [-0.48, 0.94]	Low

(a) Drossman reported data from 2 previously unpublished RCTs (no references therefore available)
(b) Use of rescue medications (laxatives) was permitted with no reporting of use by study arm. Fibre/diet/fluid/exercise/other relevant meds were not reported by study arm.
(c) No effect size or confidence intervals
(d) Unclear if ITT analysis performed. Unclear if sub analysis of scale is validated in isolation as surrogate measure of QOL.
(e) Point estimate is below MID (on 11 point scale, 30% improvement (EMA recs) = 3.3 points). CIs cross the line of effect.
(f) Total sample was 60 but was crossover study hence 60 in each arm

Table 93: GRADE Profile, Outcome: symptom severity

Quality assessment						Number of patients		Effect		
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**I = Lubiprostone**	**C = Placebo**	**Mean difference**		**Quality**
2.1 IBS SS (Symptom Severity, /500) Higher score = worse										
Whitehead 2011	RCT 14 day crossover (14 day washout)	No Serious	N/A	No serious	Very serious[a]	62[b]	62[b]	7.68 [-34.89, 50.25]		Low
2.2 Overall Responder Status (degree of relief over time) [c]						**I = Lubiprostone (%)**	**C = Placebo (%)**	**Relative (95% CI)**	**Absolute (95% CI)**	
Drossman [d] 2009	RCT	Very serious[e]	Unable to assess	No serious	No serious	138/769 (18)	39/385 (10)	1.77 [1.27, 2.47]	8 more per 100 (3 more, 15 more)	Low

(a) Point estimate below MID (on a 500 point scale, 30% improvement (EMA recs) = 150 points,) CIs cross line of effect.
(b) Total sample was 62 but was crossover study hence 62 in each arm
(c) Relief measured "How would you rate your relief of IBS symptoms over the past week compared to how you felt before you entered the study?" (7 point scale, 1=significantly worse, 2=moderately worse, 3=a little bit worse, 4=unchanged, 5=a little bit relieved, 6=moderately relieved, 7=significantly relieved). Classifications of responders:

- *Weekly – moderate or significantly relieved for that week (secondary study endpoint).*
- *Monthly – moderately relieved or better in 4 out of 4 weeks OR significantly relieved in 2 out of 4 weeks. Could not discontinue treatment during 4 week period and % of days of rescue medication did not increase from baseline (Secondary study endpoint)*
- *Overall – Monthly responders for at least 2 of the 3 months of the study (primary study endpoint).*

(d) Drossman study reported data from 2 previously unpublished RCTs
(e) Use of rescue medications (laxatives) was permitted with no report of use by study arm. Fibre/diet/fluid/exercise/other relevant meds were not reported by study arm. Outcome reporting/recall bias suspected as question asked to identify responder status was leading and retrospective, with no mention of validation.

Table 94: GRADE Profile, Outcome: abdominal pain (10 point scale) higher score = worse

Quality assessment						Number of patients		Effect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	I = Lubiprostone	C = Placebo	Mean Difference	Quality
Whitehead 2011	RCT	Serious[a]	N/A	No serious	Very Serious[b]	60	60	I = -0.80 C = -0.85 Mean difference (95%CI) 0.05 [-0.74, 0.81] Calculated by reviewer.	Very low

(a) It was not stated whether ITT analysis was performed
(b) Effect size below MID (on 10 point scale, 30% = improvement of 3 points (EMA recs)). 95% CIs cross line of effect.

Table 95: GRADE Profile, Outcome: stool score/general changes in bowel habit

Quality assessment						Number of patients		Effect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	I = Lubiprostone	C = Placebo	Mean Change (improvement)	Quality
6.1 Spontaneous Bowel Movements (frequency per week) greater frequency desirable									
Drossman[a] 2009	RCT	Serious[b]	N/A	No serious	Very serious[c]	769	385	Reported as non-significant only. No P value.	Very low
Johanson 2008	RCT	Serious[b]	N/A	No serious	Serious[d]	(all dose arms) 145	48	I : 1.9 (BL 3.6, Wk12 5.5) C : 0.5 (BL 4.3, Wk12 4.8) P=0.0296	Low
6.2 Constipation Severity (5 point scale) Higher score = worse									
Johanson 2008	RCT (phase 2)	Serious[b]	N/A	No serious	Very serious[e]	(all dose arms) 145	48	I : -0.6 (BL 2.2, Wk12 1.6)	Very low

Quality assessment						Number of patients		Effect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	I = Lubiprostone	C = Placebo	Mean Change (improvement)	Quality
								C : -0.3 (BL 2.1, Wk12 1.8) P=0.0056	
6.3 Stool Output (Days with hard/lumpy stools or no stools (%))									
Whitehead 2011	RCT 14 day crossover (14 day washout)	No Serious	N/A	No serious	Very Serious[f]	60	60	**% days without event (difference)** I : -16.7 (BL 59.4, F/UP 42.7) C : -15.9 (BL 59.4, F/UP 43.5) (no p values reported)	Low

(a) Drossman study reported data from 2 previously unpublished RCTs
(b) Use of rescue medications (laxatives) was permitted with no report of use by study arm. Fibre/diet/fluid/exercise/other relevant meds were not reported by study arm.
(c) No effect size reported
(d) MID is met in intervention arm (30% improvement (EMA recs) based on mean of baseline frequency = 1.2 movements per week). No SD or 95%CIs reported
(e) MID is not met (30% improvement (EMA recs) based on 5 point constipation severity scale =1.5 point improvement). No SD or 95% CIs reported
(f) No SD or 95%CIs and effect size does not reach MID (30% improvement in days with hard/lumpy or no stools = 5 days without event. This was not met in either arm. I = Actual days = from 16.5 to 12.2, difference 4.3 days, C = Actual days = from 16.5 to 11.9 days, difference 4.6 days)

Table 96: GRADE Profile, Outcome: bloating

Quality assessment						Number of patients		Effect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	I = Lubiprostone	C = Placebo	Mean difference	Quality
Bloating (11 point scale) Higher score = worse									
Whitehead 2011	14 day crossover RCT (+14 day washout)	No serious	N/A	No serious	Serious[a]	60[b]	60[b]	0.04 [-0.94, 1.02]	Moderate

1 *(a) Effect size does not reach MID (30% improvement (EMA recs) on 10 point scale = 3 points) and CIs cross line of effect*
2 *(b) Total sample was 60 but was crossover study hence 60 in each arm*
3

Discontinuation and Adverse Events

Table 97: GRADE profile, Outcome: discontinuation (all reasons)

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Lubiprostone (%)	Placebo (%)	Relative (95% CI)	Absolute (95% CI)	Quality
3[a]	RCTs	Serious[b]	No serious	No serious	Serious[c]	193/820 (23)	106/436 (24)	0.99 [0.81, 1.21]	0 fewer per 100 (5 fewer to 5 more)	Low

(a) Drossman 2009 (Drossman 2009 included data from two RCTs so this study is counted as 2), Johanson 2008, 48µg dose arm only.
(b) Use of rescue medications (laxatives) was permitted with no report of use by study arm. This could affect perceived efficacy and thus discontinuation.
(c) Point estimate does not reach MID (GRADE default suggestion), CIs cross line of effect

Table 98: GRADE profile, Outcome: discontinuation due to adverse event

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Lubiprostone (%)	Placebo (%)	Relative (95% CI)	Absolute (95% CI)	Quality
3[a]	RCTs	Serious[b]	Serious[c]	No serious	Serious[d]	44/820 (5)	25/436 (6)	1.08 [0.44, 2.67]	0 more per 100 (3 fewer, 10 more)	Very low

(a) Drossman 2009 (Drossman 2009 included data from two RCTs so this study is counted as 2), Johanson 2008 48µg dose arm only.
(b) Use of rescue medications (laxatives) was permitted with no report of use by study arm
(c) Significant heterogeneity. Random Effects analysis, I^2 61%, Chi^2 = 5.17 (p=0.08)
(d) Point estimate does not reach MID (GRADE default suggestion), CIs cross line of effect

Table 99: GRADE profile, Outcome: discontinuation due to lack of efficacy

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Lubiprostone (%)	Placebo (%)	Relative (95% CI)	Absolute (95% CI)	Quality
3[a]	RCTs	Serious[b]	No serious	No serious	Serious[c]	32/820 (4)	22/436 (5)	0.84 [0.49, 1.43]	1 fewer per 100 (3 fewer, 2 more)	Low

(a) Drossman 2009 (Drossman 2009 included data from two RCTs so this study is counted as 2), Johanson 2008 48µg dose arm only.
(b) Use of rescue medications (laxatives) was permitted with no report of use by study arm.
(c) Point estimate does not reach MID (GRADE default suggestion) and CIs cross line of effect

Table 100: GRADE profile, Outcome: discontinuation due to non-compliance

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Lubiprostone (%)	Placebo (%)	Relative (95% CI)	Absolute (95% CI)	Quality
3[a]	RCTs	Serious[b]	No serious	No serious	Serious[c]	22/820 (3)	6/436 (1)	1.83 [0.77, 4.34]	1 more per 100 (0 fewer, 5 more)	Low

(a) Drossman 2009 (Drossman 2009 included data from two RCTs so this study is counted as 2), Johanson 2008 48µg dose arm only.
(b) Use of rescue medications (laxatives) was permitted with no report of use by study arm.
(c) CIs cross line of no effect.

Table 101: GRADE profile, Outcome: discontinuation due to withdrawn consent

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Lubiprostone (%)	Placebo (%)	Relative (95% CI)	Absolute (95% CI)	Quality
3[a]	RCTs	Serious[b]	No serious	No serious	Serious[c]	66/820 (8.2)	38/436 (9)	0.89 [0.61, 1.29]	1 fewer per 100 (3 fewer to 3 more)	low

(a) Drossman 2009 (Drossman 2009 included data from two RCTs so this study is counted as 2), Johanson 2008 48µg dose arm only.
(b) Use of rescue medications (laxatives) was permitted with no report of use by study arm
(c) Point estimate indicates no MID (GRADE default suggestion). CIs cross line of effect.

Table 102: GRADE profile, Outcome: adverse event (at least one)

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Lubiprostone (%)	Placebo (%)	Relative (95% CI)	Absolute (95% CI)	
2[a]	RCTs	Serious[b]	No serious	No serious	Serious[c]	422/825 (51)	225/435 (52)	1.00 [0.90, 1.12]	0 fewer per 100 (5 fewer, 6 more)	Low

(a) Drossman 2009 (Drossman 2009 included data from two RCTs so this study is counted as 2), Johanson 2008 48µg dose arm only.
(b) Use of rescue medications (laxatives) was permitted with no report of use by study arm
(c) Point estimate indicates no difference. CIs cross line of no effect.

Table 103: GRADE profile, Outcome: adverse event = nausea

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Lubiprostone (%)	Placebo (%)	Relative (95% CI)	Absolute (95% CI)	Quality
2[a]	RCTs	Serious[b]	No Serious	No serious	No serious	76/825 (9)	21/435 (5)	2.14 [1.34, 3.41]	6 more per 100 (2 more, 12 more)	Moderate

(a) Drossman 2009 (data from 2 RCTs combined), Johanson 2008
(b) Use of rescue medications (laxatives) was permitted with no report of use by study arm

Table 104: GRADE profile, Outcome: adverse event = diarrhoea

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Lubiprostone (%)	Placebo (%)	Relative (95% CI)	Absolute (95% CI)	Quality
2[a]	RCTs	Serious[b]	Serious[c]	No serious	Serious[d]	58/825 (7)	17/435 (4)	2.63 [0.68, 10.23]	6 more per 100 (1 fewer, 36)	Very low

(a) Drossman 2009 (Drossman 2009 included data from two RCTs so this study is counted as 2), Johanson 2008 48µg dose arm only.
(b) Use of rescue medications (laxatives) was permitted with no report of use by study arm
(c) Significant heterogeneity. I^2 69% Chi^2 = 3.23, (p=0.07)
(d) Point estimate indicates the risk of diarrhoea is greater in the lubiprostone group but the CIs cross the threshold for MID (GRADE default suggestion).

Table 105: GRADE profile, Outcome: adverse event = abdonimal distension

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Lubiprostone (%)	Placebo (%)	Relative (95% CI)	Absolute (95% CI)	Quality
2[a]	RCTs	Serious[b]	No serious	No serious	Very serious[c]	21/825 (2)	13/435 (3)	1.01 [0.51, 2.00]	0 more per 100 (1 fewer, 3 more)	Very low

(a) Drossman 2009 (Drossman 2009 included data from two RCTs so this study is counted as 2), Johanson 2008 48µg dose arm only.
(b) Use of rescue medications (laxatives) was permitted with no report of use by study arm
(c) Point estimate indicates the risk of abdominal distension is borderline higher in the lubiprostone group but this is below the MID (GRADE default suggestion) and the CIs cross the line of effect.

Table 106: GRADE profile, Outcome: serious adverse events[a]

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Lubiprostone (%)	Placebo (%)	Relative (95% CI)	Absolute (95% CI)	
2[b]	RCTs	No serious	N/A[c]	No serious	Serious[d]	10/831 (1)	4/435 (1)	1.35 [0.47, 3.90]	0 more per 100 (0 fewer, 3 more)	Moderate

(a) Drossman 2009 n=8, cardiac arrest on background of multiple co-morbidities leading to death (1), Non-cardiac related chest pain (1), not specified (6). Johanson 2008 n=2 (48µg arm only) (out of a total of 3 across all doses), perforated appendix (1), cholecystitis (1), ectopic pregnancy (1). (NB Whitehead 2011 made no mention of SAEs)
(b) Drossman 2009 (data from 2 RCTs combined), Johanson 2008, (48 µg dose arm only)
(c) Second study has zero events in both arms
(d) CIs cross line of effect.

H.5 Review question 5a (relaxation therapy)

Table 107: GRADE profile, Relaxation vs routine clinical care/ control/ enhanced medical care (dichotomous outomes)

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	
Outcome: Adequate relief											
Shinozaki 2010	RCT	Very serious[a]	No indirectness	No inconsistency	Serious[b]	None	9/11 (81.8%)	3/10 (30%)	RR 2.73 (1.02, 7.32)	519 more per 1000 (from 6 more to 1000 more)	VERY LOW

(a) Randomisation not described, allocation concealment not reported, blinding of investigators not reported, unclear whether patients continued to take other medication during study, attrition not reported for this small study (n=21) (Shinozaki, 2010). Unclear whether outcome was a validated tool. Downgraded 2 levels.
(b) Lower limit of 95%CI crosses MID at 1.25, leading to uncertainty in clinical effectiveness of the treatment. Downgraded 1 level.

