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The Irritable Bowel Syndrome Outcome Study (IBSOS): Rationale and design of a randomized, placebo-controlled trial with 12 month follow up of self- versus clinician-administered CBT for moderate to severe irritable bowel syndrome

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Abstract

Irritable bowel syndrome is a common, oftentimes disabling, gastrointestinal disorder whose full range of symptoms has no satisfactory medical or dietary treatment. One of the few empirically validated treatments includes a specific psychological therapy called cognitive behavior therapy which, if available, is typically administered over several months by trained practitioners in tertiary care settings. There is an urgent need to develop more efficient versions of CBT that require minimal professional assistance but retain the efficacy profile of clinic based CBT. The Irritable Bowel Syndrome Outcome Study (IBSOS) is a multicenter, placebo-controlled randomized trial to evaluate whether a self-administered version of CBT is, at least as efficacious as standard CBT and more efficacious than an attention control in reducing core GI symptoms of IBS and its burden (e.g. distress, quality of life impairment, etc) in moderately to severely affected IBS patients. Additional goals are to assess, at quarterly intervals, the durability of treatment response over a 12 month period; 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 works; and evaluate the economic costs and benefits of CBT. Between August 2010 when IBSOS began recruiting subjects and February 2012, the IBSOS randomized 171 of 480

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Conflicts of interest

None

Writing Committee

Members consist of Jeffrey Lackner, Laurie Keefer, Rebecca Firth, James Jaccard, Darren Brenner, Jason Bratten, Laura Dunlap, and Mark Byroads, all of whom take full responsibility for the contents of this manuscript.

patients. Findings have the potential to improve the health of IBS patients, reduce its social and economic costs, conserve scarce health care resources, and inform evidence-based practice guidelines.

Keywords

Self-management; comparative effectiveness; pain; cognitive behavior therapy; National Institute of Diabetes and Digestive and Kidney Diseases; randomized clinical trial

Introduction

Irritable bowel syndrome (IBS) is a common, oftentimes disabling functional GI disorder whose symptoms include abdominal pain/discomfort associated with diarrhea, constipation or both in an alternating manner. As one of the most common diagnoses seen by gastroenterologists and primary care physicians [1], IBS exacts substantial economic (e.g., [2], [3]) and social (e.g., [4] [5]) costs. Making matters worse, there is no satisfactory treatment for the full range of IBS symptoms ([6]. With one exception, the few efficacious medications developed for IBS have either been withdrawn or severely restricted in response to concerns about safety, creating an urgent need to train patients to adopt effective self-management strategies for relieving unresolved symptoms. The broader disease management literature [7] indicates that effectively managing the day to day burden of chronic medical conditions involves learning specific behavioral skills (e.g., self-monitoring, goal setting and problem solving). These skills form the basis of a psychological treatment called cognitive behavior therapy (CBT).

A number of clinical trials support the efficacy of CBT for IBS when administered over multiple (weekly) sessions by trained therapists in tertiary care settings [8, 9] [10]. Treatment gains associated with CBT include improvements in key GI symptoms (pain, bowel dysfunction) [10], quality of life [4, 11], and psychological distress [10, 11]. In its standard form, however, CBT has practical limitations (high cost, shortage of adequately trained therapists, long waiting lists, time requirements) that hamper its clinical utility. As the “second generation” of IBS treatments undergoes development, 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, less time intensive and more transportable, yet one that retains the clinical efficacy of the “gold standard” CBT delivered in routine office settings.

One strategy for economizing CBT is to decrease therapist contact time through the use of primarily self-administered or “home based” treatments. In a self-administered or minimal-contact (MC) treatment (e.g., [12, 13], self-management skills are introduced in periodic clinic sessions but most of what is learned occurs at home using self-study materials with minimal professional assistance. As a result, MC-CBT requires only 4 clinic sessions rather than the 10–20 weekly sessions of standard CBT (S-CBT). Potential advantages of MC-CBT include greater patient involvement, a reduction in patient costs (e.g., time and travel costs for session attendance), expanded availability of services, lower stigma, easier scheduling and penetration into underserved areas, and easier integration into routine clinical settings. Empirical support for a MC-CBT treatment comes from a pilot study funded through the NIDDK to test the efficacy of MC- CBT [12]. After treatment, 62% of participants receiving MC-CBT described IBS symptoms as much or very much improved compared to 58% of patients receiving S-CBT and 7% on a wait list. Improvement was accompanied by significant reduction in IBS symptom severity and quality of life impairment. These data

lend preliminary support for the clinical efficacy of a self-administered version of CBT and laid the empirical foundation for the Irritable Bowel Syndrome Outcome Study (IBSOS).

Methods/Design

Study Administration

Organizational Structure—The IBSOS is an NIH-funded, multi-center, placebo-controlled randomized clinical trial with two clinical centers (University at Buffalo [UB], Northwestern University [NU]), an Administrative Core (UB), a health economics center (Research Triangle Institute [RTI]), a Data Coordinating Center (Frontier Science and Technology Research Foundation [FS]), and the NIDDK Project Office acting together to implement a common protocol and administer the trial. The organizational structure of the IBSOS is diagrammatically represented below in Figure 1

Administrative Core: The Administrative Core at the University at Buffalo (UB) has primary responsibility for developing and implementing mechanisms to ensure quality control and to coordinate the execution of the scientific goals of the study by the administrative core, clinical centers, Data Coordinating Center, health economics center, and consultants as dictated by the research plan.

Additional responsibilities of the Administrative Core include:

- Preparing (with the aid of the Steering Committee and NIH staff) the protocol, forms, manuals, and intervention materials
- Developing the experimental statistical design of the trial
- Working with the investigators in the development and pre-testing of forms and procedures, and assuming responsibility for the content of forms and their scheduling
- Collaborating in designing and monitoring the implementation of the trial interventions
- Training clinicians, data coordinators and other clinical center personnel, and monitoring clinic performance
- Developing with the UB Office of Medical Computing software for electronic daily symptom diaries (iDiaries)
- Coordinating central resources among sites and consultants
- Managing quality control aspects associated with the day to day collection and management of raw participant data
- Summarizing clinical center performance at regular intervals for the Steering Committee
- Preparing, in collaboration with the clinical investigators, various manuscripts of trial results

Clinical Centers: Each of the participating clinical centers, at the University at Buffalo and Northwestern University, has agreed to implement the IBSOS Protocol. The clinical centers will follow participants according to protocol; assume responsibility for the completion of the protocol for each participant enrolled in the study; record participant data related to the above; review and enter information from data forms using a centralized data entry and management system; and respond to edit queries from the Administrative Core. Each

clinical center has a Principal Investigator, a Research Coordinator, and additional administrative and clinical staff to carry out the protocol.

