# Research Protocol

# Irritable Bowel Syndrome Outcome Study (IBSOS)


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# 1. EXECUTIVE SUMMARY

## 1.1 Title of Study

Self-administered cognitive behavior therapy for IBS: A multi-center study

## 1.2 Trial Acronym

IBSOS (Irritable Bowel Syndrome Outcome Study)

## 1.3 Study Purpose

This multi-site clinical trial is designed to assess the short- and long-term efficacy of cognitive behavior therapy (CBT) for irritable bowel syndrome using two treatment delivery systems (self-administered, therapist-administered). Secondary aims seek to specify the conditions under which CBT may (or may not) achieve its effects (moderator questions), why and how these effects are achieved (mediator questions) and to determine the economic cost and benefits of the therapies. Long-term project goals are to develop an effective self-administered behavioral treatment program that can enhance the quality of patient care, improve clinical outcomes, and decrease the economic and personal costs of one of the most prevalent and intractable GI disorders.

## 1.4 Objectives

***Primary***: Evaluate the short-and long-term effects of a minimal-contact, home-based, patient-administered version of CBT compared to a standard, clinic-based, therapist-administered version of CBT and a psychological placebo (attention control) condition on improving global IBS symptoms.

***Secondary***: To identify clinically useful patient characteristics associated with outcome as a way of gaining an understanding of subgroups of participants for whom CBT is most beneficial; to identify theory-based change mechanisms (active ingredients) that explain how and why CBT achieves therapeutic objectives; to evaluate the economic costs and benefits of CBT relative to control conditions.

## 1.5 Population

Male and female participants 18-70 (inclusive) years of age, suffering from IBS as defined by the Rome III criteria.

## 1.6 Treatment Arms

- Minimal Contact Cognitive Behavior Therapy (MC-CBT)
- Standard Cognitive Behavior Therapy (S-CBT)
- Attention Control Condition (ACC)

# 2. STUDY SCHEDULE AND TIMELINE

IBSOS is a prospective, randomized, multi-site clinical trial comparing three types of psychotherapy delivered in an individual format for severely affected adults with IBS. After a four-week baseline data collection period, participants will be randomly assigned to receive either four-session self-administered CBT, 10-session therapist-administered CBT or a control condition emphasizing support and education (allocation 1:1:1). The acute treatment phase will last 10 weeks. Participants will undergo follow-up examinations two weeks after treatment ends (week 12) and three, six, nine, and 12 months after the end of treatment.

IBSOS requires the expeditious enrollment of a sufficient number of participants to ensure the statistical power and generalization of study results. This trial plans to recruit 480 participants over an approximately four-year treatment delivery period. Assuming a relatively conservative pre randomization dropout rate of 25%, each site will need to phone telephone screen approximately 150 participants per year and enroll (consent) 75 in order to meet yearly recruitment quotas of 60 randomized participants at each site.

## 2.1 Duration of Study and Visit Schedule

After a one-year clinical trial planning phase, the study will begin recruitment of 480 Rome diagnosed adults. Recruitment is scheduled to occur over 48 months. The acute treatment phase will be administered over 10 weeks. Participants assigned to standard CBT will attend 10 weekly sessions. Participants assigned to either the limited contact or attention control treatments will attend four clinic visits scheduled over 10 weeks. Participants will undergo post-treatment evaluation two weeks after their assigned treatment ends (week 12) and at quarterly intervals (three, six, nine, 12 months) out to 12 months. Follow-up of all participants will continue until the last participant randomized has completed 12 months of follow-up.

***See Appendix 1: IBSOS Protocol Overview***

***See Appendix 2: IBSOS Detailed Work Flow***

# 3. STUDY OBJECTIVES

The major objectives of the IBSOS clinical trial are:

## 3.1 Primary Objective

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| **Aim 1.** To evaluate the efficacy of MC-CBT compared to S-CBT and attention control for IBS. |

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| **Hypothesis 1**: Both MC-CBT and S-CBT are superior to attention-control on the primary endpoint of global improvement of IBS symptoms and secondary endpoints of satisfactory relief of IBS symptoms, quality of life, change in stool consistency, psychological distress, IBS symptom severity, participant satisfaction, and health care use.<br><br>**Hypothesis 2**: Equivalence testing will show that MC-CBT does not differ from S-CBT on primary (global IBS symptom improvement) or secondary endpoints**.** |

## 3.2 Secondary Objectives

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| **Aim 2.** To identify clinically useful participant characteristics associated with outcome as a way of gaining an understanding of subgroups of participants for whom CBT is most beneficial. |
| **Hypothesis 1**: Variables such as treatment motivation at baseline and rapid treatment response will be positively associated with treatment outcome after the acute treatment phase of CBT and through follow-up periods**.**<br><br>**Hypothesis 2**: Interpersonal distress and extra-intestinal medical problems at baseline will be negatively associated with treatment outcome after the acute treatment phase of CBT and through follow up. |

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| **Aim 3.** To identify theory-based change mechanisms (active ingredients) that explain how and why CBT achieves therapeutic objectives. |
| **Hypothesis 1**: Changes in the severity of IBS symptoms are partly mediated by changes in participants' beliefs regarding the causality (locus of control) and controllability (self efficacy) of IBS symptoms.<br><br>**Hypothesis 2**: Changes in the severity of IBS symptoms are partly mediated by nonspecific factors such as a strong therapeutic alliance and positive expectancy of improvement. |

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| **Aim 4.** To describe the cost and cost effectiveness of MC-CBT, S-CBT and attention placebo for IBS. |
| **Hypothesis 1**: MC-CBT is associated with decreased direct and indirect cost compared to SCBT and associated with increased direct and indirect cost compared to attention control.<br>**Hypothesis 2**: MC-CBT will prove cost effective relative to either S-CBT or attention control. |

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| **Aim 5.** To assess long-term durability of acute treatment effects of CBT at 3-, 6-, 9-, and 12 month follow-ups. |
| **Hypothesis**: Participants assigned to both CBT conditions will maintain treatment gains with respect to attention placebo through quarterly follow-up periods extending to 12 months after treatment completion. |

## 3.3 Primary Efficacy Endpoints

The primary efficacy endpoint is as follows:

- Participant-rated global improvement of IBS symptoms. A participant is considered to be a treatment responder if s/he rates IBS symptoms for which s/he sought treatment as markedly to moderately improved using the Clinical Global Impressions Scale–IBS version.

## 3.4 Secondary Efficacy Endpoints

Secondary efficacy endpoints include the following:

- Adequate relief of abdominal pain two weeks after the end of treatment phase and at quarterly intervals through 12 months
- Adequate relief of bowel problems two weeks after the end of treatment phase and at quarterly intervals through 12 months
- Change from pre-treatment baseline of lower GI function (i.e. stool frequency; stool consistency; severity of urgency, bloating and straining) to post-treatment, and at quarterly follow-ups
- Change from pre-treatment baseline in ratings of (a) severity of abdominal pain/discomfort and (b) global severity of IBS symptoms to post treatment and at quarterly follow-ups
- Change from pre-treatment baseline in indices of health related quality of life to post treatment, and at quarterly follow-ups
- The percent of participants who describe themselves as satisfied with assigned treatment at 2-week follow-up using the Client Satisfaction Scale.
- Change from pre-treatment baseline in psychological well-being (e.g. overall mental well-being and discrete emotional problems such as anxiety, depression, somatization) to post treatment, and at quarterly follow-ups

- Change from pre-treatment baseline in health care use to post-treatment, and at quarterly follow-ups
- Gains in estimated quality adjusted life years (QALYs) from pre- to post-treatment
- Change from pre-treatment baseline in extraintestinal symptoms to post-treatment, and at quarterly follow-ups
- The percent of participants responding positively to treatment as measured by the adequate relief of pain and adequate relief of bowel symptoms
- The percent of participants who report adequate relief, improved symptoms, and clinically significant reduction of IBS symptoms by week four (rapid response)
- Safety as measured by the occurrence of adverse events

The future status of global measures of relief/improvement as primary endpoints for IBS trials is unclear. The FDA, for example, contends that Rome recommended global endpoints (e.g. adequate relief) which IBSOS adopted are conceptually and methodologically problematic and have encouraged the development of a participant reported outcome (PRO) instrument that captures the key IBS symptoms and their day to day burden from the participants' perspective. Because the development of an IBS PRO is a time-consuming process whose completion would effectively suspend the development of novel biobehavioral treatments (CBT, drugs), the FDA has proposed interim endpoints for participants with IBS-D and IBS-C. These are described below. For IBS-C, a participant is regarded as a weekly responder on the basis of prospective improvement (from pre-treatment to post-treatment reduction during acute phase) in pain intensity *and* stool frequency.

## 3.5 Pain Intensity Responder

- Decrease in weekly average amount of "worst abdominal pain in past 24 hours" score of $\geq$ 30%
- Pain graded on a 11 point Numerical Rating Scale (NMRS) of 0-10 (where 0 = no pain, 10 = worst pain imaginable)

## 3.6 Stool Frequency Responder

- An increase of at least 1 complete spontaneous bowel movement (CSBM) per week from baseline
- For IBS-D, a participant is regarded as a weekly responder on the basis of pain intensity and stool consistency

## 3.7 Stool Consistency Responder

- Equal or less than type 5 in weekly average of the Bristol Stool Form Scale

# 4. STUDY POPULATION

## 4.1 Number of Sites and Participants

The sample will consist of 480 adult (18-70 inclusive) volunteers (240 participants x two sites) who meet Rome III diagnosis of IBS. The sites were chosen partly to yield a geographically and ethnically diverse sample that is broadly representative of individuals with IBS. The IBSOS infrastructure includes the Administrative Core (CC) at the University at Buffalo (Buffalo, New York). The AC is directed by Project PI Dr. Lackner. Northwestern University Feinberg School of Medicine (Chicago, Illinois), the other clinical site, is led by SI Dr. Keefer, who serves as vice chair of the IBSOS. The AC at UB is responsible for oversight for both clinical sites. Each clinical site is responsible for the recruitment, retention, and safety of their participants and for the acquisition and integrity of the study data.

*See Appendix 3: Study Organizations*

## 4.2 Participant Eligibility

The eligibility criteria for IBSOS identify adult participants with moderate to severe IBS who are likely to adhere to the intervention, for whom the intervention is safe, and whose data can be interpreted clearly. The inclusion and exclusion criteria are primarily based on Drs. Lackner, Krasner and Keefer's experience with NIDDK R01, "Cognitive Therapy for IBS: Process, Predication, and Outcome"; Dr. Lackner's pilot study, "Development of a limited contact CBT for IBS"; and guidelines for the conduct of clinical trials for therapies of functional GI disorders. The logic behind our eligibility criteria is to be as unrestrictive as possible while ensuring the safety of participants and maintaining the internal validity of the study.

*See Appendix 4: Eligibility Criteria*

## 4.3 Participant Recruitment

A key factor that determines the success of any clinical trial is recruitment of eligible participants of an adequate sample size. Low rates of recruitment have negative implications, such as longer duration of the clinical trial, which may lower staff and participant morale, a costlier clinical trial, since extra resources may need to be allocated to the recruitment effort, and reduced statistical power. Like all trials, the IBSOS requires the expeditious enrollment of a sufficient number of participants to ensure the statistical power and generalization of study results. This trial plans to recruit 480 participants over an approximately four-year treatment delivery period. Assuming a relatively conservative pre randomization dropout rate of 25%, each site will **need to phone telephone screen approximately 150 participants per year and enroll (consent) 75 in order to meet yearly recruitment quotas of 60 randomized participants at each site.**

Based on the PIs' (Drs. Lackner, Keefer) success in meeting accrual goals in two NIH trials with similar eligibility criteria as the proposed trial, the lead investigators anticipate no difficulty meeting enrollment goals and have formally committed to meeting yearly accrual goals as scheduled prior to grant submission. The sooner IBSOS can achieve its enrollment goals, the faster data are collected, analyzed, and shared with the larger community to improve the management of IBS.

### 4.4 Recruitment and Retention Plan

Site investigators will formally present their formal recruitment plan at the initial four- to five-day training workshop before recruitment is initiated. The sites will review their plans continually throughout recruitment in order to determine its effectiveness and report progress to the Steering Committee regarding failed screens, the productivity of recruitment strategies, and barriers to recruitment. Data shared with the SC will include number of inquiries, telephone screens, recruitment methods (self-referral, health care provider, broadcast media, etc.), and the rate of screen-to-evaluation turnover. If a center is not achieving its recruitment goals in a timely fashion, the recruitment plan may need to be modified.

It is expected that the research team at each site and across the sites will form a dynamic system of support for problem solving and developing of IBSOS-specific recruitment techniques that expeditiously meet the accrual goals of the trial.

Each clinical center will develop a formal site-specific recruitment plan for meeting the recruitment goals and requirements of IBSOS. It is expected that the plan will address any unique features of catchment area characteristics, media market outlets, anticipated barriers (participant-, investigator-, and protocol-related) and strategies for working around them, and access to IBS participants. When composing such a plan, attention should be paid to issues regarding research ethics and strategies to enhance diversity in the study population.

## 5. ASSIGNMENT TO TREATMENT GROUPS

### 5.1 Randomization

Participants in the IBSOS will be randomly assigned to one of three treatments. Random assignment is important to ensure that the different experimental treatments will be given to comparable groups of participants. Treatment assignments will be generated using an existing web-based participant registration and randomization system at Frontier Science. This system uses protocol-specific specifications files to present questions to the sites to evaluate a participant for eligibility. Only participants who meet all the eligibility requirements can be randomized to the study. The participant enrollment system also collects basic demographic information at the time of enrollment. The Protocol Data Manager at Frontier Science will work with the Principal Investigator and Project Statisticians to develop these files based on the eligibility criteria of the protocol. Treatment allocation assignments are stratified by clinic site. This will ensure initial comparability between groups of eligible participants, for whom treatments are compared, thus eliminating the impact of individual and site difference variables on outcome.

## 5.2 Blinding

In most RCTs, participants and the treating physician are "blind" or "masked" to the treatment and do not know if the participant is receiving drug or placebo. The methodological criterion of blinding participants to assigned treatments is inapplicable to psychological interventions [1]. To the extent that blinding seeks to control differential expectations and consequent demand characteristics they may generate, then we will adopt the established, surrogate practice of having participants rate credibility of the treatment to which they were assigned and their expectancy of improvement using the Treatment Expectancy Scale [2] at the conclusion of Session 1.