Table 108: GRADE profile, Relaxation vs routine clinical care/ control/ enhanced medical care

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Mean difference (95% CI)	
Outcome: SIBSQ (Total score = 98; ≥30% improvement = ≥29.4 points increase/decrease from baseline)										

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Mean difference (95% CI)	
Shinozaki, 2010	RCT	Very serious [a]	No serious	no serious	Very serious [c]	No serious	11	10	T= 48.9; C=36.3 MD=12.60 (-1.91 to 27.11) Mean change from baseline*: T=-3.2; C=-19.6 Difference: 16.4	VERY LOW
Outcome: SDS (Total score = 70; ≥30% improvement = ≥21 points increase/decrease from baseline)										
Shinozaki 2010	RCT	Very serious [a]	No serious	no serious	Very serious [c]	No serious	11	10	T=44.6; C=45.8 MD= -1.20 (-8.48 to 6.08) Mean change from baseline*: T= -1.8; C= -0.01 Difference:1.79	VERY LOW
Outcome: STAI State Anxiety (Total score= 60; ≥30% improvement =≥18 points increase/decrease from baseline)										
Shinozaki 2010	RCT	Very serious [a]	No serious	no serious	Very serious [c]	No serious	11	10	T=47.2; C=51.4 MD= -4.20 (-12.21 to 3.81) Mean change from baseline*: T= -2.8; C=-3.2 Difference:0.4	VERY LOW
Outcome: STAI Trait Anxiety (Total score= 60; ≥30% improvement =≥18 points increase/decrease from baseline)										
Shinozaki 2010	RCT	Very serious [a]	No serious	no serious	Very serious [c]	No serious	11	10	T=54.5; C=52.8 MD= 1.70 (-8.87 to 12.27) Mean change from baseline*: T= -1.5; C=-4.0 Difference: 2.5	VERY LOW

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Mean difference (95% CI)	
Outcome: SF36 Physical function- 8 weeks follow up [(*)] (Total Score 100; ; ≥30% improvement =≥30 points increase?/decrease? from baseline)										
2[≠]	RCT	Very serious[(a) ,(b)]	No serious	no serious	Very serious[(c)]	No serious	30	35	T=70.6; C=67.5 MD= 2.73 (-3.40 to 8.86) Mean change from baseline*: T=+7.5; C=-2.3 Difference:9.8	VERY LOW
Outcome: SF36 Physical function-52 weeks follow up [(*)](Total Score 100; ; ≥30% improvement =≥30 points increase/decrease from baseline)										
Shinozaki 2010	RCT	Very serious[(b)]	No serious	no serious	Very serious[(c)]	No serious	13	21	T=91.9; C=88.8 MD= 3.10 (-8.00 to 14.20) Mean change from baseline*: T=-+12.5; C=+2.3 Difference:10.2	VERY LOW
Outcome: SF36 Role physical- 8 weeks follow up[(*)](Total Score 100; ; ≥30% improvement =≥30 points increase/decrease from baseline)										
2[≠]	RCT	Very serious[(a) ,(b)]	No serious	no serious	Very serious[(c)]	No serious	30	35	T= 53.9; C= 46.6 MD= 6.59 (-8.01 to 21.19) Mean change from baseline*: T=+27.65; C=+3.3 Difference: 24.35	VERY LOW
Outcome: SF36 Role physical-52 weeks follow up[(*)](Total Score 100; ; ≥30% improvement =≥30 points increase/decrease from baseline)										
Shinozaki 2010	RCT	Very serious[(b)]	No serious	no serious	Serious [(d)]	No serious	13	21	T=38.1; C=64.5 MD= 10.50 (-16.89 to 37.89) Mean change from baseline*: T=+30.7; C=+1.6	VERY LOW

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Mean difference (95% CI)	
									Difference: 29.1	
Outcome: SF36 Bodily pain- 8 weeks follow up(*)(Total Score 100; ; ≥30% improvement =≥30 points increase/decrease from baseline)										
2≠	RCT	Very serious(a) ,(b)	No serious	no serious	Very serious(c)	no serious	30	35	T=54.64; C= 54.6 MD 1.29 (-6.41 to 8.99) Mean change from baseline*: T=+9.75; C=+5.5 Difference: 4.25	VERY LOW
Outcome: SF36 Bodily pain- 52 weeks follow up(*)(Total Score 100; ; ≥30% improvement =≥30 points increase/decrease from baseline)										
Shinozaki 2010	RCT	Very serious(b)	No serious	no serious	Very serious(c)	no serious	13	21	T=64.2; C=68 MD= -3.80 (-19.18 to 11.58) Mean change from baseline*: T=+11.2; C=+8.7 Difference: 2.5	VERY LOW
Outcome: SF36 General health- 8 weeks follow up(*)(Total Score 100; ; ≥30% improvement =≥30 points increase/decrease from baseline)										
2≠	RCT	Very serious(a) ,(b)	No serious	no serious	Very serious(c)	no serious	30	35	T=48.2; C= 49.15 MD= -1.05 (-9.40 TO 7.30) Mean change from baseline*: T=+3.4; C=+0.05 Difference: 3.35	VERY LOW
Outcome: SF36 General health - 52 weeks follow up (*)(Total Score 100; ; ≥30% improvement =≥30 points increase/decrease from baseline)										
Shinozaki 2010	RCT	Very serious(b)	No serious	no serious	Very serious(c)	no serious			T=65.9; C=66 MD= -0.10 (-15.85 TO 15.65) Mean change from baseline*:	VERY LOW

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Mean difference (95% CI)	
									T=+6.2; C=+0.6 Difference: 5.6	
Outcome: SF36 Vitality- - 8 weeks follow up(*)(Total Score 100; ; ≥30% improvement =≥30 points increase/decrease from baseline)										
2≠	RCT	Very serious(a) ,(b)	No serious	no serious	Very serious(c)	no serious	30	35	MD= 2.38 (-4.01 TO 8.78) Mean change from baseline*: T=11.7; C=+7.8 Difference: 3.9	VERY LOW
Outcome: SF36 Vitality-- 52 weeks follow up(*)(Total Score 100; ; ≥30% improvement =≥30 points increase/decrease from baseline)										
Shinozaki 2010	RCT	Very serious(b)	No serious	no serious	Very serious(c)	no serious	13	21	T= 61.5; C=59.2 MD= 2.30 (-12.48 TO 17.08) Mean change from baseline*: T=+13.5; C=+9.2 Difference:4.3	VERY LOW
Outcome: SF36 Social functioning- 8 weeks follow up(*)(Total Score 100; ; ≥30% improvement =≥30 points increase/decrease from baseline)										
2≠	RCT	Very serious(a) ,(b)	No serious	no serious	Very serious(c)	no serious	30	35	MD= -3.46 (-12.08 TO 5.16) Mean change from baseline*: T=+17.0; C=+14.7 Difference: 2.3	VERY LOW
Outcome: SF36 Social functioning- 52 weeks follow up(*)(Total Score 100; ; ≥30% improvement =≥30 points increase/decrease from baseline)										
Shinozaki 2010	RCT	Very serious(b)	No serious	no serious	Very serious(c)	no serious	13	21	T= 76.9; C=80.3 MD= -3.40 (-18.97 TO 12.17) Mean change from baseline*: T=+10.8; C=+7.2	VERY LOW

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Mean difference (95% CI)	
									Difference: 3.6	
Outcome: SF36 Role emotional- 8 weeks follow up(*)(Total Score 100; ; ≥30% improvement =≥30 points increase/decrease from baseline)										
2≠	RCT	Very serious(a) ,(b)	No serious	no serious	Very serious(c)	no serious	30	35	MD= 6.23 (-5.19 TO 17.66) Mean change from baseline*: T= +23.4; C= +2.9 Difference: 20.5	VERY LOW
Outcome: SF36 Role emotional- 52 weeks follow up(*)(Total Score 100; ; ≥30% improvement =≥30 points increase/decrease from baseline)										
Shinozaki 2010	RCT	Very serious(b)	No serious	No serious	Very serious(c)	no serious	13	21	T=66.7; C=75 MD= -8.30 (-37.70 to 21.10) Mean change from baseline*: T=+8.6; C= +4.3 Difference: 4.3	VERY LOW
Outcome: SF36 Mental health- 8 weeks follow up(*)(Total Score 100; ≥30% improvement =≥30 points increase/decrease from baseline)										
2≠	RCT	Very serious(a) ,(b)	No serious	No serious	Very serious(c)	no serious	30	35	MD= 2.24 (-4.12 to 8.60) Mean change from baseline*: T=+7.3; C=+8.9 Difference:1.6	VERY LOW
Outcome: SF36 Mental health- 52 weeks follow up(*)(Total Score 100; ≥30% improvement =≥30 points increase/decrease from baseline)										
Shinozaki 2010	RCT	Very serious(b)	No serious	No serious	Very serious(c)	no serious	13	21	T=71.4; C=77.1 MD= -5.70 (-17.06 to 5.66) Mean change from baseline*: T=+7.3; C=+12.4 Difference: 5.1	VERY LOW

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Mean difference (95% CI)	
Outcome: BSSS- Frequency- 52 weeks follow up(*)(Total Score 48; ≥30% improvement =≥16.4 points increase/decrease from baseline)										
Shinozaki 2010	RCT	Very serious(b)	No serious	No serious	Very serious(c)	no serious	13	21	T=16.2; C= 17 MD= -0.80 (-3.61 to 2.01) Mean change from baseline*: T- -4.4; C=-4.0 Difference: 0.4	VERY LOW
Outcome: BSSS-Distress- 52 weeks follow up (*)(Total Score 48; ≥30% improvement =≥16.4 points increase/decrease from baseline)										
Shinozaki, 2010	RCT	Very serious(b)	No serious	No serious	Very serious(c)	no serious	13	21	T=13.2; C=12.5 MD= 0.70 (-2.29 to 3.69) Mean change from baseline*: T=-4.5; C=-3.8 Difference: 0.7	VERY LOW
Outcome: BSSS- Interference- 52 weeks follow up (*)(Total Score 48; ≥30% improvement =≥16.4 points increase/decrease from baseline)										
Shinozaki 2010	RCT	Very serious(b)	No serious	No serious	Very serious(c)	no serious	13	21	T=13.2; C=12.5 MD= 0.70 (-2.29 to 3.69) Mean change from baseline*: T=-4.5; C=-3.8 Difference: 0.7	VERY LOW
Outcome: Automatic thoughts questionnaire- 52 weeks follow up (*)(Total Score 120; ≥30% improvement =≥36 points increase/decrease from baseline)										
Shinozaki 2010	RCT	Very serious(b)	No serious	No serious	Very serious(c)	no serious	13	21	T=40.31; C=19.56 MD= -0.17 (-9.47 to 9.13) Mean change from baseline*:	VERY LOW

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Mean difference (95% CI)	
									T= -5.9; C=-3.16 Difference: 2.74	
Outcome: Locus of control of behaviours- 52 weeks follow up (*)(Total Score 85; ≥30% improvement =≥25.5 points increase/decrease from baseline)										
Shinozaki 2010	RCT	Very serious(b)	No serious	No serious	Very serious(c)	no serious	13	21	T=24.23; C=27.9 MD=-3.67 (-13.88 to 6.54) Mean change from baseline*: T= -5.55; C=-1.19 Difference: 4.36	VERY LOW
Outcome: Hospital anxiety and depression scale- 52 weeks follow up (*)(Total Score 42; ≥30% improvement =≥12.6 points increase?/decrease? from baseline)										
Shinozaki 2010	RCT	Very serious(b)	No serious	No serious	Very serious(c)	no serious	13	21	T= 10.7; C=11 MD= -0.30 (-4.68 to 4.08) Mean change from baseline+: T=-3.3; C=-3.1 Difference: 0.2	VERY LOW

(*) *For the SF36 outcomes, one study reported the outcomes at 4 separate time points. As IBS is a chronic condition it was decided to assess the quality on the 8 week follow up (where 2 studies report results)and the latest follow up point from baseline (52 weeks).For outcomes that were not pooled, the latest time point (52 weeks follow up) is used.*

(+) Mean change from baseline calculated by analyst

(≠) Shinozaki 2010, Boyce 2003

(a) Randomisation not described, allocation concealment not reported, blinding of investigators not reported, unclear whether patients continued to take other medication during study, attrition not reported for this small study (n=21) (Shinozaki, 2010). Downgraded 2 levels.

(b) In Boyce (2003) baseline scores for all SF36 domains (apart from vitality and mental health) were lower in the Relaxation Therapy (RT) group compared to routine clinical care (RCC). Attrition at week 8 was 26.5% in RCC and 45.7% in RT; at week 52 attrition was 38% in RTT and 64% in RT. Only per protocol data was presented in the study. Downgraded 2 levels.

(c) 95%CI for mean difference between groups post treatment included both positive and negative effects making the direction of effect and the effect size very uncertain. The mean change from baseline for both groups did not reach clinical significant difference. Downgraded 2 levels.

(d) 95%CI for mean difference between groups post treatment included both positive and negative effects making the direction of effect and the effect size very uncertain.The mean change from baseline for the relaxation group was clinically significant at >30% change from baseline.Downgraded 1 level.

Table 109: GRADE profile, Relaxation vs enhanced medical care

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Mean difference from baseline difference (95% CI)	
Outcome: Impairment severity score – bodily impairment (Total Score 12; ≥30% improvement =≥3.6 points increase/decrease from baseline)										
Lahman 2010	RCT	Serious[a]	No serious	No serious	Serious[C]	no serious	40	40	T=1.69; C=0.79 MD= -0.39 (-0.77 TO -0.01) Mean change from baseline[+]: T=-0.51; C=-0.04 Difference:0.47	LOW
Outcome: Impairment severity score – psychic impairment (Total Score 12; ≥30% improvement =≥3.6 points increase/decrease From baseline)										
Lahman 2010	RCT	Serious[a]	No serious	No serious	Serious[d]	no serious	40	40	T=1.64; C= 1.88 MD= -0.24 (-0.59 to 0.11) Mean change from baseline[+]: T=-0.42; C=-0.09 Difference: 0.33	LOW
Outcome: Impairment severity score – social impairment (Total Score 12; ≥30% improvement =≥3.6 points increase/decrease from baseline)										
Lahman 2010	RCT	Serious[a]	No serious	No serious	Serious[d]	no serious	40	40	T=1.01; C=1.14 MD= -0.13 (-0.53 to 0.27) Mean change from baseline[+]: T=0.07; C=-0.08 Difference:0.15	LOW
Outcome: Overall IBS symptoms (Total Score 40; ≥30% improvement =≥12 points increase/decrease from baseline)										
Lahman 2010	RCT	Serious[b]	No serious	No serious	Serious[c]	no serious	40	40	T=26.2; C=30.6 MD= -4.40 (-7.23 to -1.57)	LOW

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Mean difference from baseline difference (95% CI)	
									Mean change from baseline[+]: T=-5.6; C=-0.04 Difference:5.56	
Outcome: Abdominal pain (Total Score 40; ≥30% improvement =≥12 points increase/decrease from baseline)										
Lahman 2010	RCT	Serious[(b)]	No serious	No serious	Very serious[(e)]	no serious	40	40	T= 25.7; C=27.3 MD=-1.60 (-6.07 to 2.87) Mean change from baseline[+]: T=-7.3; C= -4.1 Difference: 2.2	VERY LOW
Outcome: Deterioration – diarrhoea & constipation (Total Score 40; ≥30% improvement =≥12 points increase/decrease from baseline)										
Lahman 2010	RCT	Serious[(b)]	No serious	No serious	Very serious[(e)]	no serious	40	40	T= 29.1; C=29.2 MD= -0.10 (-3.45 TO 3.25) Mean change from baseline[+]: T=-4.3; C= -2.2 Difference: 2.1	VERY LOW
Outcome: Bloating (Total Score 40; ≥30% improvement =≥12 points increase/decrease from baseline)										
Lahman 2010	RCT	Serious[(b)]	No serious	No serious	Serious[(c)]	no serious	40	40	T=28.1; C=33.2 MD= -5.10 (-8.41 to -1.79) Mean change from baseline[+]: T=-7.3; C=-1.7 Difference: 5.6	LOW

For all outcomes in Table X, outcomes reported at 5 weeks and 3 months; due to chronic nature of IBS, only the outcomes for 3 month follow up reported as most clinically relevant.(+) Mean change from baseline calculated by analyst

(a) Unclear whether outcome measure BSS/ ISS is validated, paper states that it is widely used in Germany. Downgraded 1 level.

(b) Outcome measure is patient- reported subjective measurement on a scale of 10-50, lack of further detail in study. Downgraded 1 level.

