CLINCAL STUDY PROTOCOL

Efficacy of Open-label vs Double-blind Treatment in IBS.

IND Number: 126556
NCT Number: NCT02802241

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This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

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1. Study Objectives

1.1 Primary Objectives

The primary objectives of this study are to: (1) to determine whether 6 weeks of open-label placebo, double-blind placebo and no additional treatment control results in different clinical outcomes in patients with IBS and (2) assuming there are significant differences (a) to determine whether open-label placebo results in greater clinical improvement compared to no additional treatment control and (b) to determine if open-label placebo results in greater clinical outcome than double blind placebo.

1.2 Secondary Objectives

- To confirm our previous finding that the COMT val158met polymorphism is associated with placebo response.
- To replicate our previous finding that certain personality traits (extraversion, agreeableness, openness) are associated with the placebo response in IBS.
- Using ethnographic interviews to obtain insight into patients' experiences, including their views of the clinical encounter.
- An exploratory objective of the study is to obtain pilot data to assess whether double-blind peppermint oil results in greater clinical improvement compared to double-blind placebo in patients with IBS.

2. Background and Rationale

2.1 Background on IBS

IBS is one of the top 10 reasons for seeing a primary care physician, and the symptoms of IBS are present in 7-15% of the North American population. IBS is a chronic functional gastrointestinal disorder that is not a disease since there is no definitive pathophysiology or biomarker. Endpoints in clinical trials with IBS are based on subjective responses and include abdominal pain, altered bowel habits and bloating. The average placebo response in randomized double-blind placebo controlled trials in IBS is approximately 41%, making IBS a particularly good population to study placebo. The explanation for the high placebo response in clinical trials such as IBS is unclear and attempts at reducing the placebo response in clinical trials have been largely unsuccessful. To date no studies have compared double-blind placebo to open-label placebo as proposed in this study. This information is critical to understanding the effects of placebo as it relates to the design of clinical trials. Likewise, this information is critical to clinical practice, since clinical practice is unblinded yet decisions are based on inferences made from blinded randomized controlled trials. Including both blinded and open-label arms will allow us to quantify, for the first time prospectively, the difference in efficacy between these kinds of administrations. Such knowledge will strengthen inferences on clinical practice that are based on blinded randomized controlled trials.

2.2 Study Rationale

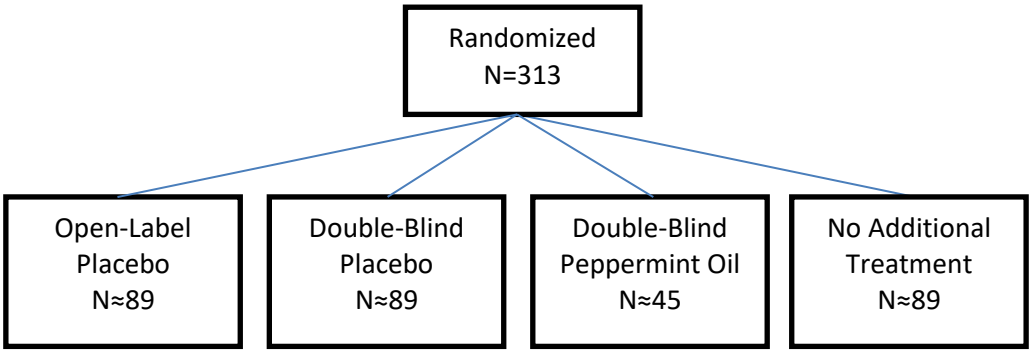
The vast majority of placebos are administered with concealment (i.e., blinded assignment in RCTs). Most clinicians and researchers believe that either deception or concealment is necessary to achieve a placebo response. To date, few studies have directly compared the effects of open-label placebo and double-blind placebo. We propose a novel, multi-disciplinary design to answer multiple clinical and research design questions concerning placebo effects.

3. Study Design

3.1 Overall Design and Plan of the Study

This study aims to investigate the effects of open-label placebos with double-blind placebos as administered in a randomized controlled trial in a 6-week trial with 313 IBS patients on standard treatment for IBS randomly assigned to one of four arms:

- open-label placebo
- double-blind placebo
- double-blind peppermint oil
- no additional treatment control.