Data Coordinating Center (DCC): The DCC for the project is Frontier Science and Technology Research Foundation (FS; Amherst, NY). FS works with study statisticians, project coordinators, and data managers at both sites to present reports to the Data Safety Monitoring Board (DSMB), prepare DSMB reports and supervise preparation of other reports. The DCC takes a leadership role in the study's design and scientific conduct. Accordingly, the DCC's responsibilities involve most aspects of the study and include: working primarily with Project PI and Lead Project Coordinator in collaboration with the clinical centers 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; developing data-management and quality assurance procedures in accordance with the final protocol and data-collection procedures; formulating a study monitoring plan along with the statisticians, producing and distributing reports, including enrollment, follow-up, protocol adherence, and data quality; preparing 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 the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) through the mechanism of the Cooperative Agreement (U01). The NIDDK Project Scientist provides program involvement as a participant in the scientific efforts of the IBSOS Research Group through development of protocols and assistance in the conduct of the IBSOS.

Steering Committee: The Steering Committee (SC) is the decision and policy making group of the IBSOS, is responsible for the overall direction of the trial, and establishes scientific and administrative policies for the study. The SC oversees all aspects of the design, execution, and publication of the study. The SC is responsible for:

- The general design and conduct of the trial and preparation of essential documents including the protocol, manual of operations and data collection forms
- Reviewing and approving data collection procedures
- Approving changes in study procedures as appropriate as for example the decision to transition from paper and pencil to electronic diary data collection of daily symptom data
- Creating, making appointments to, and disbanding subcommittees
- Allocating resources based on competing study demands (e.g., submitting ancillary study grant proposals)
- Reviewing study progress and implementing steps needed to allow the trial to meet its objectives
- Reviewing and implementing NIDDK-approved suggestions from the DSMB

The SC is comprised of the lead investigator of each clinical center, the Principal Investigator of the Administrative Core, Project Coordinators, Data Coordinating Center Chair, and NIDDK Project Scientist. All major scientific decisions will be determined by majority vote of the SC. The SC seeks the input of other IBSOS staff and consultants on an ad hoc basis to address issues beyond the immediate scope of its expertise.

Executive Committee: An Executive Committee (EC) is comprised of the IBSOS Project PI and NU Site PI Lead Project Coordinator, and the NIDDK Project Scientist. The EC is convened to manage the day-to-day operations of the study between SC meetings. The EC also develops timelines for the accomplishment of tasks, selects committee members and chairs, presents information to the DSMB, and develops SC meeting agendas.

Data and Safety Monitoring Board: An independent Data and Safety Monitoring Board (DSMB) appointed by the NIDDK Project Scientist to review and evaluate bi-annually the accumulated study data for participant safety, study conduct and progress of the IBSOS trial. The board is comprised of 4 senior investigators recognized for their expertise in biostatistics, clinical trials and methodology, behavioral medicine, and clinical gastroenterology.

Safety Officer: The Safety Officer serves 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 works with the investigators to assure that any adverse event is fully documented. Safety Officers also review adverse event data to assess if the frequency of the AEs changes dramatically from baseline. This change could be across the study or reflect a change in the AE profile at a specific site. Procedures for reporting all adverse events to the Safety Officer in a timely manner are clearly delineated in the Manual of Procedures. The frequency of safety data review and reports is also delineated.

Overall Study Aims

This paper seeks to describe the study protocol of the IBSOS whose primary goal is to assess the efficacy of two “dosages” of CBT (10 vs. 4 sessions) with reference to an active control condition for patients diagnosed with moderate to severe IBS. Additional goals are to identify clinically useful patient characteristics associated with outcomes 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 relief of GI symptoms; to evaluate the economic costs and benefits associated with the two “dosages” of CBT relative to control conditions; and to measure the durability of treatment response over 12 months post treatment.

Objectives

The major aims of the IBSOS and corresponding hypotheses are described below:

Primary Research Question—Aim 1. To evaluate the efficacy of MC-CBT compared to S-CBT and attention control for IBS

Hypothesis 1: Both MC-CBT and S-CBT are superior to attention-control (AC) 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, patient satisfaction, and health care use.

Hypothesis 2: Equivalence testing will show that MC-CBT does not differ from S-CBT on primary (global IBS symptom improvement) or secondary endpoints.

Secondary Research Questions—Aim 2. 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.

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.

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.

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.

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.

Aim 4. To estimate the cost and cost-effectiveness of MC-CBT, S-CBT and AC for IBS.

Hypothesis 1: MC-CBT is associated with lower costs compared to SCBT and associated with greater costs compared to AC.

Hypothesis 2: MC-CBT will prove cost effective relative to either S-CBT or AC.

Aim 5. To assess long term durability of acute treatment effects of CBT at 3-, 6-, 9-, and 12 month follow-ups (FU3, FU6, FU9, FU12).

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.

Study Design—As Figure 2 illustrates, the overall study design of the IBSOS includes 4 phases (pretreatment baseline [screening] assessment, baseline [symptom] monitoring, treatment and follow up phases).

Prospective subjects' initial contact with IBSOS begins with a brief phone screen that identifies obviously ineligible (e.g. previously diagnosed GI disease) volunteers and potentially viable volunteers prior to scheduling a formal, more labor- and time-intensive evaluation. The telephone screen includes a brief questionnaire regarding major exclusion criteria, collection of key demographic variable including age, duration of symptoms, referral source, and provides the potential participant with a general description of the trial. Individuals who complete initial telephone screening are either excluded from further screening and participation or are scheduled for a pretreatment baseline assessment with a gastroenterologist and health psychologist to confirm they have met eligibility criteria and to obtain baseline clinical data. At the conclusion of the baseline assessment, subjects who are deemed eligible begin the 4 week baseline symptom monitoring phase. The baseline monitoring phase consists of daily IBS symptom monitoring for a minimum of 28 days (4 weeks). Data are captured using a Dell minicomputer ("iDiary") that electronically time stamps entry of symptom diary information. Additionally, those participants who meet IBSOS eligibility criteria are randomly assigned via the DCC electronic portal to receive one of the three treatment conditions: MC-CBT, 4 session self-administered CBT; S-CBT, 10 session, therapist administered CBT; or 4 session attention control condition emphasizing supportive counseling and education (allocation ratio 1:1:1). Treatment phase begins directly

following the baseline monitoring phase, approximately 4 weeks after randomization at baseline assessment visit, and is delivered by doctoral level health psychologists or post-doctoral fellows in behavioral medicine. The acute treatment phase lasts approximately 10 weeks. Participants undergo follow-up examinations two weeks after treatment ends (12W) and 3, 6, 9, and 12 months (FU3, FU6, FU9, FU12) after the end of treatment. Follow-up phase of the IBSOS will continue until the last randomized participant has completed his/her 12 months of follow-up. At each of the 5 visits in the follow-up phase, participants provide information regarding the adequacy of relief of abdominal pain and bowel symptoms, global improvement of IBS symptoms, severity of IBS symptoms (e.g., pain, bloating etc), quality of life, psychosocial functioning. Interim assessments conducted periodically throughout treatment are designed to clarify the mechanism of change attributed to active treatments (e.g. teaching compensatory skills, belief changes, improved flexibility of problem solving responses, quality of therapeutic alliance, distress reduction, expectancy of improvement, etc). Figure 3 shows participant flow diagram consistent with the Consolidated Standards of Reporting Trials (CONSORT) statement

Definition of Outcomes

Primary Outcomes: The primary efficacy endpoint of the IBSOS is as follows:

- The key efficacy assessment is participant-rated global improvement of IBS symptoms [12]. A participant is considered to be a treatment responder if s/he rates IBS symptoms for which s/he sought treatment as moderately to markedly improved using the Clinical Global Impressions (CGI) Improvement Scale–IBS version [12, 14]. The rationale for defining treatment responders as those who report *moderately to markedly improvement* on the CGI-Improvement-IBS scale has strong precedent in multiple NIH trials [15–18] using global improvement as a primary endpoint. CGI also is a primary endpoint in a current NIH funded functional dyspepsia trial[19]. The use of the CGI satisfies Rome Foundation guidance that clinical trials use global measures that [20] “integrate ...symptom data into a single numerical index” [6]

Secondary Outcomes: Secondary efficacy endpoints include the following:

- Adequate relief of abdominal pain [21] two weeks after the end of treatment phase and at quarterly intervals through 12 months
- Adequate relief of bowel problems [12] two weeks after the end of treatment phase and at quarterly intervals through 12 months
- Change from pre-treatment baseline assessment to 2 weeks post treatment and at quarterly follow ups in ratings of (a) severity of abdominal pain/discomfort [Numerical Pain Rating Scale, Mc Gill Pain Inventory, 22, 23, 24] and (b) global severity of IBS symptoms [IBS Symptom Severity Scale, 25]
- Change from pre-treatment baseline assessment to 2 weeks post treatment and at quarterly follow ups in indices of health related quality of life [SF-12 Health Survey, EQ-5D, IBS-QOL, 26, 27, 28].
- Change from pre-treatment baseline assessment to 2 weeks post treatment and at quarterly follow ups of lower GI function (i.e. stool frequency; stool consistency [Bristol Stool Form Scale, 29]; severity of urgency and bloating using two 11-point (0–10) numerical rating scales)
- The percent of participants who describe themselves as satisfied with assigned treatment at 2-week follow-up using the Client Satisfaction Scale [30].

- Change from pre-treatment baseline to 2 weeks post treatment and at quarterly follow ups in psychological well-being (e.g. overall mental well-being [Brief Symptom Inventory, 31], and discrete emotional problems such as anxiety [State-Trait Anxiety Inventory, 32], depression [Beck Depression Inventory, 33], somatization [Screening for Somatoform Symptoms, 34])
- Change from pre-treatment baseline to 2 weeks post treatment and at quarterly follow ups in health care use (e.g. diagnostic testing, medications, ER visits, primary care, specialty care, and mental health visits)
- Change in estimated quality adjusted life years (QALYs) from pre- to post-treatment
- The proportion 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 [35])
- Safety as measured by the occurrence of adverse events

Additional Assessment: Beyond establishing the efficacy of a behavioral self-management approach for IBS, the IBSOS seeks to specify the conditions under which CBT may (or may not) achieve its effects (moderators) and why and how these effects are achieved (mediators) [36]. Moderators are temporally invariant baseline characteristics that are uncorrelated with treatment assignment but impact the relation between treatment and outcome [37, 38]. Identifying moderators is important in answering the question of what treatments work for which patients. [39]. In the IBSOS, moderator analyses will focus on a set of factors that, on the basis of existing literature, have negative prognostic value. These factors including non psychiatric medical comorbidity, interpersonal problems (IIP-36 [40]), social support, and motivation (TSRQ-IBS [41]). We will also examine predictors of outcome. We refer to predictors as baseline variables that show similar relationship with outcome irrespective of treatment assignment [36]. While predictor analyses have important clinical value, they do identify patient subgroups who respond differentially to different treatment. Only moderators address questions of the selection of treatment for a given patient [42].

While predictors and moderators refer to baseline variables associated with outcome, mediators, are temporally dynamic variables that occur during treatment and account for variability in treatment response [36, 38]. Identifying mechanism of change underpinning evidence based therapies is critical because it helps identify and refine the active ingredient of current treatments which in turn promote more robust, efficient, and disseminable interventions absent elements found to be either ineffective or redundant [43]. Because of the prominent role central factors play in governing brain gut interactions [44], the IBSOS is particularly interested in whether CBT works by correcting a rigid and negatively skewed information processing style that is believed to underlie physiological reactivity. A social learning theory (SLT) approach would predict that changes in cognitions (e.g. self-efficacy to control IBS symptoms, visceral anxiety etc.) mediate treatment changes in IBS symptoms and that greater (and more rapid) changes in cognitions occur during the course of CBT than during the attention control condition whose therapeutic focus is the provision of support and information, and not the systematic identification and disputation of negative cognitions that presumably underlie physiological reactivity. To this end, patients complete a number of cognitive measures including the IBS Management Self Efficacy Scale [45] the IBS-Specific Locus of control Scale [46], Visceral Index Index [47], and the Anxiety Sensitivity Index [48]

Firm support for the hypothesis that CBT reduces the severity of IBS symptoms by changing cognitive processes necessitates ruling out other plausible explanations that may account for the data. The effects of CBT and other psychosocial interventions are often attributed to the nonspecific factors that are “common” across different psychotherapies [49–51] [52] and not specific to CBT (e.g. skills building through formal instruction of techniques). Common factors include the provision of education, adherence and allegiance to the therapeutic protocol, provision of a convincing rationale for the treatment, support and encouragement, and, in particular, the quality of the therapeutic relationship and a positive expectancy of improvement (“placebo-expectancy” [53–58]). These variables are being measured using the Working Alliance Inventory [59] and the Expectation of Improvement/Treatment Suitability scale [60].

Participant selection—The IBSOS is scheduled to enroll 480 patients (age 18–70 at entry) who satisfy well defined eligibility requirements described below. In general, the inclusion/exclusion criteria are broadly constructed so as to acquire efficiently a sample representative of persons with IBS treated in everyday practice. This was deemed scientifically and logistically preferable to more stringent exclusion criteria (e.g., no psychiatric comorbidity, no medical comorbidity of any kind, no concomitant drug therapy) that would breach Rome III trial design recommendations to “include as broad a spectrum of patients as possible” [61], impede recruitment efforts of the very patients whose IBS imposes the greatest illness burden, increase the homogeneity of patient samples at the expense of reducing the generalizability of study results [62], and make it difficult to fulfill study aims (e.g., moderator analyses) that take advantage of the anticipated diversity of the sample.

Inclusion Criteria: With respect to inclusion criteria for entry into the study (performed at baseline screening assessment), participants include men and women of all ethnic and racial groups between the ages of 18 and 70 (inclusive). They must meet Rome III Diagnostic Criteria for Functional Gastrointestinal Disorders for the diagnosis of IBS [63], as established by a board certified gastroenterologist (GE) through medical examination. Symptom-based Rome criteria requires the presence of abdominal pain or discomfort whose onset is associated with a change in the form and/or frequency of bowel movements and/or is improved with defecation for at least 3 days/month over the past 3 months, with the symptoms first presenting at least 6 months prior to diagnosis. Symptoms must be at least moderate in severity (occur at a minimum of twice *weekly* and with some life interference). Participants are eligible if they can understand and provide informed consent, take no medications for IBS or can commit to a stable dose of all medications, during the 4-week pretreatment baseline monitoring period,. Participants must also be able to read at the 6th grade level, be willing to be randomized to treatment and to adhere to protocol requirements, attend regularly scheduled therapy sessions and follow-up visits, be able to maintain daily symptom diaries and to complete questionnaires throughout treatment and follow-ups. Finally, participants must have telephone access and be able to provide adequate tracking information should we need to locate them.