(c) *The mean change from baseline for both groups does not reach clinical significance. The confidence intervals do not cross the line of no difference indicating the estimate of the effect is precise. Downgraded 1 level.*
(d) *The mean change from baseline for both groups does not reach clinical significance. The confidence intervals do cross the line of no difference, but are narrow indicating a precise estimate. Downgraded 1 level.*
(e) *95%CI for mean difference between groups post treatment included both positive and negative effects making the direction of effect and the effect size very uncertain. The mean change from baseline for both groups did not reach clinical significant difference.Downgraded 2 levels.*

Table 110: GRADE profile, Relaxation vs hypnotherapy

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Median (Range)	
Outcome: Overall symptom score (Total score 30 ≥30% improvement =≥9 points increase/decrease from baseline)										
Forbes 2000	RCT	Very serious (a),(b)	No serious	No serious	Very serious(c)	no serious	13	12	T = 11; C =7.5 Test (p-value): NR Median change from baseline+: T= 0.0; C= -7.0 Difference: 7.0	VERY LOW
Outcome: GHQ – Sum (Total score 36 ≥30% improvement =≥14.8 points increase/decrease from baseline)										
Forbes 2000	RCT	Very serious (a)	No serious	No serious	Very serious(c)	no serious	13	12	T= 22 (11-35); C= 22.5 (5-64) Test (p-value): NR Median change from baseline+: T= +2.5; C=-4 Difference: 6.5	VERY LOW
Outcome: HADS- Anxiety (Total score 21 ≥30% improvement =≥6.3 points increase/decrease from baseline)										
Forbes 2000	RCT	Very serious (a)	No serious	No serious	Very serious(c)	no serious	13	12	T=8 (0-15); C=10.5 (2-15) Test (p-value): NR Median change from baseline+: T=+3; C=-1 Difference: 4	VERY LOW
Outcome: HADS- Depression (Total score 21 ≥30% improvement =≥6.3 points increase/decrease from baseline)										

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Median (Range)	
1 Forbes, 2000	RCT	Very serious [a]	No serious	No serious	Very serious [c]	no serious	13	12	T=4 (0-15) C=4 (0-13) Test (p-value): NR Median change from baseline+: T=0; C=-1.5 Difference: 1.5	VERY LOW
Outcome: SF36- Physical function (Total score 100 ≥30% improvement =≥30 points increase/decrease from baseline)										
Forbes 2000	RCT	Very serious [a]	No serious	No serious	Very serious [c]	no serious	13	12	T=87 (70-100) C=75 (35-100) Test (p-value): NR Median change from baseline+: T=-8; C=+8 Difference: 16	VERY LOW
Outcome: SF36- Physical role (Total score 100 ≥30% improvement =≥30 points increase/decrease from baseline)										
Forbes 2000	RCT	Very serious [a]	No serious	No serious	Very serious [c]	no serious	13	12	T= 25 (0-100) C= 50 (0-100) Test (p-value): NR Median change from baseline+: T=-50; C=+25 Difference: 75	VERY LOW
Outcome: SF36- Emotional role (Total score 100 ≥30% improvement =≥30 points increase/decrease from baseline)										
Forbes 2000	RCT	Very serious [a]	No serious	No serious	Very serious [c]	no serious	13	12	T=100 (0-100) C= 67 (0-100) Test (p-value): NR Median change from baseline+: T=0; C=0 Difference: 0	VERY LOW

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Median (Range)	
Outcome: SF36- Social function (Total score 100 ≥30% improvement =≥30 points increase/decrease from baseline)										
Forbes 2000	RCT	Very serious [a]	No serious	No serious	Very serious [c]	no serious	13	12	T= 75 (37-100) C= 44 (12-100) Test (p-value): NR Median change from baseline+: T=0; C=-6 Difference: 6	VERY LOW
Outcome: SF36- Pain (Total score 100 ≥30% improvement =≥30 points increase/decrease from baseline)										
Forbes 2000	RCT	Very serious [a]	No serious	No serious	Very serious [c]	no serious	13	12	T=56 (12-84) C= 46 (0-100) Test (p-value): NR Median change from baseline+: T=+5; C=+5 Difference: 0	VERY LOW
Outcome: SF36- Mental state (Total score 100 ≥30% improvement =≥30 points increase/decrease from baseline)										
Forbes 2000	RCT	Very serious [a]	No serious	No serious	Very serious [c]	no serious	13	12	T= 62 (40-88) C= 52 (36-84) Test (p-value): NR Median change from baseline+: T=-10; C=0 Difference: 10	VERY LOW
Outcome: SF36- Vitality (Total score 100 ≥30% improvement =≥30 points increase/decrease from baseline)										
Forbes 2000	RCT	Very serious [a]	No serious	No serious	Very serious [c]	no serious	13	12	T=50 (15-95) C= 30 (5-75) Test (p-value): NR Median change from baseline+: T=0; C=-3	VERY LOW

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Median (Range)	
									Difference: 3	
Outcome: SF36- Perception of health (Total score 100 ≥30% improvement =≥30 points increase/decrease from baseline)										
Forbes 2000	RCT	Very serious (a)	No serious	No serious	Very serious (c)	no serious	13	12	T=52 (20-100) C= 53 (5-87) Test (p-value): NR Median change from baseline+: T=-13; C=+16 Difference: 29	VERY LOW
Outcome: SF36- Health change (Total score 100 ≥30% improvement =≥30 points increase/decrease from baseline)										
Forbes 2000	RCT	Very serious (a)	No serious	No serious	Very serious (c)	no serious	13	12	T= 50 (25-100) C= 67 (0-100) Test (p-value): NR Median change from baseline+: T=0; C=+17 Difference: 17	VERY LOW

(a) Allocation concealment not reported, over 50% attrition (equal between groups), results reported on an available case basis, higher self- rating of health (SF36 and HAD) in the audiotape group compared to the hypnotherapy group (though the authors reported that this did not reach significance), the same person recorded the relaxation tape as undertook the hypnotherapy,patients were allowed to continue with pre-existing therapy for IBS, downgraded 2 levels.

(b) The primary outcome of overall symptom score is not a validated outcome measure and the overall symptom scores were not comparable at baseline. The results were calculated by the analyst and were not clearly reported in the study, downgraded 1 level.

(c) Only median values were reported in the paper, no interquartile range was reported; this meant that imprecision could not be assessed based on the specific threshold of MID. Therefore the default for continuous outcomes for GRADE was used; the optimal information size, calculated by the GRADE working group is 400; the number of events in intervention and control groups in this study did not reach this threshold, downgraded 2 levels.

H.6 Review question 5b (CCBT and Mindfulness therapy)

Table 111: GRADE profile 1a, CCBT-Mindfulness/Exposure (CCBT-M/E) vs Waitlist (online discussion forum) (W-ODF)

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other consideration	CCBT-M/E	W-ODF	Relative (96% CI)	Absolute	

Quality assessment							No of patients		Effect estimate		Quality
						s					
Outcome: IBS symptoms: GSRS-IBS[d] Responder (≥50% reduction in total score) (10-wks)											
Ljotsson 2010	RCT	Very Serious[a, b]	Serious [(d)]	Not applicable	No serious	No serious	15/42 (35.7%)	1/43 (2.3%)	RR 15.36 (2.12 to 111.13)	33 more per 100 (from 3 more to 100 more)	LOW

(a) No information on baseline use of other IBS treatments (e.g. pharmacological treatments, dietary interventions, etc.).
(b) Participants were 'self-referred', potential selection bias of participants who were more likely to experience an effect. Reason for withdrawal not reported.
(c) GSRS-IBS (Gastrointestinal Symptom Rating Scale for IBS) (total score: 13 to 91, with 13 = no discomfort at all)
(d) The study was undertaken in Sweden. There is uncertainty that the intervention would be applicable to the UK population due to the differences in delivery of CCBT in the UK compared to Sweden.

Table 112: GRADE profile 1b, CCBT-Mindfulness/Exposure (CCBT-M/E) vs Waitlist (online discussion forum) (W-ODF)

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	CCBT-M/E (T)	W-ODF (C)	Mean difference (95% CI)	
Outcome: Quality of life: IBS-QoL[d] (10-wks)										
2(a)	RCT	Very Serious[b, c]	Serious [(h)]	No serious	No serious[f]	No serious	65	70	T = 72.8, C = 52.9(at 3 months follow up) MD = 17.93 (11.25 to 24.60)	LOW
Outcome: IBS symptoms: GSRS-IBS (10-wks)										
2(a)	RCT	Very Serious[b, c]	Serious [(h)]	No serious	Serious[g]	No serious	65	70	T = 32.4 C = 47.3 (at 3 months follow up) MD = -13.6 (-17.23 to -8.88)	VERY LOW

(a) Ljotsson (2010, 2011b)
(b) No information on baseline use of other IBS treatments (e.g. pharmacological treatments, dietary interventions, etc.).
(c) Participants were 'self-referred', potential selection bias of participants who were more likely to experience an effect. Reason for withdrawal not reported.
(d) IBS-QoL (total score: 0 to 100, with 0 = minimum QoL). Drossman (2007) suggested minimum clinical important difference as ≥14 points improvement from baseline.
(e) GSRS-IBS (Gastrointestinal Symptom Rating Scale for IBS) (total score: 13 to 91, with 13 = no discomfort at all). FDA and EMA suggested MID = 30% reduction = at least 23.4 points increase from baseline.
(f) Mean difference between groups showed significant effect, treatment group reached the MID of ≥14 points improvement from baseline [Mean change from baseline: T = +20.6; C = -0.9], no downgrade.
(g) Although mean difference between groups showed significant effect, both groups end scores did not reach the ≥30% MID [Mean change from baseline: T = -16.1; C = -2.3]
(h) The study was undertaken in Sweden. There is uncertainty that the intervention would be applicable to the UK population due to the differences in delivery of CCBT in the UK compared to Sweden.

Table 113: GRADE profile 1c, CCBT-Mindfulness/Exposure (CCBT-M/E) vs Waitlist (online discussion forum) (W-ODF)

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	CCBT-M/E (T)	W-ODF (C)	Mean difference (95% CI)	
Outcome: Primary outcomes: Abdominal pain, tenderness, constipation (lower score is better): the GI symptom diary[a] (mean diary rating) (10-wks)										
Ljotsson 2010	RCT	Very serious[b,c]	Serious [(e)]	Not applicable	Serious[d]	No serious	42	43	T = 3.0; C = 5.2 MD = -2.20 (-3.33 to -1.07)	VERY LOW
Outcome: Total pain: the GI symptom diary[a] (lower score is better): (mean diary rating) (10-wks)										
Ljotsson 2010	RCT	Very serious[b,c]	Serious [(e)]	Not applicable	Serious[d]	No serious	42	43	T = 1.4; C = 1.6 MD = -1.00 (-1.66 to -0.34)	VERY LOW
Outcome: Constipation: the GI symptom diary[a](lower score is better): (mean diary rating) (10-wks)										
Ljotsson 2010	RCT	Very serious[bc]	Serious [(e)]	Not applicable	Serious[d]	No serious	42	43	T = 0.3; C = 0.6 MD = -0.40 (-0.62 to -0.18)	VERY LOW
Outcome: Diarrhoea: the GI symptom diary[a] (lower score is better): (mean diary rating) (10-wks)										
Ljotsson 2010	RCT	Very serious[b,c]	Serious [(e)]	Not applicable	Serious[d]	No serious	42	43	T = 0.4; C = 0.6 MD = -0.20 (-0.46 to 0.06)	VERY LOW
Outcome: Bloating: the GI symptom diary[a] (lower score is better): (mean diary rating) (10-wks)										
Ljotsson 2010	RCT	Very serious[b,c]	Serious [(e)]	Not applicable	Serious[d]	No serious	42	43	T = 0.9; C = 1.7 MD = -0.80 (-1.16 to -0.44)	VERY LOW
Outcome: Flatulence: the GI symptom diary[a] (lower score is better): (mean diary rating) (10-wks)										
Ljotsson 2010	RCT	Very Serious[b,c]	Serious [(e)]	Not applicable	Serious[d]	No serious	42	43	T = 0.9; C = 1.4 MD = -0.50 (-0.82 to -0.18)	VERY LOW
Outcome: Belching: the GI symptom diary[a] (lower score is better): (mean diary rating) (10-wks)										
Ljotsson 2010	RCT	Very serious[b,c]	Serious [(e)]	Not applicable	Serious[d]	No serious	42	43	T = 0.4; C = 0.5 MD = -0.10 (-0.31 to 0.11)	VERY LOW

(a) The GI symptom diary (mean daily rating) (5-point scale: 0 = not a problem; 4 = debilitating). FDA and EMA suggested MID = 30% improvement = at least 1.5 points decrease from baseline. For the composite primary outcome, 30% improvement = at least 4.5 points decrease from baseline.

(b) No information on baseline use of other IBS treatments (e.g. pharmacological treatments, dietary interventions, etc.).

(c) *Participants were 'self-referred', potential selection bias of participants who were more likely to experience an effect. Reason for withdrawal not reported.*
(d) *Both groups end scores (mean change from baseline) did not reach the ≥30% MID.*
(e) *The study was undertaken in Sweden. There is uncertainty that the intervention would be applicable to the UK population due to the differences in delivery of CCBT in the UK compared to Sweden*

CCBT-Mindfulness/Exposure vs Internet delivered stress management

Table 114: GRADE profile 2a, CCBT-Mindfulness/Exposure (CCBT-M/E) vs Internet delivered stress management (ISM)

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	CCBT-M/E	ISM	Relative (96% CI)	Absolute	
Outcome: IBS symptoms: Adequate relief[a] (responder) (10-wks)											
Ljotsson 2011	RCT	Very serious[b, c]	Serious [(f)]	Not applicable	Very serious[d]	No serious	68/98 (69.4%)	56/97 (57.7%)	RR 1.20 (0.97 to 1.49)	12 more per 100 (from 2 fewer to 22 more)	VERY LOW
Outcome: IBS symptoms: Adequate relief[a] (responder) (6-mth FU)											
Ljotsson 2011	RCT	Very serious[b, c]	Serious [(f)]	Not applicable	Serious[e]	No serious	64/98 (65.3%)	43/97 (44.3%)	RR 1.47 (1.13 to 1.92)	21 more per 100 (from 6 more to 41 more)	VERY LOW

(a) *Adequate relief (responder) [Question: "In the past week, have you had adequate relief from IBS pain or discomfort?"]*
(b) *No information on baseline use of other IBS treatments (e.g. pharmacological treatments, dietary interventions, etc.).*
(c) *Participants were 'self-referred', potential selection bias of participants who were more likely to experience an effect. Reason for withdrawal not reported.*
(d) *The RR did not reach the MID and the 95%CI crosses over 1.25.*
(e) *The 95%CI crosses over 1.25.*
(f) *The study was undertaken in Sweden. There is uncertainty that the intervention would be applicable to the UK population due to the differences in delivery of CCBT in the UK compared to Sweden*

Table 115: GRADE profile 2b, CCBT-Mindfulness/Exposure (CCBT-M/E) vs Internet delivered stress management (ISM)

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	CCBT-M/E (T)	ISM (C)	Mean difference (95% CI)	

Quality assessment							No of patients		Effect estimate	Quality
Outcome: Quality of life: IBS-QoL[a] (10-wks)										
Ljotsson 2011	RCT	Very serious[c, d]	Serious [(i)]	Not applicable	No serious[e]	No serious	97	94	T = 75.7; C = 65.7 MD = 10.00 (4.47 to 15.53)	LOW
Outcome: Quality of life: IBS-QoL[a] (6-mth FU)										
Ljotsson 2011	RCT	Very serious[c, d]	Serious [(i)]	Not applicable	No serious[f]	No serious	87	82	T = 74.9; C = 68.7 MD = 6.20 (0.20 to 12.20)	LOW
Outcome: IBS symptoms: GSRS-IBS[b] (10-wks)										
Ljotsson 2011	RCT	Very serious[c, d]	Serious [(i)]	Not applicable	Serious[g]	No serious	96	90	T = 36.3; C = 41.1 MD = -4.80 (-8.41 to -1.19)	VERY LOW
Outcome: IBS symptoms: GSRS-IBS[b] (6-mth FU)										
Ljotsson 2011	RCT	Very serious[c, d]	Serious [(i)]	Not applicable	Serious[h]	No serious	87	82	T = 33.4; C = 39.3 MD = -5.90 (-9.93 to -1.87)	VERY LOW

(a) IBS-QoL (total score: 0 to 100, with 0 = minimum QoL). Drossman (2007) suggested minimum clinical important difference as ≥14 points improvement from baseline.
(b) GSRS-IBS (Gastrointestinal Symptom Rating Scale for IBS) (total score: 13 to 91, with 13 = no discomfort at all). FDA and EMA suggested MID = 30% reduction = at least 23.4 points increase from baseline.
(c) No information on baseline use of other IBS treatments (e.g. pharmacological treatments, dietary interventions, etc.).
(d) Participants were 'self-referred', potential selection bias of participants who were more likely to experience an effect. Reason for withdrawal not reported.
(e) Mean difference between groups showed significant effect, treatment group reached the MID of ≥14 points improvement from baseline [Mean change from baseline: T = +18.6; C = +10.2], no downgrade.
(f) Mean difference between groups showed significant effect, treatment group reached the MID of ≥14 points improvement from baseline [Mean change from baseline: T = +17.8; C = +13.2], no downgrade.
(g) Although mean difference between groups showed significant effect, both groups end scores did not reach the ≥30% MID [Mean change from baseline: T = -11.2; C = -6.2]
(h) Although mean difference between groups showed significant effect, both groups end scores did not reach the ≥30% MID [Mean change from baseline: T = -14.1; C = -8.0]
(i) The study was undertaken in Sweden. There is uncertainty that the intervention would be applicable to the UK population due to the differences in delivery of CCBT in the UK compared to Sweden

Mindfulness group training vs Support group

Table 116: GRADE profile 3a, Mindfulness group training (MG) vs Support group (SG)

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	MG	SG	Relative (96% CI)	Absolute	
Outcome: IBS symptoms: IBS-SS Responder[a] (at least 50 points reduction from baseline) (10-wks)											
Gaylord 2011	RCT	Very serious[b, c]	No serious	Not applicable	Serious[d]	No serious	25/36 (69.4%)	18/39 (46.2%)	RR 1.50 (1.01 to 2.25)	23 more per 100 (from 0 more to 58 more)	VERY LOW
Outcome: IBS symptoms: IBS-SS Responder[b] (at least 50 points reduction from baseline) (3-mth FU)											
Gaylord 2011	RCT	Very serious[b, c]	No serious	Not applicable	Serious[d]	No serious	27/36 (75.0%)	21/39 (53.8%)	RR 1.39 (0.99 to 1.97)	21 more per 100 (from 1 fewer to 52 more)	VERY LOW

(a) IBS-SS (severity scale: maximum score = 500)
(b) No information on baseline use of other IBS treatments (e.g. pharmacological treatments, dietary interventions, etc.).
(c) Women only study. Reason for withdrawal not reported.
(d) The 95%CI crosses over 1.25.