3.2 Efficacy Assessments

Primary Outcome Measure

The primary outcome measure is the IBS symptom severity scale (IBS-SSS). The IBS-SSS is a questionnaire that measures the sum of the participant's evaluation on a 100 point scale of each of five items: severity of abdominal pain, frequency of abdominal pain, severity of abdominal distension, dissatisfaction with bowel habits, and interference with quality of life. All five components contribute equally to the score, yielding a theoretical range of 0-500, in which a higher score indicates a more severe condition. The responder will be considered a patient who has at least a 50 point decrease in their IBS-SSS from baseline to Visit 3. Using data from our previous IBS trial the calculated Cronbach's alpha is .70.

Secondary Outcome Measures

IBS-Adequate Relief: A single question: "In the last seven days, have you had adequate relief of your IBS symptoms? Yes/No"

IBS-Global Improvement: A single question: "Compared to the way you felt one week ago, have your symptoms over the past 7 days been: 1) Substantially Worse, 2) Moderately Worse, 3) Slightly Worse, 4) No Change, 5) Slightly Improved, 6) Moderately Improved or 7) Substantially Improved.

SF-12 Health Survey: An assessment that measures functional health and well-being.

PHQ-8: An 8-item scale that is used as a diagnostic and severity measure for depressive disorders in clinical studies.

GAD-7: A 7-item scale that is used as a diagnostic and severity measure for anxiety disorders in clinical practice and research.

Visceral Sensitivity Index: A measure of gastrointestinal symptom-specific anxiety.

Five Factor Inventory: A 60-item instrument that measures the "Big Five" dimensions of personality. Cronbach alphas for the five dimensions are: N = .79, E = .79, O = .80, A = .75, C = .83 (Costa & McCrae 1985).

Consultation and Relational Empathy Measure (CARE): Assesses physician empathy and relational skills on 10 ordinal items, which are then summed.

Expectancy Question: "If I receive placebo/peppermint oil/no additional treatment, I expect my IBS symptoms to be: "(numerical rating scale running from zero "not improved at all" to 100 "completely improved")

Balanced Inventory of Desirable Reach: Describes the tendency of respondents to answer questions that will be viewed favorably by others.

Pain Catastrophizing Scale: A scale that measures the tendency to magnify or exaggerate the seriousness of pain sensations.

Interpersonal Support Evaluation List: Designed to measure perceptions of social support among individuals in the general population

Daily Symptom Diary: Questions regarding subject symptoms will be completed daily for the seven day period prior to Visit 2 and Visit 3

Miscellaneous: Additionally, details of demographics, medical history, symptoms and adverse events will be recorded.

4. Selection and Enrollment of Participants

Approximately 313 IBS patients who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled.

4.1 Inclusion Criteria

To be eligible for enrollment, male and female patients must meet all of the following inclusion criteria:

1. Provide signed and dated informed consent and understand the nature of the study sufficiently to allow completion of all study assessments.
2. Be ambulatory, community dwelling, 18 to 80 years, inclusive
3. Meet Rome IV diagnostic criteria for IBS
4. Have IBS of at least moderate severity, i.e., have a score on the IBS-SSS of $\geq$ 175 (0-500) at the baseline visit
5. If the patient is on medications which affect the gastrointestinal tract or visceral sensation (e.g., tricyclic antidepressants, fiber, antispasmodics, etc.), must be on a

stable dose for at least 1 month prior to entering the study and for the duration of the study.

4.2 Exclusion Criteria

If any of the following exclusion criteria are met, the patient is not eligible for the study:

1. Self-reported pregnancy or planned pregnancy within the next two months.
2. Have an established diagnosis of any concomitant bowel disturbance that would interfere with the assessment of efficacy or safety in the study (e.g., Hirschsprung's disease, diverticulitis, colonic ischemia).
3. Report warning symptoms (e.g., rectal bleeding, weight loss >10%, iron deficiency anemia, etc.) otherwise not explained
4. Have undergone previous abdominal surgery of the intestines (with the exception of uncomplicated appendectomy, cholecystectomy, hysterectomy, or polypectomy $\geq$ 6 months prior to enrollment).
5. Have a history of drug, excluding nicotine or caffeine, or alcohol abuse within 2 years of entry into the study
6. Exhibit abnormalities on physical examination, unless judged to be clinically insignificant by the Investigator. Such cases will be noted.
7. Current, within the past 30 days, therapeutic use of enteric coated peppermint oil for the treatment of IBS
8. Known or suspected peppermint or soybean oil allergy
9. Severe acid reflux (> 3 episodes of heartburn or regurgitation per day on average over a week)
10. Inability to speak or read English
11. Unable or unwilling to cooperate with the study protocol or considered by the Investigator to be unsuitable for the study.