Exclusion criteria: Participants are deemed ineligible for the IBSOS if they present with evidence of current structural (due to abdominal surgery or idiopathic) or biochemical abnormalities, medication use, or other primary GI illnesses/maladies that better explains their gastrointestinal symptoms (e.g. laxative dependence, history of colon resection, radiation to the abdomen, etc.); if they have been diagnosed and/or treated for a malignancy other than localized basal or squamous cell carcinomas of the skin in the past 5 years; are currently undergoing psychotherapy *for IBS*; cannot commit to completing all scheduled screening visits, psychotherapy sessions and follow-up visits; have either an unstable

extraintestinal condition or a major psychiatric disorder (e.g., depression associated with high risk of suicidal behavior, psychotic or delusional disorders or gross cognitive impairment) that would realistically impede the conduct of the trial, interfere with completion of study demands, and/ or affect the interpretation of data; report a current gastrointestinal infection or an infection within the 2 weeks prior to the evaluation that would otherwise obscure IBS symptoms; or if they have taken a gut-sensitive antibiotic such as Rifaximin or Neomycin for IBS during the 12 weeks prior to baseline assessment. In the case of infection, baseline assessment to confirm eligibility is delayed until 2 weeks after complete recovery. In the case of antibiotic use, final determination of eligibility status is suspended for 12 weeks from the date the gut-sensitive antibiotic was first consumed.

There are several notable eligibility issues that warrant elaboration because they bear on both behavioral trials in general and the conduct of trials for functional GI disorders.

Comorbidity: Because we are interested in understanding the prognostic value of nonpsychiatric medical comorbidities on outcome, the IBSOS does not exclude patients with coexisting illnesses provided they are relatively stable at pre-treatment and have a low likelihood of interfering with fulfillment of study demands (e.g. frequent hospitalizations, surgeries, impaired ambulation). We reasoned that the randomization should balance the three treatment arms on dimensions of coexisting medical problems such that any group difference can be attributed to the effect of treatment.

We also made the decision not to routinely assess patients for organic GI disease such as celiac disease. First, in patients whose symptoms meet Rome criteria and have no alarm features (e.g., rectal bleeding, unintended weight loss, anemia) suggestive of organic GI disease, this combination of a positive Rome diagnosis for IBS and no alarm symptoms have 100% sensitivity and positive predictive value [64, 65]. These data argue strongly that in a clinical research setting, routine diagnostic testing in general is not necessary for patients who have typical IBS symptoms, satisfy Rome criteria and present with no alarm symptoms. With respect to celiac testing in particular, cost effectiveness studies [66] [67] indicate that testing is not inexpensive and has limited incremental value (the risk of missing celiac disease is about 1 percent) for the great majority of patients with IBS symptoms over a positive (ie symptom based) diagnostic approach “unless one works in a high prevalence area or clinically suspects the diagnosis on other grounds”[68].

Concomitant Treatments: Unlike in previous CBT trials [12, 69], we do not exclude patients who are undergoing psychotherapy unless their treatment specifically targets relief of IBS symptoms. Patients who are currently involved in marital therapy or psychodynamic therapy, for example, are not necessarily deemed ineligible. After consulting with other investigators who oversee large NIH funded behavioral trials, we came to the conclusion that if ancillary treatments had robust, clinically significant impact on IBS these patients would not be seeking treatment for relief of IBS symptoms from a psychological treatment specific to IBS. In other words, the probability that patients would experience meaningful symptom change due to an ancillary therapy that yielded no symptom improvement prior to study enrollment was regarded as low.

Similarly, while we request that with the exception of gut-specific antibiotics patients maintain stable dosages of ancillary medications during the four week pretreatment baseline, we do not require them to maintain a stable dosage throughout the acute treatment phase for multiple reasons. First, one proposed measure of the therapeutic benefit of CBT is the extent to which patients’ health care utilization decreases as their symptom self-management skills improve. By requiring patients to maintain a stable regimen of ancillary treatments we run the risk of artificially inflating levels of an important clinical variable that is subject to

change. Second, because of random assignment to conditions, it is likely that concomitant medication use will be equivalent in all conditions. In other words, randomized patients on concomitant medication are unlikely to be disproportionately distributed to a specific arm. Therefore, any change in the dependent variable (e.g. symptom relief or improvement) can be confidently attributed to treatment and not ancillary medication use. To verify this assumption, IBSOS developed a formal plan for tracking ancillary treatments through baseline, acute treatment phase, and follow up periods. This plan involves (1) interviewing patients at each clinic visit about any new medications or changes to existing ones, as well as significant non drug therapies (e.g., physical therapy, chiropractic care) taken after randomization; (2) carefully tracking medication use patterns through the course of the trial; and (3) statistically analyzing and controlling for their influence by comparing the treatment groups to determine if there are differential patterns of post-randomization therapies that may influence outcome; and (5) if pre-randomization and/or post-randomization therapy patterns are differential by group, conduct sensitivity analyses to assess whether the effects of treatment on the primary outcome measure vary by either of these patterns.

Recruitment of Subjects: Delivery of treatment is being carried out at two clinical sites: The University at Buffalo School of Medicine (Buffalo, NY) and Northwestern University Feinberg School of Medicine (Chicago, IL). The multisite organizational structure of the IBSOS confers several methodological and logistical advantages over single site trials: (1) ability to recruit a more heterogeneous pool of subjects, thereby enhancing generalizability of findings and an opportunity to evaluate a broader range of subjects characteristics that may modify treatment response; (2) generate larger sample sizes with greater power to test hypotheses and more precise estimation of population parameters; and (3) rapid recruitment in a shorter period of time to provide sponsor, health care organizations and policy makers with timely results to inform policy regarding contentious issues in the field (e.g., the therapeutic benefit of CBT for IBS). Based on over a decade of NIH-funded IBS clinical research carried out at the University at Buffalo that has been effective in recruiting a broad spectrum of IBS patients from primary care, tertiary care, and the local community, the IBSOS has adopted a two pronged recruitment strategy that emphasizes both direct-to-patient and indirect methods.

Direct approaches are pitched directly to prospective participants through newspaper, magazine, radio, television and internet promotion as well as the distribution of fliers, and posters in areas with high patient traffic, such as waiting rooms, pharmacies, beauty salons, restaurants, community centers, gyms, laundromats, coffee shops, bookstores/record stores, places of worship, and grocery stores. Innovative direct approaches used by the IBSOS include

- The Northwestern site of the IBSOS has partnered with the Institute for Women's Health Research (IWHR), a multidisciplinary department, whose mission is to promote research in women's health. One of its hallmark programs is the Illinois Women's Health Registry, created in March of 2008 as a way to provide two-way communication between women and scientists to facilitate a better understanding of how and why illnesses develop differently or similarly in men vs. women, how to best treat diseases in women and what women can specifically do to prevent illness. The IBSOS-NU site has used the registry to identify women who endorse symptoms of IBS in their annual health surveys in order to send them study brochures and field phone calls to assess their potential eligibility. The Northwestern site PI also wrote an article about IBS for the April, 2012 issue of IWHR's monthly e-newsletter to coincide with IBS Awareness Month. The electronic newsletter was distributed to all 5000+ members.