***See Appendix 5: Adverse Event Reporting***

***See Appendix 6: Interruption or Discontinuation of Therapy***

# 6. DESCRIPTION OF THERAPY

The IBSOS features two specific types of psychological treatment, either Education Supportive Counseling (Attention Control Condition) or Cognitive Behavior Therapy (CBT). Cognitive Behavior Therapy will be delivered in two “dosages”: a home-based, self-administered version (four sessions) or a clinic-based, therapist delivered version (10 sessions). In this respect, the trial features three discrete treatment conditions:

- Ten-session, therapist-administered CBT
- Four-session, participant-administered CBT
- Four-session Attention Control Condition

The Attention Control Condition represents a credible attention-placebo condition that provides adequate control for the non-specific factors (e.g. attention from university-based medical staff and faculty) that foster improvement in participants treated with CBT. Thus, the trial will feature three treatment arms. All treatments will be manualized and conducted on an individual, outpatient basis by a highly trained therapist.

Complete explanations of these therapies can be found in the Treatment Manuals. The following section provides a brief summary of the nature, structure, and format of featured treatments:

## 6.1 Standard CBT (S-CBT)

S-CBT is a skills-based training program [3] that involves 10 weekly, one-hour individual sessions. Treatment is structured around six overlapping phases:

1. Information and education regarding stress and its relationship to IBS
2. Self-monitoring of stressful situations associated with IBS episodes
3. Muscle relaxation exercises both to increase physiological self regulation and to cultivate a sense of mastery or self control over symptoms

4. Learning to identify, reevaluate, and change negatively skewed thoughts associated with IBS
5. Changing underlying schemas or “core” beliefs (e.g. perfectionism)
6. Formal training in problem solving to strengthen the ability to cope more effectively with realistic stressors associated with IBS weekly home exercises are assigned to facilitate skills acquisition.

## 6.2 Minimal-Contact CBT (MC-CBT)

MC-CBT covers the same range of procedures featured in S-CBT but relies extensively on self-study materials to facilitate skills building. Additionally, whereas the S-CBT condition involves 10 one-hour clinic visits, MC-CBT meets for only four, one-hour clinic visits over a 10-week period.

1. At the first MC-CBT session, treatment is explained, self-study materials are provided and muscle relaxation and self-monitoring are introduced.
2. The second treatment session introduces cognitive coping techniques (e.g. decatastrophizing through prediction testing).
3. At the third session, participants learn problem-solving techniques and more advanced cognitive coping skills (e.g. modifying core beliefs such as perfectionism).
4. The fourth session introduces relapse prevention skills.

In the MC-CBT condition, two 10-minute phone contacts are scheduled at weeks 3 and 7 to troubleshoot around any problems encountered between clinic visits.

## 6.3 Attention Control Condition (ACC)

ACC is an educational and supportive counseling-based program that is administered in the format of four, one-hour individualized sessions over 10 weeks. It has been closely adapted from the psychological placebo intervention used by various psychosocial researchers [4, 5, 6] to control for nonspecific therapeutic influences inherent in CBT. The attention placebo procedure features a combination of educational presentations and supportive psychotherapy. The educational component presents information about IBS, its clinical features, epidemiology, diagnostic criteria, medical tests, and treatment options. This condition specifically avoids relaxation training, cognitive restructuring, or problem-solving techniques featured in CBT. Therapists will be trained to avoid disseminating specific behavioral instructions or routines that would directly facilitate behavioral self change. Instead, the attention control condition provides attention, a credible therapeutic rationale (i.e. that learning information about IBS, sharing one’s personal experiences of having a chronic illness, and having access to an understanding health care provider can help alleviate the burden of IBS), and other common elements of a psychotherapeutic relationship, while avoiding the theoretical and procedural elements specific to CBT. In this respect, the attention control satisfies key requirements of an “active” control condition [7].

The format of the attention control condition parallels the MC-CBT condition (four

monthly sessions with two 10-minute phone calls and self-study materials). Previous studies demonstrate that an education/supportive psychotherapy condition whether administered in group, individual, brief or extended format produces evaluations of credibility and outcome expectations similar to those generated by CBT [6, 8-10]. It is recognized as a best available placebo control condition for IBS and other comparable disorders [9, 11-13].

To control for receipt of self-help materials, participants will receive a copy of *IBS: Learn to Take Charge of It* [14], an evidence-based participant education book that accentuates the therapeutic value of information ("It all comes down to this: An informed participant is an empowered one") over structured behavioral skills instruction featured in CBT.

# 7. DATA ANALYSIS

## 7.1 Overview of Data Collection Schedule

In general, clinical interviews and questionnaires constitute the primary method of obtaining clinical data. The assessments described below were chosen according to the following principles:

- Use of standard, widely used or recommended assessment measures to maximize acceptance and comparability of findings with other studies
- Measures of multiple outcome criteria
- Psychometric properties, including established reliability and validity

The assessment will generate the following information:

- Data to be used for the screening of participants based on the inclusion and exclusion criteria
- Data to be used to evaluate the outcomes of treatment
- Outcome mediators and predictors

Data will be collected at three main stages of the trial: pre-treatment baseline, during active treatment, and at follow-up.

The main purpose of baseline assessment data is: (1) to confirm eligibility and (2) to obtain a reference level of functioning against which immediate and long-term treatment effects are to be judged. For this reason, most baseline measures will be re-administered at the end of treatment (two-week follow-up) and at quarterly follow-ups. Because a major goal of the IBSOS trial is to identify the active ingredient of CBT (i.e. mechanisms of change), a limited number of symptom measures *will be periodically assessed during the active treatment phase* along with a variety of "process" measures that tap psychosocial processes believed to account for treatment effects.

***See Appendix 7: Data Collection Schedule***

***See Appendix 8: Description of Assessment Measures***

## 7.2 Approach to Data Integrity

To ensure the study runs effectively, a number of steps have been taken:

1. Standardized outcome measures will be applied.
2. The manual of operations: a detailed manual has been prepared listing all staff responsibilities, staff training, coordination between sites, quality control, handling of reports, data coding and entry, data access restrictions, protocol for contingencies, and preparation of progress reports.
3. Training and study monitoring: standardized training has been given to ensure consistency across sites. This includes: all personal undergoing various training seminars, ongoing consultation with regular bi-weekly conference calls between sites, and standardized monitoring.
4. Data collection and entry: comprehensive Case Report Forms (CRFs) will be entered at each site by trained graduate and undergraduate assistants. Data entry will be performed on secure computers and networks and sent to the study's data coordinating center at Frontier Science. At Frontier Science, the data will be reviewed, missing data checked with the study site if required, and the information will be stored for data analysis.

### 7.2a Data Coordination and Backup

Consistency checks will be routine across forms and visits. Data files will be backed up regularly. Frontier Science has extensive infrastructure to support the data collection, entry, and management needs of the IBSOS study.

### 7.2b Data Queries and Reports

Monthly reports will be generated by Frontier Science to each study site summarizing recruitment, compliance, errors, changes, clarifications, and other relevant information.

## 7.3 Preliminary Data Analysis

Prior to formal analysis, preliminary analyses will be conducted to provide perspectives on missing data, intent-to-treat analyses, attrition, normality of distributions, variance heterogeneity, non-model based outliers, *a priori* factor structures of multi-item instruments, reliability, and clustering (due to site).

For the primary questions, one set of analyses will establish whether the effects of MC-CBT and S-CBT are comparable. This will be pursued from two perspectives: a traditional hypothesis testing framework and an equivalence testing framework. For each outcome variable, there are assessments at baseline (BL), an immediate posttest (12W FU) and at three-, six-, nine-, and 12-month follow-ups (FU3, FU6, FU9 and FU12) for each of three groups (MC-CBT, S-CBT and an attention control, AC). The traditional analysis for a given outcome variable is a two-way analysis of covariance using the three groups as a between-participants factor, time as a within-participants factor (12W FU, FU3, FU6, FU9 and FU12) and the baseline score as a covariate. Single degree of freedom contrasts focus on the pairwise comparisons of adjusted

means within a given time period (e.g. comparing MC-CBT, S-CBT and the AC). These analyses will reveal group differences on outcomes at different points in time. Because of the limitations of null hypothesis testing for asserting equivalence between two conditions, we will apply equivalence testing strategies to evaluate functional equivalence between conditions using methods described in Welleck [15]. These methods will be applied in the context of the above analysis-of-covariance framework.

Another important analysis will be formal modeling of the long-term durability of acute treatment effects at three, six, nine, and 12 months post-treatment. Analyses will compare the decay functions of the different groups to determine if the decline (or improvement) in treatment effects from IM to FU12 differ depending on the type of treatment received. This will be pursued using SEM based growth curve modeling methods. The statistical technology for these analyses is described by Duncan et al [16].

Another set of analyses will identify baseline participant characteristics that predict response to treatment and identify time varying mediators of response to treatment. For mediation analyses, both mediators and outcomes are measured at baseline as well as IM, FU3, FU6, FU9 and FU12. Most of the mediators also are measured during treatment, typically every other week as is an outcome proxy, the IBS symptom severity scale. One analytic strategy can be illustrated using IBS self-efficacy to predict within treatment variability in response to outcome at the immediate posttest (IM). An early response mediation model states that IBS self-efficacy gains experienced early in treatment (e.g. from B to W1 and W3) are the primary determinants of the ultimate response to treatment at IM. A recency mediation model states that the level of IBS self-efficacy at the last treatment session (W12) is the primary mediator of IM response to treatment. A growth curve mediation model states that it is the general acceleration/deceleration of IBS self-efficacy across the entire treatment session (as well as the shape of the curve) that best predicts response to treatment at IM (with IBS self-efficacy being as parameterized as a growth curve per Figure 1). A fourth model is one that incorporates all three types of mediational influence into a single estimating equation, with linear coefficients attached to each to reflect their relative influence in impacting treatment response. The baseline outcome variable is used as a covariate and the IM outcome is used as the criterion. All three sources of influences will be parameterized and modeled as predictors of change at IM as well as the decay functions characterizing change from IM to FU12. Models also will be pursued that include multiple mediators in the same model. Moderator analyses will be pursued by including product terms in the models.

## 7.4. Formal Data Analysis

### Aim 1

The primary focus of Aim 1 is to establish whether the effects of MC-CBT and S-CBT are comparable. We will pursue this from two perspectives: a traditional hypothesis testing framework and an equivalence testing framework. For the core outcome variables, we have assessments at baseline (BL), immediate post-test (FU W12) and at three-, six-, nine-, and 12-month follow-ups (FU3, FU6, FU9 and FU12) for each of three groups (MC-CBT, S-CBT and the active comparison control (attention control)). The traditional analysis for a given outcome variable is a two-way analysis of covariance

using the three groups as a between-participants factor, time as a within-participants factor (IM, FU3, FU6, FU9 and FU12) and the baseline score as a covariate. Single degree of freedom contrasts focus on the pair-wise comparisons of adjusted means within a given time period (e.g. comparing MC-CBT, S-CBT, and the attention control condition). Of interest is whether there are statistically significant pair-wise contrasts between the groups. We will pursue such contrasts using non-pooled error terms across time (because of the likely violation of sphericity), but with pooled error terms across groups within time (unless diagnostics suggest otherwise). We will use the program M Plus to estimate the single degree of freedom contrasts (by translating the analysis of covariance model into an SEM framework). M Plus has the capability to take into account cluster effects, should that be necessary, and it also offers robust algorithms.

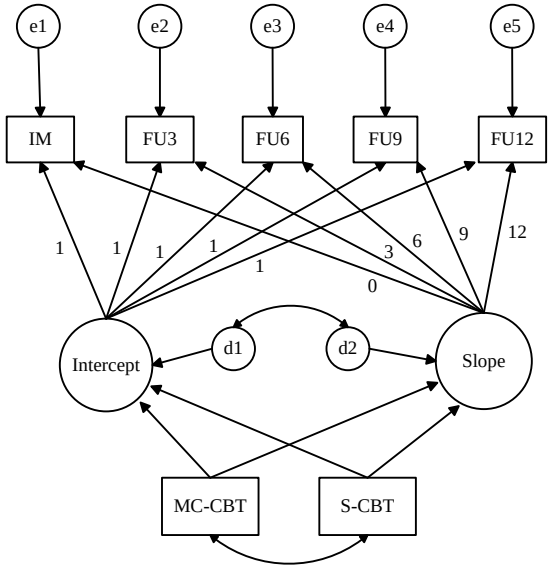
In terms of statistical power, for a single degree of freedom contrast between two independent groups with a single covariate, the approximate sample size needed to achieve power of 0.80 for an adjusted mean difference of d = 0.50 (using Cohen's d) is approximately 65 per group. To achieve power of 0.90 requires a sample size of 85 per group. Our sample sizes easily meet these standards.

## Aim 5

Aim 5 emphasizes evaluating the long-term durability of acute treatment effects at three, six, nine, and 12 months post-treatment. Accordingly, a second type of analysis will compare the decay functions of the different groups, to determine if the decline (or improvement) in treatment effects from IM to FU12 differ depending on the type of treatment received. For example, it might be found that the beneficial effects of MC-CBT decline more rapidly than S-CBT in the months following the completion of the formal treatment regimen. This can be tested using growth curve analysis in an SEM framework. For a single outcome and a linear growth curve, the basic growth curve model is parameterized using figure 1. The three treatment groups are represented by two dummy variables. The intercept represents the score at IM and the slope represents the linear decay function. The path coefficients from the dummy variables to the latent slope variable represents group differences in the average slope characterizing the decay function. The statistical technology for executing these analyses is straightforward and well-developed [16, 17]. It is possible that the decay functions are non-linear. One strategy for modeling non-linear trajectories is to use quadratic regression, but this can yield parameter estimates that are difficult to interpret or the non-linearity may not be quadratic in form. An alternative approach is to use spline regression in which meaningful spline knots are identified and then slopes are measured between knots. This approach is readily incorporated into growth curve analyses and involves representing each slope defined by knots as a distinct latent variable. We will use M Plus to estimate the parameters of the growth curve. The program has the capability to take into account cluster effects due to site, should that be necessary, and it also offers robust algorithms.

In terms of statistical power, using the power analysis methods described by Raudenbush [18], we set the duration parameter at 4, the frequency of observations at 1, the standardized effect size reflecting the ratio of the group mean difference to the standard deviation of the true change component at 0.50, the within-person variance at

1.0 and the growth parameter variance at 1 (all creating a rough approximation to standardized effects). For a linear growth curve, statistical power of 0.80 is achieved with a sample size of approximately 75 per group in a two-group contrast of growth curves, and power of 0.90 is achieved for a sample size of approximately 95 per group. For a quadratic growth curve, the sample size required under the same conditions for power of 0.80 is approximately 90 per group and for power of 0.90 it is approximately 110 per group. These estimates map favorably onto the sample sizes for the proposed research.




