Irritable Bowel Syndrome Outcome Study (IBSOS) Manual of Operations, Policies and Procedures (MOPP)

Protocol:
Irritable Bowel Syndrome Outcome Study (IBSOS)

Sponsored by:
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

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Disclaimer

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List of Abbreviations

ACC	Attention Control Condition
AC	Administrative Core
ASI	Anxiety Sensitivity Index
ARQ	Adequate Relief Questionnaire
ATT	Attitudes Towards Treatment Questionnaire – IBS
BDI II	Beck Depression Inventory II
BSI 18	Brief Symptom Inventory 18
BSFS	Bristol Stool Form Scale
CA	Controllability Awareness
CBC	Complete Blood Count
CBT	Cognitive Behavior Therapy
CDC HRQOL-4	Centers for Disease Control and Prevention Health-Related Quality of Life – 4 Questionnaire
CGI	Clinical Global Impression Scale
CNS	Central Nervous System
CRF	Case Report Form
CSQ	Abbreviated Coping Strategies Questionnaire
CSQ-8	Client Satisfaction Questionnaire-8
DCC	Data Coordinating Center
DIS	Discomfort Intolerance Scale
DSMB	Data and Safety Monitoring Board
ERQ	Emotional Regulation Questionnaire
EQ-5D	Euro-Quality of Life Questionnaire
FCC	Federal Communications Commission
FDA	Food and Drug Administration
FMS	Fibromyalgia
FMBS	Frankfurt Monitoring and Blunting Scale Questionnaire
GE	Gastroenterologist
GI	Gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act of 1996
HMO	Health Maintenance Organization
IB	Irritable Bowel
IBD	Inflammatory Bowel Disease
IBS	Irritable Bowel Syndrome
IBSOS	Irritable Bowel Syndrome Outcome Study
IBS-LOC	Irritable Bowel Syndrome Locus of Control Questionnaire
IBS-SE	Irritable Bowel Syndrome Self-Efficacy Scale
IBS-PRO	Irritable Bowel Syndrome Patient Reported Outcomes
IBS-QOL	Irritable Bowel Syndrome Quality of Life Questionnaire

IBS-SSS	Irritable Bowel Syndrome Symptom Severity Scale
IFFGD	International Foundation for Functional Gastrointestinal Disorders
IIP	Inventory of Interpersonal Problems
IRB	Institutional Review Board
ITT	Intent to Treat
K-ESS	Krause – Emotional Social Support Scale
LEV	Life Events Scale
MC-CBT	Minimal Contact CBT
MCS	Mental Component Summary SF 12
MINI	Mini-International Neuropsychiatric Interview
MOP	Manual of Operations
NCI	National Cancer Institute
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
NPCM-IBS	Non-Psychiatric Medical Comorbidity - IBS
NU	Northwestern University
OTC	Over the Counter
PSWQ-A	Penn State Worry Questionnaire – Abbreviated
POMS	Reduced Profile of Mood States Questionnaire
PCS	Physical Component Summary SF 12
PI	Principal Investigator
PSA	Public Service Announcement
QALY	Quality Adjusted Life Years
QOL	Quality of Life
RCT	Randomized Clinical Trial
ROI	Research Project Grant
RTI	Research Triangle International
SAE	Serious Adverse Event
SAS	Sub Studies and Ancillary Studies
SC	Steering Committee
SEM	Structural Equation Modeling
S-CBT	Standard CBT
SF-MPQ	Short-Form McGill Pain Questionnaire
SI	Site Investigator
STAI	State-Trait Anxiety Inventory
PC	Project Coordinator
SOAP	Subjective Objective Assessment Plan
TSRQ	Treatment Self-Regulation Questionnaire
TSS	Therapist Skillfulness Scale
UB	University at Buffalo
U01	Cooperative Agreement
VAS	Visual Analog Scale
VSI	Visceral Sensitivity Index
WRAT-4	Wide Range Achievement Test-4

Synopsis and Schema

Title of Study

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

Trial Acronym

IBSOS (Irritable Bowel Syndrome Outcome Study)

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.

