Research Protocol

FORTITUDE

Face-to-face versus online hypnotherapy for the treatment of Irritable Bowel Syndrome, according to a non-inferiority design.

Three-armed randomized controlled trial

FORTITUDE

PROTOCOL TITLE 'Face-to-face versus online hypnotherapy for the treatment of Irritable Bowel Syndrome, according to a non-inferiority design. Three-armed randomized controlled trial (FORTITUDE)'

Protocol ID	**NL67607.068.18**
Short title	**FORTITUDE**
Version	**2.7**
Date	**19.12.2022**
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
BFI	**Big Five Inventory**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CRF	**Case Report File**
CTCM	**Clinical Trial Center Maastricht**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EQ-5D	**Euro-Quality of Life – 5 domains**
FDA	**Food and Drug Administration**
GAD-7	**Generalized Anxiety Disorder 7**
GCP	**Good Clinical Practice**
GP	**General Practitioner**
IB	**Investigator's Brochure**
IBS	**Irritable Bowel Syndrome**
IBS-SSS	**Irritable Bowel Syndrome Symptom Severity Scale**
IBS-QoL	**IBS Quality of Life**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
MCQ	**Medical Consumption Questionnaire**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
MLDS	**Gastroenterology Foundation; in Dutch: Maag Lever Darm Stichting**
NRS	**Numerical Rating Scale**
NVMDL	**Dutch association for gastroenterologists; in Dutch: Nederlandse Vereniging van Maag-Darm-Lever artsen**
OTC	**Over The Counter-non prescription drug**
PAM	**Patient Activation Measurement**

PCQ	**Productivity Cost Questionnaire**
PDSB	**Irritable Bowel Syndrome patient organisation; In Dutch: Prikkelbare Darm Syndroom Belangenvereniging**
PHQ-9	**Patient Health Questionnaire-9**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

1. SUMMARY

Rationale: Psychological therapies are effective in reducing irritable bowel syndrome (IBS) symptom severity and increasing quality of life and are recommended for the management of IBS by guidelines. Evidence appears strongest for the efficacy of hypnotherapy as psychological treatment. However, therapist-led interventions are time consuming and relatively costly. Approaches based on e-health are cost saving and appear more attractive to patients as no visits to a therapist are necessary. Therefore, we plan to conduct a multicentre randomised controlled trial to examine whether the effectiveness of online hypnotherapy is non-inferior compared to individual face-to-face hypnotherapy delivered by a therapist, according to current FDA guidelines. Online psychoeducation will be used as control condition. In addition, we hypothesize that treatment with online hypnotherapy is a more cost-effective therapy than face-to-face hypnotherapy in IBS patients.

Objective:
Primary objective:
To compare the efficacy of online hypnotherapy versus face-to-face according to a non-inferiority design for the treatment of IBS.
Hypothesis: Hypnotherapy delivered in the form of online exercises has non-inferior efficacy to face-to-face hypnotherapy delivered by a hypnotherapist for the treatment of IBS.

Secondary objectives:
1. To compare the efficacy of hypnotherapy vs. online psychoeducation
2. To evaluate the cost-effectiveness of face-to-face hypnotherapy as compared to online exercises of hypnotherapy
3. To evaluate the effect of treatment after discontinuation
4. To evaluate the effect of treatment on quality of life
5. To evaluate the use of OTC and rescue medication
6. To evaluate the adherence to therapy
7. To evaluate the response rates in relation to patient expectation prior to the start of treatment
8. To evaluate the response rates in relation to comorbid anxiety and/or depression

Study design: A randomised controlled clinical trial with three parallel study arms (online psychoeducation, face-to-face hypnotherapy and online hypnotherapy) for 12 weeks with a follow up of 1 year.

Study population: 285 patients with IBS (according to Rome IV criteria) aged 16 - 75 years.

Intervention: Group 1 will receive 12 weeks treatment with online psychoeducation, group 2 will receive 12 weeks treatment with individual face-to-face hypnotherapy (6 individual, bi-weekly sessions), group 3 will receive 12 weeks treatment with online hypnotherapy.

Main study parameters/endpoints:

Primary parameter:

According to FDA recommendation:

1. Abdominal pain response rate after 12 weeks of treatment.
    a. A responder is defined as a patient who experiences at least a 30 percent decrease in the weekly average of worst daily abdominal pain (measured daily, on an 11 point NRS) compared to baseline weekly average in at least 50 percent of the weeks in which the treatment in given.

Secondary parameters:

- Degree of relief response rate after 12 weeks of treatment, according to EMA recommendation: 'A responder is defined as a patient who experiences a weekly relief of 1 or 2 (on a 7 point NRS) in at least 50 percent of the weeks in which treatment is given.'
- Response rate directly after completion of the 12-week treatment period
- Improvement of symptom severity as determined by the IBS-SSS by 50 points or more
- Longitudinal change in IBS-SSS at baseline (run-in), t=12 weeks, t=16 weeks, t=6 months follow-up and t=1 year follow-up
- Cost-utility, as determined by calculations incorporating total treatment costs and changes in EQ-5D-5L (QALYs gained) and MCQ/PCQ results (savings from reduced medical resource use and increased work productivity respectively)
- Quality of life, as determined by the EQ-5D-5L and IBS-QoL (change from baseline)
- Use of OTC and rescue medication
- Adherence to therapy
- Response rates in relation to patient expectation prior to the start of treatment
- Response rates in relation to comorbid anxiety and/or depression
- Number and severity of adverse events

All endpoint analyses will be based on the intention to treat population. The proportion of responders in each treatment group will be compared using logistic regression to provide covariate adjustments for centers, gender, age etc. in the analyses.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Subjects may be confronted with certain inconveniences. There are three (digital) visits (screening visit, randomisation visit and post-treatment visit). The screening will take up to 1 hour, including different questionnaires and a pregnancy test for women of fertile age. During the run-in period patients are asked to report their daily symptom scores with the use of an electronic diary (mobile phone application), this takes approximately 30 seconds each day. A similar smartphone application has previously been developed for IBS trials by investigators from the study group (PERSUADE study, NL 56000.068.16 / METC 162009), completion of the questionnaire does not result in substantial interference with everyday life. During the treatment period, participants are asked to report daily symptom scores using the same mobile phone application as during the run-in period, and complete three questionnaires electronically each week. Participants in the online psychoeducation group will be requested to use the online instrument for 15-30 minutes per day for 5 days a week. Participants randomized to face-to-face hypnotherapy will receive treatment that is delivered in a series of 6, bi-weekly 45-minute sessions in which patients receive protocol-based structured hypnotherapy. In addition, these participants are asked to exercise at home, for 15-30 minutes per day for 5 days a week, using a CD or other electronic data storage equipment provided by their therapist. Participants in the online hypnotherapy group will be requested to do home-work exercises using the online instrument for 15-30 minutes per day for 5 days a week.
During the post-treatment measurement and follow-up participants several questionnaires have to be completed at several time-points. In total, to complete all the questionnaires during the study period take several hours.
Participants in each group may experience relief of IBS symptoms. We don’t expect any side effects. Side effects of hypnotherapy can occur in participants with any psychiatric condition, we will screen for anxiety and depression with the GAD-7 and PHQ-9 questionnaires during the screening visit, subjects which scores corresponds with moderate anxiety and depression are excluded from the study.

2. INTRODUCTION AND RATIONALE

Irritable bowel syndrome (IBS) is a highly prevalent gastrointestinal disorder characterized by recurrent abdominal pain and altered bowel habits. IBS affects up to 15% of the population in Western countries and is associated with high healthcare utilisation and reduced quality of life.(1) In addition, IBS is associated with significant morbidity and work-absenteeism.(2) Healthcare seeking behavior is largely related to symptom severity and psychological complaints. The majority of patients (80%) seeking medical care is treated in primary care practice, where they account for 12% of all patients seen.(3) When initial treatment fails or when organic pathology is suspected, patients are referred to secondary care. IBS represents at least 15-20% of referrals to gastroenterologists in the Netherlands (survey data, Dutch Society for Gastroenterologists, 2015). In addition, IBS is associated with high healthcare consumption and decreased quality of life.(1)

IBS is thought to be a multifactorial functional disorder lacking a single unifying explanation for the symptoms toward which therapy can be targeted. Patients with IBS often demonstrate visceral hypersensitivity to painful stimuli, and abnormal central nervous system processing of pain.(4) Psychological therapies are effective in reducing the IBS symptom severity and increasing quality of life and are recommended for the management of IBS by guidelines. Evidence appears strongest for the efficacy of hypnotherapy as psychological treatment. In a recent study in primary and secondary care patients, hypnotherapy was demonstrated to be superior to educational control intervention and group-therapy was non-inferior to individual hypnotherapy.(5) However, therapist-led interventions are time consuming and relatively costly. Approaches based on e-health are cost saving and appear more attractive to patients as no visits to a therapist are necessary. Herewith, many IBS patients may be effectively treated in primary care which will reduce costs associated with hospital referral. Recent evidence from a Dutch study in adolescent patients with IBS suggests that hypnotherapy using a CD is non-inferior to therapist-delivered hypnotherapy.(6) No such study has been performed in an adult population.
Hypnotherapy has been shown to have long-term benefits, with 83% of responders in one study maintaining treatment benefits for 1–5 years after the course of treatment (7) and 75% of responders showing additional benefit after 2-7 years in another study (both uncontrolled trials).(8)