In sum, we will use traditional analysis of covariance to compare the treatment groups at a given point in time and growth curve modeling to compare the decay functions in groups after treatment.

**Figure 1. Basic Growth Curve Model**

## Equivalence Testing

A premise of the proposed research is that the brief version of CBT (MC-CBT) for IBS will be about as effective as the extended version (S-CBT). A problem with traditional null hypothesis testing is that one can never accept the null hypothesis; i.e., one can never declare that two means or two average growth curves are exactly equal. All one can do is fail to reject the null hypothesis. The problem of declaring equivalence between treatments has been addressed in the statistical literature on bio-equivalence testing and we will adapt this perspective in the current research. The spirit of the approach is to specify an *a priori* population threshold value (TV) where meaningful differences between groups can be said to emerge. To take a commonplace example, if we compare the annual incomes of males and females and the mean difference in salary is $3, this is a trivial difference that for all practical purposes does not matter. The mean annual salaries are "functionally equivalent." However, a mean difference in annual income of $3,000 is meaningful and has important implications for the lifestyles of the two groups. The key to equivalence testing is specifying a TV such that if a population difference is between –TV and +TV, then one concludes that the group difference is trivial and that the two groups are "functionally equivalent." If the population difference exceeds +TV or is lower than –TV, then the groups are declared non-equivalent. Equivalence testing is implemented by testing two directional hypotheses with respect to a predefined value of TV using standard tests of significance; one hypothesis that the population mean difference is greater than –TV and the other that

the population mean difference is less than +TV. If both null hypotheses are rejected relative to the alternative hypotheses, then one is confident that the true population difference is somewhere between –TV and +TV. This leads to a formal assertion of functional equivalence in the groups. A statistically equivalent form of this test is to compute confidence intervals about the mean difference in the sample data. If the upper limit of the interval is less than +TV and the lower limit of the interval is greater than –TV, then functional equivalence is declared.

The issues involved in applying equivalence testing are well known and discussed in Wellek [15]. The confidence interval approach can be easily adapted to comparing adjusted mean differences in the analysis of covariance framework described earlier, as well as comparing decay functions in the growth curve analyses. A key issue in this portion of the research is the development and specification of conceptually and empirically justifiable threshold values. For example, for the IBS-SS scale, it is commonly argued that a 50-point reduction represents the cutoff for meaningful change[19]. This suggests that a TV of 50, such that if the population mean difference between the treatments is between -50 and +50, then the interventions are deemed functionally equivalent. Stated more formally, if the lower limit of the relevant confidence interval for the mean difference in the sample data is greater than -50 and if the upper limit is less than +50, then the interventions are declared functionally equivalent. Our previous research with the IBS-SS yielded scores that ranged from 82 to 422 with a standard deviation of approximately 78. The estimated half-width of a 95% confidence interval for a two group mean difference with a sample size of 160 per group (using a tolerance value of 90%) is approximately 18, indicating our sample size will yield interval widths that are viable for making statements of functional equivalence for this measure. As another example, the accepted standard in the field for a clinically meaningful change on the IBS Quality of Life measure (which ranged from 15 to 92 in our previous work, with a standard deviation of 19.5) is 14 units [20]. If two treatments yield a population difference between -14 and 14, then they can be declared functionally equivalent. The estimated half-width of a 95% confidence interval for this measure given our sample size is approximately 4, again indicating our sample sizes can sustain this type of analysis. The statistical and methodological issues for building empirical support for threshold values can be complex and are discussed elsewhere [21, 22].

## Aims 2 and 3

Aims 2 and 3 emphasize identifying baseline participant characteristics that predict response to treatment (hence reflecting moderators of the effects of the interventions) and also identifying time-varying mediators of response to treatment. Response to treatment can be defined in terms of: (1) group differences in an outcome at a given point in time, (2) variation in decay functions after treatment, or (3) variations in change from baseline to the immediate post-test within a given group (i.e. within MC-CBT or within S-CBT). Statistical strategies vary depending on how response to treatment is operationalized.

With respect to mediation, an important facet of mediation analysis is specifying the correct time interval between the change in a mediator and change in the outcome of interest. Changes in a mediator may translate into instantaneous changes in an

outcome or, alternatively, it may take some time before the change in the mediator translates into change in the outcome. If one assesses the mediators after changes have occurred, but measures the outcome *before* the changes in the mediators have manifested themselves in the outcome, one is at risk of misdiagnosing the importance of the mediator. Unfortunately, the time dynamics by which mediator effects translate into outcome effects are not well understood in the IBS area. We will measure our mediators and outcomes at baseline as well as IM, FU3, FU6, FU9 and FU12. We also will measure most of the mediators during treatment, typically every other week, and we will gather a weekly assessment of an outcome proxy, the IBS symptom severity scale. This frequent assessment of mediators and outcomes has the advantage of allowing us to formally explore temporal dynamics with mediators and outcomes within the context of SEM frameworks.

The richness of the data can be illustrated by considering one example; namely, IBS self efficacy used to predict within-treatment variability in response to outcome at the immediate post-test (IM), pooling the MC-CBT and S-CBT groups to bolster the stability of parameter estimates. IBS self efficacy is measured at baseline (BA) and during weeks 1, 3, 5, 7, 8 and 12 of the acute treatment phase (i.e. W1, W3, W5, W7,W8, W12). There are several plausible mediation models that may bear on results. An ***early response mediation model*** states that IBS self efficacy gains experienced early in treatment (e.g. from B to W1 and W3) are the primary determinants of the ultimate response to treatment at IM. A ***recency mediation model*** states that the level of IBS self efficacy at the last treatment session (W12) is the primary mediator of IM response to treatment. A **growth curve mediation model** states that it is the general acceleration/deceleration of IBS self efficacy across the acute treatment phase (as well as the shape of the curve) that best predicts response to treatment at IM (with IBS self efficacy being as parameterized as a growth curve per Figure 1). A fourth model is one that incorporates all three types of mediational influence into a single estimating equation, with linear coefficients attached to each to reflect their relative influence in impacting treatment response. The baseline outcome variable is used as a covariate and the IM outcome is used as the criterion. It is possible to use the M Plus software to parameterize all three sources of influences and then test their relative contributions. Note that this can be done to predict response to treatment as measured at IM or it can be used to predict decay functions characterizing change from IM to FU12. Models also can be pursued that include multiple mediators in the same model, thereby permitting complex multivariate explorations of the data.

## Aim 4

The following section outlines the steps for the economic analysis of the costs and cost-effectiveness of S-CBT and MC-CBT relative to the attention control group.

***Aim 4A (Cost Hypothesis)*:** The MC-CBT intervention will have lower costs per person than the S-CBT.

***Aim 4B (Cost Hypothesis)*:** Both S-CBT and MC-CBT will be cost-effective relative to the less costly but also less effective attention control. MC-CBT will be at least as effective as S-CBT, and given its lower costs, MC-CBT will be cost-effective relative to S-CBT.

Hypotheses 4A and 4B require us to estimate the costs of each intervention and then to combine the cost and effectiveness data to estimate the cost-effectiveness of each intervention relative to the studied alternatives. Cost-effectiveness analysis compares the differences in cost with effectiveness across alternative policy options. The results are expressed as the incremental cost per unit of incremental outcome change, yielding ratios such as the incremental cost per reduction in health care utilization (e.g. days of inpatient hospital stay).

## Cost Collection

To perform a cost-effectiveness analysis, we need estimates of both the effectiveness of the interventions and the costs of each intervention. Because most of the data required for the cost-effectiveness analyses will already be collected for the effectiveness analysis, we will estimate the costs of the interventions, regardless of whether the interventions are found to be effective. Our cost study methodology will follow the micro-costing approach recommended by [23] and [24] and which was implemented in [25] and [26] for costing of methadone treatment services and in [26] in the context of the Combining Medications and Behavioral Interventions for Alcoholism (COMBINE) randomized control study of alternative alcohol treatments. This approach identifies, measures, and values the resources associated with each activity of the intervention. Our primary perspective for the cost analysis is the provider and includes only the provider costs and excludes costs incurred by private consumers or households. We recognize that the societal perspective is often cited as the appropriate perspective to use [23-24]; however, as there is no social decision maker, most cost-effectiveness analyses adopt the provider perspective to make the analysis more relevant to real-world situations. However, another primary decision-maker is the participant. Few studies consider the participant's perspective in estimating costs and cost-effectiveness even though these costs may have a substantial impact on a participant's treatment choice, his or her ability to access treatment, or his or her treatment adherence. As part of our sensitivity analysis, we will expand our analysis to estimate participants' costs such as time, travel expenses, and out-of-pocket health care expenses and to analyze the impact these costs have on the interventions' cost-effectiveness.

Estimating the costs directly attributable to the intervention conditions requires collecting both variable and fixed costs incurred in providing the interventions. Variable costs vary directly with the services provided and include time spent providing participants with M-CBT or S-CBT sessions and the cost of session materials. Fixed costs do not vary with the provision of services; they include expenditures on building space, utilities, and general office supplies.

The first step in conducting this type of cost analysis is to define fully the interventions being delivered and to identify all the associated activities. Once intervention activities are identified, the next step is to identify the resources that may be used to deliver the intervention (e.g. type of labor, space). The final step is to identify the costs of the resources used in the intervention. The analysis will make a distinction between one-time startup costs and ongoing implementation costs.

## Cost Analysis

Once data on resources used and the unit costs of those resources are gathered, we will derive cost estimates for various intervention activities, including both startup and ongoing implementation activities, following the methodology in [27]. The labor costs of each activity are equal to the product of the amount of time spent by each person on the activity and his/her hourly wage. For salaried staff, salary will include the actual hourly wage plus a fringe rate that covers all benefits. To estimate space costs, the size of the room used for each activity will be multiplied by the annual market rental price per square foot prorated by the time for which the room is used for that activity. Finally, we will multiply the unit cost of materials used during the delivery of the intervention with the quantity used per intervention session. For each participant in a given intervention, the total cost of the intervention is simply the cost per activity multiplied by the number of activities or services received by the participant during the intervention, and taking the mean across participants in a given intervention yields the mean per-participant cost of that intervention.

## Cost-Effectiveness

In the event that the two studied interventions are effective relative to the attention control group, we will implement a cost-effectiveness analysis. Our cost-effectiveness methodology will follow the approach described in the literature [23, 28-29] and that has been implemented in [26, 30-31] in the context of randomized control trials (RCTs). We will combine the cost estimates described above with intervention effectiveness measures of changes in outcomes related to IBS. To perform the cost-effectiveness analysis, the costs and outcome measure for each intervention under study will be tabulated in increasing order of effectiveness (or cost). Starting with the intervention with the smallest effectiveness (or cost), cost-effectiveness ratios will then be computed for each intervention relative to the next most effective option after eliminating intervention options that are dominated by other interventions [23, 32]. To derive the cost-effectiveness ratios, we will calculate the difference in costs and outcomes between each intervention. The incremental cost-effectiveness ratio will then be calculated as the ratio of the difference in costs to the difference in outcomes. An intervention may be dominated in either a simple sense (higher cost and lower effectiveness than another option) or in an extended sense (higher cost-effectiveness ratio than a more effective option). In either case, the cost of achieving a given level of the outcome is lower if the dominated intervention is eliminated.

We will calculate cost-effectiveness acceptability curves (CEACs) as an alternative to confidence intervals for ICERs [33-34]. The CEACs incorporate the inherent variability of the cost and effectiveness estimates and they show the probability that an intervention is the most cost-effective as a function of the policymaker's intrinsic valuation or willingness to pay for the outcome. We will use nonparametric bootstrap methods to calculate CEACs. (See also [26, 35-36].)

## Sensitivity Analysis

After we have conducted the CEA, we will conduct a sensitivity analysis. The objective of a sensitivity analysis is to assess whether the cost-effectiveness results are affected

by changes in model parameters, such as key assumptions made in the cost analysis. We will perform one-way sensitivity analyses in which we examine the effect of changing one of the model parameters, holding all other parameters constant. We will also perform n-way sensitivity analyses in which n parameters of the model are varied jointly, holding all other parameters constant.

## 8. BACKGROUND AND RATIONALE

Irritable bowel syndrome (IBS) is a common, painful, and often disabling gastrointestinal (GI) disorder characterized by abdominal pain/discomfort associated with alterations in bowel habits. As a functional disorder, IBS lacks a reliable biomarker and is therefore best understood from a biopsychosocial perspective [37]. The bowel abnormalities may manifest in constipation, diarrhea, or both in alteration. IBS is estimated to afflict 6-14 million of the adult population in the U.S. [38]. Even though most IBS participants do not seek medical attention, IBS remains one of the most common GI disorders and more common than such important disease as diabetes, asthma, ischemic heart disease, and hypertension [39-40]. IBS accounts for 40% of the referrals made to gastroenterologists (GE) and is the 7$^{th}$ leading diagnosis made by primary care physicians in the U.S. [40]. IBS is also costly in terms of medical treatments and diagnostic procedures [41], time lost from work [42], and non-monetary costs such as diminished quality of life [42-43] and activity limitations [44]. A conservative estimate of the combined social and economics costs of IBS is $20 billion annually [45-46]. It is believed that the lack of a satisfactory medical treatment partly drives these costs [47].

There is therefore a demand among primary care physicians, gastroenterologists, health insurance providers, participants [48-49] and their employers for effective self-management treatments for those who are most burdened by IBS, derive limited relief from conventional medical options, and consume a disproportionate share of scarce health care resources.

Our previous research has provided a strong, empirical foundation for performing a randomized clinical trial of the effects of MC-CBT, relative to those evoked by S-CBT and an appropriate attention-control (psychological placebo) condition, on participants' reports of overall improvement as well as improvement in clinical symptoms, psychological distress, and related measures of quality of life and health care usage. This clinical trial also will address five critical aims that have not been examined in previous outcome studies involving CBT or other behavioral therapies. These issues are: (a) the extent to which the CBT conditions produce outcomes that are superior to those produced by a credible attention-placebo condition that adequately controls for the non-specific effects of CBT; (b) identification of baseline participant characteristics, psychosocial variables, and extra-intestinal medical problems that may predict or moderate participant outcomes; (c) identification of cognitive and psychosocial variables that may mediate the outcomes produced by CBT interventions; (d) determining the cost-effectiveness of MC-CBT relative to those produced by S-CBT and attention-placebo control conditions, and e) clarifying the long-term durability of treatment effects.

## 8.1 Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) is a time-limited, highly structured, problem-focused, and prescriptive therapy based on two central underlying assumptions:

1) Symptoms are acquired (learned) and reflect specific skills deficits in domains of cognitive and behavioral functioning
2) Teaching and rehearsing skills for modifying maladaptive behaviors and thinking patterns can remediate these deficits which, in turn, relieves symptoms.