- Recognizing the popularity of social media and the influence of the internet as an information channel, the IBSOS produced a recruitment audio slide show to supplement other components of a print and online recruitment campaign. To gather content for the slide show, multimedia producers at UB photographed and interviewed IBSOS team members, as well as a female and male grant patients who had completed the CBT for IBS. The final product, uploaded to YouTube (<http://youtu.be/gbF75zp-DbE>), presents prospective patients with useful information about the IBSOS and its possible clinical value. The slide show also humanized IBS by presenting the stories of real patients who both struggled with the disorder and achieved symptom relief through the IBSOS. Referring MDs report that the YouTube is a convenient, informative way to orient prospective referrals to the IBSOS.
- In response to epidemiological data showing that 50–70% of individuals with IBS symptoms do not visit physicians and a growing awareness that a large number of chronically ill patients turn to pharmacists for guidance on disease management ([70]), the IBSOS initiated a local pharmacist outreach campaign. The campaign began by partnering with three free standing pharmacies in the greater Buffalo area and has expanded to include 17 additional pharmacies including those of a large national supermarket chain. Recognizing the value of behavioral self-management approaches for unresolved IBS symptoms, participating pharmacists have agreed to provide counter space for distribution of study brochures that describe the IBSOS trial and include an easy-to-use perforated reply piece to give prospective participants the opportunity to request information and/or a follow-up call from IBSOS staff.

Indirect methods have been aimed at enlisting support (e.g. referrals, generating positive word of mouth, building brand identity of the IBSOS) of physicians, and other health care professionals who are in a position to influence prospective participants' decision to enter the IBSOS.

- One indirect recruitment strategy is through the *Enterprise Data Warehouse* (EDW) at Northwestern, an electronic medical record data storage facility that can be queried to identify all patients who have been diagnosed with IBS seen within the NU faculty practice. Similar to the IWHR, these patients are sent direct mailings inviting them to consider participating in the IBSOS.
- NU created a “best practice alert” popup within the electronic medical record platform to alert gastroenterologists in real-time whenever their patients are potentially eligible for participation in IBSOS. This approach helps reduce the barrier to recruitment most cited by physicians—not enough time to recruit and/or forgetting to recruit in a busy clinic. If physicians click on the “Yes” button to refer a patient to the trial, the patient receives a brochure printed out at checkout and the NU patient liaison forwards the referral to NU research coordinators so they can call the patient directly.
- The IBSOS collaborated with the American Academy of Family Physicians to develop CME materials on CBT for IBS for the March 2012 edition (CBT for IBS) as part of its *FP Audio* program [71]. FP Audio is a continuing medical education designed to provide family physicians with high quality, cost effective CME options. Each edition of *FP Audio* contains authoritative, unbiased, and peer-reviewed clinical information regarding important clinical topics. After listening to a CD or mp3 tape of a studio recorded interview and completing an online quiz, participants earn CME credits.

The effectiveness of patient recruitment initiatives are regularly measured using a variety of metrics:

- Number of phone calls
- Number of initiated and completed phone screens
- Reasons for caller ineligibly
- Conversion of phone calls to scheduled evaluations
- tracking how participants heard about the study
- tracking media coverage
- reporting the number of hits to the trial website and YouTube clip\comparing the number of telephone calls received before rolling-out recruitment initiatives to the number received during and after
- Cost of print/TV/radio ad per screen

Treatments

Follow up: Data collection for efficacy endpoints occurs at 5 points after the end of acute 10 week treatment phase: 2 weeks post treatment (12W); 3, 6, 9, and 12 months post treatment (FU3, FU6, FU9, FU12). Assessing treatment benefit at 12W is designed to gauge whether treatment response is sustained after the withdrawal of treatment at week 10. We believe that this is a more rigorous way of assessing treatment benefit than defining treatment response based on the proportion of weeks (e.g., 50%, 75%) a patient reported symptom relief/improvement. The latter approach is problematic because there is no universally accepted rule of what proportion of weeks defines a responder or which weeks are critical to a positive treatment response definition. Further, patients' judgments of efficacy may be influenced by nonspecific factors if efficacy ratings are assessed during treatment. This practice may overstate the treatment specific effects.

The major goal of quarterly follow ups is to assess both the immediate and long-term benefits of CBT for IBS as well as its clinical course. Follow up visits require patients to complete a set of self-report questionnaires administered previously during the pre-treatment baseline screening assessment phase and to undergo post treatment evaluation by the study gastroenterologist who evaluates severity of symptoms without knowledge of treatment allocation. Each follow up phase includes a semi structured health care utilization interview concerning IBS symptoms, their impact, and health care use.

Data collection to establish mediation is more complicated. The data of a conventional outcome study that schedules data collection pre- and post treatment does not allow causal interpretations regarding the association between therapeutic benefit and change on putative mediators as observed. Changes in putative mediators should temporally precede substantial changes in the outcome measure being used. An outcome study that collects data pre and post treatment does not collect data regularly enough to assess temporal precedence and determine the causal significance of changes in mediators on a clinical outcome. Because the effects of treatment on outcome are likely to occur as early as the first four weeks treatment for a significant proportion of IBS patients undergoing CBT [72], it is important to assess the putative mediator and outcome variable at frequent intervals throughout the early part of treatment when change is likely to occur. A key consideration in structuring the IBSOS assessment schedule is systematically assessing whether change in the mediator precedes the effects of treatment on outcome (i.e. temporal precedence). This means that assessment of mediators occurs prior to assessment of outcomes. If temporal precedence is

not established, then it is difficult to rule out the notion that change in the mediator is a consequence versus cause of change in outcome [36]. For these reasons, proposed mediators are assessed at the pretreatment baseline screening assessment, weeks 1, 3, 5, and 8 of the acute treatment phase as well as 12W of the follow up phase of the IBSOS.

Study Interventions: The IBSOS features two specific types of psychological treatment, either Education Supportive Counseling (Attention Control Condition or AC) or Cognitive Behavior Therapy (CBT). Cognitive Behavior Therapy is delivered in two “dosages”: a clinic-based, therapist delivered version (Standard CBT (S-CBT), 10 sessions) and a home-based, self-administered version (Minimal Contact CBT (MC-CBT), four sessions).

Standard CBT (S-CBT) is a skills-based training program [73] based on the principles of social learning theory [74]. In SLT, health and behavior is explained in terms of a continuous reciprocal interaction between cognitive, behavioral, biological, and environmental influences. These are very dynamic relationships where the person can shape the environment as well as be shaped by the environment. Individual differences across health outcomes are strongly determined by the way patients perceive and think about their illness, particularly their beliefs regarding the capacity to control or influence illness parameters (self-efficacy). Treatment involves 10 weekly, 1 hr. individual sessions and 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 aimed 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 schema or “core” beliefs (e.g., perfectionism), and (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.