4.3 Screen Failures

Patients will be allowed to rescreen once if they do not meet inclusion criteria #4 or #5 at the initial screening visit.

5. Study Interventions

5.1 Interventions, Administration, and Duration

The study involves four groups as follows:

- open-label placebo 1 softgel TID (N~80)
- double-blind placebo 1 softgel TID (N~80)
- double-blind peppermint oil 1 softgel TID (N~40)
- no additional treatment control (N~80)

Placebo will be supplied as soybean oil (manufactured by SoftGel Technologies Inc.), matched to peppermint oil softgels (Pepogest™). The open-label and double-blind placebo are identical and both are matched to the peppermint oil. Each peppermint oil dose is 0.2mL. Study drug should be administered approximately 30 minutes before meal times.

5.2 Concomitant Interventions

Patients will be allowed to continue their IBS medications (e.g., fiber, anti-spasmodics, loperamide, etc.) as long as they had been on stable doses for at least 30 days prior to entering the study and agree not to change medications or dosages during the trial. Any non-pharmacological treatments for IBS (e.g. meditation, acupuncture, etc.) will be allowed as long

as they were on a stable pattern/behavior for at least 30 days prior to entering the study. All concomitant interventions will be recorded. Patients will be asked to refrain from making any major life-style changes (e.g., starting a new diet, changing their exercise pattern or starting a stress reduction program) during the study.

5.3 Study Drug Accountability

Accountability for the study drug will be the responsibility of the Research Pharmacy at Beth Israel Deaconess Medical Center. Drug accountability records indicating the study drug delivery date to the study center, inventory at the study center, and use by each subject will be maintained at the Research Pharmacy. These records will document that the subjects were provided the study drug as specified in the protocol.

All unused study drug will be retained at the study center.

6. Study Procedures

The study will consist of a screening telephone call no more than 60 days prior to the screening visit during which subjects will be assessed for study qualification. Eligible subjects will then undergo three visits – screening visit (baseline assessments and randomization will occur at this visit); midpoint visit; and endpoint visit.

6.1 Schedule of Evaluations

Assessment	**Screening Visit**	**Week 3 (± 5 business days)** **Midpoint Visit**	**Week 6 (± 5 business days)** **Endpoint Visit**
Informed Consent Form	X		
Clinician Interaction	X	X	X
Demographics	X		
Medical History	X		
Inclusion/Exclusion Criteria	X		
Physical Exam	X	X	X
Vital Signs	X		X
Current Medications	X		
Randomization	X		
Blood for Genetic Analysis	X		X
Questionnaires	X	X	X
Concomitant Medications		X	X

Adverse Events		X	X

6.2 Description of Evaluations
Potential participants will be screened by telephone to determine if they meet the Rome IV Criteria for IBS and do not suffer from other active diseases or are on medications that would disqualify them for enrollment.

6.2.1 Enrollment, Baseline and Randomization

Visit 1 (Baseline & Randomization): The informed consent will clearly indicate that the study is testing placebo; it will also clearly indicate that the placebo pills are inert, "like sugar pills." Subjects, who provide informed consent and fulfill the inclusion and exclusion criteria, including an IBS-SSS of at least 175, will be eligible to enter the trial. A research coordinator will assist in completion of questionnaires and collection of blood. A clinician with expertise in IBS will review the patient's history, perform a physical exam and confirm the diagnosis of IBS. Subjects will be randomly assigned to one of the four groups. Randomization will be accomplished by using sequentially numbered opaque sealed envelopes provided to the clinician. All assessments with the exception of blood collection will occur prior to randomization.

Depending on the assignment, subjects will be given a semi-scripted discussion regarding their assignment. The clinician will make every effort to assure equal attention, encouragement and patient-clinician relationship.