1 **Table 117: GRADE profile 3b, Mindfulness group training (MG) vs Support group (SG)**

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	MG (T)	SG (C)	Mean difference (95% CI)	
Outcome: Quality of life: IBS-QoL[a] (10-wks)										
Gaylord 2011	RCT	Very serious[c, d]	No serious	Not applicable	Serious[e]	No serious	36	39	T = 74.99; C = 70.92 MD = 4.07 (-3.30 to 11.44)	VERY LOW
Outcome: Quality of life: IBS-QoL[a] (3-mth FU)										
Gaylord 2011	RCT	Very serious[c, d]	No serious	Not applicable	Serious[f]	No serious	36	39	T = 76.73; C = 71.05 MD = 5.68 (-2.39 to 13.75)	VERY LOW
Outcome: IBS symptoms: IBS-SS Abdominal pain severity[b] (10-wks)										
Gaylord 2011	RCT	Very serious[c, d]	No serious	Not applicable	Serious[g]	No serious	36	39	T = 35.00; C = 50.49 MD = -15.49 (-28.42 to -2.56)	VERY LOW
Outcome: IBS symptoms: IBS-SS Abdominal pain severity[b] (3-mth FU)										
Gaylord 2011	RCT	Very serious[c, d]	No serious	Not applicable	Serious[g]	No serious	36	39	T = 31.11; C = 45.49 MD = -14.38 (-26.61 to -2.15)	VERY LOW
Outcome: IBS symptoms: IBS-SS Bloating severity[b] (10-wks)										
Gaylord 2011	RCT	Very serious[c, d]	No serious	Not applicable	Serious[g]	No serious	36	39	T = 42.57; C = 49.22 MD = -6.65 (-19.84 to 6.54)	VERY LOW
Outcome: IBS symptoms: IBS-SS Bloating severity[b] (3-mth FU)										
Gaylord 2011	RCT	Very serious[c, d]	No serious	Not applicable	Serious[g]	No serious	36	39	T = 37.46; C = 47.55 MD = -10.09 (-23.55 to 3.37)	VERY LOW
Outcome: IBS symptoms: IBS-SS Dissatisfaction with bowel habit[b] (10-wks)										
Gaylord 2011	RCT	Very serious[c, d]	No serious	Not applicable	Serious[g]	No serious	36	39	T = 49.94; C = 65.15 MD = -15.21 (-28.27 to -2.15)	VERY LOW
Outcome: IBS symptoms: IBS-SS Dissatisfaction with bowel habit[b] (3-mth FU)										
Gaylord 2011	RCT	Very serious[c, d]	No serious	Not applicable	Serious[g]	No serious	36	39	T = 45.69; C = 62.56 MD = -16.87 (-29.60 to -4.14)	VERY LOW

(a) *IBS-QoL (total score: 0 to 100, with 0 = minimum QoL). Drossman (2007) suggested minimum clinical important difference as ≥14 points improvement from baseline.*
(b) *IBS-SS (severity scale for individual symptoms: maximum score = 100, with ≥30% MID = 30 points change from baseline)*
(c) *No information on baseline use of other IBS treatments (e.g. pharmacological treatments, dietary interventions, etc.).*
(d) *Women only study. Reason for withdrawal not reported.*
(e) *Mean difference between groups showed no significant effect, both groups end scores did not reach the MID of ≥14 points improvement from baseline [Mean change from baseline: T = +10.19; C = +3.7]*
(f) *Mean difference between groups showed no significant effect, both groups end scores did not reach the MID of ≥14 points improvement from baseline [Mean change from baseline: T = +11.93; C = +3.83]*
(g) *Mean change from baseline did not reach the MID of ≥30 points change.*

Mindfulness-based stress reduction vs Treatment as usual

Table 118: GRADE profile 4a, Mindfulness-based stress reduction (MBSR) vs Treatment as usual (TAU)

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	MBSR	TAU	Relative (96% CI)	Absolute	
Outcome: IBS symptoms: IBS-SS Responder[a] (at least 50 points reduction from baseline) (8-wks)											
Zernicke 2012	RCT	Very serious[b, c]	No serious	Not applicable	Very serious[e]	No serious	10/43 (23.3%)	10/47 (21.3%)	RR 1.09 (0.50 to 2.37)	2 more per 100 (from 11 fewer to 29 more)	VERY LOW

(a) *Zernicke (2012)*
(b) *IBS-SS (severity scale: maximum score = 500)*
(c) *Medication for IBS was allowed but no information was provided regarding usage between groups.*
(d) *No information on what consisted of the Treatment As Usual arm.*
(e) *The 95%CI crosses over both MIDs of 0.75 and 1.25.*

Table 119: GRADE profile 4b, Mindfulness-based stress reduction (MBSR) vs Treatment as usual (TAU)

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	MBSR (T)	TAU (C)	Mean difference (95% CI)	
Outcome: Quality of life: IBS-QoL (8-wks)										
Zernicke 2012	RCT	Very serious[c, d]	No serious	Not applicable	Serious[e]	No serious	43	47	T = 75.0; C = 63.1 MD = 11.90 (1.91 to 21.89)	VERY LOW
Outcome: Quality of life: IBS-QoL (6-mth FU)										
Zernicke	RCT	Very	No serious	Not	Serious[f]	No serious	43	47	T = 74.3; C = 66.5	VERY

Quality assessment							No of patients		Effect estimate	Quality
2012		serious[c, d]		applicable					MD = 7.80 (-2.77 to 18.37)	LOW
Outcome: IBS symptoms: IBS-SS (6-mth FU)										
Zernicke 2012	RCT	Very serious[c, d]	No serious	Not applicable	Serious[g]	No serious	43	47	T = 193.6; C = 213.8 MD = -20.20 (-71.57 to 31.17)	VERY LOW

(a) IBS-QoL (total score: 0 to 100, with 0 = minimum QoL). Drossman (2007) suggested minimum clinical important difference as ≥14 points improvement from baseline.
(b) IBS-SS (severity scale: maximum score = 500, with ≥30% MID = 150 points change from baseline)
(c) Medication for IBS was allowed but no information was provided regarding usage between groups.
(d) No information on what consisted of the Treatment As Usual arm.
(e) Although mean difference between groups showed significant effect, both groups end scores did not reach the MID of ≥14 points improvement from baseline [Mean change from baseline: T = +9.7; C = +1.5]
(f) Mean difference between groups showed no significant effect, both groups end scores did not reach the MID of ≥14 points improvement from baseline [Mean change from baseline: T = +9.0; C = +4.9]
(g) Mean change from baseline did not reach the MID of ≥150 points change (mean change from baseline: T = -55; C = -35.2)

CCBT-Exposure vs Waitlist control

Table 120: GRADE profile 5, CCBT-Exposure (CCBT-E) vs Waitlist control (WC)

Table 121: <Insert Table Title here> Quality assessment							No of patients		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**CCBT-E (T)**	**WC (C)**	**Mean difference (95% CI)**	
Outcome: Quality of life: IBS-QoL[a] (6-wks)										
Hunt 2009	RCT	Very serious[c, d]	No serious	Not applicable	No serious[e]	No serious	13	18	T = 84.0; C = 111.0 MD = -27.00 (-45.25 to -8.75)	LOW
Outcome: IBS symptoms: GSRS-IBS[b] (6-wks)										
Hunt 2009	RCT	Very serious[c, d]	No serious	Not applicable	Serious[f]	No serious	13	18	T = 35.0; C = 52.0 MD = -17.00 (-26.19 to -7.81)	VERY LOW

(a) IBS-QoL (only raw score reported, total score: 0 to 170, with 0 = minimum QoL). Drossman (2007) suggested minimum clinical important difference as ≥14 points improvement from baseline based on the 0 to 100 scale. For the raw score of 170, the calculated MID would be ≥23.8 points improvement from baseline.

(b) GSRS-IBS (Gastrointestinal Symptom Rating Scale for IBS) (total score: 13 to 91, with 13 = no discomfort at all). FDA and EMA suggested MID = 30% reduction = at least 23.4 points increase from baseline.
(c) Participants were 'self-reported' as being diagnosed as having IBS by a medical professional. No information on exclusion criteria.
(d) No information on baseline use of other IBS treatments (e.g. pharmacological treatments, dietary interventions, etc.). No information on what is the 'waitlist control' group.
(e) Mean difference between groups showed significant effect, treatment group end scores reached the ≥23.8 points from baseline MID [Mean change from baseline: T = -38; C = -12], no downgrade.
(f) Although mean difference between groups showed significant effect, both groups end scores did not reach the ≥23.8 points from baseline MID [Mean change from baseline: T = -22; C = -9]

CCBT-Mindfulness vs CCBT-Mindfulness/Exposure

Table 122: GRADE profile 6a, CCBT-Mindfulness (CCBT-M) vs CCBT-Mindfulness/Exposure (CCBT-M/E)

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	CCBT-M (T)	CCBT-M/E (C)	Mean difference (95% CI)	
Outcome: Quality of life: IBS-QoL[a] (10-wks)										
Ljotsson 2014	RCT	Serious[c]	Serious[(h)]	Not applicable	No serious[d]	No serious	146	146	T = 73.6; C = 79.2 MD = -5.60 (-9.88 to -1.32)	MODERATE
Outcome: Quality of life: IBS-QoL[a] (6-mth FU)										
Ljotsson 2014	RCT	Serious[c]	Serious[(h)]	Not applicable	No serious[e]	No serious	134	133	T = 76.5; C = 81.4 MD = -4.90 (-9.46 to -0.34)	MODERATE
Outcome: IBS symptoms: GSRS-IBS[b] (10-wks)										
Ljotsson 2014	RCT	Serious[c]	Serious[(h)]	Not applicable	Serious[f]	No serious	146	146	T = 38.2; C = 31.8 MD = 6.40 (3.41 to 9.39)	LOW
Outcome: IBS symptoms: GSRS-IBS (6-mth FU)										
Ljotsson 2014	RCT	Serious[c]	Serious[(h)]	Not applicable	Serious[g]	No serious	135	134	T = 37.3; C = 32.2 MD = 5.10 (2.03 to 8.17)	LOW

(a) IBS-QoL (total score: 0 to 100, with 0 = minimum QoL). FDA and EMA suggested MID = 30% improvement = at least 30 points increase from baseline.
(b) GSRS-IBS (Gastrointestinal Symptom Rating Scale for IBS) (total score: 13 to 91, with 13 = no discomfort at all). FDA and EMA suggested MID = 30% reduction = at least 23.4 points increase from baseline.
(c) No information on baseline use of other IBS treatments (e.g. pharmacological treatments, dietary interventions, etc.).
(d) Mean difference between groups showed significant effect, both groups end scores reached the MID of ≥14 points improvement from baseline [Mean change from baseline: T = +16.1; C = +19.6], no downgrade.
(e) Mean difference between groups showed significant effect, both groups end scores reached the MID of ≥14 points improvement from baseline [Mean change from baseline: T = +19.0; C = +21.8], no downgrade.
(f) Although mean difference between groups showed significant effect, both groups end scores did not reach the ≥30% MID [Mean change from baseline: T = -9.3; C = -14.3]

(g) Although mean difference between groups showed significant effect, both groups end scores did not reach the ≥30% MID [Mean change from baseline: T = -10.2; C = -13.9]
(h) The study was undertaken in Sweden. There is uncertainty that the intervention would be applicable to the UK population due to the differences in delivery of CCBT in the UK compared to Sweden

Table 123: GRADE profile 6b, CCBT-Mindfulness (CCBT-M) vs CCBT-Mindfulness/Exposure (CCBT-M/E)

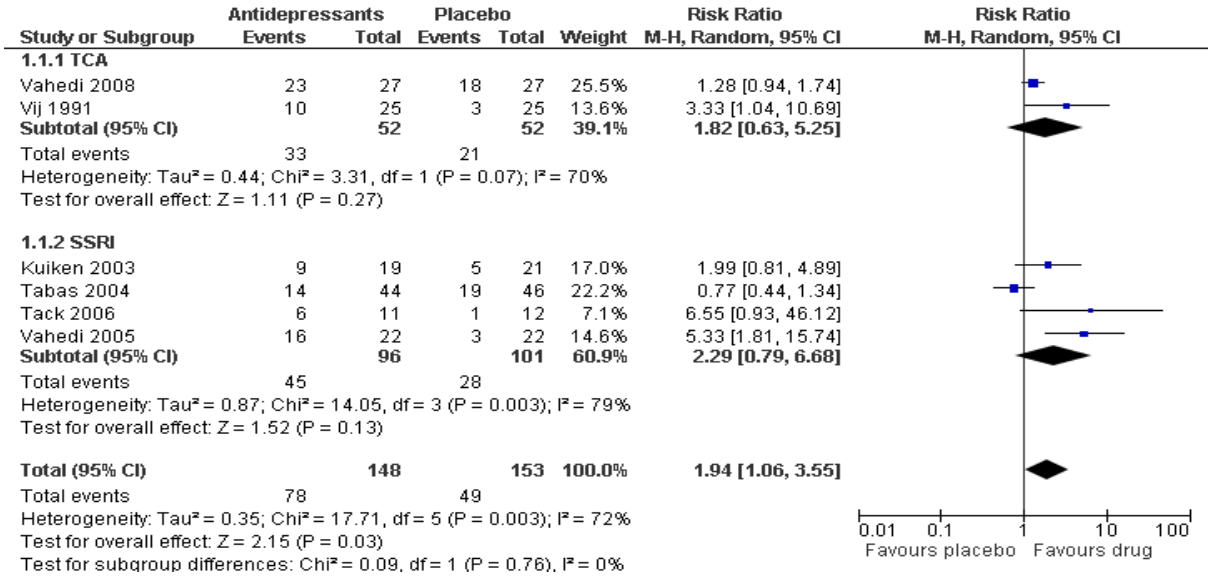
Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	CCBT-M	CCBT-M/E	Relative (96% CI)	Absolute	
Outcome: Adverse events (cluster)[a] (10-wks)											
Ljotsson 2014	RCT	Serious[b]	Serious[(e)]	Not applicable	Serious[c]	No serious	19/145 (13.1%)	29/142 (20.4%)	RR 0.64 (0.38 to 1.09)	7 fewer per 100 (from 13 fewer to 2 more)	LOW
Outcome: Adverse events (cluster)[a] (6-mth FU)											
Ljotsson 2014	RCT	Serious[b]	Serious[(e)]	Not applicable	Serious[d]	No serious	9/127 (7.1%)	3/131 (2.3%)	RR 3.09 (0.86 to 11.17)	5 more per 100 (from 0 fewer to 23 more)	LOW

(a) Adverse events (No. of participants reported) [Cluster of residual discomfort, worsening of symptoms, stress because of the study, depressed or anxious mood]
(b) No information on baseline use of other IBS treatments (e.g. pharmacological treatments, dietary interventions, etc.).
(c) The 95%CI crosses over the MID of .0.75
(d) The 95%CI crosses over the MID of 1.25.
(e) The study was undertaken in Sweden. There is uncertainty that the intervention would be applicable to the UK population due to the differences in delivery of CCBT in the UK compared to Sweden

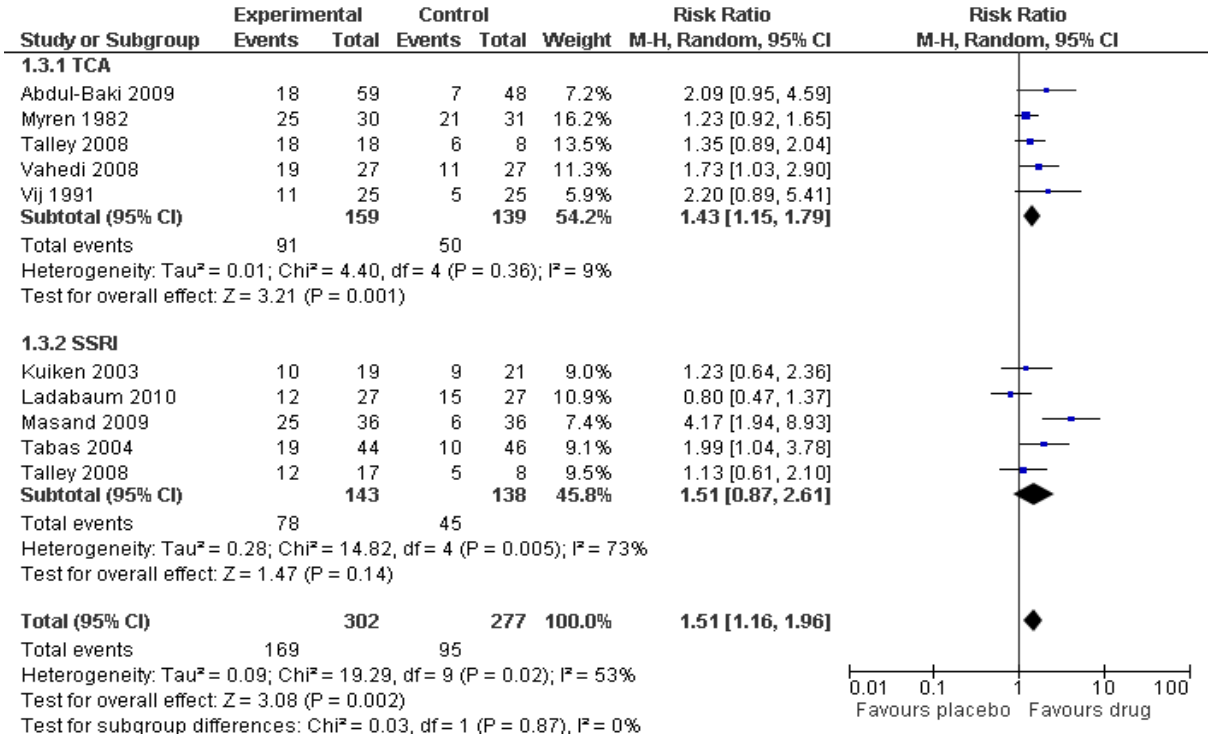
Appendix I: Forest plots

I.1 Review question 1 (antidepressants)

I.1.1 Abdominal pain, number of successfully treated patients



I.1.2 Global assessment, number of successfully treated patients



I.2 Review question 2 (low FODMAP diet)

No forest plot was produced, please see full GRADE profiles in appendix H.