Specific technical components of CBT protocols typically include:

- Information about stress and its relationship to IBS
  - Self-monitoring of antecedent and consequent events associated with IBS
- Problem solving strategies around stressors that aggravate symptom flare-ups
- Muscle relaxation exercises for cultivating lower physiological arousal and increased sense of mastery over symptoms
- Cognitive restructuring for modifying faulty threat appraisals that underlie physiological and emotional reactivity.

These techniques administered either singly (e.g. cognitive therapy techniques alone) or in combination with other interventions have been featured in 24 randomized clinical trials (RCTs) between 1985 and 2005. The first generation of CBT trials suffered from many methodological flaws. However, as the quality of trials have improved [50], a more positive picture of CBT's therapeutic value emerges. In comparison with passive control conditions (e.g. waiting list, no-treatment conditions), CBT generally yields broad improvements in key GI symptoms (pain, bowel dysfunction), quality of life [43], and psychological distress [50]. Less impressive, albeit statistically significant, results have emerged from the few trials [5, 51] that have pitted CBT against an active control (attention placebo) condition that controls for nonspecific therapy effects. These data underscore the importance of adding an attention placebo arm to determine whether CBT's effects are due to particular techniques specified by cognitive behavioral theory (i.e. social learning theory [52]) or to nonspecific therapy effects.

CBT has practical limitations restricting its clinical utility. Assuming an hourly charge per 50-minute session of $90 [53], a 12-week regimen of individual CBT [5] costs $1,090. The average wholesale price of a 12-week regimen [5] of desipramine, [one of the more efficacious pharmacological agents [5]], is $221.76 per participant [54]. Beyond cost, logistical problems add to CBT's utility problems. Access to CBT is currently restricted by its time intensiveness (median treatment hours = 16 hours [55]), high level of demand and limited availability of adequately trained therapists [56], especially in geographical areas not served by the 5 academic medical centers (US) which deliver CBT for IBS. Clearly, CBT suffers from a very significant technology transfer problem. As the "second generation" of IBS treatments emerges, it is increasingly clear that efficacy demonstration is a necessary but not sufficient condition of treatment viability. An unmet need exists for a brief form of CBT that is less costly, time intensive and more transportable, yet retains the clinical efficacy of the "gold standard" CBT delivered in routine office settings.

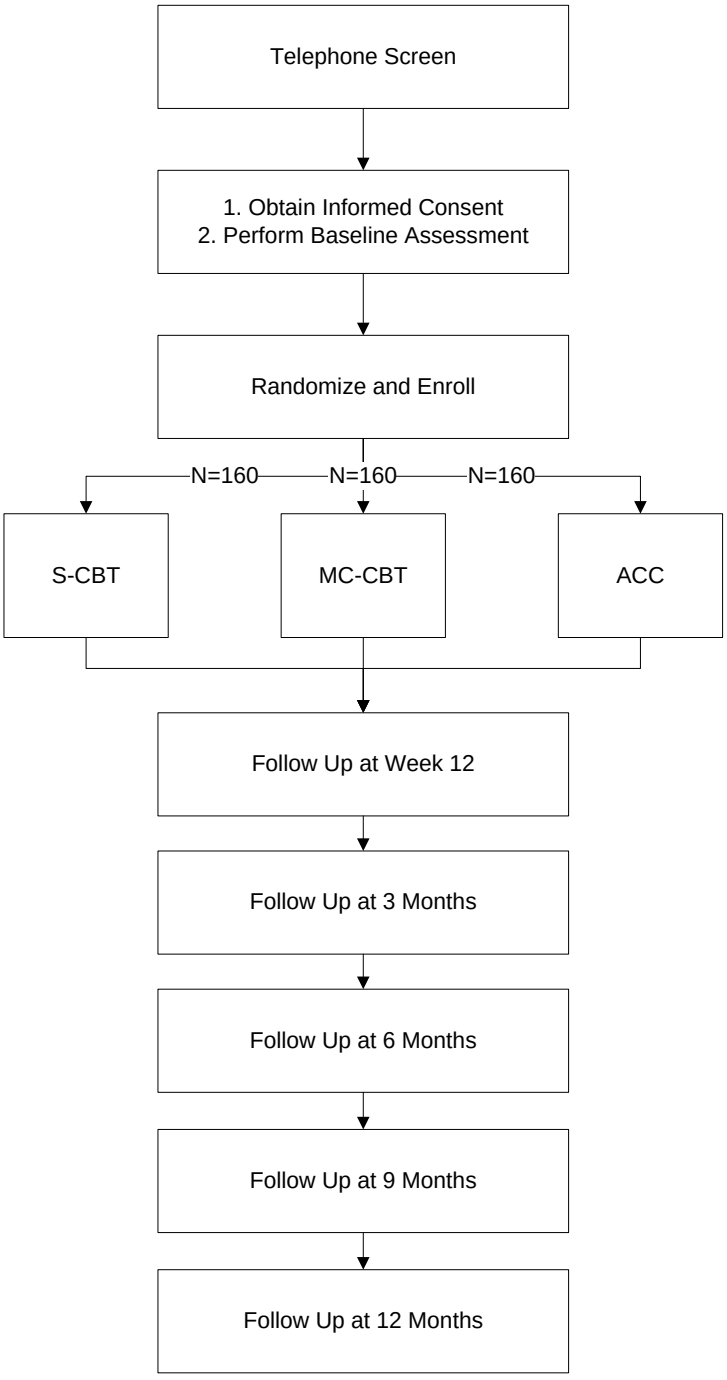
One strategy for tackling high treatment delivery costs involves decreasing therapist contact time through the use of primarily self-administered or “home-based” treatments. A self-administered version of CBT could (1) increase the numbers and types of symptomatic people who attain relief from IBS symptoms at relatively low cost and (2) help conserve and allocate scarce health care resources to those participants who require more intensive, clinic-based care. If self-administered CBT is found to be effective, this line of research would represent a major advance in the treatment of this common, often intractable GI disease.

## 8.2 Minimal-Contact CBT

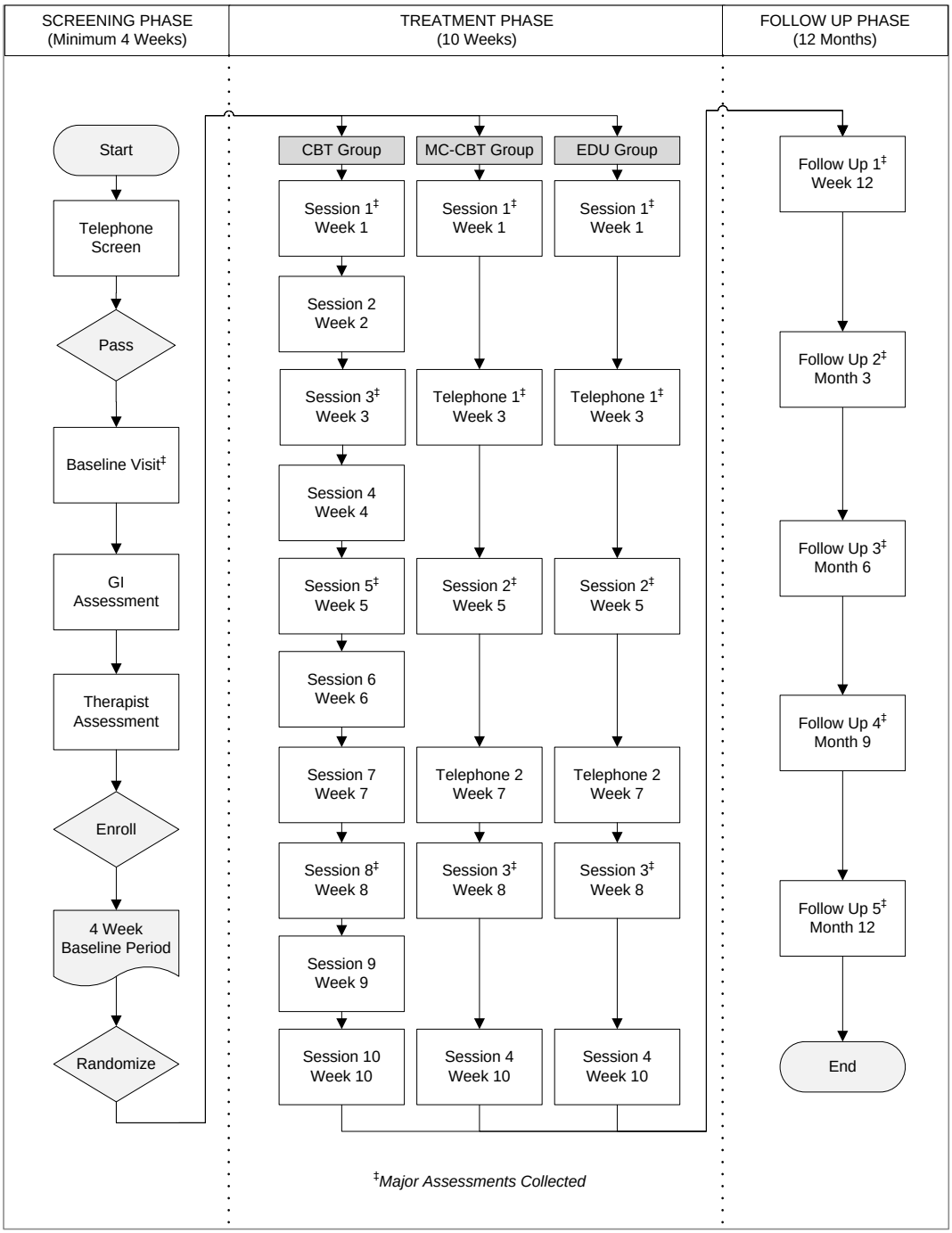
In a minimal-contact (MC) treatment (e.g. Holroyd [57]), self-management skills are introduced in periodic (e.g. monthly) clinic sessions but most of what is taught in clinic-based CBT is learned at home using self-study materials developed by the PI. As a result, MC-CBT requires only four clinic sessions rather than the 10-20 weekly sessions featured in the literature. Potential advantages of an MC-CBT approach include: compatibility with the number (six) of sessions most psychotherapy participants attend[58]; greater participant involvement; a reduction in participant costs (direct and opportunity); expanded availability of services; lower stigma; easier scheduling and penetration into underserved areas; and more rapid integration into routine clinical settings participant to yearly HMO limits on outpatient counseling visits. Research exploring the monetary benefit of limited contact treatments in general indicates that the cost effectiveness index of limited contact treatments is more than five times larger than that of clinic-based therapies [59]. In a health care culture emphasizing a stepped care approach, an MC-CBT treatment may represent a logical first step intervention for individuals who require more than advice, reassurance, or simple lifestyle changes, but a less complex, restrictive, and costly option than specialty care settings typically provide. Potential disadvantages of an MC-CBT approach include greater investment of time, effort, and motivation for the participant at home, and fewer opportunities for corrective feedback. Research that has directly pitted MC-CBT against S-CBT for behavioral medicine problems shows that MC-CBT generally perform at least as well as more time- and labor-intensive versions on primary clinical endpoints [59-60].

These findings provide a data-based rationale for performing tests of the feasibility of a brief CBT for IBS.

# APPENDIX 1: IBSOS Protocol Overview



# APPENDIX 2: IBSOS Detailed Work Flow



# APPENDIX 3: Study Organizations

Participating institutions include the Administrative Core (UB) and two clinical centers: Northwestern University (NU) and University at Buffalo (UB). Frontier Science functions as the trial's Data Coordinating Center (DCC). The Behavioral Health Economics Program of RTI International (RTI) supports the health economic analysis goals of the study.

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# List of Participating Clinics, Data Centers, Resource Centers

## Clinical Centers

Each clinical center at UB and NU consists of an interdisciplinary team of clinical investigators who provide the areas of expertise necessary for the successful execution and completion of the IBSOS protocol. Clinical center responsibilities include:

- Recruiting participants for the trial
- Confirming eligibility of all participants
- Implementing the interventions in a systematic and standardized fashion consistent with the study protocol
- Collecting high quality data according to the study protocol
- Making provisions to ensure the safety of trial participants
- Collaborating in design and monitoring of the study, including regular attendance at Steering Committee meetings
- Collaborating in the analysis and dissemination of study results

## Health Economics Center

The health economics center will be led by Dr. Laura Dunlap, Director of the Behavioral Health Economics Program at RTI. RTI International is a nonprofit research organization headquartered in Research Triangle Park, NC. Dr. Dunlap will be responsible for designing and performing the economic analysis which will include a cost analysis of the IBS intervention, and cost-effectiveness and cost-benefit analyses as appropriate. RTI will contribute to the production of reports, publications, presentations and other needs related to the economic analysis as well as developing publications and presentations of the economic findings. RTI also will interact with the Steering Committee, Executive Committee, Data Coordinating Center, and the Data and Safety Monitoring Board as needed on all procedures involving the assessment of economic variables as well as economic data quality and collection, and the economic analyses.

## Data Coordinating Center (DCC)

Kenneth Wood of Frontier Science is the DCC's lead investigator for the project. He will supervise the DCC's operations and will work with study statisticians and data managers to present reports to the DSMB. He will direct and actively participate in preparations of DSMB reports and supervise preparation of other reports. The DCC will take a leadership role in the study's design and scientific conduct. Communication, cooperation, and frequent interaction with investigators are essential ingredients in executing DCC responsibilities. Accordingly, the DCC's responsibilities involve most aspects of the study and include: working with Project PI to develop and refine trial architecture and design study forms; establishing and maintaining data-collection procedures and documenting them in the Manual of Operations; implementing and operating the randomization system; develop data-management and quality assurance procedures in accordance with the final protocol and data-collection procedures; formulation of a study monitoring plan along with the statisticians, producing and

distributing reports, including enrollment, follow-up, protocol adherence, and data quality; analyzing study data for reports, publications, presentations and other needs; and assisting in writing publications and presentations.

## The National Institute of Diabetes and Digestive and Kidney Diseases

IBSOS is funded through a cooperative agreement (U01) with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). Details of the relationship between the NIDDK and the IBSOS are included in the “Terms and Conditions for Large Scale Research Project Applications.”