Subjects in all groups will be reminded not to make changes to their diet, exercise, and IBS medications, which may be continued during the study, provided that they are on a stable dose for 1 month. Subjects will be told to return in 3 weeks. (Note: Approximately 42 patients will be randomly selected to participate in the nested qualitative study and will undergo a detailed interview at the conclusion of Visit 3).

Subjects will be instructed on the completion of the daily diary to be completed nightly for the seven days prior to both Visit 2 and Visit 3.

6.2.2 Follow-up Visits

Visits 2 and 3: At these visits, the following procedures will be performed: vital signs (Visit 3 only), brief physical examination with clinician interaction, dispensation of pills (if appropriate), pill counts (if appropriate), review of concomitant medications, and documentation of adverse events. A research coordinator will assist in completion of questionnaires and collection of blood. Whenever possible, the same treatment provider will see the patient for all visits.

Vital signs will not be recorded in the source documents, as they are done to mirror a standard clinic visit from the subject perspective and will not be analyzed.

6.2.3 Sample Collection
Genetic variation in genes encoding proteins involved in several neurotransmitter pathways has been shown to modify response to placebo treatment. This study will build on these findings to examine how placebo treatment modifies gene, protein and miRNA expression as well as changes in metabolism that may be associated with differential response to placebo treatment.

Although all these genomic studies will not be run in the primary study, it is important to collect samples that will allow these analyses to be done in the future. Aliquots of plasma, serum, white cells and red cells will be de-identified and stored at -80C. Samples will be collected at baseline and at the end of the study.

GWAS will be conducted to identify genes implicated in modifying placebo response.

6.2.4 Blinding

Blinding of the double-blind treatment groups will be maintained throughout the study by using procedures that are identical in method and appearance. The assessor who administered the questionnaires will be blinded to all groups. For patients randomized to either of the double blind administration groups, the clinician will be blinded to the treatment administered (peppermint oil or placebo).

The Investigator and study center personnel will not have access to the randomization code during the study except in the case of an emergency. Breaking the blind for a subject will only be done in the event of a medical emergency where the identify of study drug is necessary to appropriately treat the subject. If the blind is broken, the reason and date will be documented. Every attempt will be made to maintain the blind throughout the study.

6.2.5 Completion/Final Evaluation

Efforts will be made to complete data collection on all subjects regardless of compliance with treatment. Those who are not compliant will be noted.

There will not be any additional study procedures done for subjects that discontinue early.

7. Safety Assessments

7.1 Adverse Events and Serious Adverse Events

Adverse Event: An AE is any untoward medical occurrence in a patient administered a study product and which does not necessarily have a causal relationship to the study product. Patients will be instructed to contact the Study Team at any time if any symptoms develop.

Serious Adverse Event: An SAE is an event that:

- Results in death
- Is immediately life threatening
- Requires inpatient hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability and/or incapacity, or
- Is a congenital anomaly/birth defect

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

At every study visit, patients will be asked questions to elicit medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens. Any difference in responses to any question on the side effects questionnaire between visits will not be considered an adverse event unless the subject verbally informs the research team.

7.2 Reporting Procedures

All AEs observed from the time the patient receives the first treatment until the last follow-up visit will be recorded on the CRF. The description of the AE will include the type of event, onset date, assessment of severity, date of resolution of event, seriousness, any required treatment of evaluations, and outcome.

All SAEs will be reported to the Beth Israel Deaconess Medical Center Institutional Review Board (IRB). In addition, the FDA will be notified of all serious and unexpected AEs in an IND safety report no later than 15 calendar days after awareness of the event and 7 days after a suspected unexpected serious adverse event that results in death.

A formal report from the DSMB will be supplied to NCCIH, which will be communicated to the PI and the Beth Israel Deaconess Medical Center. Each report will conclude with a recommendation to either 1) continue the study without changes; 2) continue the study with changes; or 3) terminate the study. This recommendation will be made by formal majority vote and fully justified by the preceding report.

Any AEs observed that are unanticipated will be reported under the following schedule:

1. Unanticipated problems that are serious adverse events will be reported to the IRB within 1 week of the investigator becoming aware of the event.