Minimal Contact 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, 1 hour clinic visits, MC-CBT meets for only 4, 60-minute clinic visits over a 10 week period. MC CBT sessions occur during the first, fifth, eighth and tenth week of the acute treatment phase. At the 1st MC-CBT session, treatment is explained, self-study materials are provided and muscle relaxation and self-monitoring are introduced. The 2nd treatment session introduces cognitive coping techniques (e.g. decatastrophizing, negative prediction testing). At the 3rd session, patients receive problem solving training and learn more advanced cognitive coping skills (e.g., modifying core beliefs such as perfectionism). The 4th session introduces relapse prevention skills. In the MC-CBT condition, two 10 minute phone contacts are scheduled at week 3 and 7 to troubleshoot around any problems encountered between clinic visits.

Attention-control is closely adapted from the psychological placebo intervention used by various psychosocial researchers [75, 76] [77] to control for nonspecific therapeutic influences inherent in CBT. Attention-control conditions have two important features in common with the experimental conditions(s): the provision of a credible therapeutic rationale and a psychotherapeutic relationship. In the IBSOS intervention, participants were provided with the rationale that learning information about IBS, sharing one’s personal experiences of having a chronic illness, and having access to a knowledgeable and understanding health care provider could help alleviate the burden of IBS. Therapists were expected to maintain the common elements of the psychotherapeutic relationship while avoiding the technical elements specific to CBT (e.g. prescribing behavioral changes). In this respect, the attention control satisfies key requirements of an “active” control condition [72].

The format of the attention condition parallels the MC-CBT condition (4 sessions with 2 10-minute phone calls over ten week treatment phase and self-study materials). The sessions are structured around education and reflection. The educational component (usually administered at the beginning of the session) emphasizes imparting accurate, up-to-date information about IBS, its clinical features, epidemiology, diagnostic criteria, medical tests, and treatment options. To maintain credibility around the educational component, the developers of the manual determined that information that was easily accessible by the patient (e.g. internet, self-help books, employee assistance program websites) could be included as long as it did not encourage specific behavior change. For example, information about the role of stress in IBS was included in Session 2, but stress management skills were neither discussed nor prescribed. Instead, the patient is asked to reflect on ways that stress affects them with the therapist providing support around the emotional unpleasantness of stress. Studies demonstrate that an education/supportive psychotherapy condition produces evaluations of credibility and outcome expectations similar to those generated by CBT [77–80]. It is recognized as a best available psychological placebo control condition for IBS and other comparable disorders [79, 81–83]. To control for receipt of self-help materials, patients receive a copy of *IBS: Learn to Take Charge Of It* [84], a patient education book that accentuates the therapeutic value of information (“It all comes down to this: An informed patient is an empowered one”) over structured behavioral skills instruction featured in CBT. During the planning phase, IBSOS negotiated with the publisher to print off a special edition of the book that extracted any pages that discussed proscribed behavioral techniques (e.g. step by step relaxation exercises) featured in the CBT conditions.

Treatment Assignment: Participants in the IBSOS who have provided written informed consent and fulfill eligibility criteria are randomly assigned to one of the three treatments at the end of pre-treatment baseline screening assessment by the site’s research coordinator. Treatment assignments are generated using a web-based subject registration and randomization system developed by the DCC (Frontier Science). This system uses protocol-specific specifications files to present eligibility questions to the sites to evaluate a subject for enrollment. Only participants who meet all the eligibility requirements can be randomized to the study. Treatment allocation assignments are stratified by clinic site. This ensures initial comparability between groups of eligible participants for whom treatments are compared, thus eliminating the impact of individual and site difference variables on outcome.

Treatment 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 whose content is known to therapists [85]. To the extent that blinding seeks to control differential expectations and consequent demand characteristics they may generate, we adopted 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 [86] at the conclusion of session 1. Participants are never informed of the condition to which they were assigned. All conditions are described as symptom self-management treatments.

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 hypotheses one set of analyses will establish whether the effects of MC-CBT and S-CBT are comparable. This will be pursued from both a traditional hypothesis testing framework and

an equivalence testing framework. Generally speaking, endpoints are assessed at baseline screening assessment visit, at immediate post-treatment (12W) and at the follow-ups FU3, FU6, FU9 and FU12 for each of three groups (MC-CBT, S-CBT and, AC). The traditional analysis for a given outcome variable is a two way analysis of covariance using the three groups as a between-subjects factor, time as a within-subjects factor (12W FU, FU3, FU6, FU9 and FU12) and the baseline assessment 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 elsewhere[87]. 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 3, 6, 9, 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 12W follow up 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 [88].

Another set of analyses will identify baseline patient 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 assessment as well as 12W, FU3, FU6, FU9 and FU12. Most of the mediators also are measured during treatment, (weeks 1, 3, 5 and 8) 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 post-treatment test (12W). An early response mediation model states that IBS self-efficacy gains experienced early in treatment (e.g., from baseline assessment to weeks 1 and 3 in treatment) are the primary determinants of the ultimate response to treatment at 12W. Alternatively, a recency mediation model states that the level of IBS self-efficacy at the two week post treatment follow up (12W) is the primary mediator of treatment response. A growth curve mediation model states that it is the general acceleration/deceleration of IBS self-efficacy across the entire treatment course (as well as the shape of the curve) that best predicts response to treatment at 12W with IBS self-efficacy being as parameterized as a growth curve. 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 on treatment response. The baseline assessment outcome variable is used as a covariate and the 12W outcome is used as the criterion. All three sources of influences will be parameterized and modeled as predictors of change at 12W as well as the decay functions characterizing change from 12W to FU12. Models also will be pursued that include multiple mediators in the same model. Moderator analyses will be conducted by including product terms in the models.

With respect to establishing the relative economic value of the three conditions, we will conduct an economic evaluation of the three conditions to evaluate the costs, cost-effectiveness, and cost-benefit associated with each of these conditions. Our perspective for the economic evaluation is a societal perspective and will include both provider costs (e.g., labor time for treatment provider staff, building space, and treatment-related supplies and materials) and participant costs (e.g., value of participant's time in treatment and travel time to/from treatment and other treatment-related expenses).

Costs for each of the conditions will be estimated for all participants following the micro-costing approach recommended by Drummond et al. (2005) and Gold et al. (1996). This approach identifies, measures, and values the resources associated with each activity performed under each treatment condition. The total treatment cost for each participant is simply the cost per activity multiplied by the number of activities or services received by the participant during treatment, and taking the mean across participants in a given treatment condition yields the mean per participant cost of that treatment.