I.3 Review question 3 (linaclotide)

No forest plot was produced; please see full GRADE profiles in appendix H.

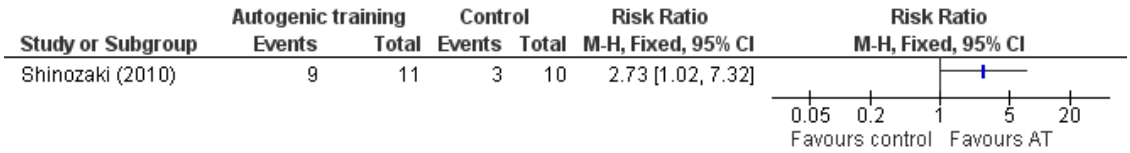
I.4 Review question 4 (lubiprostone)

No forest plot was produced; please see full GRADE profiles in appendix H.

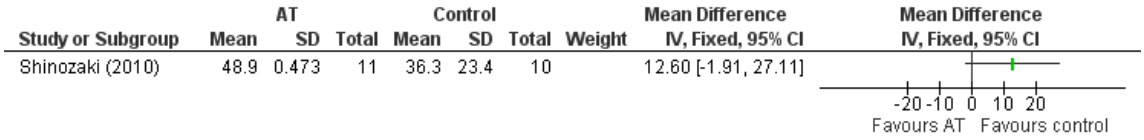
I.5 Review question 5a (relaxation therapy)

I.5.1 Relaxation vs routine care/control

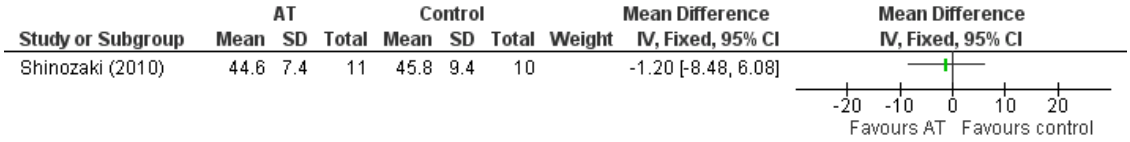
Adequate relief



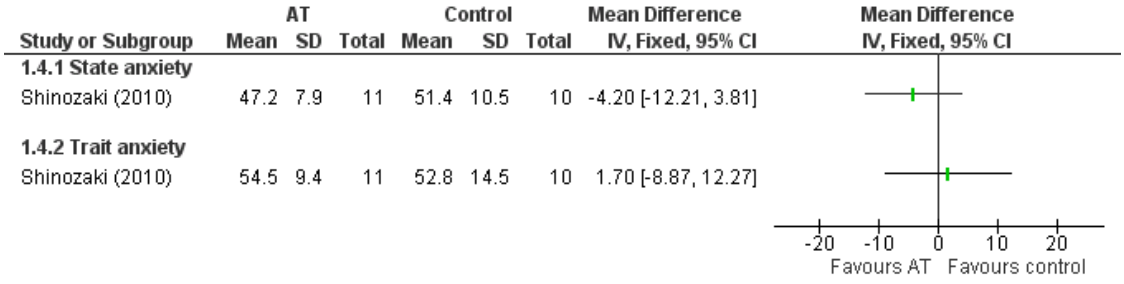
SIBSQ (scored out of 98)



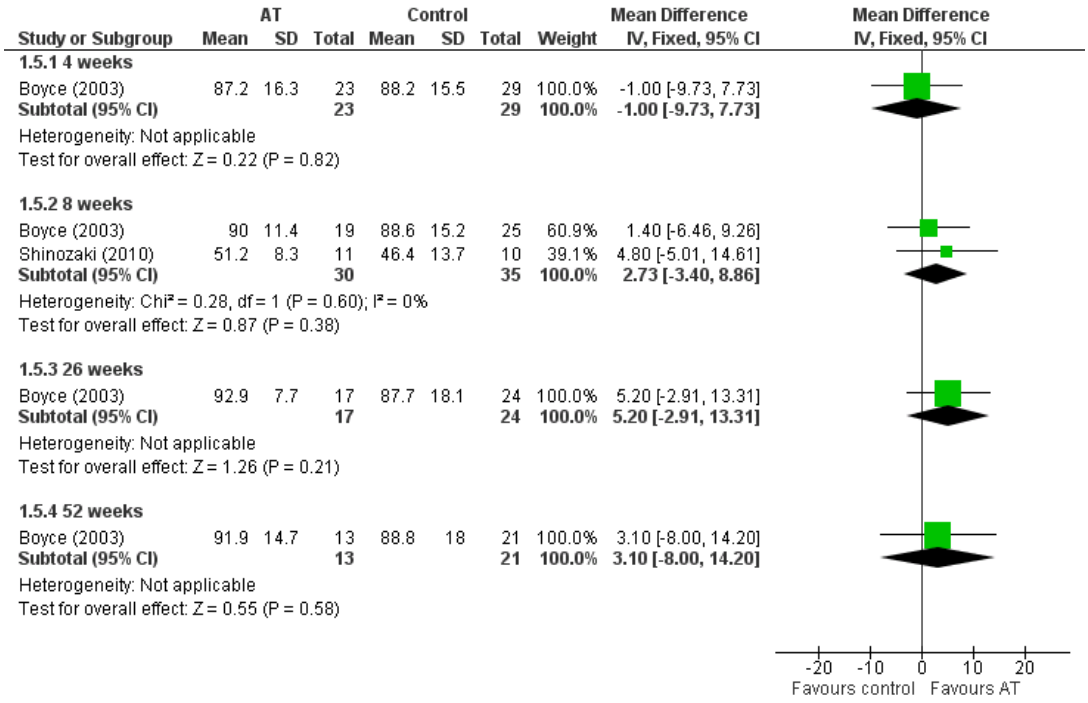
SDS (scored out of 80)



STAI – (each section scroed between 20-80 [60 total])

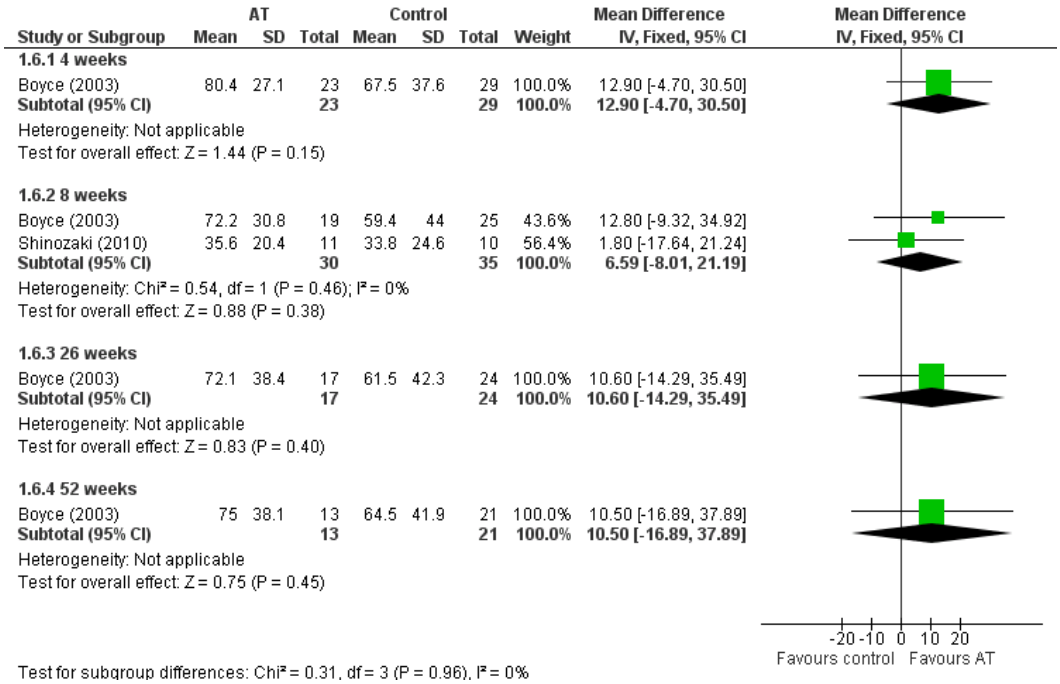


1 SF36 Physical function



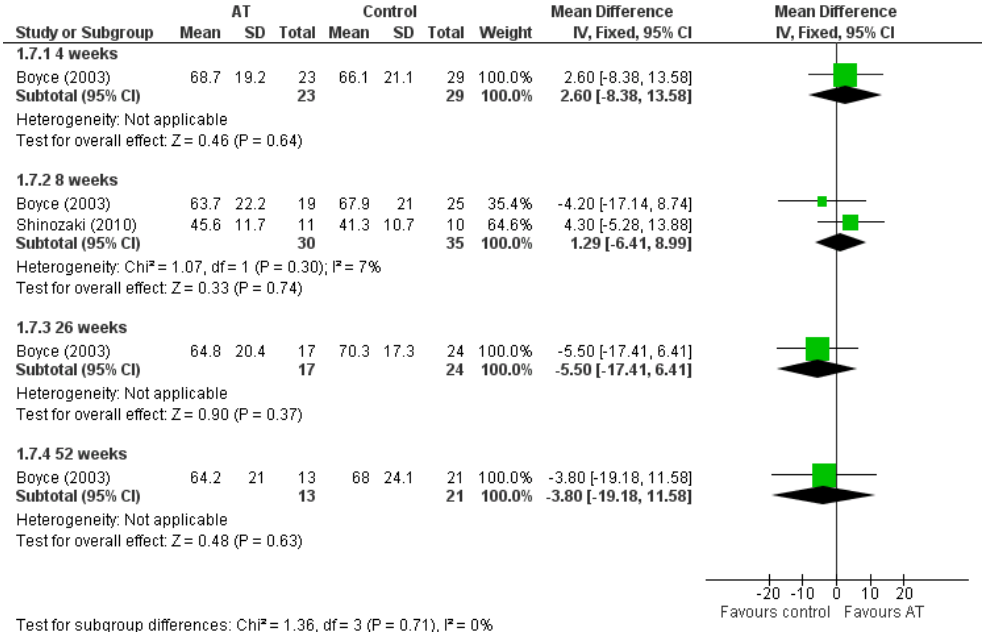
2

3 SF36 Role physical



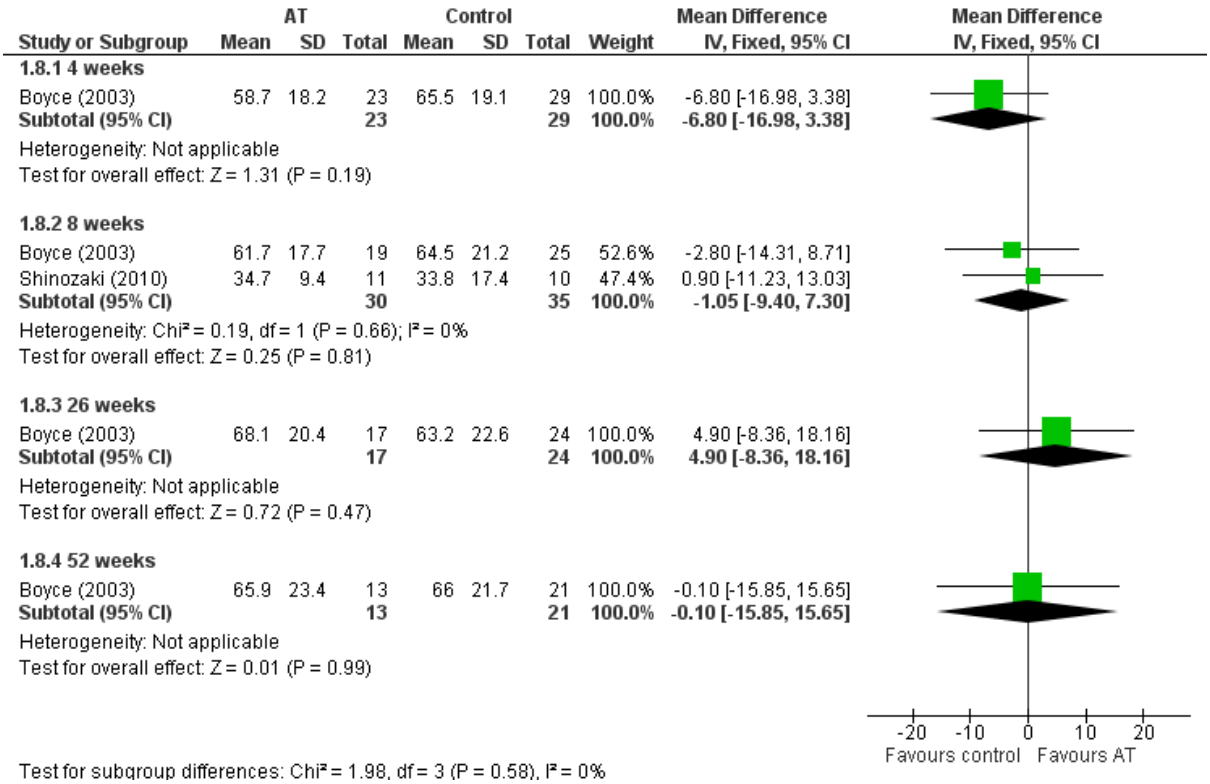
4 Test for subgroup differences: Chi² = 0.31, df = 3 (P = 0.96), I² = 0%