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 (i.e. attention control condition that emphasizes patient education and supportive counseling) 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.

Population

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

Treatment Arms

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

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
• The participant demonstrates an ability to speak, understand and read English at the sixth grade level or higher.
• 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

Study Design

After undergoing a pre-treatment evaluation to confirm eligibility and obtain baseline data (approximately four weeks before randomization), participants will be randomly assigned to receive either four-session, self-administered CBT; 10-session, therapist-administered CBT; or an active control condition emphasizing supportive counseling and education (allocation ratio 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. At each follow-up phase, participants will 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, etc.

Interim assessment will be 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). The duration of the study is designed to last 67 weeks: (one week pre-treatment evaluation, four weeks pre-treatment baseline, 10 weeks treatment, 52 weeks follow-up).

Efficacy Assessment

The primary endpoint will be global improvement of IBS symptoms. A clinically significant response will be operationalized *a priori* as whether a patient describes symptoms for which s/he sought treatment as markedly to moderately improved using the Clinical Global Impressions Scale — IBS version.

Secondary clinical endpoints will include adequacy of relief from pain and bowel symptoms, pre- to post-treatment changes in psychological distress, changes in health care utilization, changes in quality of life, change in the severity of IBS symptoms, change in stool consistency, change in the intensity of abdominal pain and discomfort (e.g. bloating, urgency), stool frequency, health care use, and treatment satisfaction.

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 3, 6, 9 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-subjects factor, time as a within-subjects 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 [1]. 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 [2].

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 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.