## APPENDIX 4: Eligibility Criteria

| Inclusion Criteria |
|---|
| • Gender: male or female |
| • Ages 18-70 years (inclusive) |
| • All ethnic groups |
| • Meet Rome III criteria for IBS |
| • Moderate to severe IBS symptoms (symptom frequency ≥ 2 days/wk) |
| • Ability to understand and provide informed consent |
| • With the exception of antibiotics, participant is willing to remain on a stable dose throughout the 4-week pretreatment baseline period prior to randomization |
| • Participant either not taking medications or if taking medications willing to suspend starting any new medications during the initial 4-week pre-treatment baseline period |
| • A minimum 6$^{th}$ grade reading level based on the Wide Range Achievement Test (WRAT 4) if necessary |
| • Participant is willing to be randomized to CBT or Support/Education to which s/he has been assigned and to adhere to protocol requirements |
| • Participant is willing to attend regularly scheduled therapy sessions during active phase of the trial |
| • Participant is willing to be contacted and scheduled for follow-up assessments at week 12 and 3, 6, 9, and 12 months after the conclusion of acute treatment phase |
| • Participant is able to a maintain daily symptom diary and complete questionnaires through treatment and at regularly scheduled follow ups |
| • Participant has access to a telephone |
| • Participant is willing and able to provide adequate information for locator purposes |

| Exclusion Criteria |
| --- |
| • Evidence of current structural or biochemical abnormalities or medication use that better explain the participant's IBS symptoms (e.g. IBD) |
| • Evidence of a current infection or infection of any type within the 2 weeks prior to the study gastroenterologists' evaluation which would obscure the presentation of IBS symptoms. In such cases the baseline can be delayed until 2 weeks after complete recovery |
| • Participant has received antibiotics (e.g. rifaximan and/or neomycin) specifically targeted to treat IBS symptoms. In this instance, eligibility will be suspended for 12 weeks from the initial date the antibiotic was consumed |
| • Participant has undergone previous abdominal surgery that would have caused significant alteration of the anatomy/physiology of the digestive/GI tract, which adequately explains GI symptoms |
| • Participant has been diagnosed and/or treated for malignancy in the past 5 years with exception of localized basal or squamous cell carcinomas of the skin |
| • Participant has an unstable extraintestinal medical condition whose immediate or foreseeable treatment needs (e.g. hospitalization, conflicting physician visits) would realistically interfere with study demands (e.g. consistent attendance at treatment sessions and/or ability to participate in telephone interventions) or may affect the interpretation of clinical efficacy data |
| • Participant has a major psychiatric disorder, which in the opinion of the senior clinical staff may impede conduct of the clinical trial. These disorders include but are not limited to major depression with a high risk of suicidal behavior (i.e. intent or plan), alcohol or substance abuse/dependence within the past year, a lifetime history of schizophrenia or schizoaffective disorder or gross cognitive impairments |
| • Participant has other conditions which in the opinion of the senior clinical staff would influence negatively the conduct of the clinical trial |
| • Participant is currently receiving targeted psychotherapy for IBS and is unwilling or unable to discontinue his/her treatment for the acute treatment phase of this study |
| • Participant is unable to complete all scheduled screening visits |
| • Participant is inaccessible for interventions and/or follow-up evaluations |

# APPENDIX 5: Adverse Event Reporting

## Completing the Adverse Event Case Report Form (CRF)

- Each adverse event must be reported using the Adverse Event (AE) CRF. If necessary, multiple AE CRF forms may be used for participants.

- After completing the header fields, the clinician should write a brief description of the event on the AE CRF and use the standard definitions provided to indicate:

  (a) the maximum severity of the AE
  (b) the current status of the AE
  (c) date of onset of the AE and, if AE has been resolved, date of resolution
  (d) whether the AE was expected or unexpected the likelihood that the AE is related to the study treatment intervention.

  These ratings are described in detail below.

- If a participant did not experience an AE at the end of his/her study period (including follow-up), the clinician will indicate this on the AE CRF. In this case, the clinician will not fill out any other fields on the AE CRF except for the header fields, the Source Document Language field, and Form Completion Status field (filled in as 'Form Completed as Required'). There should be at least one AE CRF completed for each participant, even if a participant did not experience an adverse event during the course of the protocol.

## AE Severity Rating

The clinician will rate the severity of each AE using a four-category scale. These categories are defined below. This rating should represent the maximum severity of the adverse event. For example, a participant may report multiple headache events over a short period of time or a prolonged period of chest pain that may vary in intensity. The clinician should provide a rating of the most severe episode of headache or a rating of the chest pain at its maximum severity. The numerical rating of the appropriate category should be recorded in the box marked "Severity."

1. **Mild**: Does not interfere with participant's usual function
2. **Moderate:** Interferes to some extent with participant's usual function
3. **Severe:** Interferes significantly with participant's usual function
4. **Life-Threatening:** Poses a significant threat to the life or functioning of the participant

It should be noted that judgments of AE severity should be independent of judgments regarding whether or not an AE is considered "serious." The term "severe" is typically used to describe the intensity (severity) of an event (as in mild, moderate, or severe pain); the event itself may be of regarded as medically benign (such as severe migraine

headache). This use of “severe” is not the same as "serious," the latter of which is based on participant/event outcome or action criteria usually associated with events that pose a threat to the participant’s life or vital functions. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

## Adverse Event Current Status

The clinician will indicate the current status of the AE at the time of the report using a four-category scale. These categories are described below. The numerical rating of the appropriate category should be recorded in the box marked “Status.” In addition, the recorder should indicate the date of the onset of the AE in the boxes provided on the AE CRF.

1. **New:** This report represents the first occurrence of the adverse event
2. **Resolved**: The event is no longer ongoing although there still may be lasting problems or complications. If event is resolved, please record the Date and Time of Resolution in the boxes provided on the AE CRF.
3. **New and Resolved In Same Interval**: The AE meets criteria for both *New* and *Resolved* AE.
4. **Ongoing**: The AE has not been resolved at the time of report.

## The Expected or Unexpected Nature of the AE

The clinician will check the appropriate box to indicate whether the AE is expected or unexpected based on the following criteria:

- **Unexpected Adverse Event**: An adverse event that occurs during the research protocol in which the nature, severity, or frequency of the event is not consistent with either:

    a. the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, or the current IRB-approved informed consent document, and (b) other relevant sources of information; or

    b. the expected natural progression of the underlying disease, disorder, or condition of the participants(s) experiencing the adverse event and the participant’s predisposing risk factor profile for the adverse event.

- **Expected Adverse Event:** Any event that does not meet the definition of unexpected adverse event.

## Adverse Event Related to Protocol Treatment

The clinician will rate the likelihood that the adverse event was caused by the procedures involved in the research using the following categories and definitions:

- **Reasonable Possibility**: There is a reasonable possibility that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research. A *reasonable possibility* is defined as more likely than not the event is causally and consequentially related to the research procedures or, in other words, there is a strong (>50%) likelihood of the event having been caused by the procedures involved in the research

- **Not Reasonable Possibility**: There is not a reasonable possibility that the adverse event may have been caused by study participation.

# APPENDIX 6: Interruption or Discontinuation of Therapy

## Definitions of "Withdraw Consent" & "Lost to Follow-Up"

A participant can partially or totally withdraw consent. If s/he totally withdraws consent, then IBSOS Study personnel may not attempt to collect any further data. But a participant may withdraw consent only for collection of specific data items; for example, quality of life, health care utilization, etc.

Likewise, a participant can be partially or totally lost to follow-up. A participant is partially lost to follow-up if s/he is unable to attend further follow-ups at the clinic but is still willing to provide questionnaire data administered via mail. This can happen if the participant moves away from the clinical center's city, or has a condition (e.g. unstable heart disease) that conflicts with the aims of the trial that was not disclosed during pre-treatment evaluation.

A participant is totally lost to follow-up if s/he dies or his/her whereabouts are unknown, that is, s/he has disappeared according to all available contacts. In this case, generally no further data can be collected.

## Withdrawal from the Study

Following enrollment, participants may discontinue or be discontinued from study participation for the following reasons:

1. **Voluntary withdrawal** of consent by participant/volunteer/participant.

2. **Withdrawal requested by the study site's Principal Investigator** — S/he may remove a participant from the trial if, in his or her opinion, it is not in the best medical interest for the volunteer to continue in the IBSOS trial.

   Examples include situations where participants experience significant clinical deterioration (e.g. significant cognitive or medical deterioration, suicidal attempts or significant suicidal ideation, or significant substance use) during the 'active' (i.e. acute) phase of treatment that may require treatment that is outside the scope of study protocol (e.g. hospitalization). In such cases, participants are withdrawn from the treatment arm of the study and encouraged to seek appropriate treatment at a qualified facility.

3. **Protocol violation and noncompliance with trial procedures** — The investigator may believe that the volunteer is not complying with the protocol or has violated protocol criteria and may therefore wish to withdraw him/her from the trial.

   Examples of noncompliance arise if a participant fails to attend two consecutive MC-CBT or S-CBT sessions, or three consecutive EDU sessions without a reason deemed appropriate by his or her therapist and site PI. Non-compliance with homework is not regarded as an acceptable basis for withdrawal.

4. **Administrative error** — Participants who do not meet all study inclusion or exclusion criteria may enter the study in error.

   For example, a participant who does not disclose concurrent targeted psychotherapy for IBS or the presence of a medical condition that makes it unsafe or impractical for the participant to continue may be withdrawn at the PI's discretion. These participants may be replaced because they would not have satisfied eligibility criteria had the participant fully disclosed information regarding health status at the time eligibility was determined.

# DATA COLLECTION FORMS SCHEDULE

00-00-00

## STUDY IBSOS1

## BOOK 1

| NOTE: The columns are marked with an "X" to indicate data and evaluations required at each visit. | | PRE-TREATMENT BASELINE | PREMATURE DISCONTINUATION |
|---|---|---|---|
| **eData/ HAND-ENTERED FORMS** | **Frontier Form #/ Reference** | | |
| IBS0S1 Study Participant Intake Form | QLW01 | X | |
| IBS - Symptom Severity Scale | QLW03 | X | |
| LEV- BL | QLW10 | X | |
| IBSOS Comorbid Disease Form | QLW13 | X | |
| MD Rating - Baseline | QLW15 | X | |
| Concomitant Medications/Supplements and Non-Drug Therapies | CMW1 | X | |
| IBS Module (IBS-PRO) | QLW14 | X | |
| IBSOS1 Study Participant Economic Form | QLW06 | X | |
| FMBS | QLW12 | X | |
| Euroqol EQ- 5D | QLW02 | X | |
| Adverse Events | IBS0021 | | X |
| Off Study / Drop Out | IBS1601 | | X |
| Missed Visit | ST0010 | | |
| Death Form | SP1411 | | |
| **FLIPS FORMS** | **Frontier Form #/ Reference** | | |
| IBS - LOC | ibsloc | X | |
| IBS SE Questionnaire | ibsse | X | |
| PSS | pss | X | |
| PCSQ-2 Item | pcsq2 | X | |
| IBS-QOL Instrument | ibsqol | X | |
| McGill - SF | mcgsf | X | |
| The SF - 12 Health Survey | sf12 | X | |
| Restorative Activities | restact | X | |
| SOMS-7 | soms7 | X | |
| ASI | asi | X | |
| VSI | vsi | X | |

Continued on page 2.

# DATA COLLECTION FORMS SCHEDULE

00-00-00

STUDY IBSOS1

BOOK 1

| NOTE: The columns are marked with an "X" to indicate data and evaluations required at each visit. | | PRE-TREATMENT BASELINE | PREMATURE DISCONTINUATION |
|---|---|---|---|
| **FLIPS FORMS (continued)** | **Frontier Form #/ Reference** | | |
| DIS | dis | X | |
| PSWQ-A | pswqa | X | |
| ER | er | X | |
| BDI-II | bdiii | X | |
| BSI-18 | bsi18 | X | |
| STAI-SF | staisf | X | |
| K-ESS | kess | X | |
| ISEL-12 | isel12 | X | |
| IIP-32 | iip32 | X | |
| NIS | nis | X | |
| TSRQ (A) | tsrqa | X | |
| **Non-Form Evaluation (Exported to Database)** | | | |
| MINI International Neuropsychiatric Exam Plus | mini | X | |
| **Site-Use Only forms (Not Entered into Database)** | | | |
| Health Care Coverage f Form | | X | |
| Locator Form | | X | |

# DATA COLLECTION FORMS SCHEDULE

00-00-00

## STUDY IBSOS1 - BOOK 2

**NOTE:** The columns are marked with an "X" to indicate data and evaluations required at each visit.

| | | MC-CBT and Educational Support Treatment | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Clinic Visit 1 | | Tel. Visit 1 | | Clinic Visit 2 | | Tel. Visit 2 | Clinic Visit 3 | | Clinic Visit 4 | |
| | | FC-CBT - Treatment | | | | | | | | | | PREM. |
| | Weeks → | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | DISC. |
| **eData/ HAND-ENTERED FORMS** | **Frontier Form #/ Reference** | | | | | | | | | | | |
| IBS - Symptom Severity Scale | QLW03 | | | | | X | | | | | | X |
| IBSOS Comorbid Disease Form | QLW13 | | | | | | | | | | | X |
| Concomitant Medications/Supplements and Non-Drug Therapies | CMW1 | X | X | X | X | X | X | X | X | X | X | X |
| IBS Module (IBS-PRO) | QLW14 | | | | | | | | | | | X |
| IBSOS1 Study Participant Economic Form | QLW06 | | | | | | | | | | | X |
| FMBS | QLW12 | | | | | | | | | | | X |
| Euroqol EQ-5D | QLW02 | | | | | | | | | | | X |
| IBSOS Daily Diary | LGW1 | X | X | X | X | X | X | X | X | X | X | X |
| IBSOS1 Study Participant Follow Up Form | QLW17 | | | | | | | | | | | X |
| LEV-FU | QLW11 | | | | | | | | | | | X |
| MD Rating- Follow Up | QLW16 | | | | | | | | | | | X |
| Adverse Events | IBS0021 | | | | | | | | | | | X |
| Off Study / Drop Out | IBS1601 | | | | | | | | | | | X |
| Missed Visit | ST0010 | | | | | | | | | | | |
| Premature Discontinuation of Study Treatment | IBS4000 | | | | | | | | | | | |
| Death Form | SP1411 | | | | | | | | | | | |
| **FLIPS FORMS** | **Frontier Form #/ Reference** | | | | | | | | | | | |
| IBS - LOC | ibsloc | X | | X | | X | | | X | | | X |
| IBS SE Questionnaire | ibsse | X | | X | | X | | | X | | | X |
| PSS | pss | X | | X | | X | | | X | | | X |
| PCSQ-2 Item | pcsq2 | X | | X | | X | | | X | | | X |
| IBS-QOL Instrument | ibsqol | | | | | | | | | | | X |
| McGill - SF | mcgsf | | | | | | | | | | | X |
| The SF - 12 Health Survey | sf12 | | | | | | | | | | | X |
| Restorative Activities | restact | | | | | | | | | | | X |

Continued on page 2.