1 SF36 Bodily pain



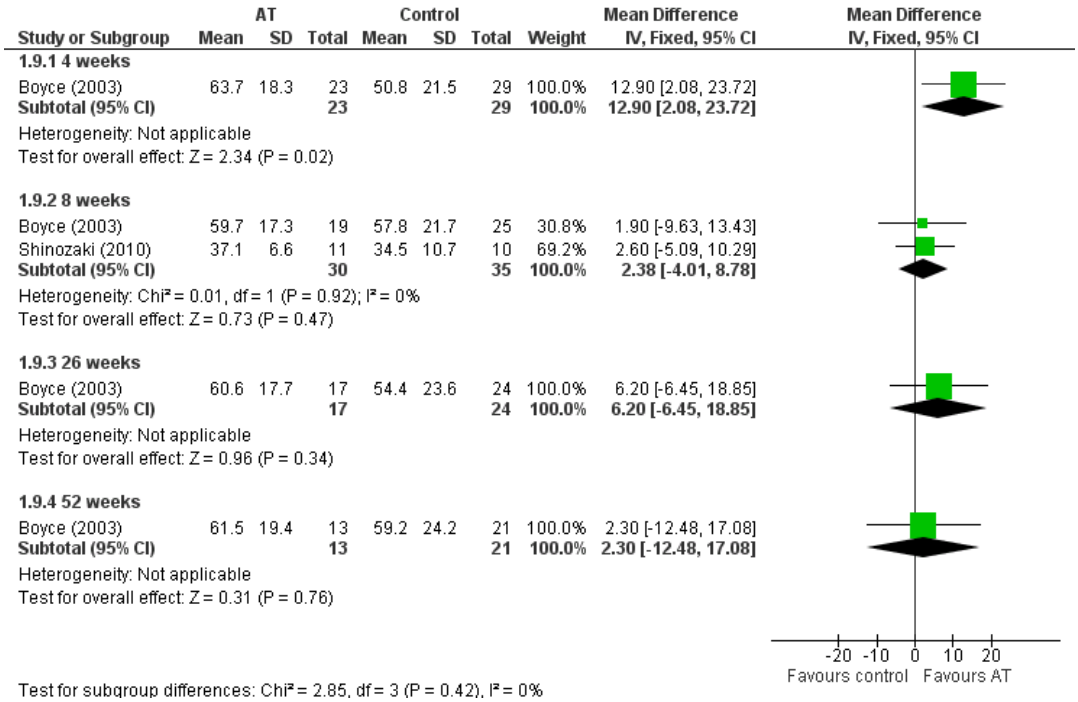
2 Test for subgroup differences: Chi² = 1.36, df = 3 (P = 0.71), I² = 0%

3 SF36 General health



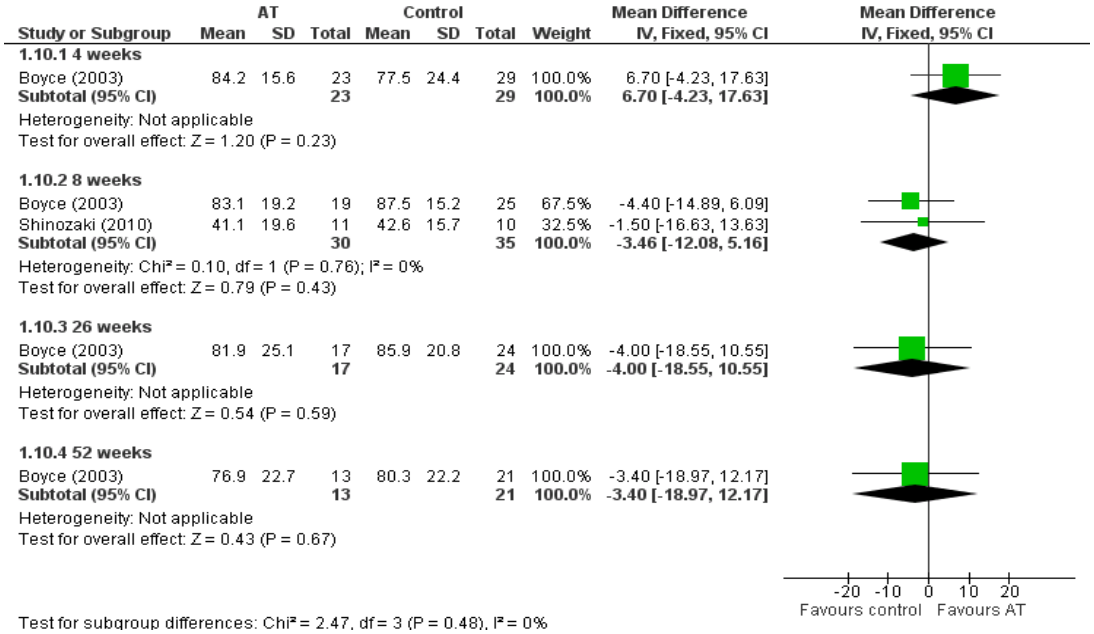
4 Test for subgroup differences: Chi² = 1.98, df = 3 (P = 0.58), I² = 0%

1 SF36 Vitality



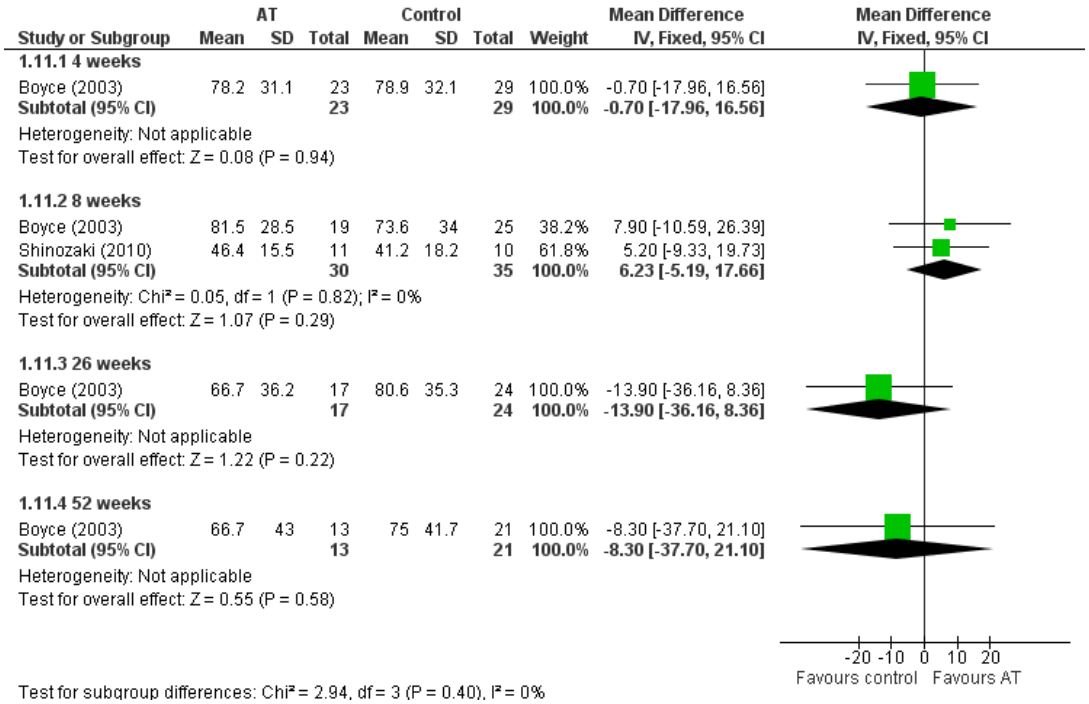
2 Test for subgroup differences: Chi² = 2.85, df = 3 (P = 0.42), I² = 0%

3 SF36 Social functioning



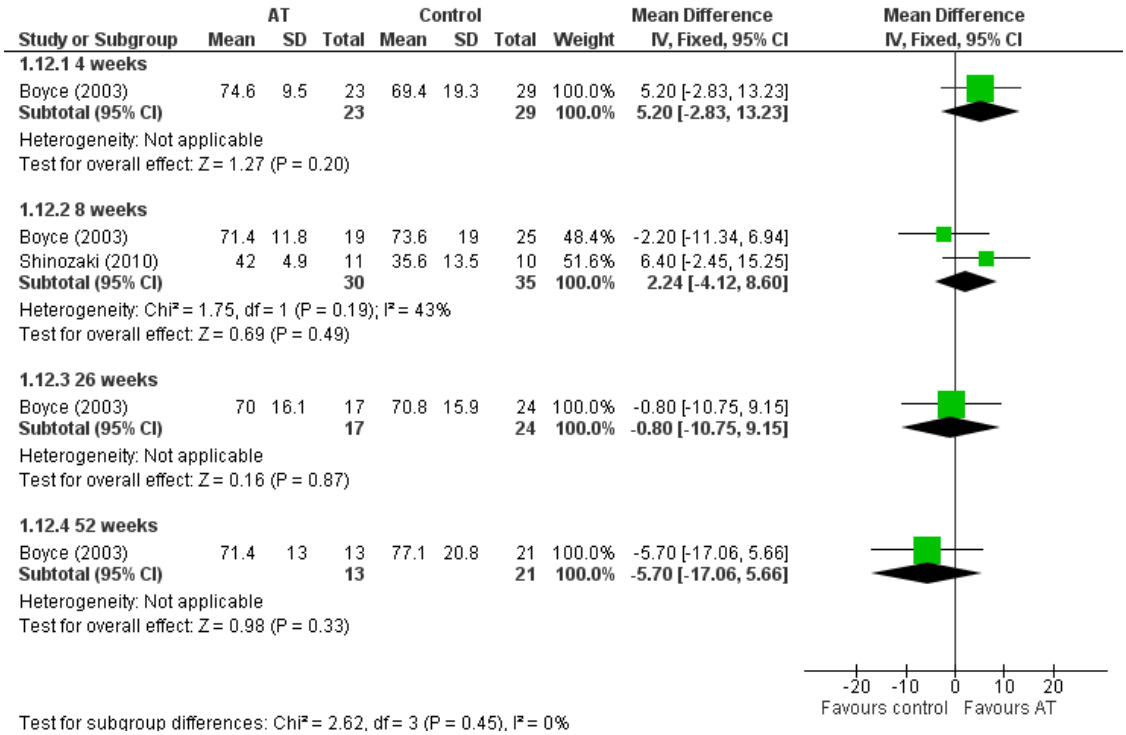
4 Test for subgroup differences: Chi² = 2.47, df = 3 (P = 0.48), I² = 0%

1 SF36 Role emotional



2 Test for subgroup differences: Chi² = 2.94, df = 3 (P = 0.40), I² = 0%

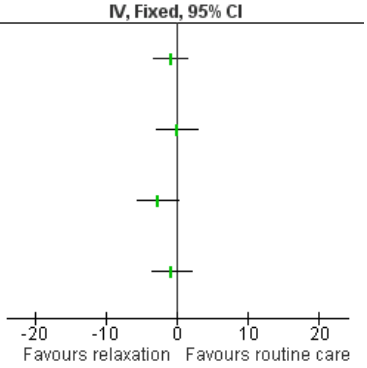
3 Mental health



4 Test for subgroup differences: Chi² = 2.62, df = 3 (P = 0.45), I² = 0%

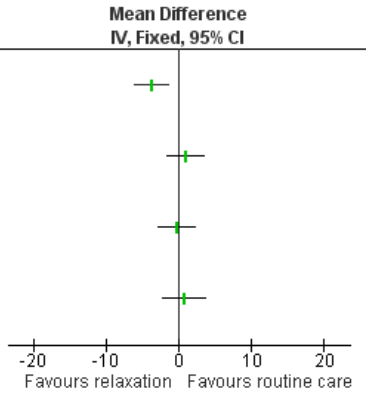
1 BSSS Frequency

Study or Subgroup	Relaxation Mean	SD	Total	Routine clinical care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.13.1 4 weeks							
Boyce (2003)	18.1	4.2	23	19	4.4	29	-0.90 [-3.25, 1.45]
1.13.2 8 weeks							
Boyce (2003)	18	5	19	18	5	25	0.00 [-2.98, 2.98]
1.13.3 26 weeks							
Boyce (2003)	16.1	4.3	17	18.8	4.8	24	-2.70 [-5.50, 0.10]
1.13.4 52 weeks							
Boyce (2003)	16.2	3.7	13	17	4.6	21	-0.80 [-3.61, 2.01]



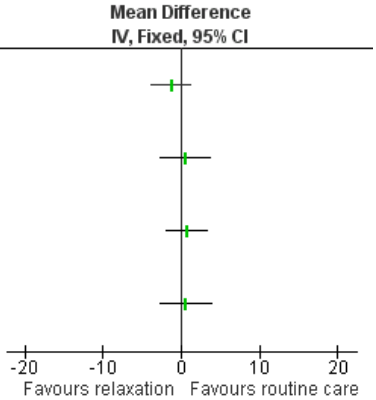
3 BSSS Distress

Study or Subgroup	Relaxation Mean	SD	Total	Routine clinical care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.14.1 4 weeks							
Boyce (2003)	14.2	4	23	17.9	4.7	29	-3.70 [-6.07, -1.33]
1.14.2 8 weeks							
Boyce (2003)	14.4	4.2	19	13.4	4.4	25	1.00 [-1.56, 3.56]
1.14.3 26 weeks							
Boyce (2003)	13.1	3.8	17	13.4	4.4	24	-0.30 [-2.82, 2.22]
1.14.4 52 weeks							
Boyce (2003)	13.2	4.8	13	12.5	3.4	21	0.70 [-2.29, 3.69]



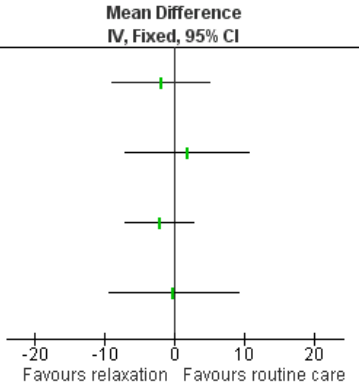
5 BSSS Interference

Study or Subgroup	Relaxation Mean	SD	Total	Routine clinical care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.15.1 4 weeks							
Boyce (2003)	12.5	3.9	23	13.8	5.2	29	-1.30 [-3.77, 1.17]
1.15.2 8 weeks							
Boyce (2003)	13.1	5.7	19	12.6	4.9	25	0.50 [-2.70, 3.70]
1.15.3 26 weeks							
Boyce (2003)	12.5	4.3	17	11.8	4.3	24	0.70 [-1.97, 3.37]
1.15.4 52 weeks							
Boyce (2003)	12	5	13	11.4	4	21	0.60 [-2.61, 3.81]



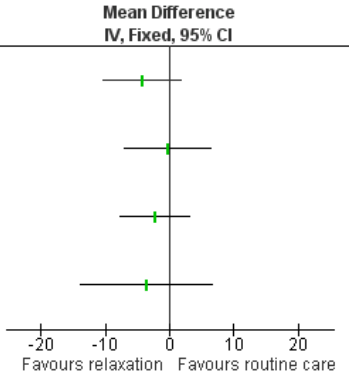
1 Automatic thoughts on questionnaire

Study or Subgroup	Relaxation Mean	SD	Total	Routine clinical care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.16.1 4 weeks							
Boyce (2003)	41.39	10.13	23	43.38	15.46	29	-1.99 [-8.98, 5.00]
1.16.2 8 weeks							
Boyce (2003)	42.83	16.35	19	40.97	12.7	25	1.86 [-7.02, 10.74]
1.16.3 26 weeks							
Boyce (2003)	37.82	6.27	17	39.96	9.65	24	-2.14 [-7.02, 2.74]
1.16.4 52 weeks							
Boyce (2003)	40.31	7.47	13	40.48	19.56	21	-0.17 [-9.47, 9.13]



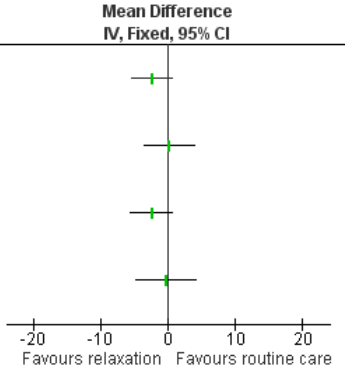
3 Locus of control of behaviours

Study or Subgroup	Relaxation Mean	SD	Total	Routine clinical care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.17.1 4 weeks							
Boyce (2003)	23.28	10.74	23	27.55	11.7	29	-4.27 [-10.39, 1.85]
1.17.2 8 weeks							
Boyce (2003)	26.49	10.98	19	26.82	11.25	25	-0.33 [-6.95, 6.29]
1.17.3 26 weeks							
Boyce (2003)	27.76	7.28	17	30.04	10.46	24	-2.28 [-7.71, 3.15]
1.17.4 52 weeks							
Boyce (2003)	24.23	8.93	13	27.9	21.01	21	-3.67 [-13.88, 6.54]



5 HADS total

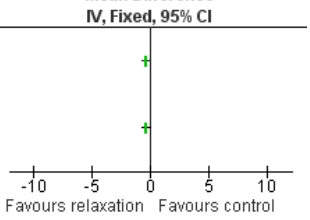
Study or Subgroup	Relaxation Mean	SD	Total	Routine clinical care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.18.1 4 weeks							
Boyce (2003)	10.2	5.2	23	12.6	6	29	-2.40 [-5.45, 0.65]
1.18.2 8 weeks							
Boyce (2003)	11.2	5.9	19	11	6.5	25	0.20 [-3.48, 3.88]
1.18.3 26 weeks							
Boyce (2003)	9.6	4.6	17	12	5.5	24	-2.40 [-5.50, 0.70]
1.18.4 52 weeks							
Boyce (2003)	10.7	5.4	13	11	7.6	21	-0.30 [-4.68, 4.08]