Health care efficiency problem
The evidence from clinical trials is inadequate and/or insufficient to support the efficacy of many of the therapies currently used routinely to treat IBS. At best, there is limited evidence to

suggest some degree of efficacy in individual IBS symptoms.(9) Most therapies used to treat IBS target only one symptom and research indicates that less than 25% of patients report complete relief of any one symptom with existing treatments.(10) The effect of pharmacotherapy of IBS is often disappointing and hardly exceeds placebo effect. Several studies have pointed to a high percentage of IBS patients using some form of medication, but almost half considered their treatment ineffective and were therefore unsatisfied.(11) Psychological therapies are more effective but are costly and access to therapists is limited. It is clear that current practice of IBS management is suboptimal and leads to repeat consultations and increased direct and indirect disease-related costs. In addition, previous studies have shown that the majority of IBS patients felt that they are insufficiently informed on their condition and were not provided with an adequate explanation for their symptom.(12) This seems particularly relevant since patients may often have considerable misconceptions about IBS. For instance, in a US study it was found that over 40% of IBS patients thought that colonoscopy can diagnose IBS and one in seven patients stated that IBS turns into cancer.(13)

Usual/standard care

IBS treatment should begin by explaining the condition, providing reassurance as to the benign nature of the condition, and educating the patient about the utility and safety of diagnostic tests, and treatment options. Education includes information on lifestyle modifications that may improve IBS symptoms, e.g. regular physical exercise, relaxing or stress reducing activities and a healthy diet.(2) Education about IBS might result in improvement of IBS symptoms even to such an extent that patients do not ask for further treatment. Medical treatments for IBS symptoms vary greatly depending on symptom severity, patient preference and the treating physician’s own experience – no uniform approach exists. The majority of patients receive drug prescriptions, with antispasmodics being most frequently prescribed.(9) In addition, self-medication with over-the-counter drugs is common.(14) Those who are not yet sufficient helped are referred to secondary care. Patients with more severe symptoms are generally treated with psychoactive medication or psychological treatment.

3. OBJECTIVES

Primary objective:

1. To compare the efficacy of online hypnotherapy versus face-to-face hypnotherapy according to a non-inferiority design for the treatment of IBS.

Hypothesis: Hypnotherapy delivered in the form of online exercises has non-inferior efficacy to face-to-face hypnotherapy delivered by a hypnotherapist for the treatment of IBS. This will not lead to a difference in total percentage of responders, as defined by FDA recommendations.

Secondary objectives:

1. To compare the efficacy of hypnotherapy (regardless of the form in which it is delivered) versus online psychoeducation for the treatment of IBS.

Hypothesis: We hypothesize hypnotherapy (in either form) is superior to online psychoeducation in IBS patients. This will lead to a higher total percentage of responders, as defined by FDA recommendations, in the hypnotherapy arms compared to online psychoeducation.

2. To evaluate the cost-effectiveness of face-to-face hypnotherapy delivered by a therapist as compared to online exercises of hypnotherapy (according to non-inferiority design) for the treatment of IBS.

Hypothesis: We hypothesize hypnotherapy delivered in the form of online exercises is a more cost-effective therapy compared to face-to-face hypnotherapy delivered by a hypnotherapist for the treatment of IBS.

3. To evaluate the effect of treatment on quality of life

Hypothesis: We hypothesize that treatment of IBS with hypnotherapy will lead to an increased quality of life as compared to online psychoeducation. We hypothesize that treatment with online hypnotherapy will lead to an increased quality of life as compared to face-to-face hypnotherapy because less visits to a therapist are necessary.

4. To evaluate the effect of treatment after discontinuation

Hypothesis: We hypothesize that some rebound of symptoms will occur after discontinuation of treatment. However, we expect that abdominal pain scores will remain lower than at baseline as hypnotherapy has been found to be effective on long-term. Overall medical consumption will be less than at baseline and quality of life and work productivity will remain higher than baseline.

5. To evaluate the use of OTC and rescue medication between online psychoeducation, face-to-face hypnotherapy and online hypnotherapy
Hypothesis: We hypothesize that treatment of IBS symptoms with hypnotherapy will lead to fewer use of rescue medication for pain.

6. To evaluate the adherence to therapy
Hypothesis: We hypothesize that adherence to online therapy is lower considered to face-to-face visits as the former is entirely driven by the intrinsic motivation of the patient.

7. To evaluate the response rates in relation to patient expectation prior to the start of treatment
Hypothesis: We hypothesize that response rates are higher when patients are randomized to the treatment of choice.

8. To evaluate the response rates in relation to comorbid anxiety and/or depression
Hypothesis: We hypothesize that patients with comorbid anxiety and/or depression have lower responder rates compared to those patients without as the interventions are primarily driven by gut-related health and not psychological well-being.

4. STUDY DESIGN

This study is a multicenter, randomized controlled trial with three parallel treatment arms. The trial will be executed in accordance with the current FDA and EMA guidelines for IBS trials. Patients with IBS will be randomised into one of the three arms based on a 1:1:1 randomisation:

1. Online psychoeducation
2. Face-to-face hypnotherapy
3. Online hypnotherapy

Centers where recruitment will commence include the Maastricht University Medical Center, AMC Amsterdam, Alrijne Hospital Leiden, Bernhoven Hospital Uden, Diakonessenhuis Utrecht, Gelderse Vallei Ede-Wageningen, Jeroen Bosch Hospital Den Bosch, Maasziekenhuis Pantein, Martini Hospital Groningen, MMC Veldhoven, Medical Center Leeuwarden, MST Enschede, Rijnstate Hospital Arnhem, Tergooi Hospital Hilversum, VUMC Amsterdam. In addition, patients from primary care setting will be recruited from GP practices in South Limburg.

An overview of the study design is provided below. Total study duration will be approximately 4 years (1 year preparation, 3 years inclusion). A total of 228 completers will be needed (see sample size calculation below).