# DATA COLLECTION FORMS SCHEDULE

00-00-00

## STUDY IBSOS1 - BOOK 2

**NOTE:** The columns are marked with an "X" to indicate data and evaluations required at each visit.

| | | MC-CBT and Educational Support Treatment | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Clinic Visit 1 | | Tel. Visit 1 | | Clinic Visit 2 | | Tel. Visit 2 | Clinic Visit 3 | | Clinic Visit 4 | |
| | | FC-CBT - Treatment | | | | | | | | | | PREM. DISC. |
| | Weeks → | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| **FLIPS FORMS (continued)** | **Frontier Form #/ Reference** | | | | | | | | | | | |
| SOMS-7 | soms7 | | | | | X | | | | | | X |
| ASI | asi | X | | X | | X | | | X | | | X |
| VSI | vsi | X | | X | | X | | | X | | | X |
| DIS | dis | X | | X | | X | | | X | | | X |
| PSWQ-A | pswqa | X | | X | | X | | | X | | | X |
| ER | er | X | | X | | X | | | X | | | X |
| BDI-II | bdiii | | | | | | | | | | | X |
| BSI-18 | bsi18 | | | | | | | | | | | X |
| STAI-SF | staisf | | | | | | | | | | | X |
| K-ESS | kess | | | | | | | | | | | X |
| ISEL-12 | isel12 | | | | | | | | | | | X |
| IIP-32 | iip32 | | | | | | | | | | | X |
| NIS | nis | | | | | | | | | | | X |
| WAI-SR-PATIENT | waisrpt | X | | X | | X | | | X | | | X |
| WAI-SR-THERAPIST | waisrth | X | | X | | X | | | X | | | X |
| ATT | QLW1 | X | | | | | | | | | | |
| IBS Treatment Suitability and Patient Expectation Form | patexppt | X | | | | | | | | | | |
| IBS Treatment Suitability and Patient Expectation Form Therapist Version | patexpth | X | | | | | | | | | | |
| Homework Compliance Form | hwcf | | X | X | X | X | X | X | X | X | X | |
| Adequate Relief | adqrel | | | | | X | | | | | | X |
| Global Impression of Change | gloc | | | | | X | | | | | | X |
| TSRQ (B) | tsrqb | | | | | X | | | | | | X |
| Client Satisfaction Questionnaire4 | csq | | | | | | | | | | | X |
| **Site-Use Only forms (Not Entered into Database)** | | | | | | | | | | | | |
| Locator Form | ------- | | | | | | | | | | | |

# DATA COLLECTION FORMS SCHEDULE

00-00-00

## STUDY IBSOS1 - BOOK 3

| NOTE: The columns are marked with an "X" to indicate data and evaluations required at each visit | | FOLLOW-UP PERIODS | | | | | |
|---|---|---|---|---|---|---|---|
| | Months → | 1 | 3 | 6 | 9 | 12 | Premature Discontinuation |
| | Weeks → | 12 | 22 | 34 | 46 | 52 | |
| **eData/ HAND-ENTERED FORMS** | **Frontier Form #/ Reference** | | | | | | |
| IBS - Symptom Severity Scale | QLW03 | X | X | X | X | X | X |
| IBSOS Comorbid Disease Form | QLW13 | X | X | X | X | X | X |
| Concomitant Medications/Supplements and Non-Drug Therapies | CMW1 | X | X | X | X | X | X |
| IBS Module (IBS-PRO) | QLW14 | X | X | X | X | X | X |
| IBSOS1 Study Participant Economic Form | QLW06 | X | X | X | X | X | X |
| FMBS | QLW12 | X | | | | | X |
| Euroqol EQ-5D | QLW02 | X | X | X | X | X | X |
| IBSOS Daily Diary | LGW1 | X | X | X | X | X | X |
| IBSOS1 Study Participant Follow Up Form | QLW17 | X | X | X | X | X | X |
| LEV-FU | QLW11 | X | X | X | X | X | X |
| MD Rating- Follow Up | QLW16 | X | X | X | X | X | X |
| Adverse Events | IBS0021 | | | | | | X |
| Off Study / Drop Out | IBS1601 | | | | | | X |
| Missed Visit | ST0010 | | | | | | |
| Premature Discontinuation of Study Treatment | IBS4000 | | | | | | |
| Death Form | SP1411 | | | | | | |
| **FLIPS FORMS** | **Frontier Form #/ Reference** | | | | | | |
| IBS - LOC | ibsloc | X | X | X | X | X | X |
| IBS SE Questionnaire | ibsse | X | X | X | X | X | X |
| PSS | pss | X | X | X | X | X | X |
| PCSQ-2 Item | pcsq2 | X | X | X | X | X | X |
| IBS-QOL Instrument | ibsqol | X | X | X | X | X | X |
| McGill - SF | mcgsf | X | X | X | X | X | X |
| The SF - 12 Health Survey | sf12 | X | X | X | X | X | X |
| Restorative Activities | restact | X | X | X | X | X | X |
| SOMS-7 | soms7 | X | X | X | X | X | X |

Continued on page 2.

# DATA COLLECTION FORMS SCHEDULE

00-00-00

## STUDY IBSOS1 - BOOK 3

| NOTE: The columns are marked with an "X" to indicate data and evaluations required at each visit | | FOLLOW-UP PERIODS | | | | | |
|---|---|---|---|---|---|---|---|
| | Months → | 1 | 3 | 6 | 9 | 12 | Premature Discontinuation |
| | Weeks → | 12 | 22 | 34 | 46 | 52 | |
| **FLIPS FORMS (continued)** | **Frontier Form #/ Reference** | | | | | | |
| ASI | asi | X | X | X | X | X | X |
| VSI | vsi | X | X | X | X | X | X |
| DIS | dis | X | X | X | X | X | X |
| PSWQ-A | pswqa | X | X | X | X | X | X |
| ER | er | X | X | X | X | X | X |
| BDI-II | bdiii | X | X | X | X | X | X |
| BSI-18 | bsi18 | X | X | X | X | X | X |
| STAI-SF | staisf | X | X | X | X | X | X |
| K-ESS | kess | X | X | X | X | X | X |
| ISEL-12 | isel12 | X | X | X | X | X | X |
| IIP-32 | iip32 | X | X | X | X | X | X |
| NIS | nis | X | X | X | X | X | X |
| WAI-SR-PATIENT | waisrpt | X | | | | | X |
| WAI-SR-THERAPIST | waisrth | X | | | | | X |
| Adequate Relief | adqrel | X | X | X | X | X | X |
| Global Impression of Change | gloc | X | X | X | X | X | X |
| TSRQ (B) | tsrqb | X | X | X | X | X | X |
| Client Satisfaction Questionnaire4 | csq | X | | | | | X |
| **Site-Use Only forms (Not Entered into Database)** | | | | | | | |
| Locator Form | ------ | X | X | X | X | X | X |

# APPENDIX 8: Description of Assessment Measures

## Pre-treatment Assessment

The measures that comprise the pre-treatment assessment can be divided into the following domains: descriptive, diagnostic; outcome, mediation, and moderation.

### Descriptive

We plan to use the **IBSOS Intake Form** (Lackner & Keefer, 2009) to capture descriptive information on clinically relevant variables including, basic demographic variables (age, gender, education, SES, etc) treatment history (diagnostic procedures, OTC and prescription medications, alternative and complementary treatments, mental health services, etc), symptom duration, lifestyle factors (smoking, alcohol consumption), family history of GI disease, abuse history.

### Diagnostic

#### *Psychiatric Diagnosis*

The **Mini-International Neuropsychiatric Interview** (MINI; Sheehan et al., 1998) will serve as the primary instrument of psychodiagnostic assessment.

The MINI is an abbreviated psychiatric structured interview that uses decision tree logic to assess the major adult Axis I disorders in DSM-IV and ICD-10. These include the primary psychiatric (Axis I) diagnoses for IBS participants (e.g. mood disorders, anxiety disorders, somatoform disorders[55]). Moreover, the MINI allows the investigator to classify each disorder for which the patient meets criteria as current, past, or lifetime. The MINI has been validated in the U.S. and Europe. Psychometric examination of the MINI shows acceptable test-retest and inter-rater reliability [56]. We selected the MINI-Plus over other psychodiagnostic instruments (e.g. SCID) because of its ease (i.e. computerization) of administration, the relatively brief training needed for its use, its broad coverage, and a relatively quick administration time of 20-30 minutes.

#### *IBS Diagnosis*

**The IBSOS will adhere to Rome III diagnostic criteria for confirming IBS.**

a. Recurrent abdominal pain or discomfort occurring at least three days per month in the last three months associated with two or more of the following criteria:
   i. Improvement in pain/discomfort with defecation
   ii. Onset of pain/discomfort associated with a change in stool frequency
   iii. Onset of pain/discomfort associated with a change in stool consistency

   These criteria fulfilled for the last three months with symptom onset at least six months prior to diagnosis.

   Adapted from Longstreth et al., Gastroenterology 2006;130:1481.

The **Patient-Reported Outcome Interview** (IBS Module PRO-IBS) [57] is a semi-structured interview whose 7 core items and 9 associated items correspond to Rome III criteria for IBS.

The IBS-PRO, in conjunction with physician decision making, can be used to support a current diagnosis of IBS in accordance with Rome III criteria. In addition to assessing the frequency and impact (distress, functional limitations) of key IBS symptoms (abdominal pain/discomfort, altered defecation, and associated symptoms such bloating, incomplete evacuation, nausea, urgency), the PRO-IBS taps the global impact of IBS symptoms on social, home/family, and occupational functioning, improvement in symptoms since baseline administration, overall response validity, and overall IBS severity. For each item, standardized questions and probes are provided to elicit description of symptom. These probes are designed to elicit the experience of IBS symptoms and their impact from the patient's perspective. The PRO-IBS is designed to be administered by clinicians and clinical researchers who have a working knowledge of IBS and Rome diagnostic criteria as well experience performing semi-structured diagnostic evaluations. The less clinical experience the potential interviewer has had, the more training required.

## Outcome Assessment

### Global Improvement / Relief

Consistent with Rome III recommendations [58], the primary endpoint will be global improvement/relief of IBS symptoms. Global improvement of IBS symptoms will be based on a patient's response to the seven-point ordinal **Clinical Global Improvement Scale** (CGI-I)[59]: "Compared to how you felt prior to entering the study, how would you rate the IBS symptoms for which you sought treatment during the past week?" (1 = very much improved, 7 = very much worsened).

We will adopt the practice [44, 47, 60] of defining responders as participants with a score of 1 (much improved) or 2 (very much improved) on the CGI-I. At post-treatment assessments, the study gastroenterologists (blind to treatment allocation) will complete a clinician-rated version of the CGI-I [48] to estimate how much the participants' IBS symptoms improved or worsened relative to his or her baseline state.

We will measure *global relief* of symptoms using two adequate relief measures. The original adequate relief measure was explicitly focused on adequacy of pain relief [43, 61] and does not necessarily estimate treatment response for IBS participants seeking relief from non-painful GI symptoms (e.g. diarrhea, urgency, bloating, etc). In our previous work (Lackner et al., 2008), we therefore developed and validated a second adequate relief measure assessing adequacy of relief from bowel symptoms. Participants who respond affirmatively to the two adequate relief question(s) will be classified *a priori* as responders.

### IBS Symptom Severity

We will adhere to the recommendation of Rome III to use the IBS-SSS [49] to measure

IBS symptom severity. The **IBSSS** is a multidimensional patient-based rating scale of four domains (pain, distention, bowel dysfunction, and general well-being) deemed important to gauging overall IBS severity. Participants will complete the IBS-SS at baseline, and at each of the 5 follow-up assessments. Because the psychometric properties of the IBSSS are not firmly established[62], participants will rate the overall severity of symptoms at the end of each week using a single-item global severity scale ("How severe have your IBS symptoms been in the last week?" with responses ranging from 0 = Absent; 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very severe).

The study GE will rate the global severity of IBS symptoms using the clinician version of the **CGI Severity of Illness Scale** [59] (1 = normal, 7 = severely ill) at each of the main assessment periods.

## Abdominal Pain / Discomfort

The **McGill Pain Inventory-Short Form** [63] will measure pain sensation, pain affect, and current pain intensity at each of the 6 assessment periods. The main component of the SF-MPQ consists of 15 descriptors (11 sensory, 4 affective) that participants rate on a 4-point intensity scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Three pain scores are derived from the sum of the intensity rank values of the words chosen for sensory, affective, and total descriptors. The SF-MPQ scores obtained from participants in post-surgical and obstetrical wards and physiotherapy and dental departments were compared to the scores obtained with the standard MPQ. The correlations were consistently high and significant. The SF-MPQ was also shown to be sufficiently sensitive to demonstrate differences due to treatment at statistical levels comparable to those obtained with the standard form. The SF-MPQ is a useful measure for studies or clinics in which the standard MPQ would require too much time to administer. We will also assess the intensity (worst, average) of pain/discomfort on a daily basis using an 11-point Numerical Rating Scale (where 0 = none, 10 worst imaginable). Respondents will rate the intensity of other types of unpleasant visceral sensations (e.g. bloating, urgency) using similar numerical ratings scales embedded in GI Diaries.

## Somatization

The seven day version of the **Screening for Somatoform Symptoms** *(*SOMS-7) [64] is a self-rated checklist that assesses the severity of 53 unexplained medical symptoms. The questionnaire includes all 33 physical complaints of the DSM-IV somatization disorder symptom list, the symptoms of ICD-10 somatization disorder, and the ICD-10 somatoform autonomic dysfunction symptom list. Participants are asked whether they had experienced the listed physical symptoms during past seven days. They were instructed only to describe rate the degree of impairment for medical symptoms for which "*no clear causes have been found by physicians and which have affected your well-being".* The SOMS-7 measures somatization and therefore has conceptual and psychometric advantages over self described "somatization" measures (e.g., PHQ-15) that assess severity of somatic symptoms[65]

## Altered Bowel Function

### *Stool consistency*

Per Rome III guidelines [66], the seven-item **Bristol Stool Consistency Form** [67], will be used to characterize the consistency (form) of participants' stool. Information from the Bristol Stool Form will subtype IBS type by predominant stool pattern at baseline and post treatment assessment periods. The Bristol Stool Scale is regarded as a surrogate marker of gastrointestinal transit time with stool type 1 or 2 defined as slow colonic transit; stool of type 3-5 defined as normal colonic transit; and stool of type 6 and 7 defined as fast colonic transit.