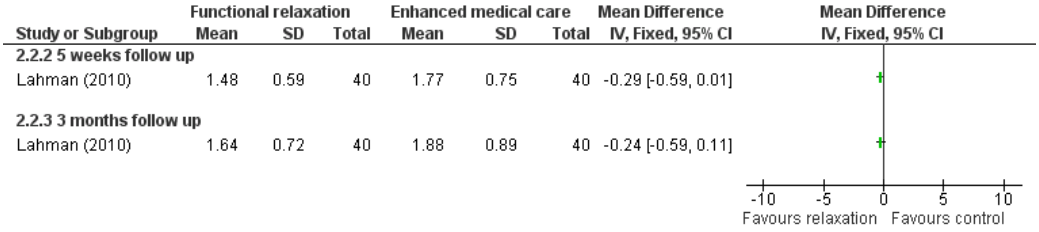
I.5.2 Relaxation vs enhanded medical care

8 Impairment severity score – bodily impairment

Study or Subgroup	Functional relaxation Mean	SD	Total	Enhanced medical care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
2.1.2 5 weeks follow up							
Lahman (2010)	1.59	0.73	40	2.03	0.7	40	-0.44 [-0.75, -0.13]
2.1.3 3 months follow up							
Lahman (2010)	1.69	0.95	40	2.08	0.79	40	-0.39 [-0.77, -0.01]

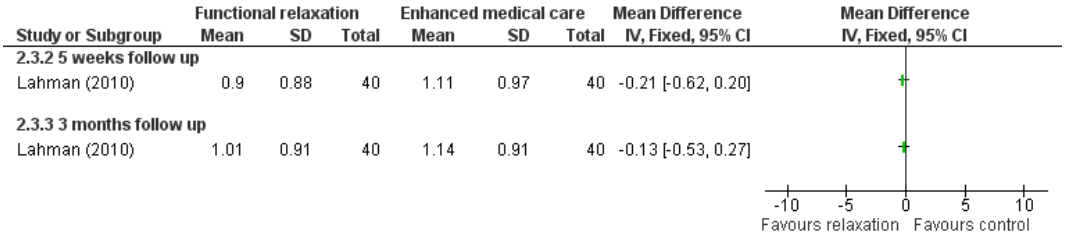


1 Impairment severity score – psychic impairment



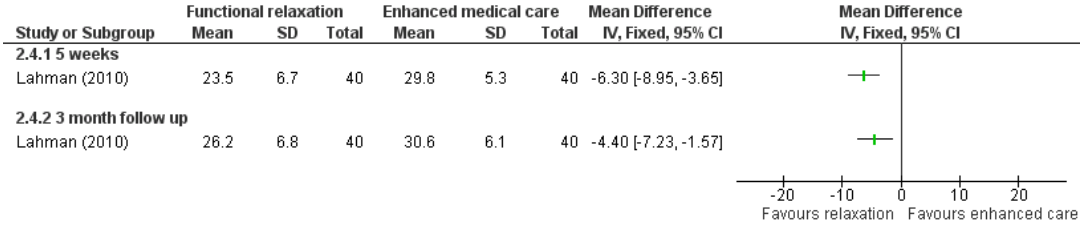
2

3 Impairment severity score – social impairment



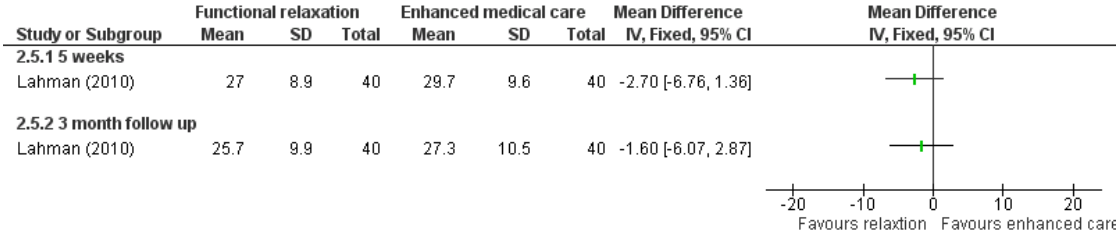
4

5 Overall IBS symptoms



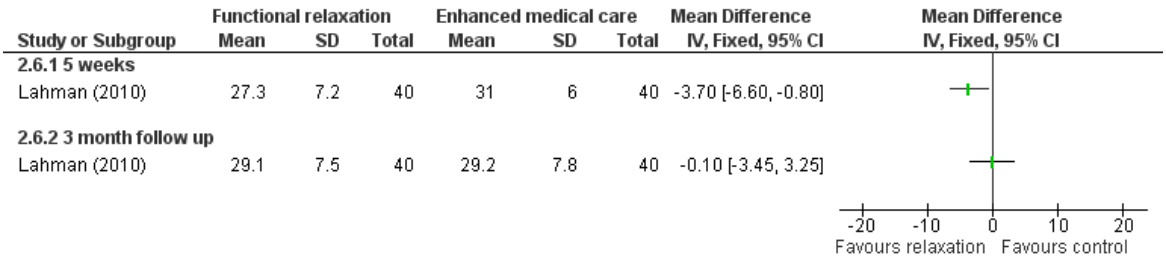
6

7 Abdominal pain



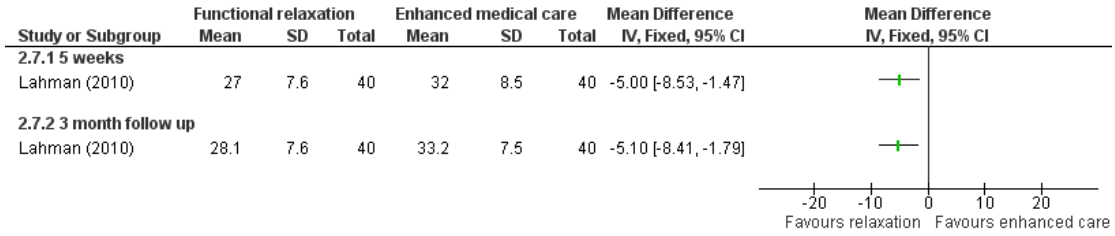
8

9 Deterioration – diarrhoea & constipation



10

1 **Bloating**



2

I.5.3 3 Relaxation vs hypnotherapy

4 Data reported as median (range)

5 **Overall symptom score**

	Audiotape			Hypnotherapy		
	Baseline	Follow up	Difference	Baseline	Follow up	Difference
ITT (n=52)	14*	13	-1	14*	11	-3
ients completing diaries (n= 45)	13	13	0	14	8.5	-5.5
Available case (n=25)	11	11	0	14.5	7.5	-7

6 **GHQ**

GHQ domain	Audiotape (n=13)			Hypnotherapy (n=12)		
	Baseline	Follow up	Difference	Baseline	Follow up	Difference
Somatisation	7 (4-11)	5.5 (1-10)	-1.5	9.5 (2-18)	4.5 (2-13)	-5
Anxiety/ insomnia	4.5 (0-10)	6 (0-13)	+1.5	7 (2-16)	6 (1-18)	-1
Social dysfunction	7 (6-10)	7(6-12)	0	10.5 (5-16)	6.5 (1-17)	-4
Depression	0 (0-9)	1 (0-7)	+1	2.5 (0-16)	2.5 (0-18)	0
Sum	19.5 (12-29)	22 (11-35)	+2.5	26.5 (11-63)	22.5 (5-64)	-4

Psychiatric "case-ness" (scored on Likert 1-4)	N=9	NS	-	N=10	NS	-

1 **HADS**

HADS domain	**Audiotape (n=13)**			**Hypnotherapy (n=12)**		
	Baseline	Follow up	Difference	Baseline	Follow up	Difference
Anxiety	5 (0-13)	8 (0-15)	+3	11.5 (3-21)	10.5 (2-15)	-1
Depression	4 (0-7)	4 (0-15)	0	5.5 (0-13)	4 (0-13)	-1.5
Possible psychiatric disorder	N=3	-	-	N=4	-	-
Probable psychiatric disorder	N=5	-	-	N=8	-	-

2 **SF36**

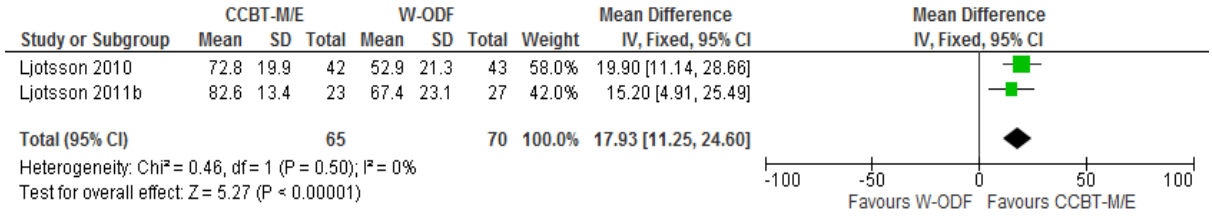
SF36 domain	**Audiotape (n=13)**			**Hypnotherapy (n=12)**		
	Baseline	Follow up	Difference	Baseline	Follow up	Difference
Physical function	95 (60-100)	87 (70-100)	-8	67 (35-100)	75 (35-100)	+8
Physical role	75 (0-100)	25 (0-100)	-50	25 (0-100)	50 (0-100)	+25
Emotional role	100 (0-100)	100 (0-100)	0	67 (0-100)	67 (0-100)	0
Social function	75 (50-100)	75 (37-100)	0	50 (12-87)	44 (12-100)	-6
Pain	51 (0-84)	56 (12-84)	+5	41 (0-84)	46 (0-100)	+5
Mental state	72 (44-84)	62 (40-88)	-10	52 (32-84)	52 (36-84)	0
Vitality	50 (20-100)	50 (15-95)	0	27 (10-85)	30 (5-75)	+3
Perception of health	65 (10-95)	52 (20-100)	-13	37 (5-92)	53 (5-87)	+16

SF36 domain	Audiotape (n=13)			Hypnotherapy (n=12)		
	Baseline	Follow up	Difference	Baseline	Follow up	Difference
Health change	50 (0-75)	50 (25-100)	0	50 (0-100)	67 (0-100)	+17

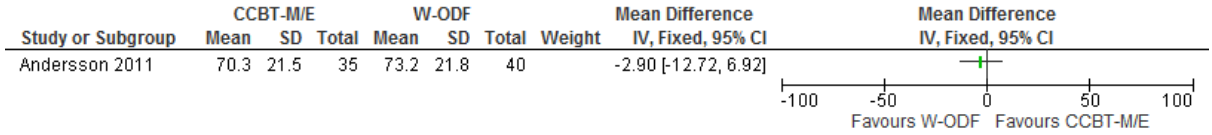
I.6 Review question 5b (CCBT and Mindfulness therapy)

I.6.1 CCBT-Mindfulness/exposure vs Waitlist (online discussion forum)

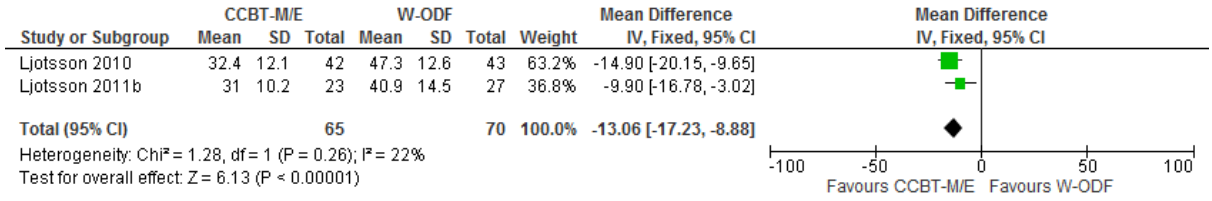
IBS-QoL (10-weeks)



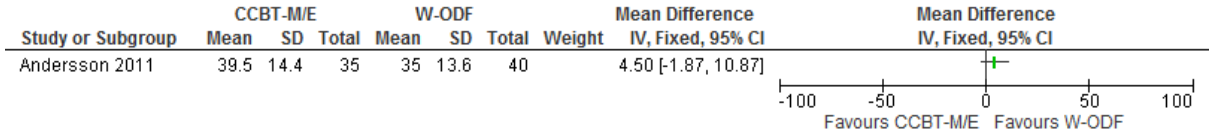
IBS-QoL (12-mth FU)



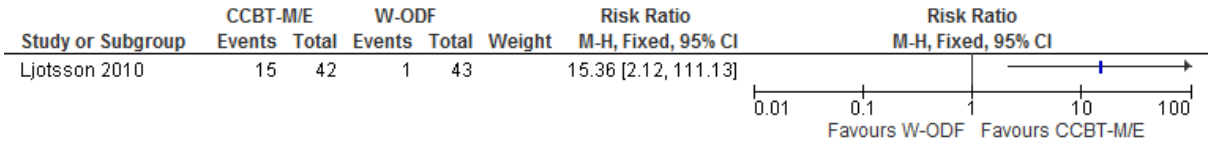
GSRS-IBS (10-wks)



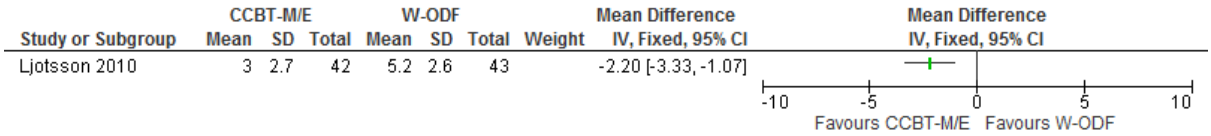
GSRS-IBS (12-mth FU)



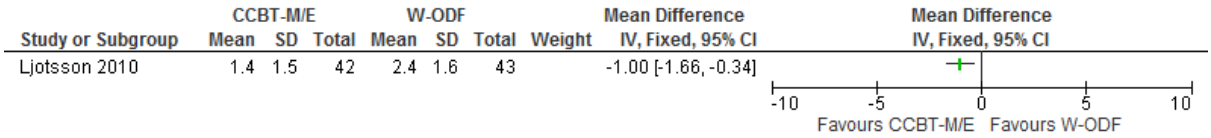
GSRS-IBS Responder (10-wks)



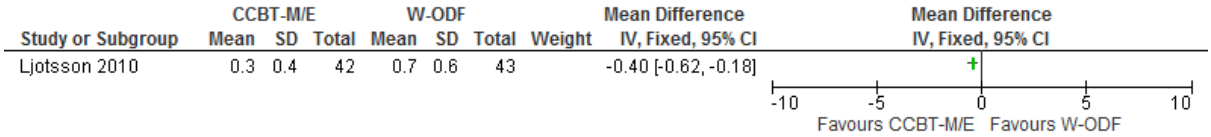
Primary outcomes: Abdominal pain, tenderness, constipation (10-wks)



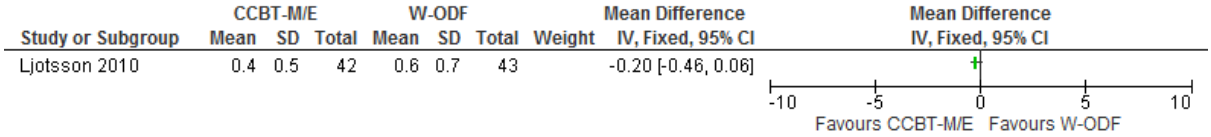
Total pain: the GI symptom diary (mean dairy rating) (10-wks)



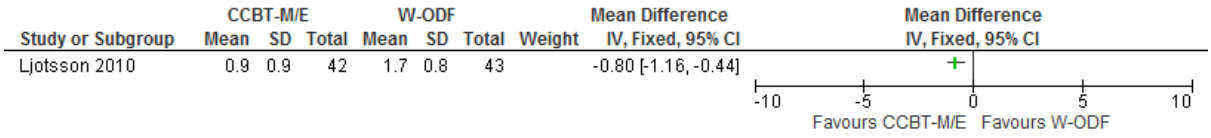
Constipation: the GI symptom diary (mean dairy rating) (10-wks)



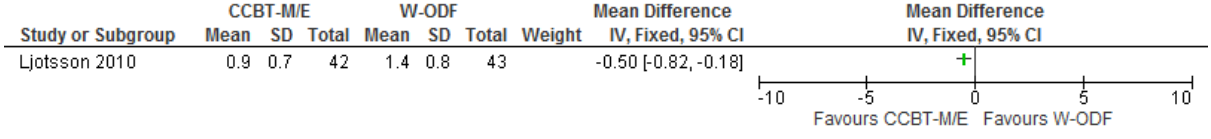
Diarrhoea: the GI symptom diary (mean dairy rating) (10-wks)