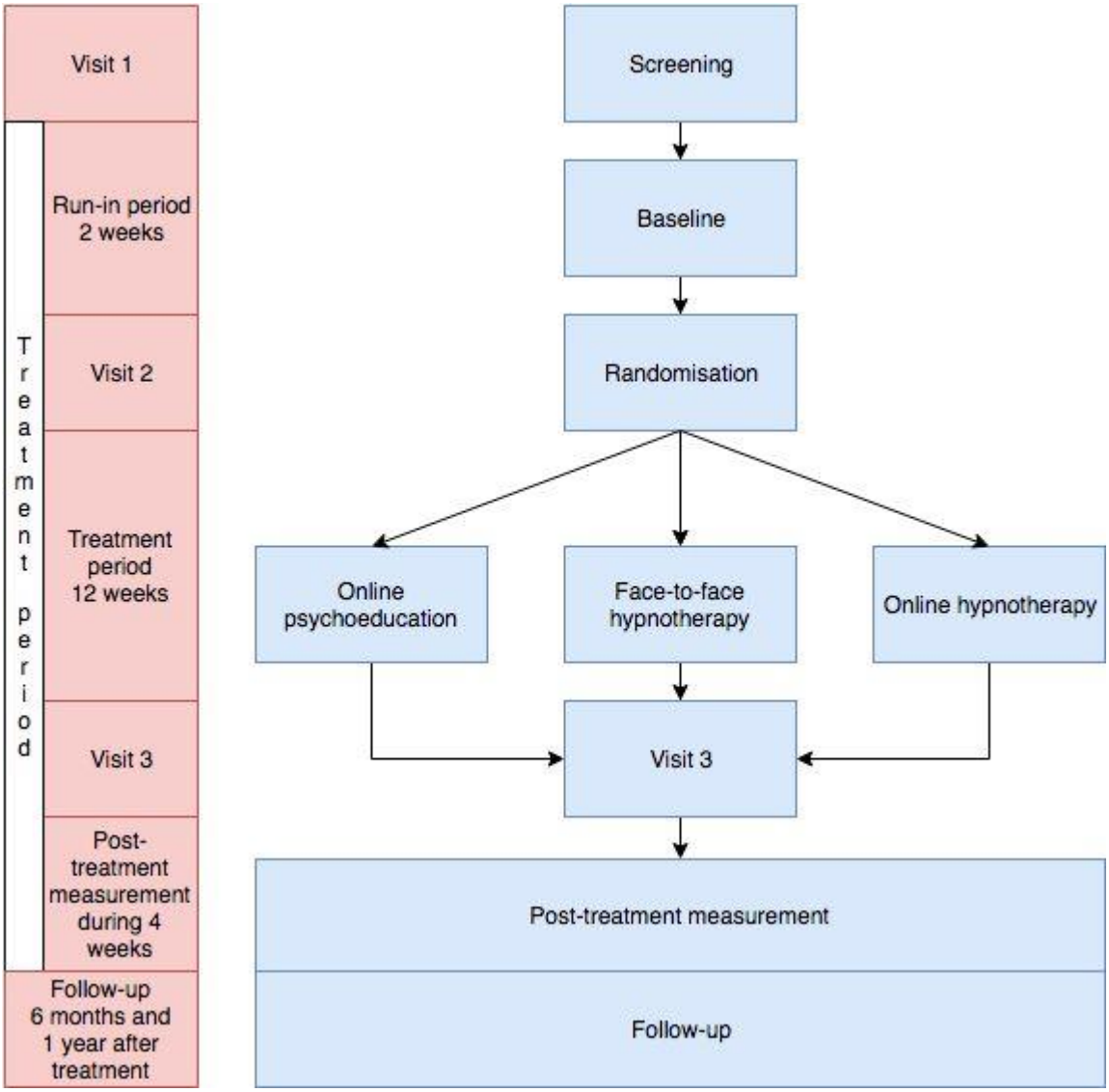

Figure 1 Study design

1) Recruitment

In order to include a representative population of patients, subjects will be recruited from both primary care as well as secondary/tertiary care. Patients in the primary care setting will be recruited by their general practitioner and secondary/tertiary care patients will be recruited by their gastroenterologist in the GI-outpatient clinic. The treating physicians will briefly inform eligible IBS patients about the study. If the patient is interested, detailed oral and written study information will be given by the researcher. In addition, an announcement will be put on the website of the 'Prikkelbare Darmsyndroom Belangenvereniging', local newspapers (of areas of participating centers), social media and in GP practices in the Maastricht area. (See E3. Poster_FORTITUDE_2.0 for advertisement info) Patients that are interested to participate in the study can contact the researcher directly. A screening visit will then be planned, at the earliest, seven days after patients have received detailed study information to allow sufficient

time for consideration. If the patient does not contact the investigator however after receiving the written information brochure, the coordinating investigator will contact the patient once (at the earliest 7 days after sending the written information brochure, and only if the patient has given permission to do so during the first conversation).
Also subjects that participated in the Maastricht IBS Cohort study (NL24160.068.08/ METC 08-2-066), that gave consent to be approached in the future for further research, will be contacted by email or letter. (See E3. Wervingstekst_FORTITUDE_IBSCohort_Versie 2.0)

2) Screening

Patients aged 16-75 years old with a diagnosis of irritable bowel syndrome according to the Rome IV criteria are considered eligible for the current study. In the presence of alarm symptoms, organic pathology of the gastrointestinal tract has to been excluded sufficiently prior to inclusion. If an IBS patient is willing to participate in the study, an informed consent will be signed. In- and exclusion criteria will be checked. Women in fertile ages that are suitable for inclusion will undergo a simple (urine) pregnancy test to exclude pregnancy. Subjects are asked to complete the GAD-7 (Generalized Anxiety Disorder-7) and PHQ-9 (Patient Health Questionnaire-9) in order to screen for anxiety and depression using electronic questionnaires (all questionnaires are discussed in section 8.3.7). A cut-off value of 10 is used for both the GAD-7 and PHQ-9, as this corresponds to moderate anxiety and depression, respectively. Patients with a score of 10 or higher on either questionnaire will be interviewed by the investigator. The investigator decides (if needed, in consultation with the coordinating investigator and/or principal investigator) if there is indeed a presence of anxiety or depression. If this is the case, patients are excluded from the study. In addition, the general practitioner and/or referring gastroenterologist will be informed in these cases, as additional/alternative treatment may be required. However, if scores of 10 or higher on the PHQ-9 or GAD-7 appear to be unrelated to depression or anxiety, the patient can still participate in the study. A separate questionnaire addressing expectations with regard to the effects of interventions will be administered. Finally, subjects will be asked to complete some electronic questionnaires: IBS-SSS (IBS Symptom Severity Scale), IBS-QoL (IBS-Quality of Life), MCQ (Medical Consumption Questionnaire), PCQ (Productivity Cost Questionnaire), EQ-5D-5L (Euro-Quality of Life, 5 domains), Big Five Inventory.

3) Run-in period

Following inclusion, potential study participants are enrolled in a 2 week run-in period. Symptoms will be recorded daily using a smartphone application. Subjects are required to have reported a minimal average score of 3 for all symptoms during the run-in period (on an 11-point NRS scale). After two weeks, the average symptom score will be calculated. Subjects with an average symptom score below 3 will be excluded from the study and will be informed by telephone. This approach is in line with FDA guidelines on other treatment trials in irritable

bowel syndrome. For participants with a symptom score of 3 or higher a randomisation visit (in person or by telephone) will be planned.

4) Randomisation

Participants will be randomly assigned in equal proportions to one of the three groups: face-to-face hypnotherapy, online hypnotherapy or online psychoeducation. Randomisation will be performed by the coordinating investigator using the online TENALEA software, see paragraph 8.2. Subjects randomized to online psychoeducation, will be asked to complete two electronic questionnaires: PAM (Patient Activation Measurement) and Health literacy.

5) Treatment

The treatment period will be 12 weeks. During the treatment period patients will again be asked to report symptoms daily using a smartphone application, including the same symptoms as during the run-in period. Patients are asked weekly to complete electronic questionnaires (adequate relief of symptoms (AR), IBS-SSS, therapy compliance).

6) Visit

An in-person visit or appointment by telephone will be organized following the 12-week treatment period further counseling of the study procedures, evaluation and for administrative handling of reimbursement payments.

7) Post-treatment measurement

During 4 weeks after treatment is completed, patients will again be asked to complete weekly electronic questionnaires (AR and IBS-SSS) and to report symptoms daily using a smartphone application. This because the maximum effect of the intervention is potentially reached after the 12-week intervention period. At t=16 weeks patients will be asked to complete electronic questionnaires (satisfaction, IBS-SSS, GAD-7, PHQ-9, MCQ, PCQ, EQ-5D-5L, IBS-QoL) and for patients randomized to online psychoeducation two additional questionnaires (PAM and recall of information).

8) Follow-up

After a follow-up of 6 months after treatment is completed, patients will again be asked to complete electronic questionnaires sent by email (IBS-SSS, GAD-7, PHQ-9, MCQ, PCQ, EQ-5D-5L, IBS-QoL) and for patients randomized to online psychoeducation one additional questionnaire (PAM). In addition, patients will be asked to report symptoms daily during the last 4 weeks of follow-up. After a follow-up of 1 year after treatment is completed, patients will again be asked to complete the same electronic questionnaires sent by email (IBS-SSS, GAD-7, PHQ-9, MCQ, PCQ, EQ-5D-5L, IBS-Qol, PAM).