2. Any other unanticipated problem will be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.

8. Statistical Considerations

8.1 Randomization

Treatment assignments will be generated using permuted block randomization with randomly varying block sizes. Randomization will be done in a 2:2:2:1: ratio (open-label placebo; double-blind placebo; no treatment control; double blind peppermint oil). Randomization for the qualitative sub-study will be done. Randomized assignments to one of the four groups will be sealed in sequentially numbered opaque envelopes.

A random subset of approximately 57 of the participants will be selected for participation in the nested qualitative study. The participants will be randomly selected in the same ratio as the primary randomization. Care providers will be blinded to participation in the sub study. A list of selected randomization IDs and access to the REDCap patient scheduling module will be provided to the interviewer so that he or she can conduct the qualitative interview after the participant has completed the final clinical evaluation.

8.2 Stratification

Stratification will be based on IBS symptom severity score (< 300 and ≥ 300) and gender, resulting in 4 strata. Each stratum will have a different color randomization envelope and a unique set of randomization ID numbers.

8.3 Analyses

All tests will be two-tailed with α=.05. For our primary analyses, we will use a modified intention-to-treat analysis including any patient who was randomized and provided a baseline assessment and at least one post-baseline primary outcome assessment. We will also run per protocol analyses, and any substantive differences between the two methods will be reported.

We will examine the amount of missing data and the nature of the missingness (missing completely at random, missing at random, and missing not a random). If necessary, we will conduct a full intention to treat analysis.

Aim 1. To determine whether 6 weeks of open-label placebo, double-blind placebo and no-treatment results in different clinical outcomes. To test this aim, we will conduct a one-way analysis of covariance. In addition to treatment group, the model will include baseline IBS-SSS and stratification factors for gender and symptom severity.

Assuming that there is a significant difference between the 3 groups, Dunnett's analysis will be used to do pairwise analyses of the following aims

1a. To determine if 6 weeks of open-label placebo results in superior clinical outcome than no treatment control. Hypothesis: open-label placebo > no treatment control.

1b. To determine if 6 weeks of open-label placebo results in superior clinical outcome than double blind placebo. Hypothesis: open-label placebo > double-blind placebo.

Secondary Aims Analysis Plan: There are three secondary multi-disciplinary aims in this study.

Secondary Aim 1 (Genetics Aim): In our previous large RCT we found that the number methionine alleles in COMT val158met was associated with placebo responses especially to a combined placebo and supportive patient-provider relationship. We plan to confirm these findings and extend them by evaluating additional candidate genes implicated in placebo. Exploratory analyses will be performed in other candidate genes associated with placebo including: the mu-opioid receptor polymorphism (OPRM1 A118G), FAAH polymorphisms Pro129Thr. monoamine oxidase gene polymorphisms, and serotonin-related polymorphism CGTTLPR and G-703T (polymorphism in the tryptophan hydroxylase-2 (TPH-2) gene promoter)**.**

DNA will be extracted from those study participants who agree to the genetic screening and will be analyzed by a TaqMan allele discrimination assay. Subsequently, COMT and other candidate genotypes will be correlated with response to placebo or active drug treatment using the above mentioned outcomes. Furthermore, potential correlations of the COMT and other genotypes and patient-disease characteristics, for instance pain experience at baseline, will be examined.

Secondary Aim 2 (Psychological Aim): In our previous large RCT in IBS we found that higher levels of extraversion, agreeableness, and openness to experience are associated with increased response to placebo treatment, especially with an augmented patient-practitioner relationship. We will use the Five Factor Inventory (FFI) to measure these personality traits and

then use multiple regression to examine their association with outcomes after controlling for baseline severity.

Secondary (exploratory) Aim: To determine if 6 weeks of double-blind peppermint oil results in greater improvement than double-blind placebo in patients with IBS. Hypothesis: Double-blind peppermint oil > Double-blind placebo. To test this aim, we will conduct an analysis of covariance. In addition to treatment group, the model will include baseline IBS-SSS and stratification factors for gender and symptom severity.

8.4 Power Calculations: To estimate the effect size for Aim 1, we used our previous pilot trial in IBS. In that study, the effect size for the difference between open-label placebo and no-treatment on the IBS Symptom Severity Scale was d=0.53. For this comparison, there will be 88 patients in each group, and using ANCOVA to control for baseline scores leaves the power for the 3 group comparison at .96. To estimate the power for secondary (exploratory) aim using ANCOVA to control baseline scores leaves the power of .60; however, using more recent data that suggest an effect size of d=0.50, the power would be .78.