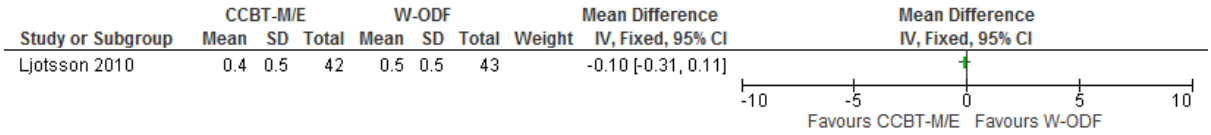
Bloating: the GI symptom diary (mean dairy rating) (10-wks)



Flatulence: the GI symptom diary (mean dairy rating) (10-wks)

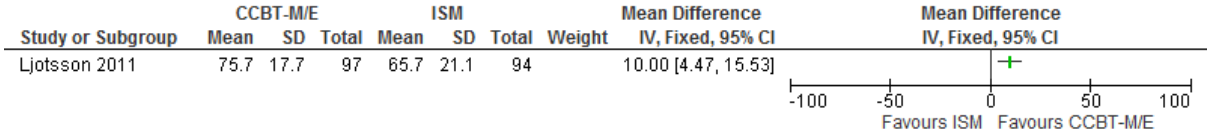


Belching: the GI symptom diary (mean dairy rating) (10-wks)

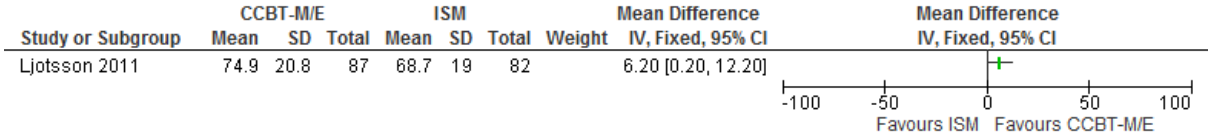


I.6.23 CCBT-Mindfulness/exposure vs Internet delivered stress management

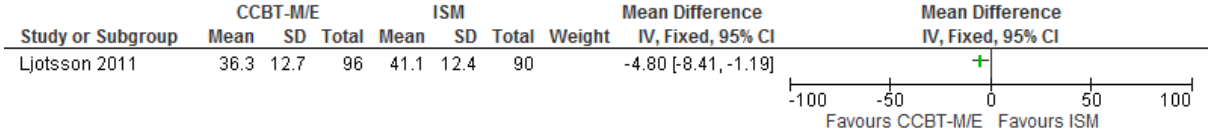
IBS-QoL (10-wks)



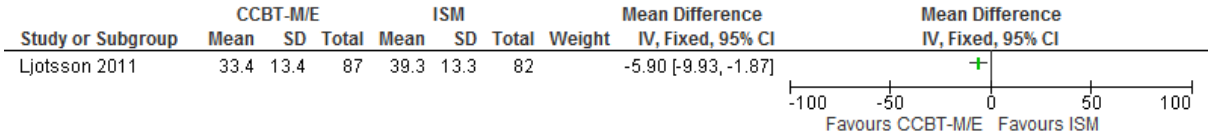
IBS-QoL (6-mth FU)



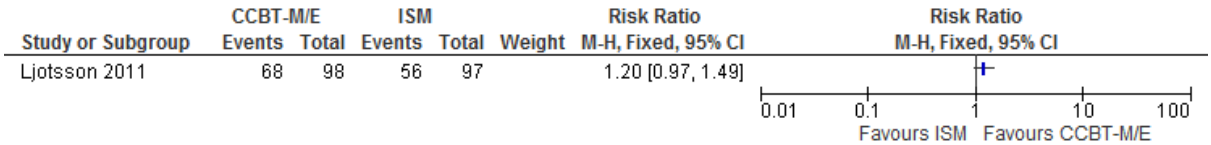
GSRS-IBS (10-wks)



GSRS-IBS (6-mth FU)



Adequate relief (responder) (10-wks)

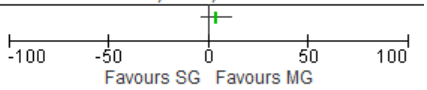


Adequate relief (responder) (6-mth FU)

I.6.31 Mindfulness group training vs Support group

2 IBS-QoL (10-wks)

Study or Subgroup	MG Mean	MG SD	MG Total	SG Mean	SG SD	SG Total	Weight	Mean Difference IV, Fixed, 95% CI
Gaylord 2011	74.99	15.14	36	70.92	17.4	39		4.07 [-3.30, 11.44]



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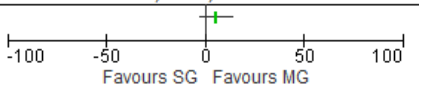
4 IBS-QoL (3-mth FU)

Study or Subgroup	MG Mean	MG SD	MG Total	SG Mean	SG SD	SG Total	Weight	Mean Difference IV, Fixed, 95% CI
Gaylord 2011	76.73	17.42	36	71.05	18.25	39		5.68 [-2.39, 13.75]



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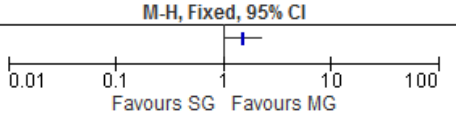
6 IBS-SS Responder (10-wks)

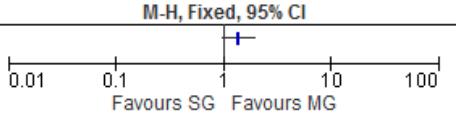
Study or Subgroup	MG Events	MG Total	SG Events	SG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gaylord 2011	25	36	18	39		1.50 [1.01, 2.25]



7

8 IBS-SS Responder (3-mth FU)

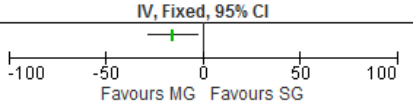
Study or Subgroup	MG Events	MG Total	SG Events	SG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gaylord 2011	27	36	21	39		1.39 [0.99, 1.97]



9

10 IBS-SS Abdominal pain severity (10-wks)

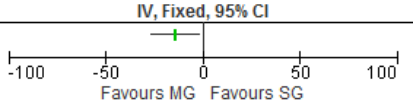
Study or Subgroup	MG Mean	MG SD	MG Total	SG Mean	SG SD	SG Total	Weight	Mean Difference IV, Fixed, 95% CI
Gaylord 2011	35	28.24	36	50.49	28.85	39		-15.49 [-28.42, -2.56]



11

12 IBS-SS Abdominal pain severity (3-mth FU)

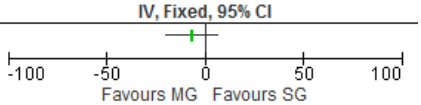
Study or Subgroup	MG Mean	MG SD	MG Total	SG Mean	SG SD	SG Total	Weight	Mean Difference IV, Fixed, 95% CI
Gaylord 2011	31.11	25.69	36	45.49	28.33	39		-14.38 [-26.61, -2.15]



13

14 IBS-SS Bloating severity (10-wks)

Study or Subgroup	MG Mean	MG SD	MG Total	SG Mean	SG SD	SG Total	Weight	Mean Difference IV, Fixed, 95% CI
Gaylord 2011	42.57	28.86	36	49.22	29.39	39		-6.65 [-19.84, 6.54]



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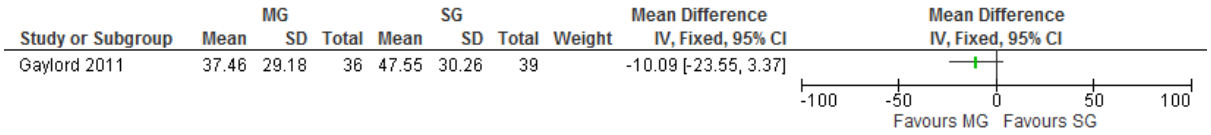
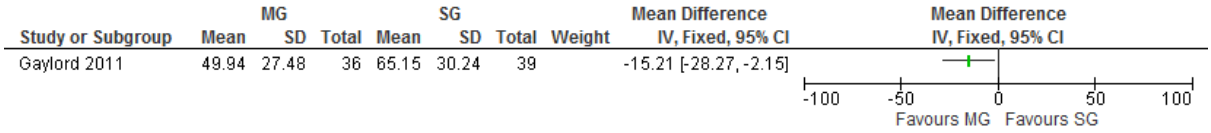
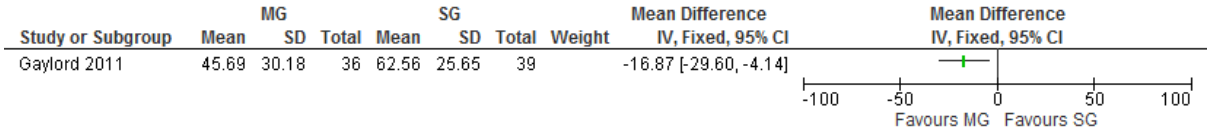
IBS-SS Bloating severity (3-mth FU)



IBS-SS Dissatisfaction with bowel habit (10-wks)

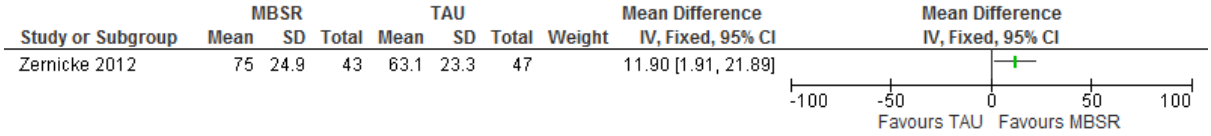


IBS-SS Dissatisfaction with bowel habit (3-mth FU)

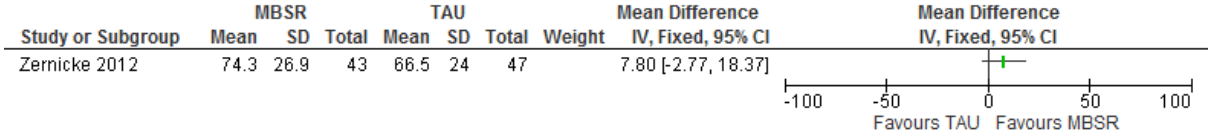


I.6.47 Mindfulness-based stress reduction vs Treatment as usual

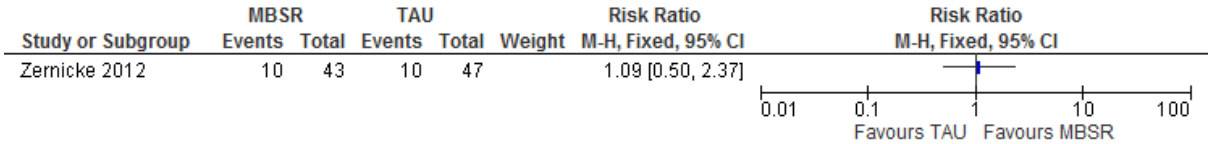
IBS-QoL (8-wks)



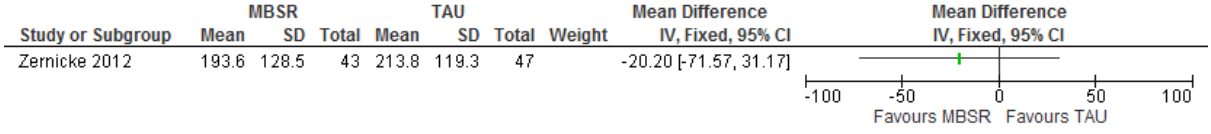
IBS-QoL (6-mth FU)



IBS-SS Responder (8-wks)

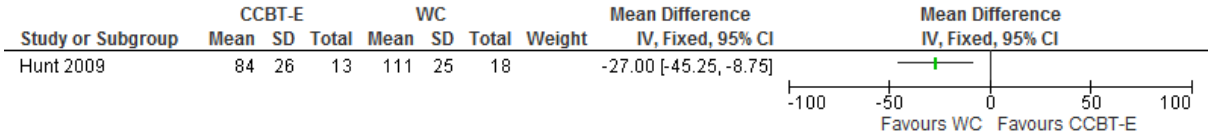


IBS-SS (6-mth FU)



I.6.51 CCBT-Exposure vs Waitlist control

2 IBS-QoL (6-wks)



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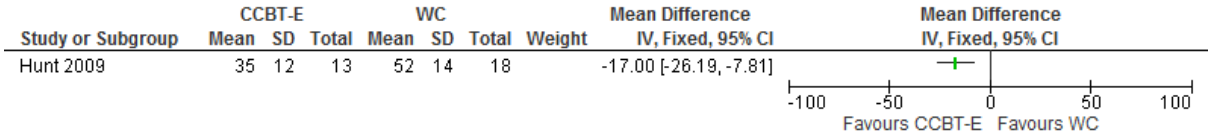
4 GSRS-IBS (6-wks)



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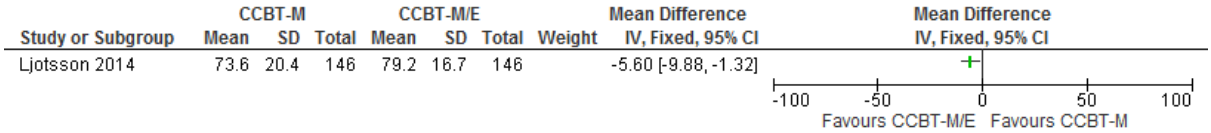
I.6.66 CCBT-Mindfulness vs CCBT-Mindfulness/Exposure

7 IBS-QoL (10-wks)



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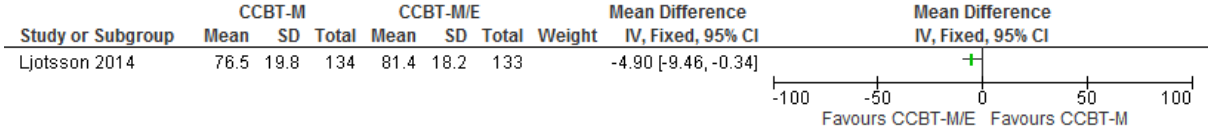
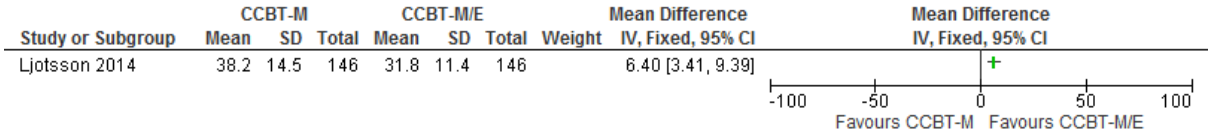
9 IBS-QoL (6-mth FU)



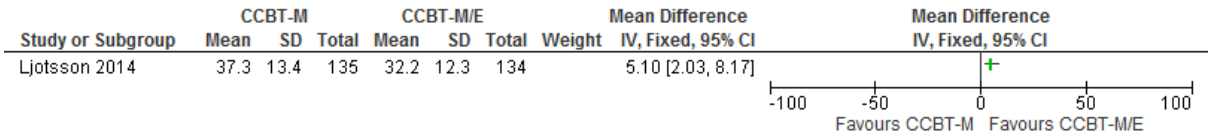
10

11 GSRS-IBS (10-wks)



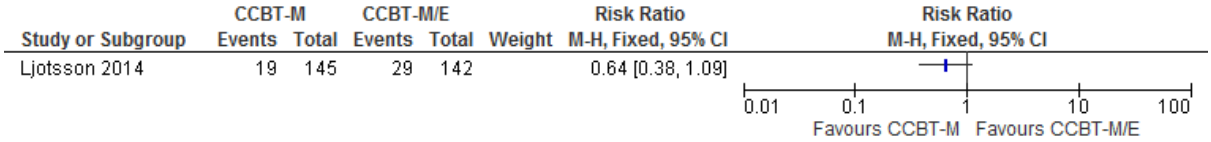
12

13 GSRS-IBS (6-mth FU)



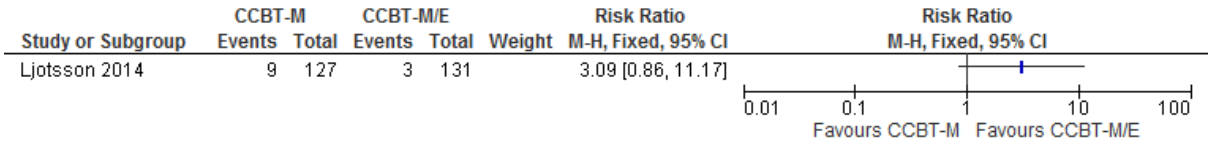
14

1 **Adverse events (cluster) (10-wks)**



2

3 **Adverse events (cluster) (6-mth FU)**



4