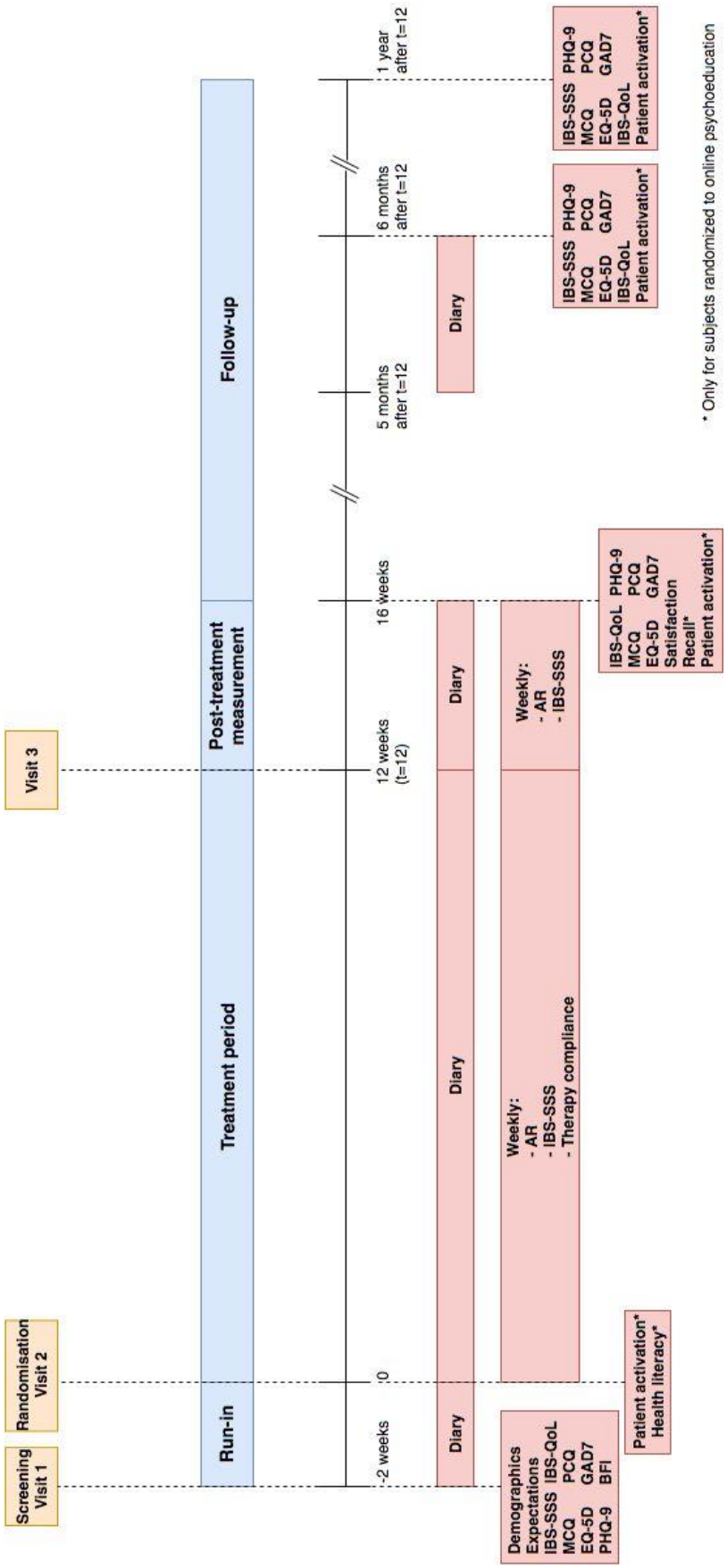

Figure 2 Timeline

5. STUDY POPULATION

5.1 Population (base)

IBS patients aged 16-75 years will be recruited in both the primary and secondary/tertiary healthcare setting for a representative population of patients. The Rome IV criteria are used for a diagnosis of IBS. These criteria include:

Recurrent abdominal pain on average at least 1 day a week in the last 3 months, associated with 2 or more of the following:

- Related to defecation
- Associated with a change in frequency of stool
- Associated with a change in form (appearance) of stool

Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

5.2 Inclusion criteria for run-in period

In order to be eligible to participate in the run-in period of this study, a subject must meet all of the following criteria:

- Age 16-75 years
- A diagnosis of IBS according to the Rome IV criteria
- In the presence of alarm symptoms, such as rectal blood loss, weight loss, anemia, first onset of symptoms above 50 years of age, patients will be first referred for further investigation by their treating physician to exclude organic disorders, conform current Dutch guidelines for IBS.(15)
- Women in fertile age must use contraception or be postmenopausal for at least two years.

5.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Insufficient command of the Dutch language
- No access to internet
- Evidence of current anxiety and/or depression disorder as defined by a score ≥10 on the GAD-7 and/or PHQ-9 questionnaire, supported by a detailed interview by the investigator (i.e. the investigator is required to confirm suspicion of anxiety or depressive disorder). In this case it is conceivable that the IBS symptoms are strongly related to psychopathology for which different treatment might be more appropriate.
- History of ulcerative colitis, Crohn’s disease, coeliac disease or significant liver disease

- Major surgery to the lower gastrointestinal tract, such as partial or total colectomy, small bowel resection or partial or total gastrectomy
- Past or present radiotherapy to the abdomen
- Current pregnancy or lactation
- Using of psychoactive medication in case there's no stable dose for at least 3 months prior to inclusion
- Use of over-the-counter or prescription antidiarrheals, analgesics and laxatives in case there's no stable dose during the study period
- Hypnotherapy treatment received in the last 3 months prior to inclusion
- Using more than 20 units of alcohol per week
- Using drugs of abuse

5.4 Inclusion criteria for randomisation and the actual treatment period

During the run-in period, patients are asked to report their daily symptom scores with the use of an electronic diary (mobile phone application). If after the run-in period patients meet the inclusion criteria, they will enter the treatment period. A minimal average score of 3 for all core symptoms is required for inclusion (on an 11-point NRS scale). Subjects with a lower average score will be excluded from the study, and will be referred back to their clinician. This approach is in line with FDA guidelines on treatment trials in irritable bowel syndrome.

5.5 Sample size calculation

Sample size calculation is based on a non-inferiority design, with an anticipated response rate of 60% and 50% in the face-to-face hypnotherapy and the online hypnotherapy, respectively. The non-inferiority margin was defined as 10% (which corresponds to a clinically meaningful difference). We applied the following values: significance level (α two-sided) = 0.05; power = 0.80. According to this calculation, 76 patients per arm are needed, i.e. 228 patients in the three intervention groups. Calculation can be found at the following web address: http://powerandsamplesize.com/Calculators/Compare-2-Proportions/2-Sample-Non-Inferiority-or-Superiority. In a previous trial conducted by our group (PERSUADE NL56000.068.16/METC 162009) there were 43 drop-outs during screening and run-in period, this corresponds to ~20%. The subjects in the PERSUADE study are comparable with the subjects in our study and inclusion criteria after the run-in period are equal. In order to account for drop-outs during the treatment period, we will include an additional 5%. This results in 95 subjects per arm and a total of 285 subjects.

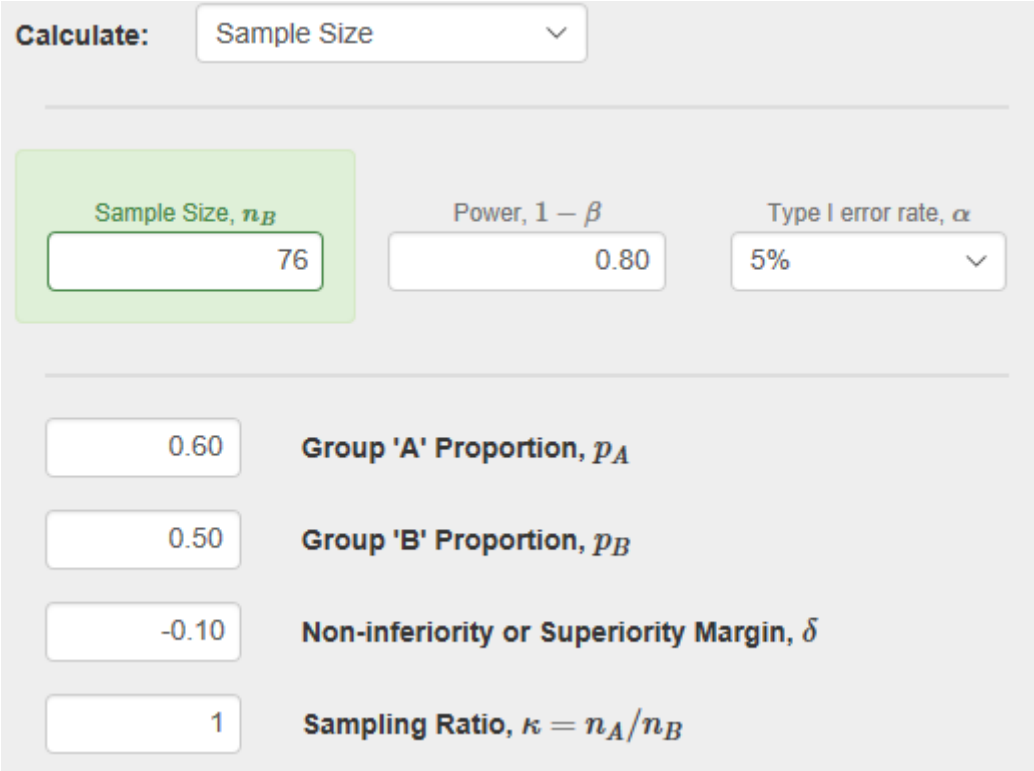

Figure 3 Sample size calculation

6. TREATMENT OF SUBJECTS

6.1 Investigational product/treatment

1. Online psychoeducation.

Psychoeducation will be self-administered using an interactive online web application (website available in mobile format) with learning modules addressing different aspects of IBS designed by an expert psychologist Drs. Cynthia Elderson (Erasmus University Rotterdam). The Web Application serves education purposes about IBS and is a generic instrument that can be applied to all IBS patients. It begins by explaining the condition, educating the patient about diagnostic tests and treatment options. No specific patient-related data is collected using the web-application. All data are collected separately using a smartphone application specifically designed for this study (see section 12.1). The Web application also supports the patient in discovering which lifestyle and diet choices may trigger their symptoms. The patient can choose between goals and practice with these goals such as regular exercise, healthy diet alterations and activities to promote relaxation. The Web Application uses persuasive technology, an e-coach avatar and gamification to improve adherence. This approach is designed to influence coping by education patients to stimulate self-management. A recent systematic review performed by Dorn (16) about self-management support for IBS, emphasizes the fact that self-management is an essential component of care for IBS. However, many studies in the past were of subpar quality, and most of the interventions did not seem feasible for “real world” clinical practice, suggesting that the key challenge for improving self-management in IBS is to develop practical self-management interventions that can be applied across various settings.