### *Stool frequency*

We will also measure the frequency of bowel movements (BM), spontaneous bowel movements (SBM) and complete spontaneous bowel movements (CSBM) compared to baseline [68]. An SBM is a bowel movement that occurs in the absence of laxative, enema or suppository usage within the preceding 24 hours. A CSBM is operationalized as an SBM (i.e., BM without use of laxative, enema or suppository usage within the preceding 24 hours) that is accompanied by a feeling of complete evacuation. The frequency of bowel movements will be measured at baseline, daily during the acute treatment phase, and for the two weeks before each post treatment follow-ups.

## Health-Related Quality of Life (QOL)

We will be administering four questionnaires to assess discrete dimensions of quality of life [69-72]. The psychometric properties of the proposed QOL measures are well established [69-72].

### Generic QOL

The **SF-12 v2 Health Survey** [70] is an abbreviated (12-item) version of the SF 36 generic quality-of-life instrument. The SF 12 contains one or two items that measure each of the eight domains included in the SF-36: physical functioning, role limitations resulting from physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations resulting from emotional problems, and mental health. It yields scale scores for each of these eight health domains and two summary measures of physical and mental health, the Physical Component Summary (PCS) and Mental Component Summary (MCS). Subscale scores yield two summary scores: Physical Component Summary (PCS) and Mental Component Summary (MCS) scales. Scores are transformed to have a mean value of 50, standard deviation (SD) 10, where scores above or below 50 are above- or below-average physical or mental well-being, respectively

**The EQ-5D** [71] is a standardized, non disease-specific instrument for evaluating participants' preference-based valuations of health-related quality of life. There are two sections to the EuroQol: the EQ-5D and the EQ thermometer. The EQ-5D assesses health across five domains: anxiety/depression (AD), mobility (M), pain/discomfort (PD), self-care (SC), and usual activities (UA). Each domain has one item and a three-point

categorical response scale; health 'today' is assessed. Weights based upon societal valuations of health states are used to calculate an index score of –0.59 to 1.00, where –0.59 is a state worse than death and 1.00 is maximum well-being. A score profile can be reported. The EQ thermometer is a single 20 cm vertical visual analogue scale with a range of 0 to 100, where 0 is the worst and 100 the best imaginable health. The EQ 5D is added to testing battery for the purpose of gauging economic impact of treatments (Aim 4) in terms of quality-adjusted life year (QALY) [73].

**CDC HRQOL-4 ("Healthy Days")** The core items of the CDC HRQOL-4 [9, 74] (also referred to as "Healthy Days") include four questions. Question 1 is a global self-perceived health item (from excellent to poor) regarded as a valid synthesis of individuals' appraisals about their past, present, and anticipated health problems; for secondary analyses, question 1's five ordinal levels were collapsed into two dichotomous levels: 1) excellent, very good, and good, or 2) fair and poor. Three "days" questions measure poor physical health (question 2), poor mental health (question 3), and activity limitation resulting from poor physical or mental health (question 4) in the past 30 days. The sum of the responses to the second and third questions yields an "overall unhealthy days" measure that estimates the overall number of recent days when physical or mental health was not good with the restriction that the total number of days does not exceed 30 days. For example, a person who reports four physically unhealthy days and two mentally unhealthy days is assigned a value of six unhealthy days; someone who reports 30 physically unhealthy days and 30 mentally unhealthy days is truncated at the maximum of 30 unhealthy days to maintain the same timeframe as that of its components.

### Disease-Specific QOL

The **IBS-QOL**[75, 76] is a 34-item measure constructed specifically to assess the subjective well-being of participants with IBS. Each item is scored on a five-point scale (1 = not at all, 5 = a great deal) that represents one of eight dimensions (dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual dysfunction, and relationships). Items are scored to derive an overall total score of IBS-related quality of life. To facilitate score interpretation, the summed total score is transformed to a zero to 100 scale ranging from zero (poor quality of life) to 100 (maximum quality of life). In addition, participants will rate their difficulty performing activities across multiple domains relevant to IBS (e.g. eating, travel, activity interference) and the extent to which these limitations are due to IBS. These items will be embedded into the end-of-week section of the daily diaries.

### Psychological Distress

The **Global Severity Index** of the **Brief Symptom Inventory-18 (**BSI-18) [77] will assess levels of overall emotional distress. Self-reported anxiety and depression will be measured using the abbreviated version o**f State-Trait Anxiety Inventory** [78] and the **Beck Depression Inventory-II** [79] respectively. End-of-week positive and negative affect will be measured using an abbreviated version of the **Profile of Mood States** (POMS [80]). This 18-item scale instrument representing each of three negative mood factors (anxiety, depression, anger) and three adjectives representing each of three positive

mood factors (vigor, well-being, calm). Participants are presented with the 18 adjectives, randomly ordered, and asked to rate how often they felt this way during the past week. Each item is rated on a scale of zero to five (0 = not at all accurate, 5 = extremely accurate).

The **Perceived Stress Scale-4** [81, 82] is a four-item version of the full-length (10-item) Perceived Stress Scale [82] that assesses the degree to which situations in one's life are appraised as stressful. High levels of perceived stress are associated with poor self-reported health, nonpsychiatric and psychiatric medical problems (e.g. hypertension, susceptibility to infection, depression, et al). The PSS assesses the amount of stress in one's life rather than in response to a specific stressor.

## Treatment Satisfaction

The **Client Satisfaction Questionnaire-8** ( CSQ-8) [83] is an eight-item instrument of general satisfaction with treatment. It will only be administered at week 12. In addition, respondents will complete a single-item treatment satisfaction scale ("During the past week, how satisfied are you with the level of IBS relief your current treatment provides?"), with treatment responses ranging from 0 = very dissatisfied to 4 = very satisfied, that will be embedded in the end-of-week section of the daily diary.

### Health Care Utilization/Cost

A critical component of the study is an economic evaluation (e.g. cost, cost-effectiveness, and benefit-cost analyses) of the CBT treatment options. Some of the data needed for the economic evaluation will be collected in the **Economic Form-IBS**[84]. This form includes a series of questions on health status and activity limitations, labor market activity, and health care insurance coverage. In addition, the form collects detailed information on health care utilization including the type and amount of new, or previously administered, treatments (including prophylactic), their focus, and associated costs (e.g. direct costs for diagnosing, treating, prescriptions, OTC agents, physician visits, alternative and complementary therapies) and patient costs of accessing these services (e.g. transportation, child care). Information from this form will be used to estimate the economic benefits and costs associated with the CBT treatment options. We will administer the Economic Form-IBS at major assessment periods (baseline, post-acute treatment phase, and quarterly follow-up visits).

## Treatment Mediator Assessment

This set of measures is designed to help clarify the psychological processes that explain why CBT works or how it produces change (i.e. active ingredients) in IBS symptoms. These measures are completed at regularly scheduled times during the active treatment phase and at follow-up periods.

### Control Beliefs

The 25-item **IBS Management Self Efficacy Scale** (IBS-SE) measures participants' confidence in their ability to control and manage IBS episodes using a seven-point Likert scale (1 = strongly disagree, 7 = strongly agree) [41]. The **IBS-Specific Locus of**

**Control Scale** (IBS-LOC) [41] is a 33-item scale (five-point, 1 = strongly disagree, 5 = strongly agree) whose three subscales measure participants' beliefs that IBS symptoms are internally controlled, controlled by health care professionals, or dictated by chance. The IBS-SE and IBS-LOC subscales demonstrate high internal consistency (LOC Internal Control α = 92; Health Care Professionals α = .82; Chance α = .80; IBS SE α = .83). Convergent and discriminant validity coefficients indicate that the IBS-SE and LOC perform as expected against established measures of distress, coping, QOL, and each other [41].

## Symptom Beliefs

The **Anxiety Sensitivity Inventory**[85] measures the extent to which symptoms of physiological arousal (e.g. rapid heartbeat) cause fear or anxiety. Each item consists of a possible negative consequence of arousal symptoms. Items are rated on a 0- to 4-point Likert scale and are summed to compute a total score. The ASI has demonstrated high internal consistency and satisfactory test-retest reliability [86]. A related construct, visceral sensitivity, will be measured using the **Visceral Sensitivity Index** (VSI). The VSI [87, 88] is a 15-item self-report questionnaire that assesses GI symptom anxiety including worry, fear, vigilance, and avoidance related to visceral sensations and contexts. The Discomfort Intolerance Scale [89, 90] (DIS) measures ability to tolerate pain and discomfort. The DIS is a five-item, self-report questionnaire, in which participants respond to questions such as ''I am more sensitive to physical discomfort compared to most people'" on a scale ranging from 0 = not at all like me to 6 = extremely like me.

## Threat Appraisal

The **Penn State Worry Questionnaire** (PSWQ-A) [91] is an eight-item instrument that measures worry severity independent of worry content. The measure is scored on a five-point Likert scale (1 = not at all typical, 5 = very typical). The PSWQ-A was statistically derived from the full-length PSWQ[92] and the construct validity of this measure was supported via a strong correlation with the original PSWQ (r = .92) and relatively equivalent correlations of these instruments with alternate measures of negative affect [91]. The PSWQ-A items have good internal consistency (a = .87), with convergent validity supported through moderate correlations of the PSWQ-A with various anxiety measures [91]. A single item from the 10-item version of the Perceived Stress Scale inquiring whether patient was feeling particularly "nervous/stressed" is embedded in the daily diaries as an additional measure of threat appraisal.

## Self-Regulation/Coping Strategies

The **Emotion Regulation Questionnaire** [93] is a 10-item instrument designed to assess two aspects of emotion regulation: suppression and reappraisal. The reappraisal scale, comprising six items, assesses the ability to modify or change the emotions one experiences in a way that alters its emotional impact [94]. Sample item of this scale includes "I control my emotions by changing the way I think about the situation I'm in." The suppression scale, consisting of four items, involves the tendency to avoid or prevent the expression of emotions [95]. Sample items include: "I control my emotions by

not expressing them." Reappraisal strategies are associated with more adaptive health behaviors including better social functioning [93].

The abbreviated version of the original **Coping Strategies Questionnaire** [96 97] will be used to assess the frequency of use each of six cognitive coping strategies and one behavioral strategy when one feels pain: diverting attention, reinterpreting pain sensations, ignoring pain, praying and hoping, coping self-statements, increasing behavioral activities, and catastrophizing. Of particular interest is the pain catastrophizing scale as pain catastrophizing is associated with greater pain and functional limitations in participants with a range of persistent painful medical disorders including IBS [98-101]. The two items of the catastrophizing subscale ask participants to rate the frequency with which they, during an episode of pain, engage in various beliefs thought to index catastrophizing (e.g. "When I am in pain, I feel I can't stand it anymore," "It's awful and I feel it overwhelms me"). Respondents rate how characteristic each item is of them using a six-point Likert scale (0 = never do, 6 = always do).

## Treatment Expectancies

At the end of session 1, participants' expectancies that they will respond successfully to treatment will be measured using the **Expectation of Improvement/Treatment Suitability Form** [102, 103], asking "Which of the following best describes how successful you think your treatment will be?" Responses are rated using an 11-point visual analog scale (0 = not at all, 10 = completely). The form's second question ("How suitable do you think your treatment will be for your IBS symptoms?") measures suitability of treatment. In consultation with behavioral treatment efficacy expert Dr Steven Hollon, we developed a therapist version of the form that requires clinicians to rate their estimation of the suitability of their participants' assigned treatment and the likelihood that treatment will be successful as a way of assessing potential allegiance effects [104], an important nonspecific variable whose role in shaping outcomes has received scant attention by clinical researchers. The therapist version of the treatment suitability questionnaire should be completed before randomization to minimize the extent to which treatment allocation shapes judgments of suitability.

## Therapeutic Alliance

The **Working Alliance Inventory Short Form** (WAISF) [105] is a 12-item self-report questionnaire of the quality of the therapeutic alliance. The WAISF comprises three subscales, with respondents rating their level of agreement to statements using a five-point scale. The subscales assess the goals of therapy, the tasks of therapy, and the bond that develops between the therapist and patient. The WAI, full and short forms, are the most widely used assessment for measuring the therapeutic alliance[106-108]. The WAISF has sound reliability and validity and has been recommended over the WAI by its developer, Dr. Adam Horvath. The IBSOS will administer the patient version and has a modified therapist version.

## Homework Compliance

At the end of clinic and telephone session after week 1, the therapists will complete a

coding form [109, 110] indicating whether the participant attended the current session and the participant's degree of adherence to the homework assignment for the previous week(s). Adherence is rated by the therapist on a six-point scale (1 = participant did not attempt homework, 6 = participant did more of the assigned homework than requested). The amount of time (hours, minutes) participants spent doing homework assignments will be recorded as part of end-of-week diary section of the daily diary.

## Treatment Moderator Assessment

This group of instruments is designed to answer the question of which patient, therapist, treatment and contextual factors moderate treatment outcome. These instruments are completed at baseline and at follow-up periods.

### Interpersonal Functioning

Three conceptually discrete aspects of interpersonal functioning (interpersonal problems, negative interactions, social support) will be assessed.

The 32-item version of the **Inventory of Interpersonal Problems** (IIP) [111, 112] measures *interpersonal deficiencies and excesses*. The IIP requires participants to rate interpersonal problems using a five-point response format (0 = not at all, 4 = extremely) on phrases beginning "It is hard for me to..." or "I am too...". The IIP has eight subscales that maps onto eight octants on the interpersonal problems circumplex graph. A person's interpersonal problems can be represented by the octant which their most severe problem occupies. These octants are (too) dominant, vindictive, cold, socially-avoidant, submissive, exploitable, overly nurturing and intrusive. Example items from the intrusive (NO) scale are "It is hard for me to stay out of other people's business" and "I want to be noticed too much."

*Negative interaction* will be assessed with four items that were taken from the work of Krause [113] and Newsom et al[114]. These items have been used to assess four domains of negative interactions: unwanted advice/intrusion, failure to provide help, unsympathetic/insensitive behavior, and rejection/neglect. The four items are averaged to form a negative interactions index. A high score on these measures represents more frequent negative interaction.

A related construct, *social support*, will be measured using a brief index consisting of four items that assess how often family members and friends provide study participants with perceived emotional support (e.g. love and caring; respect, approval, and acceptance; encouragement and reassurance; listening; understanding and empathy).

There are several reasons why we focused only on emotional support and not other sources of support such as instrumental support. First, research [115] suggests that different types of received support are highly inter-correlated and that emotional support may form the core of this conceptual domain (see also Hobfoll & Vaux, 1993) [116]. Second, there is some evidence that more consistent stress-buffering effects have been observed with measures of emotional support than with other types of assistance received from others, e.g. [117].