8.5 Missing Data Minimization Strategies: Missing data minimization strategies includes patient retention efforts and a modified intent-to-treat analysis. Each individual patient reported assessment will be captured electronically at each visit with missing responses prohibited by the electronic system.

9. Administrative Requirements

9.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Files will be established at the beginning of the study, maintained for the duration of the study, and retained according to appropriate regulations.

9.2 Data Management

Data will be recorded and stored via REDCap. Data will be recorded on REDCap as the study is in progress. All passwords will be strictly confidential.

9.3 Protocol Deviations/Violations

If a subject does not complete a daily diary entry, it will not be considered a protocol deviation/violation. If blood is not obtained at either Visit 1 or Visit 3, it will not be considered a protocol deviation/violation.

Appendix 1

Schedule of Study Procedures

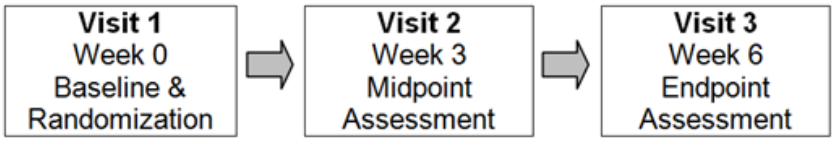


Figure 6: Study Flow Diagram

Appendix 2

IBS-Severity Scoring System

Instructions
These questions are designed to enable us to record and monitor the severity of your IBS. It is to be expected that your symptoms might vary over time, so please try and answer the questions based on how you currently feel (i.e. over the last 10 days or so). All information will be kept in **strict** confidence.

1. For questions where a number of different responses are a possibility please circle the response appropriate to you.
2. Some questions will require you to write in an appropriate response.
3. Some questions require you to put a cross on a line which enables us to judge the severity of a particular problem.

Please place your cross (X) anywhere on the line between 0-100% in order to indicate as indicate as accurately as possible the severity of your symptom.

This example shows a severity of approximately 90%.

0%|----------X-----| 100%
no pain not very quite severe very
or discomfort severe severe severe

1. Do you currently suffer from abdominal pain? ☐ Yes ☐ No

1b. If yes, how severe is your abdominal pain? *Please make an "X" anywhere on the line.*

0%|----------| 100%
no pain not very quite severe very
or discomfort severe severe severe

1c. Out of 10 days, how many days do you experience abdominal pain? _____

2. Do you currently suffer from abdominal distention (bloating, swelling, or tightness)?

☐ Yes ☐ No

2b. If yes, how severe is your abdominal distention? *Please make an "X" anywhere on the line.*

0%|----------| 100%
no distention not very severe quite severe severe very severe

3. How satisfied are you with your bowel habit? *Please make an "X" anywhere on the line.*

0%|----------| 100%
very happy quite happy unhappy very unhappy

4. How much does your IBS affect or interfere with your life in general? *Please make an "X" anywhere on the line.*

0%|----------| 100%
not at all not much quite a lot completely

Appendix 3

List of Evaluations to be Completed at Each Visit

Paper Source Documents

Evaluation	Visit 1	Visit 2	Visit 3
Telephone screening			
Original signed ICF	X		
Physical Examination	X	X	X
Rome IV Diagnostic Criteria	X		
IBS-SSS	X	X	X
Visit 1 Template	X		
Visit 2 Template		X	
Visit 3 Template			X
Concomitant Medication Log	X	X	X
Adverse Event Log		X	X
Blood Collection	X		X

Entered Directly into RedCap

Evaluation	Visit 1	Visit 2	Visit 3
Rome IV Module	X		
Symptom Questionnaire		X	X
Why are you participating?	X		
IBS-ARS	X	X	X
IBS-GIS	X	X	X
Blinding Question		X	X
Expectancy Question	X		
Medication Adherence Questionnaire		X	X
Side Effects Questionnaire	X		X
PHQ-8	X		
GAD-7	X		
VSI	X		X
SF-12	X		
FFI	X		
CARE			X
PCS	X		X
BIDR			X
ISEL-12	X		X
Daily Questionnaire			

* All questionnaires above are completed by the subjects. The demographic and Visit 1 IBS-SSS data in RedCap is completed by stuff staff.