This instrument has been developed in collaboration with the study group, the task force Neurogastroenterology of the NVMDL, the PDSB, dieticians, psychologists, patient input and the MLDS in order to comply to patients’ need and to assure scientific quality and soundness of the information and advice provided.

2. Individual face-to-face hypnotherapy.

Patients randomized for face-to-face hypnotherapy will receive treatment that is delivered in a series of 6, bi-weekly 45-minute sessions in which patients receive protocol-based structured hypnotherapy. In each treatment session, a hypnotic state (trance) and relaxation is induced and patients are led through a series of scripted, gut-focused imageries with specific hypnotic suggestions to normalize motility of the gut, and to reduce pain and feelings of discomfort. Each of the following sessions target a specific symptom of IBS are titled ‘Tension and relaxation’, ‘Beach and waves,’ ‘Hands on belly,’ ‘Murmuring

brook'/'Streaming river' and 'Soft cloths'. Patients are asked to exercise at home for 15-30 minutes per day for 5 days a week using a CD provided by their therapist. All repeat sessions start with discussing home assignments.

The treatment procedure has been developed previously for the Dutch IMAGINE study (17) and is based on the Manchester protocol. Treatment is given by qualified psychologists who are educated as hypnotherapists and have specifically been trained previously for the intervention. Supervision will be provided from within the study team by Dr. Carla Flik, expert hypnotherapist. The network of hypnotherapists who recently participated in the Dutch IMAGINE study will be involved in the current study as well. This insures a standardized approach among therapists during the treatment period. All hypnotherapist participating in the trial will be specifically trained by Dr. Carla Flik.

3. Home-based self-administered online hypnotherapy

The online hypnotherapy uses a generic protocol and script of the face-to-face hypnotherapy. All exercises are given in the same order to patients, there are no patient-specific algorithms used. Using a smartphone application, designed by Drs. Louis Zantema, psychologist at Medisch Centrum Leeuwarden, a senior hypnotherapist (Dr. Flik) trained in the treatment of IBS will explain on video the rationale and principles of hypnosis for IBS and guide the induction of a hypnotic state (trance) and lead the patients through the same series of scripted, gut focused imageries with specific hypnotic suggestions. The treatment procedure is the same as discussed above and is based on the IMAGINE study.(5) Additional patient input was obtained for development from patient focus groups. Patients will be requested to do home-work exercises using the online instrument for 15-30 minutes per day for 5 days a week. No patient-related data are stored in the smartphone application for hypnotherapy, as this is done via the use of separate smartphone application, as described previously.

6.2 Use of co-intervention

No new treatment (such as antidepressants or other form of psychotherapy) can be started throughout the treatment period (12 weeks) of the study or else the patient will be excluded from participation. Patients that are on a gluten or lactose free diet should have been on this for at least two months already and continue with this throughout the study. Lifestyle and dietary measures for treating IBS should be stabilized prior to study entry (i.e. prior to the run-in period) and will be maintained during the course of the clinical trial. The use of psychoactive medication is allowed, provided that dosing has been stable for at least 3 months before enrolment (i.e. prior to the run-in period). Women in fertile ages should use

contraception continuously. The use of concomitant medication is restricted: drugs with analgesic action or with specific effects on bowel function are not allowed (unless adequately justified as rescue medication, see paragraph 6.3).

6.3 Escape medication

In accordance to EMA guidelines on IBS trials, drugs with analgesic action or with specific effects on bowel function such as laxatives and antidiarrhoeals will generally be avoided during the course of the treatment period, and may only be allowed as specific “rescue medication” if adequately justified and documented. The rescue medication will be clearly specified and evaluated as efficacy parameter (and for safety/side effects).

7. INVESTIGATIONAL PRODUCT

No medicinal products are used in this trial and no investigational product.

The web-application for psychoeducation and the smartphone application for hypnotherapy are not considered medical devices, because of the fact that only generic information is provided and no personal or individual data are used (Nictiz advice document and flowchart (https://www.nictiz.nl/wp-content/uploads/2018/04/Infographic-medical-apps.pdf and checklist http://www.ce-markeren.nl). The psychoeducation application serves purposes of education about a certain condition (IBS) and by no means does it represent a diagnostic tool or a specific therapeutic instrument, it merely provides insight into ones condition in a generic way based on predefined algorithms for self-management.

The smartphone application for hypnotherapy assists patients to perform self-hypnosis in a generic way and the sequelae of hypnosis exercise is the same for all patients. No use is made of patient-derived data. The Medical Devices Degree therefore is not applicable.

The digital diary will be provided to the patients in a smartphone application format, similarly to previous trials conducted by our group (PERSUADE and TENDER trials, NL56000.068.16/METC 162009 and NL62932.068.17/METC 173051 resp.) The mere purpose of this application is data storage and is therefore not considered a medical device (see further under point 12).

8. NON-INVESTIGATIONAL PRODUCT

Not applicable

9. METHODS

9.1 Study parameters/endpoints

9.1.1 Main study parameter/endpoint

According to FDA recommendation:

1. Abdominal pain response rate after 12 weeks of treatment.

    a. A responder is defined as a patient who experiences at least a 30 percent decrease in the weekly average of worst daily abdominal pain (measured daily, on an 11 point NRS) compared to baseline weekly average in at least 50 percent of the weeks in which the treatment in given.

9.1.2 Secondary study parameters/endpoints

- Degree of relief response rate after 12 weeks of treatment, according to EMA recommendation: 'A responder is defined as a patient who experiences a weekly relief of 1 or 2 (on a 7 point NRS) in at least 50 percent of the weeks in which treatment is given.'
- Response rate directly after completion of the 12-week treatment period
- Improvement of symptom severity as determined by the IBS-SSS by 50 points or more;
- Longitudinal change in IBS-SSS at baseline (run-in), t=12 weeks, t=16 weeks, t=6 months follow-up and t=1 year follow-up
- Cost-utility, as determined by calculations with EQ-5D-5L, direct costs, indirect costs and social tariff;
- Quality of life, as determined by the EQ-5D-5L and IBS-QoL;
- Use of OTC and rescue medication;
- Number and severity of adverse events;
- Adherence to therapy;
- Response rates in relation to patient expectation prior to the start of treatment
- Response rates in relation to comorbid anxiety and/or depression
- (Negative) mood; assessed with the use of the PHQ-9 and GAD-7 (change from baseline).

9.2 Randomisation, blinding and treatment allocation

When a patient can be included after completing the run-in period, the coordinating investigator will receive a notification in Ldot. Ldot is a certified and secure database build by MEMIC, all personal details of the subjects will be registered here. After the notification, the coordination investigator will confirm eligibility and will then randomize the patient in an online environment provided by the CTCM (TENALEA). The patient will be randomized into one of the three treatment arms using the online TENALEA software based on the

minimization method. Minimization is a largely nonrandom method of treatment allocation, aiming to balance treatment arms with respect to predefined patient factors. This trial will be balanced in the three treatment arms for the following factors: inclusion center, age (16-30; 31-50; 51-75) and gender.

9.3 Study procedures

9.3.1 Screening visit

If a patient with IBS is willing to participate in the study after a minimum time for consideration of 7 days, an informed consent will be signed during the screening visit*. At t = -2 week, a medical screening will be performed to assess the eligibility of the patient to participate in this study. In- and exclusion criteria will be checked. In the presence of alarm symptoms, organic pathology of the gastrointestinal tract has to been excluded sufficiently prior to inclusion. Subjects are asked to complete the GAD-7 and PHQ-9 in order to screen for anxiety and depression using electronic questionnaires. A cut-off value of 10 is used for both the GAD-7 and PHQ-9, as this corresponds to moderate anxiety and depression, respectively. Patients with a score of 10 or higher on either questionnaire will be interviewed by the investigator. The investigator decides (if needed, in consultation with the coordinating investigator and/or principal investigator) whether the scores indeed correspond to anxiety or depression. If this is the case, the patient will be excluded from the study. In addition, the general practitioner and/or gastroenterologist will be informed in these cases, as additional/alternative treatment may be required. However, if scores of 10 or higher on the PHQ-9 or GAD-7 appear to be unrelated to depression or anxiety, the patient can still participate in the study.
Finally, subjects will be asked to complete some other electronic questionnaires: IBS-SSS, IBS-QoL, MCQ, PCQ, EQ-5D-5L, Big Five Inventory, expectations. All questionnaires are discusses in detail below in section 8.3.7. Completion of these questionnaires takes approximately 45 minutes.

* Informed consent can also be obtained without an on-site appointment (digital screening visit). After the researcher provided verbal information over the phone, participants will sign the informed consent form during a video call and send this to the researcher. Upon receiving the informed consent form, the researcher will also sign the informed consent form. After obtaining the informed consent the screening will be performed via a video call.