Separate cost-effectiveness analyses will be conducted for the primary outcome (i.e., proportion of patients responding to treatment) and selected secondary outcomes (e.g., proportion of patients with improved psychological well-being; QALYs gained). To estimate the cost-effectiveness associated with the three conditions for a given outcome we will tabulate the costs and effectiveness measure for each condition in increasing order of cost (or effectiveness). Starting with the treatment with the lowest cost (or effectiveness), incremental cost-effectiveness ratios (ICER) will be computed for each treatment condition relative to the next most costly option after eliminating treatment options that are dominated by other treatments [89, 90]. A treatment 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). ICERs are calculated by dividing the difference in costs of two alternatives by the difference in the effectiveness of the two alternatives. The estimated ICER can be interpreted as dollars spent per unit of desired outcome gained (e.g., \$5,000 per QALY gained). To aid in interpretation of the results, we also will estimate cost-effectiveness acceptability curves (CEACs) for the ICERs to show the probability that a treatment condition is cost-effective as a function of a policy maker's intrinsic valuation or willingness to pay for the clinical outcome [91–93].

As a final step in the economic evaluation, we will perform a cost-benefit analysis (CBA) to examine the monetized benefits relative to costs for each of the three conditions. The CBA primarily will focus on benefits related to post-treatment health care utilization as this measure is hypothesized to be a key driver associated with IBS costs. To perform the CBA, we will calculate the net benefit (i.e., the dollar value of benefits less costs) for each condition and then compare these estimates across conditions to evaluate which condition is optimal regarding future health care utilization. The unit costs to be used in valuing these economic outcomes will be drawn from various literature and public data sources.

Sample size determination: The projected sample sizes at the two sites are 276 and 204, for UB and NU, respectively. For traditional null hypothesis testing, the alpha level is 0.05 for a two-tailed test. We do not anticipate conducting interim analyses for possible termination of the study as there is much to be gained in modelling of data irrespective of the treatment outcome.

Because we use structural equation modelling (SEM) for some analyses, sample size considerations are relevant for the use of asymptotic theory and the stability of the covariance matrices. Simulation studies suggest that sample sizes of 125 to 150 often yield adequate results for asymptotic theory for a range of latent variable models, given that reasonably reliable measures are used with well-defined factor structures [94, 95] (269–268). The sample size in our study exceeds this standard.

The primary focus of Aim 1 is establishing whether the effects of MC-CBT and SCBT are comparable. This is pursued from two perspectives, a traditional hypothesis testing framework and an equivalence testing framework. For the core outcome variables, we have assessments at baseline (screening assessment), an immediate posttest 12W and at 3, 6, 9 and 12 month follow-ups (FU3, FU6, FU9 and FU12) for each of three groups (MC-CBT, S-

CBT and AC). The traditional analysis for a given outcome variable is a two way analysis of covariance using the three groups as a between-subjects factor, time as a within-subjects factor (12W, FU3, FU6, FU9 and FU12) and the baseline assessment 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 AC). Of interest is whether there are statistically significant pairwise contrasts between the groups. These contrasts will use non-pooled error terms across time (because of the likely violation of sphericity), but will use pooled error terms across groups within time (unless diagnostics suggest otherwise). 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 meet these standards.

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 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 adopt 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. Equivalence testing is implemented by testing two directional hypotheses with respect to this predefined value of TV using standard tests of significance; one hypothesis stating 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 [96]. The confidence interval approach can be adapted to allow comparison of adjusted mean differences in the analysis of covariance framework described earlier as well as decay functions in growth curve analyses described below. For the IBS-SS scale, it is commonly argued that a 50 point reduction represents the cut-off for meaningful change. This suggests that if the population mean difference between the treatments [25] 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 (using a tolerance value of 90%) for a two group mean difference with a sample size of 160 per group is approximately 18, indicating our sample size will yield interval widths that are viable for making statements of functional equivalence for this measure. For the 12 month intent-to-treat follow-up analyses with a project N of 149 per group, the estimated half width is approximately 19 and for the dosage response sample size of 115 per group it is approximately 21. 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 [97]. 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 intent-to-treat analysis sample size at the immediate post-test (12W) is approximately 4, again indicating our sample sizes can sustain this type of analysis. For the twelve month

follow-up ITT analysis the estimated half width is 4.7 and for the dosage response analysis it is 5.4.

Aim 5 emphasizes evaluating the long term durability of acute treatment effects at 3, 6, 9, and 12 months post treatment. Accordingly, a second type of analysis is to compare the decay functions of the different groups, to determine if the decline (or improvement) in treatment effects from 12W 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. The three treatment groups are represented by two dummy variables. A latent intercept is defined to represent the score at IM and a latent slope is defined to represent the linear decay function. Paths from the dummy variables to the latent slope variable represents group differences in the average slope characterizing the decay function. It is possible, of course, that the decay functions are non-linear. We will use either quadratic regression or split regression to deal with this, as needed. Using the power analysis methods described by Raudenbush & Liu [98], 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 map favourably onto our proposed final sample sizes.

Aims 2 and 3 emphasize identifying baseline patient characteristics that predict response to treatment (hence reflecting moderators of the effects of the interventions) and 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 assessment to the immediate post-test (12W) within a given group (i.e., within MC-CBT or within S-CBT). Statistical strategies vary depending on how response to treatment is operationalized. The sample size calculations described above apply directly to the analyses that will be pursued for these aims, so they are not repeated here.

Missing data is handled through full information maximum likelihood (FIML) methods, MCMC multiple imputation, or is formally modelled in the SEM structures, depending on characteristics of the data. We plan to collect follow-up data on all respondents initially enrolled in the study independent of whether they complete treatment so that we can perform both per-protocol and intent-to-treat (ITT) analyses.

Many of the traditional tests we plan to use rely on maximum likelihood or least squares analytic schemes that make population level assumptions. When either theory or data suggest that the assumptions are questionable, robust estimation methods are desirable. We will use either bootstrapping or Huber-White sandwich estimators to deal with such cases. The data are collected at multiple sites, so there is a potential for clustering effects due to site. We do not believe there will be clustering effects but we will test for them through the analysis of intraclass correlations. If we observe non-trivial clustering, then this will be taken into account using algorithms based on Huber-White adjustment.

Treatment Integrity: Treatment integrity is the degree to which a particular intervention is delivered as intended. The two key components of treatment integrity are adherence (the extent to which the therapist implements the prescribed techniques and avoids techniques that are proscribed) and competence (the skill with which the therapist delivers the treatment). Failure to preserve treatment integrity threatens both the internal and external validity of an outcome study. Determining whether specific treatment procedures are causally related to treatment outcome depend in part on the integrity of treatments. Unfortunately, while few would argue that treatment integrity is unimportant as a principle in outcome research, systematic evaluation of treatment integrity is “extremely rare” in behavioral research [99]. The IBSOS has incorporated a number of methods for monitoring and optimizing treatment integrity, which map onto the domains (e.g., study design, training, treatment delivery) the NIH Behavioral Change Consortium deems important to preserving treatment fidelity [100]. Some of these methods are described below

Therapist Selection: IBSOS has applied the “gold standard” for treatment delivery through the identification, training and maintenance of qualified therapists. IBSOS therapists have doctoral degrees in clinical or counseling psychology with a minimum of 3 years of clinical experience in the practice of CBT or supportive psychotherapy. In addition, therapists, regardless of treatment condition must be:

- Willing to learn manualized versions of treatments and follow manual guidelines for the duration of the protocol
- Willing to be assigned to deliver each of the treatment conditions and participate in any initial and ‘refresher’ training sessions
- Willing to have their sessions audio recorded for review by clinical supervisor and adherence/competence raters, to attend regular supervision sessions and to complete process ratings (e.g., ratings of the therapeutic alliance and techniques used during sessions)
- Be approved by the IBSOS administrative/supervisory staff as appropriate for the study (e.g., sufficiently reliable, performs clinical and administrative duties competently)

Therapist Training/Supervision: All therapists attend an intensive didactic training seminar at the primary site prior to delivering treatment for randomized subjects. Training includes review of cognitive behavioral theory and techniques, topic-by-topic review of the manuals, listening to a sample of audiotapes, several role play and practice exercises, discussion of case examples, modeling of competent administrative tasks, and rehearsing strategies for difficult or challenging cases. Therapists received similarly rigorous training for delivering the AC condition. After training each therapist is assigned a minimum of two training cases for each condition which are closely supervised by site PIs. Therapists who demonstrate an ability to deliver competently each intervention are then certified and able to receive randomly assigned patients. Remediation through additional didactic instruction and training cases is assigned as necessary.