To assess the perceived availability of social support, we will use the 12-item version of the **Interpersonal Support Evaluation List** [118], which consists of a list of 12 statements regarding the perceived availability and quality of potential social support. In addition to providing an overall score, it has three subscales that measure the perceived availability of three types of social support: 1) appraisal support, which assesses the perceived availability of confidants to talk to about one's difficulties; 2) belonging support, which examines the availability of people one can do things with; and 3) tangible support, which refers to the availability of practical or instrumental help. The ISEL-12 includes a list of statements regarding available social support to which participants are asked to indicate whether each is "definitely true," "probably true," "probably false," or "definitely false".

## Treatment Credibility / Expectancy of Improvement

Participants will complete an IBS version [119] of the 10-point **Attitudes to Treatment Questionnaire** [120] at the end of session 1 to assess the credibility of the assigned treatment's rationale and participant's baseline expectations for treatment's success.

## Negative Life Events

Participants will complete the **Life Events Scale** [121, 122] to describe which of a list of 15 major events happened to them during the three months prior to each of the major assessment periods. Examples of events include: death of a loved one, loss of a job, being divorced, moving, death of close friend or family member. In general, the idea of life events instruments is that whatever major events do to us (e.g. require adaptation, induce negative affect and cognition), this accumulates as the number of events accumulate. The more events the respondent reports, the greater the stress. The items assessing recent stressful life events were selected from two sources [121, 122].

## Treatment Motivation

Motivation for treatment will be measured using a modified version of the 15-item **Treatment Self Regulation Questionnaire** (TSRQ) [123]. The TSRQ assesses autonomous vs. externally controlled motivation for particular health behaviors. In collaboration with Dr. Edward Deci (Deci and Ryan 1987; Aaron, Bradley et al. 1996; Senecal, Nouwen et al. 2000; Deci and Ryan 2002), Director of the Human Motivation Laboratory at the University of Rochester and co-developer of the TSRQ, the Project PI developed an IBS-specific version of the TSRQ that assesses motivation for adopting behavioral strategies for managing IBS symptoms. Psychometric analyses indicate that the TSRQ demonstrates excellent internal consistency ($\alpha = 89$) and validity [124].

## Non-Psychiatric Comorbidity

We will assess nonpsychiatric medical comorbidity using the **IBSOS Nonpsychiatric Medical Comorbidity Inventory** [125], a 112-item (12 domains), self-administered questionnaire. This questionnaire asks participants to identify medical conditions for which they have been formally diagnosed by or received treatment from a physician or other medical professional (e.g. nurse, physician assistant). Participants then rate the

severity of each condition they have had during the past three months on a five-unit category scale with the following verbal anchors: (1) Absent, (2) Mild, (3) Moderate, (4) Severe, and (5) Very Severe. Participants are asked to base severity ratings on three dimensions: the intensity and frequency of the symptoms and the extent to which the symptoms interfere with their lives (e.g. daily routine, job, family activities).

Items included in the IBSOS Comorbidity Form are grouped into three of 12 conceptually distinct categories (e.g. skin or dermatologic disorders, respiratory or lung disorders, cardiovascular) and parallel with those included in other comorbidity questionnaires such as those developed by Whitehead et al [126]and Charlson et al [127]. The IBSOS Comorbidity Form, however, differs from those used in previous studies of IBS participants that have produced only frequency counts of comorbid medical complaints (vs. diagnoses). That is, in addition to producing a frequency count of comorbid diseases, the IBSOS measure provides a mean comorbidity severity score, a feature that is unique to our instrument.

## Miscellaneous Measures

### Restorative Activities

**The Restorative Activities Scale** will be used to assess the frequency of engaging in restorative activities. Restorative activities refer to activities that rejuvenate or restore individuals to some equilibrium such as value hobby, physical exercise, or sleep. Restorative activities have been linked to both improved mental and physical health outcomes.

### Coping Flexibility

The **Frankfort Monitoring Blunting Scale** (FMBS) [128] is designed to assess rigid vs. adaptive coping styles. Rigid coping refers to either Monitoring or Blunting in situations implying threat and thereby disregarding situational control contingencies. Adaptive coping pertains to the employment of Monitoring strategies in controllable situations and Blunting strategies in uncontrollable situations. The FMBS is composed of four uncontrollable and threatening vignettes (waiting for surgery, threat [129] of being laid off work, turbulent flight, being stuck in an elevator) and four controllable and stressful vignettes (important job interview, icy road conditions, losing one's way in New York City, applying for a mortgage). Controllability is defined as the possibility to change the outcome of a situation through active intervention. Each FMBS situation is followed by eight behavioral choices. Of these, four items pertain to a Monitoring (information seeking) and four to a Blunting (reinterpretation of and distraction from the threatening aspects of a situation) style of coping with aversive events. Participants are instructed to respond to each item on a four-point rating scale (1 = complete disagreement, 4 = complete agreement). Individuals are classified as rigid "monitors" (high monitoring scores in controllable and uncontrollable situations) or "blunters" (high blunting scores in controllable and uncontrollable situations) or "adaptive copers" (high monitoring scores in controllable situations and high blunting scores in uncontrollable situations) or "unspecified types" on the basis of their scores. Unspecified types refer to participants who are neither monitors nor blunters nor adaptive copers.

### Concomitant Medications

The names and dosing regimens of all medications and significant non-drug therapies (e.g. physical therapy, dietary supplements, OTC agents) administered after the patient begins treatment will be recorded (week 1, 3, 5, 7, 8, 10) and at each follow-up assessment period on the Concomitant Medications Log.

## Follow-up Assessments

The IBSOS is designed to assess both the immediate and long-term follow-up benefits of CBT for IBS, as well as its clinical course. To achieve these objectives, it is essential that each participant be examined regularly at follow-up visits until the study is terminated. Follow-up assessments are scheduled two weeks after treatment ends and every three months thereafter (three, six, nine, and 12 months).

### Study Visit Windows

Follow-up assessments will be conducted in person, at appointments scheduled by the PC specifically for this purpose. Scheduling should occur by telephone when possible; participants who do not have telephones will be contacted by mail and asked to make arrangements for an appointment. Participants may also make appointments in person. A minimum of three contact attempts should be made and documented before a patient is considered unreachable. If a patient cannot be contacted, inform the SI after two attempts have been made, and before ruling a patient unreachable. Every conceivable effort must be made before a participant is deemed unreachable. Participants who are lost to follow-up during the active treatment phase, however, are allowed and should be encouraged to participate in regularly scheduled follow-up assessments. ***All participants, regardless of whether or not they completed therapy, should be contacted for all follow-up assessments and compensated for their time.***

We ask that every effort be made to adhere to the specific time windows when performing the follow-up assessments. If this is not possible, the window can be extended for purposes of recording the visit. However, ***extensions should be regarded as the exception and not the rule***.

- *Two-week post-treatment* — Post-treatment assessment should occur two weeks following the end of active therapy. However, it is permitted for post-treatment follow-up visits to occur within the two weeks preceding or following the scheduled appointment (i.e. weeks 10-14).
- *Interim assessment* — Participants will describe their daily bowel habits using the Bristol Stool form and rate the intensity of pain, bloating, and urgency (11-point VAS) at the end of each day through the 10-week acute treatment phase. At the end of each week of the acute treatment phase, they will rate global symptom severity, satisfaction with IBS symptoms, life interference, and mood using the abbreviated POMS, and time spent completing homework assignments. In addition, participants will complete process measures (IBS SE, WAI, IBS LOC, etc) at regularly scheduled times during active treatment phases. Participants should complete process measures within seven days of their being assigned.

- *Two-week follow-up assessment* — The two-week assessment should occur two weeks from the date of the last active treatment session, plus or minus (±) two weeks.
- *Three-month assessment* — The three-month assessment should occur three months ± two weeks from the date of the last active treatment session.
- *Six-month assessment* — The six-month assessment should occur six months ± two weeks from the date of the last active treatment session.
- *Nine-month assessment* — The nine-month assessment should occur nine months ± two weeks from the date of the last active treatment session.
- *12-month assessment* — The 12-month assessment should occur 12 months ± two weeks from the date of the last active treatment session.

# APPENDIX 9: Human Subjects Protection

## Informed Consent

Because the study will rely on intent to treat (ITT) (vs. completer) approach for data interpretation, all randomized participants will be included in study analyses. Therefore, it is important to have information on as many participants as possible. If a participant is unwilling to continue full engagement in the study, every effort should be made to strongly encourage the participant to undergo regularly scheduled follow-up clinic evaluations, and, if this is impossible, a minimum-level contact (telephone interview).

## Documenting Withdrawal of Consent

If a participant indicates that s/he wishes to withdraw consent, his/her wish must be honored. Just as it is a severe ethical breach to enroll a participant without her consent, so it is a severe ethical breach not to honor her withdrawal of consent.
At all times during this process, the participant should be treated with the utmost respect and courtesy. This is his/her due, of course, but also, participants sometimes change their minds and may return to the study if they are shown respect and courtesy.

## Procedures for Discontinuation

A participant's decision to withdraw from a clinical trial should be documented in the study records using the Off Study (i.e. drop out) Form. At a minimum, such documentation should include:

- Whether the discontinuation of the participant's participation resulted from a decision by the participant or by the investigator;
- Whether the discontinuation involves some (e.g. treatment but not follow up assessments) or all types of participation;
- The reason for the discontinuation.

An individual report should be promptly submitted to the site IRB if the discontinuation was related to an unanticipated problem involving serious risks to the participant. Otherwise, premature discontinuations can be summarized in regularly scheduled reports for DSMB.

## Follow-Up

Once participants have signed on to the study, we become responsible for following them up to five times over the following 12 months — regardless of whether they enter or complete treatment. The first challenge is simply maintaining contact; the second is getting them to come in and complete the assessments.

All potential candidates for the study will be given a current copy of the IRB-approved Informed Consent Form to read. The PI investigator, sub-investigators or their designees (e.g. supervised graduate students, research coordinator, project coordinator) will explain all aspects of the study in lay language and answer all of the

candidate's questions regarding the study. If the candidate desires to participate in the study, s/he will be asked to sign the Informed Consent. Informed consent is obtained from each participant before they are enrolled in the study. The consent form describes the potential risk and benefits of study participation as well as the responsibilities of the participants and the investigators. Participants who refuse to participate or who withdraw from the study will be treated without prejudice. In the event a significant protocol change occurs, the informed consent should be modified appropriately and sites will need to submit the revised documents to their IRB for approval. It should be noted that the overall content of initial consent form submitted for IRB approval at each site will be standard across clinical sites. It may be necessary to address unique questions/issues raised by the local IRB boards in the consent forms. Nevertheless, we will endeavor to maximize consistency in content across all consent forms.

## Participant Safety and Confidentiality

### Introduction

The psychosocial interventions consist of individual cognitive behavioral therapy or supportive counseling. The acute treatment phase will last 10 weeks with follow-up periods occurring every three months for one year following the end of treatment. Neither psychosocial treatment is expected to pose any particular risk. Each Site Investigator has primary responsibility for the individual participants under his or her care.

### Protocol review and study monitoring

An independent Data and Safety Monitoring Board (DSMB) is appointed by NIDDK and is charged with monitoring the progress of the study. The DSMB reviews and approves the protocol prior to study initiation. During the study, the DSMB meets biannually (one face-to-face, one telephone conference) to review study progress and trouble shoot around any problems that threaten study aims. These reviews include evaluation of interim data as well as the monitoring of participant safety and the quality of all aspects of study operations.

The PI and Site Investigators continually monitor safety issues at his/her site and report any problem to the Administrative Core at the University at Buffalo. As noted in the Chapter on Trial Governance, the IBSOS will identify a safety officer who functions as an independent evaluator (external to the study) of all adverse events (AEs), both serious and non-serious. In the case of this unmasked trial, the safety officer will work with the investigators to assure that the event is fully documented. Safety officers also review adverse event data to assess if the frequency of the AEs changes dramatically from baseline during treatment delivery phase of the trial. This change could be across the study or a change in the AE profile at a specific site.

### Exclusions

Persons with medical or psychological contraindications will be deemed ineligible to be enrolled.

### Institutional Review

Prior to study implementation, the protocol, informed consent forms, and all advertising materials must be approved by the IRB of each participating study site. All protocol amendments effecting the safety and welfare of study participants must be approved by the IRB prior to implementation. The study site PI is responsible for all submission documents and for periodic review reports required by the IRB.

## Data Security and Confidentiality

All participant information, and even the fact that an individual is participating in the study, is considered confidential. This confidentiality is assured in IBSOS through several mechanisms. First, each participant is assigned an anonymous study ID, which is then used on all study forms. Second, all study forms, and paper records that contain participant information (e.g. consent forms, address lists, phone lists) are kept in secured, locked areas when not in use. In addition, such materials, when in use, are kept away from public scrutiny. Materials and specimens that can be discarded are destroyed. Third, access to all participant data and information, including laboratory specimens, is restricted to authorized personnel. In the case of computerized data, this restricted access is assured in several ways. At the clinical centers, the data are maintained on personal computers (PCs) that are password-protected. Staff members receive individualized account numbers and passwords that allow them access only to those elements of the data management system to which they are authorized. At the Administrative Core, access to computerized data is restricted in two ways. First, only authorized personnel are granted access to the data, and, second, this access is further restricted by password protection.

When the study database is made available to clinical centers and to the Project Office, it does not include actual identities and contact information of participants. Such information is retained at the individual clinical centers for use in the event that future follow-up of the study participants is necessary. Finally, participants are not identified by name in any reports or publications, nor are data presented in such a way that the identity of individual participants can be inferred.

All members of the research team are required to complete a confidentiality certification procedure upon employment. Policies regarding the confidential nature of the data collected, processed and stored are explained to all personnel who must then sign a “confidentiality certification” before being allowed access to confidential information.

The CC and each SI will continually reinforce the need for careful and confidential handling of data at staff meetings and trainings. In addition, key personnel are required annually to sign a confidentiality statement affirming that they agree to abide by the Center for Health Research’s policies on research confidentiality and ethics.

## Protection of Participant Privacy

Privacy in the context of this study includes confidentially of data and personal information at the participating sites and in the handling and reporting of data obtained by sites. It also includes discretion of the part of the clinical center staff and

arrangements or physical privacy during interviews and examinations. Each site is responsible for ensuring physical privacy of participants and ensuring that data are stored in a secured area accessible only to IBSOS staff. These provisions and arrangements will be monitored during periodic visits from the CC.

## APPENDIX 10: Literature Cited


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