Pregnancy test

Women in fertile ages that are suitable for inclusion will undergo a simple (urine) pregnancy

test to exclude pregnancy. When completed, the pregnancy tests and urine samples will be destroyed immediately at the end of the screening visit. No personal information will be visible on the samples.

9.3.2 Run-in period

Potential study participants are enrolled in a 2 week run-in period. Symptoms will be recorded daily using a smartphone application. Symptom scores in these two weeks will be used define baseline values. The daily questionnaire takes approximately 30 seconds to complete and patient receive a reminder at the end of the day via their smartphone. A similar smartphone application has previously been developed for IBS trials by investigators from the study group (PERSUADE study, NL 56000.068.16 / METC 162009). Completion of the questionnaire does not result in substantial interference with everyday life. In the currently running study, we have noticed a compliance rate of around 90% of filling in the daily questionnaires. Those patients who do not process a smartphone will receive a tablet for the study period.

Subjects are required to have reported a minimal average score of 3 for all symptoms during the run-in period (on an 11-point NRS scale). After two weeks, the average symptom score will be calculated. Subjects with an average symptom score below 3 will be excluded from the study and will be informed by telephone. This approach is in line with FDA guidelines on other treatment trials in irritable bowel syndrome. For participants with a symptom score of 3 or higher a randomisation visit (in person or by telephone) will be planned. After randomisation, a separate questionnaire addressing expectations with regard to the effects of interventions will also be administered.

9.3.3 Treatment period

Following inclusion, participants will be randomly assigned in equal proportions to one of the three groups (online psychoeducation, face-to-face hypnotherapy, online hypnotherapy). Patients randomized to online psychoeducation will be asked to complete two additional questionnaires (patient activation and health literacy). Participants will have to start with the treatment period within 4 weeks after the run-in period. This will be communicated with patients prior to the run-in period, in order to prevent exceedance of the time-window. If enrolment within this 4-week time-window is not possible, participants will have to undergo the run-in period again. For participants randomised into the face-to-face hypnotherapy arm, an appointment will be arranged with the hypnotherapist at the earliest possible time point following the run-in period. The treatment period will commence starting with the first appointment with the therapist. In case of online psychoeducation or online hypnotherapy, the participant will receive further instructions at time of randomisation. The

web application will be downloaded with the assistance of the study team representative. The treatment period will be 12 weeks. During the treatment period participants will again be asked to report symptoms daily using the same smartphone application, including the same symptoms as during the run-in period. On the basis of the daily symptom score, responders rates will be determined according to FDA/EMA guidelines on IBS. Participants are asked weekly to complete electronic questionnaires (adequate relief of symptoms (AR), IBS-SSS, therapy compliance). In addition, the time spent logged into the web application to use the online intervention will be monitored. For the participants randomized to the face-to-face hypnotherapy arm, the hypnotherapist will keep record of the time spent with the participant. Any specific knowledge on IBS obtained by the participants during psychoeducation or hypnotherapy will not be tested for, as this may decrease enthusiasm from the participant and have negative effects on compliance. Nevertheless, the psychoeducation module will have the option for participants to test their knowledge, in case they wish to do so.

The final visit will take place after the treatment period, to evaluate treatment.

9.3.4 Visit

An in-person visit or appointment by telephone will be organized following the 12-week treatment period further counseling of the study procedures, evaluation and for administrative handling of reimbursement payments.

9.3.5 Post-treatment measurement

During 4 weeks after treatment is completed, participants will again be asked to complete weekly electronic questionnaires (AR and IBS-SSS) and to report symptoms daily using the smartphone application. This because the maximum effect of the intervention is potentially reached after the 12-week intervention period. At the end of the post-treatment measurement (t=16 weeks) patients will be asked to complete some electronic questionnaires (IBS-QoL, GAD-7, PHQ-9, MCQ, PCQ, EQ-5D-5L, satisfaction) and for patients randomized to online psychoeducation two additional questionnaires (patient activation and recall).

9.3.6 Follow- up

After a follow-up of 6 months after treatment is completed, participants will again be asked to complete electronic questionnaires sent by email (IBS-SSS, IBS-QoL, GAD-7, PHQ-9, MCQ, PCQ, EQ-5D-5L) and for patients randomized to online psychoeducation one additional questionnaire (patient activation). In addition, participants will be asked to report symptoms daily during the last 4 weeks of follow-up. After a follow-up of 1 year after treatment is completed, patients will again be asked to complete the same electronic

questionnaires sent by email (IBS-SSS, IBS-QoL, GAD-7, PHQ-9, MCQ, PCQ, EQ-5D-5L) and for patients randomized to online psychoeducation one additional questionnaire (patient activation).

9.3.7 Questionnaires

All questionnaires will be filled out in a secure, electronic environment that can be accessed via Internet by telephone or computer. A hyperlink to access the questionnaires is sent to the patients' email address at each time point discussed above. This electronic based environment in which subjects can fill out all the required questionnaires, named 'Castor', has previously been created by the Maastricht Center and Information and Data Management (MEMIC), affiliated to Maastricht University. Castor uses a NEN7510 and ISO 27001:2005 certified server called "True".

• **Rome IV criteria IBS See F1.1_Rome_IV_criteria**

At t = -2, subjects will fill out this questionnaire for inclusion to the study.

• **Baseline characteristics questionnaire See F1.2_Algemene_Vragenlijst**

At t = -2, subjects will fill out this questionnaire regarding baseline characteristics, demographics and life-style.

• **IBS-SSS: IBS symptom severity score See F1.3_IBS-SSS**

The IBS-SSS assesses five features of IBS (pain severity and frequency; abdominal distension; bowel satisfaction; interference with life in general) and their intensity, using visual analogue scales.(18) The IBS-SSS will be completed at the screening visit (t = -2), one time a week for 18 weeks and after 6 months and 1 year follow-up.

• **MCQ: Medical Consumption Questionnaire See F1.4_MCQ**

The MCQ is a questionnaire developed by the Institute for Medical Technology Assessment (Rotterdam) and is designed to measure healthcare consumption.(19) The MCQ will be completed at the screening visit (t = -2), at the end of the post-treatment measurement (t= 16) and after 6 months and 1 year follow-up.

• **PCQ: Productivity Cost Questionnaire See F1.5_PCQ**

The PCQ is a questionnaire developed by the Institute for Medical Technology Assessment (Rotterdam) and is designed to measure work productivity and absenteeism.(20) The PCQ will be completed at the screening visit (t = -2), at the end of the post-treatment measurement (t= 16) and after 6 months and 1 year follow-up.

• EQ-5D-5L: Euroqol See F1.6_EQ-5D-5L

The EQ-5D-5L assesses five dimensions of quality of life: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. (21)The EQ-5D-5L will be completed at the screening visit (t = -2), at the end of the post-treatment measurement (t= 16) and after 6 months and 1 year follow-up.

• GAD-7: Generalized Anxiety Disorder-7 See F1.7_GAD7

Subjects will be asked to complete the GAD-7 in order to screen for anxiety (exclusion criterion). The GAD-7 is a validated 9-item questionnaire which has been demonstrated to be an efficient tool for screening for generalized anxiety disorder and assessing its severity in clinical practice and research.(22) A cut-of value of 10 is used for screening purposes (which is subsequently complemented with a detailed interview by the researcher). The GAD-7 will be completed at the screening visit (t = -2), at the end of the post-treatment measurement (t= 16) and after 6 months and 1 year follow-up.

• PHQ-9: Patient Health Questionnaire See F1.8_PHQ9

During the screening visit, subjects will be asked to complete the PHQ-9 in order to screen for depression (exclusion criterion). The PHQ-9 is a validated multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression. It incorporates DSM-IV depression diagnostic criteria with other leading major depressive symptoms into a brief self-report tool.(23) A cut-of value of 10 is used for screening purposes (which is subsequently complemented with a detailed interview by the researcher). The PHQ-9 will be completed at the screening visit (t = -2), at the end of the post-treatment measurement (t= 16) and after 6 months and 1 year follow-up.

• BFI: Big Five Inventory See F1.9_BFI

The BFI will be completed at the screening visit (t = -2). This questionnaire is intended to identify personality traits which will later be analysed for correlation with treatment outcome.

• Expectations questionnaire See F1.10_Expectations

Before start of treatment there will be a questionnaire addressing expectations with regard to the effects of intervention, it will be completed at the screening visit (t = -2).

• Adequate symptom relief question (AR) See F1.11_AR

During the treatment period and post-treatment measurement, patients will be asked to complete the 'adequate relief' query. This is one question concerning patients' symptom relief.

• Compliance See F1.12_Compliance

Compliance to therapy will be monitored using end-of-week questionnaires wherein participants will be asked if they had used the online therapeutic instrument in the respective week or whether they had been to their appointment with the hypnotherapist. During treatment period (t = 0 t/m t = 12), at the end of each week.