Ongoing training and monitoring of all therapists: To monitor implementation of IBSOS treatment, facilitate consistent treatment quality and delivery across sites, and prevent therapist “drift,” all sessions are taped and a proportion of each participants’ sessions are reviewed by site supervisors. Therapy monitoring focuses both on the degree to which the therapist delivers the treatment in adherence with manual guidelines and on the level of therapists’ skill in delivering treatment. IBSOS supervision emphasizes two components (1) continuous monitoring of treatment delivery and (2) provision of corrective feedback

regarding adherence and competence [101] through regular supervisory meetings, review of audiotapes, and therapist self-monitoring of their clinical activity. The importance attached to supervision reflects research showing that the therapeutic benefit of CBT in clinical trials is highly dependent on the quality and persistence of supervision. Lax supervision is often identified as a reason for why CBT has not proven clinically superior to a control condition in the NIMH Treatment of Depression Collaboration Research program [102]. Controlled trials that have incorporated more intensive supervision (e.g., weekly supervision) have yielded stronger outcome data [103, 104]. In addition to regularly scheduled supervision and opportunity to receive booster training sessions, all therapists attend monthly clinical telephone conferences with the clinical staff of both sites. The goal of these clinical teleconferences is to identify clinical issues that may affect treatment implementation, to strengthen provider skills and treatment delivery, and to discuss clinical process issues whereby the therapist had to choose from several options. The analysis of such “choice points” provides the supervisor and therapists an opportunity to explore how the needs of a particular patient can be met within the context of a specific treatment protocol. Junior level therapists receive weekly supervision as well as “real-time” supervision when appropriate.

Audiotaping of therapists: Close attention to the therapists’ delivery of study treatment and level of competence is emphasized in the IBSOS. This is partly achieved by audio taping all sessions. Audio taping enables objective verification of dosage and treatment content according to criteria developed a priori; provides a mechanism for providing specific corrective feedback during supervision; and optimizes standardization within and between providers at both clinical sites. Independent raters use condition specific Therapist Adherence Scales, which were developed as a way to determine the extent to which a particular treatment has been delivered in the manner specified. In addition to adherence, the quality of the treatment provided (competence) is also rated. Coders use a 5 point scale to rate therapists on their degree of effectiveness across various domains of the therapy (e.g. MC-CBT and S-CBT domains include self-monitoring, homework, labeling cognitive errors). AC domains include appropriate coverage of educational material and reflective listening without engaging in proscribed behaviors from other manuals, time management, therapist style and maintenance of positive expectancy/motivation. Overall session scores below 4 are considered out-of-protocol and require further remediation.

Manualized Treatments: During the pilot study [12], detailed treatment manuals were developed for the two CBT conditions. These manuals were refined and a manual for the AC condition was developed during the clinical trial planning phase,. The purpose of the manuals is to specify and discriminate treatments, outline session goals, describe therapeutic activities and strategies to meet these goals, and provide guidance for troubleshooting around common clinical problems encountered during each session. These manuals follow a “flexibility within fidelity” approach ([105] of manual development that struck a balance between providing detailed and concrete guidance without inhibiting therapeutic creativity, was sensitive to individual needs of patients, and fostered a quality therapist-patient alliance.

Session-by-session checklists: Checklists are used by the therapist at each session to record if key ingredients from each session are or are not implemented as prescribed in the manual, that homework is correctly assigned and that study procedures are followed. Therapists “sign off” on their adherence to these checklists and protocol violations are reported to the site supervisor when needed.

Current Study Status—The IBSOS enrolled its first subject in August, 210. To date, 565 individuals have undergone a phone screen to determine eligibility for an evaluation. Of the 335 callers who passed telephone screening, 252 (signed an informed consent for

participation and underwent baseline evaluation. One hundred and seventy one (of callers who passed telephone screen) were successfully enrolled and randomized to treatment. UB has enrolled 105 subjects, NU 66. One hundred and twenty subjects have successfully completed the 10 week acute treatment phase. Fourteen subjects dropped out either during pretreatment baseline or acute treatment phase. One hundred and eight have completed the 2 week post treatment follow up, 82 subjects have completed their 3 month follow up, 55 completed their 6 month follow up, 42 completed the 9 month, and 21 subjects have completed their 12 month follow up (study completer).

Summary

The IBSOS is a landmark clinical trial funded by the NIDDK with the primary goals of determining the therapeutic benefit of a self-administered behavioral treatment for patients with unresolved IBS. Additional goals include determining the active ingredients of treatment, identifying the subgroups of individuals for whom treatment is most and least beneficial, assessing the durability of treatment response, and calculating the costs associated with treatment. In the absence of a satisfactory medical or dietary treatment for the full range of IBS symptoms that exact a heavy burden both on the individual sufferer and society as a whole, data emanating from the IBSOS will help fill a critical gap in our understanding of IBS and its treatment and potentially may lead to enhanced quality of patient care, improved clinical outcomes, and decreased costs of one of the most prevalent and intractable GI disorders. The trial architecture is designed to assure successful recruitment and patient retention, optimal data collection, coordination of sites in delivering treatment and training and monitoring of competent therapists of all experimental conditions. These features stand to make the IBSOS a model for other randomized clinical trials for other complex chronic illnesses that defy medical cure and whose symptoms rely on patient self management.

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Abbreviations

CBT	Cognitive behavior therapy
MC-CBT	Minimal contact CBT
S-CBT	Standard-CBT
GI	gastrointestinal
QALY	Quality Adjusted Life Years
IBSOS	Irritable Bowel Syndrome Outcome Study
IBS	irritable bowel syndrome
DSMB	data safety monitoring board
SEM	structural equation modeling
DCC	data coordinating center
NIDDK	National Institutes of Diabetes and Digestive and Kidney Diseases
SLT	social learning theory
AC	attention control
NIH	National Institutes of Health
SC	Steering Committee
EC	Executive Committee
12W	2 week post treatment follow up
FU3, FU6, FU9, FU12	3, 6, 9 and 12 month post treatment follow up periods, respectively

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Figure 1.

Figure 2.

Figure 3.