• IBS-QoL: IBS-Quality of Life See F1.13_IBS-QoL

The IBS-QoL has a recall period of 30 days and includes 30 items and consists of nine scales (dysphoria; interference with activity; body image; health worry; food avoidance; social reaction; sexuality; relationships; overall scale).(24) The IBS-QoL will be completed at t= -2, t= 16 weeks and after 6 months and 1 year follow-up.

• PAM: Patient Activation Measurement See F1.14_Patientactivatie

Patient activation is determined by the Dutch version of the Short Patient Activation Measure and consists of 13 items.(25) The PAM will be completed by patients randomized to online psychoeducation at t= 0, t= 16 and after 6 months and 1 year follow-up.

• Health literacy See F1.15_Gezondheidsvaardigheden

The Dutch version of the Newest Vital Sign (NVS-D) is used to measure participants' health literacy ability, it consists of 6 items assessing the ability to read and apply information from a nutrition label.(26, 27) Two subscales of the Digital Health Literacy Instrument (operation skills and navigation skills) are used to measure digital health literacy.(28) It will be completed by patients randomized to online psychoeducation at t= 0.

• Satisfaction See F1.16_Tevredenheid

General satisfaction is measured by one question about treatment satisfaction and will completed at the end of the post-treatment measurement (at t= 16 weeks).

• Recall of information See F1.17_Kennisvragen

Recall of information is measured using an adapted version of the Netherlands Patient Information Recall Questionnaire (NPIRQ).(29) It will be completed by patients randomized to online psychoeducation at the end of the post-treatment measurement (at t= 16).

• Symptom diary See F2_Symptom_diary

Study participants will be asked to fill out a daily symptom diary during run-in period, treatment period, post-treatment measurement and 5th month of follow up (t = -2 t/m t= 16, t = 5 months follow-up t/m t = 6 months follow up).

9.3.8 Missing data from questionnaires/electronic diary

Questionnaires should be completed within a predefined time-window. If not completed within this window, questionnaires for that specific time-point are closed and the answers are considered as missing data.

Time-windows are the following:
1. Weekly questionnaires that should be completing during the entire study period (treatment, post-treatment measurement and last month of follow-up), have to be completed within 1 week after the questionnaires have been sent to the patient. Other questionnaires that should be completed during the entire study period have to be completed within 3 weeks after the questionnaires have been sent to the patient.
2. The electronic diary should be completed each day during the run-in and treatment period. Questions from each day can be answered from 7pm until 12pm. If the diary entry has not been completed within this time-window, (residual) answers for that day will be considered as missing data.

9.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

9.5 Replacement of individual subjects after withdrawal

We anticipated dropouts within our sample size calculation.

9.6 Follow-up of subjects withdrawn from treatment

Subject withdrawn from the study will not be followed up, unless it seems necessary in case of any urgent medical reason.

9.7 Premature termination of the study

We don’t expect that this study will be terminated prematurely. However, if certain urgent medical problems occur during the study (for example SAEs that result in death or are life threatening) the investigator (if necessary together with METC or CCMO) can decide to halt the study to check whether it is safe to proceed or that termination is preferred.

10. SAFETY REPORTING

10.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

10.2 AEs, SAEs and SUSARs

10.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the trial procedure or study treatments. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

10.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator. An elective hospital admission will not be considered as a serious adverse event.

(S)AEs are reported from the moment of signing the informed consent until 4 weeks after discontinuation of treatment. During every hospital visit or call, patients will be asked about the occurrence any (S)AE.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to

complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

10.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

10.3 Annual safety report

Not applicable

10.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

10.5 Data Safety Monitoring Board (DSMB) / Safety Committee

Not applicable

11. STATISTICAL ANALYSIS

Statistical analyses will be carried out using IBS SPSS statistics 22.0 for Windows (Chicago IL, USA). Demographics, baseline characteristics (including the outcomes of the questionnaires at baseline) will be analysed and summarised using descriptive statistics. Dichotomous variables will be analysed using the Chi-square test. A Yates correction (continuity correction) or Fisher exact test will be performed if necessary. Normality of continuous or ordinal variables will be evaluated by the Kolmogorov-Smirnov test and histograms. The dependent variables will be analysed with the Wilcoxon signed-ranked test if the variables are not normally distributed. If the variables are normally distributed a paired t-test will be performed. The independent variables will be analysed with the Mann-Whitney test if the variables are not normally distributed. If the variables are normally distributed an independent sample t-test will be done. Correlations will be assessed according to Spearman or Pearson and regression analyses will be done. A p-value < 0.05 is considered to be statistically significant. A Bonferroni correction will be applied for multiple testing.

11.1 Primary study parameters

All endpoint analyses will be based on the intention to treat population. The proportion of responders (as defined by FDA recommendations) in each treatment group will be compared using multiple logistic regression to provide covariate adjustments for center, IBS subtype, gender, age and BMI in the analyses. The differences in responder rates, corresponding 95% confidence intervals (CIs) and two sided P-values will be calculated. An observed case approach to missing data will be applied for responder variables and continuous efficacy variables: if a patient does not have a score (responder/non-responder) for a particular treatment period week the patient will be considered a non-responder for that particular treatment period week. Patients are required to complete at least 4 diary entries (of 7) within one week, to be considered a responder. This approach is conservative and any bias is against treatment. A sensitivity analysis will be conducted using Baseline Observation Carried Forward (BOCF).

An interim analysis will be performed, when recruitment is completed, for t=16 weeks and t=6 months follow-up.

11.2 Secondary study parameters

Changes from baseline in scores for IBS-SSS, IBS-QoL, MCQ, PCQ, EQ-5D-5L will be analyzed longitudinally using a generalized linear model, based on the observed cases during the treatment period; treatment group, inclusion center, period, period by treatment interaction and subject as fixed effects and baseline values as covariates.

An interim analysis will be performed, when recruitment is completed, for t=16 weeks and t=6 months follow-up.

11.3 Cost-utility analysis

A trial based cost-utility analysis will be performed from a societal perspective with a time horizon of 1 year after completion of the 12-week treatment period. The outcome measure for the cost utility analysis will be the incremental costs per QALY (Quality Adjusted Life Year) gained. Patients will also fill in the generic quality of life questionnaire EQ-5D-5L at 6 months and 1 year in order to examine quality of life after patients stopped the treatment. The scores of patients on the EQ-5D-5L will be converted to utility scores by using the Dutch tariff based on the preferences from a general population.(30) Subsequently, QALY's are calculated by multiplying the utility score relating to a certain health state with the length of time a patient spent in that state. Decision analytic modelling will be used to examine the cost effectiveness of the treatment strategies. Resource use within and outside healthcare will be collected using the MCQ and PCQ, using a reference period of 1 year. In line with the guidelines for cost research, costs of productivity loss (both absenteeism and presenteeism) will be calculated by means of the friction cost method, based on the average standardized wages per hour. The friction cost method takes into account the time needed to replace a sick employee in order to restore the production at the original level.(31) With regards to the cost-effectiveness analysis, data will be analysed according to the intention-to-treat principle. Since the distribution of costs is general skewed, non-parametric bootstrap analysis will be used. This method estimates the sampling distribution of a statistic with replacement from original data.(32) In addition, bootstrap analysis will also be used to quantify the uncertainty surrounding the incremental cost-effectiveness ratio (ICER). Probabilistic sensitivity analysis will be performed to estimate for example the impact of parameters (like different cost-prices, utility) on the incremental cost-effectiveness ratio. Missing data will be imputed by a using a multiple imputation approach.

12. ETHICAL CONSIDERATIONS

12.1 Regulation statement

The study will be conducted according to the Declaration of Helsinski (last version October 2013, Brazil), the Medical Research Involving Human Subjects Act (WMO) and the FDA guidelines for the conduct of clinical trials.

12.2 Recruitment and consent

Patients with IBS (diagnosed according to the Rome IV criteria, the most widely accepted scientific criteria) will be recruited in both the primary and secondary/tertiary healthcare setting. In addition to recruitment via the treating physician, announcements will be placed on the website of the 'Prikkelbare Darmsyndroom Belangenvereniging', local newspapers (of areas of participating centers), social media and in GP practices in the Maastricht area.

Recruitment will start in 14 hospitals: Maastricht University Medical Center, AMC Amsterdam, Alrijne Hospital Leiden, Bernhoven Hospital Uden, Diakonessenhuis Utrecht, Gelderse Vallei Ede-Wageningen, Jeroen Bosch Hospital Den Bosch, Maasziekenhuis Pantein, Martini Hospital Groningen, MMC Veldhoven, Medical Center Leeuwarden, MST Enschede, Rijnstate Hospital Arnhem, Tergooi Hospital Hilversum and VUMC Amsterdam. All visits and study procedures will take place in the center the subject was included. Recruitment in the primary care will primarily take place in the south of Limburg. Patients included there will visit the MUMC for their screening and checkups.

Treating physicians will notify eligible IBS patients about the current study. If a patient is potentially interested in the study, the treating physician will ask the patient for permission to be contacted by the coordinating researcher (by telephone or email). Permission to contact the patient by telephone will be logged in the subject screening and enrolment log. If allowed by the patient, the treating physician will provide the coordinating researcher with the patient's telephone number either by telephone or via a designated e-mail address (specifically created for the current study). Further information will be provided verbally by telephone by the investigator and the written information brochure will be sent by regular mail or email. A time period of one week (minimum) is provided to decide whether the subject would like to participate. The subject is asked to contact the investigator by telephone or email if he or she would like to participate. If the patient does not contact the investigator however, the coordinating investigator will contact the patient once (at the earliest 7 days after sending the written information brochure, and only if the patient has given permission to do so during the first conversation). If the patient wishes to participate,

an appointment with the coordinating investigator or research nurse will be made for the medical screening. All subjects will have to sign an informed consent before screening can commence.

12.3 Benefits and risks assessment, group relatedness

Not all subject may benefit directly from participating this study. There is evidence given treatment cause relief of IBS symptoms.(16, 17) Therefore, it is expected that at least a part of patients will have some sort of benefit from participating in this study. Hypnotherapy has been shown to have long-term benefits, with 83% of responders in one study maintaining treatment benefits for 1–5 years after the course of treatment (7) and 75% of responders showing additional benefit after 2-7 years in another study.(8)

Hypnotherapy, when performed by an appropriately, is considered safe.(33) Multiple studies reported that no adverse events were observed. (34-36) One study reported that one patient complained of slight dizziness after the first session but continued the therapy.(37) One study reported one dropout due to panic attack during hypnosis sessions. Only in certain circumstances such as when a patient has a significant psychological co-morbidity (such as schizophrenia, epilepsy or bipolar disorder) is hypnotherapy contraindicated.(38)

Participating in this study will cost some time. There are three (digital) visits. The screening will take up to 1 hour. To report daily symptom scores in the electronic diary, takes approximately 30 seconds each day. Treatment with face-to-face hypnotherapy is delivered in a series of 6, bi-weekly 45-minute sessions. In addition, participants are asked to exercise at home for 15-30 minutes per day. Participants in the online hypnotherapy group will be requested to do home-work exercises using the online instrument for 15-30 minutes per day. To complete all the questionnaires during the study period take several hours.

The risks associated with participation are of such small extent that they are in proportion to the scientific value of the study. Because the efficacy of online hypnotherapy have not sufficiently been tested in IBS patients, it is essential to conduct this randomized controlled trial. This study can thereby yield useful information for doctors and IBS patients and thereby pave the way for a wider use of online hypnotherapy.

12.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

12.5 Incentives

Subjects completing the study will receive 100 euro compensation. Furthermore, we will compensate them for their travel expenses, reimbursing €0.19 per kilometre (with a maximum distance of living address to hospital of 100 km). If a subject visits the hospital for the medical screening, but does not meet the in- and exclusion criteria, travel expenses will be compensated. If a subject completes the run- in period, but can't be included for the treatment period due to an insufficient symptom score, the subject will be paid €12.50.

13. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

13.1 Handling and storage of data and documents

Data will be handled confidentially (coded) and the privacy of the subjects will be guaranteed. All subjects will receive an individual study ID-number, coded depending on the inclusion site:

- Maastricht University Medical Center: MUMC-001, MUMC-002 etc.
- AMC Amsterdam: AMC-001, 002 etc.
- Alrijne Hospital Leiden: AHL-001, AHL-002 etc.
- Bernhoven Hospital Uden: BHU-001, BHU-002 etc.
- Diakonessenhuis Utrecht: DIU-001, DIU-002 etc.
- Gelderse Vallei Ede-Wageningen: GVE-001, GVE-002 etc.
- Jeroen Bosch Hospital Den Bosch: JBH-001, JBH-002 etc.
- Maasziekenhuis Pantein Boxmeer: PAN-001, PAN-002 etc.
- Martini Hospital Groningen: MHG-001, MHG-002 etc.
- MMC Veldhoven: MMC-001, MMC-002 etc.
- Medical Center Leeuwarden: MCL-001, MCL-002 etc.
- MST Enschede: MST-001, MST-002 etc.
- Rijnstate Hospital Arnhem: RHA-001, RHA-002 etc.
- Tergooi Hospital Hilversum: THH-001, THH-002 etc.
- VUMC Amsterdam: VUA-001, VUA-002 etc.
- GP practices in South Limburg: GP-001, GP-002 etc.

Case Report Files (CRFs) will be coded and will not contain personal details of the subjects. Together with members of the project team, assigned monitors from the CTCM, IGJ and members of the medical ethical committee will have access to research data. In addition, ZonMw will have access to the coded research data (no original documents or personal patient information). All primary documents and data shall be kept for 15 years for possible inspection. The electronic CRF, electronic diary and electronic questionnaires will be build and stored by qualified organizations such as the Clinical Trial Center Maastricht (CTCM) and MEMIC, taking into account current regulations. Personal details of the subjects will be registered in Ldot, also a certified and secure database build by MEMIC. Data from the electronic diary (mobile phone application) will be stored on the NEN-7510 certified ITS-azM database. Data from the additional questionnaires and electronic CRF are acquired with Castor, which uses “True”, a NEN7510 and ISO 27001:2005 certified server, as per previous studies performed by our group (PERSUADE and TENDER, NL56000.068.16/METC 162009 and NL62932.068.17/METC 173051 resp.)

In the study, we specifically aim to create a data storage environment where only personal data are stored (Ldot), separately from patient-derived data (Castor and the smartphone daily dairy). In addition, the applications used as a part of the study intervention do not use any personal data and are generic instruments primarily aimed at education and assistance in self-management.

13.2 Monitoring and Quality Assurance

A qualified monitor of the CTCM will monitor the conduct of the study. A monitoring plan will be drafted after the first application to the METC.

13.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

13.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

13.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the sponsor will submit a final study report with

the results of the study, including any publications/abstracts of the study, to the accredited METC.

13.6 Public disclosure and publication policy

Results from this project will be published in international peer-reviewed journals, in the field of Gastroenterology and presented at national and international congresses. In accordance to specifications from the subsidizing party (ZonMw), these publications will all be open access. To further promote knowledge transfer and implementation, and in particular to reach general practitioners, results (and resulting recommendations) will also be disseminated in national journals. Results and recommendations will be presented to scientific societies responsible for national guidelines relevant for IBS (guidelines of the Dutch College of General Practitioners 'NHG richtlijnen'). The results will also be incorporated into continuous medical education for general practitioners and gastroenterologists and published in Dutch Medical Journals. Furthermore, the IBS patient federation (PDS Belangenvereniging) will assist in dissemination of study results among patients. Publication will be done in accordance with the CCMO-statement 'Publicatie beleid'.

14. STRUCTURED RISK ANALYSIS

14.1 Potential issues of concern

a. Level of knowledge about mechanism of action

Patients with IBS often demonstrate visceral hypersensitivity to painful stimuli, and abnormal central nervous system processing of pain.(4) Hypnotherapy has proven efficacious in IBS. The mechanisms responsible for the therapeutic success of hypnotherapy are partially unknown, but there are suggestions that is may act by affecting visceral sensitivity, gastrointestinal motor function and psychological distress.(39) Previous studies show that altering the emotional state of a patient with IBS using hypnosis can lead to a change in rectal sensation.(40, 41)

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

Psychological therapies are effective in reducing the IBS symptom severity and increasing quality of life and are recommended for the management of IBS by guidelines. Evidence appears strongest for the efficacy of hypnotherapy as psychological treatment. In a recent study in primary and secondary care patients, hypnotherapy was demonstrated to be superior to educational control intervention and group-therapy was non-inferior to individual hypnotherapy.(5)

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

Not applicable

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Not applicable

e. Analysis of potential effect

Hypnotherapy, when performed by an appropriately, is considered safe.(33) Only in certain circumstances such as when a patient has a significant psychological co-morbidity (such as schizophrenia, epilepsy or bipolar disorder) is hypnotherapy contraindicated.(38)

f. Pharmacokinetic considerations

Not applicable.

g. Study population

All participants are IBS patients aged 16-75 years.

h. Interaction with other products
Not applicable

i. Predictability of effect
The meta-analysis by Ford et al.(42) included 5 studies with 278 patients and concludes that hypnotherapy is effective with a NNT of 4 (confidence interval 3-8). A meta-analysis by Schaefert et al. included 8 randomized controlled trials with a total of 464 patients and concludes hypnotherapy was superior to control conditions in producing adequate symptom relief and reducing global gastrointestinal score with a NNT of 5.(34)

j. Can effects be managed?
See 13.1.e above.

14.2 Synthesis

Hypnotherapy, when performed by an appropriately, is considered safe.(33) Side effects of hypnotherapy can occur in participants with any psychiatric condition, we'll screen for anxiety and depression with the GAD-7 and PHQ-9 questionnaires during the screening visit, subjects which scores corresponds with moderate anxiety and depression are excluded from the study.

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