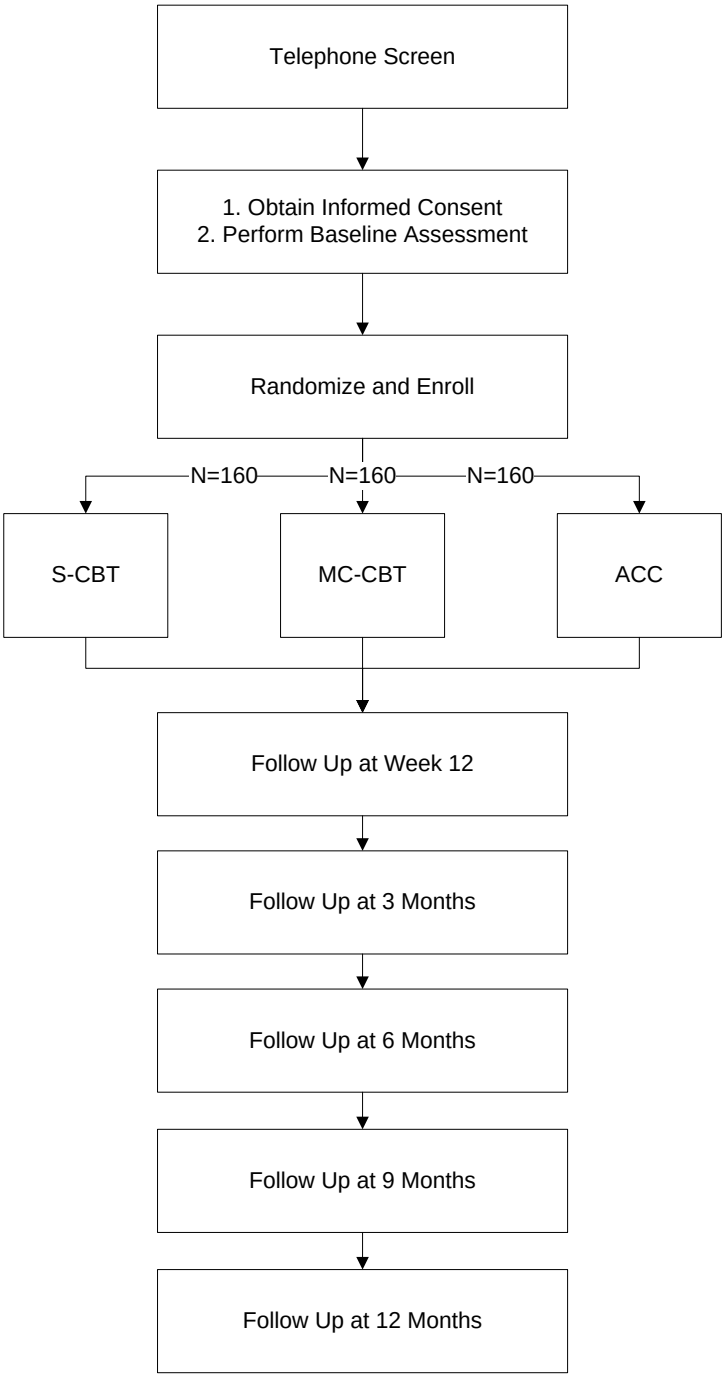

Figure 1: IBSOS Study Flow

Using the Manual of Operations

The IBSOS Manual of Operations (MOP) is a handbook that details the study's conduct and operations. It aims to transform the study's protocol into a set of guidelines that describe the study's organization, operational data definitions, recruitment, screening, enrollment, randomization, follow-up procedures, data collection methods, data flow, Case Report Forms and quality control procedures. The MOP is intended to serve as the IBSOS "cookbook" to facilitate research in the following study procedures. Its goal is to describe the procedures with sufficient clarity to ensure that all clinical centers use the same examination procedures, participant management, intervention schedules, definitions, and, as much as possible, the same equipment in a uniform, predictable manner.

An electronic version is available on the internal IBSOS website: https://www.fstrf.org/apps/cfmx/apps/common/Portal/index.cfm .

Additional scientific information is contained in the study protocol. If you have problems or questions that the MOP does not adequately address, these issues should be raised directly and resolved collectively on biweekly telephone conferences.

Table 1: Administrative Core Primary Contacts

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The Administrative Core at the University of Buffalo is responsible for any and all revisions to the MOP. **Substantive changes require approval of the Steering Committee or an IBSOS subcommittee.**

The IBSOS MOP is a dynamic, "working" document that will be updated throughout the conduct of the study to reflect any significant protocol or consent amendments as well as the refinement of the case report forms (CRFs) and study procedures. Changes to the MOP and relevant forms are made as soon as practical and, unless otherwise noted, become effective as soon as the clinical sites are notified of the change. Once accepted, the policies in the protocol and the procedures described in the MOP must be followed at each clinical center. **The importance of uniform adherence to the policies and procedures outlined in the MOP cannot be overemphasized**. Standardization of procedures is no less important than the quality of treatment delivery.

Indeed, it provides the firm foundation upon which quality treatment is delivered, quality data is collected, quality results are interpreted, and quality changes in health care policy are made. The MOP should be centrally maintained by the study Project Coordinator (Rebecca Firth) in a format that allows it to be easily viewed, revised, and accessed (e.g. three-hole binder as well as electronic file accessible online).

Organization of the MOP

We have organized the MOP around the roles and responsibilities of study personnel (i.e. psychologists, gastroenterologists, study coordinators, graduate assistants, postdocs, etc.). While members of IBSOS will be responsible for **all of the content** in the MOP, they will be able to easily reference the sections that are particularly relevant to their responsibilities on the trial through the use of hyperlinks. Thus, while sections of the MOP are redundant, we felt it important that we maintain this organization structure to improve usability for the different types of individuals involved. The manual also has a fair amount of ancillary and theoretical background for individuals who wish to receive more information on the design of the trial, the choice of assessment measures, etc. This information will be also be available online through hyperlinks.

Study Purpose

The Irritable Bowel Syndrome Outcome Study (IBSOS) is a multi-site clinical trial 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 their economic cost and benefits. 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.

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PARTICIPATING SITES

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.

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.

TRIAL GOVERNANCE

IBSOS is an NIH-funded, multi-center, randomized clinical trial with two clinical centers, an Administrative Core, and the NIDDK Project Office acting together to implement a common protocol and to administer the trial. The organizational structure of the IBSOS is diagrammatically represented below:

IBSOS Organizational Structure

NIDDK U01 DK0077738

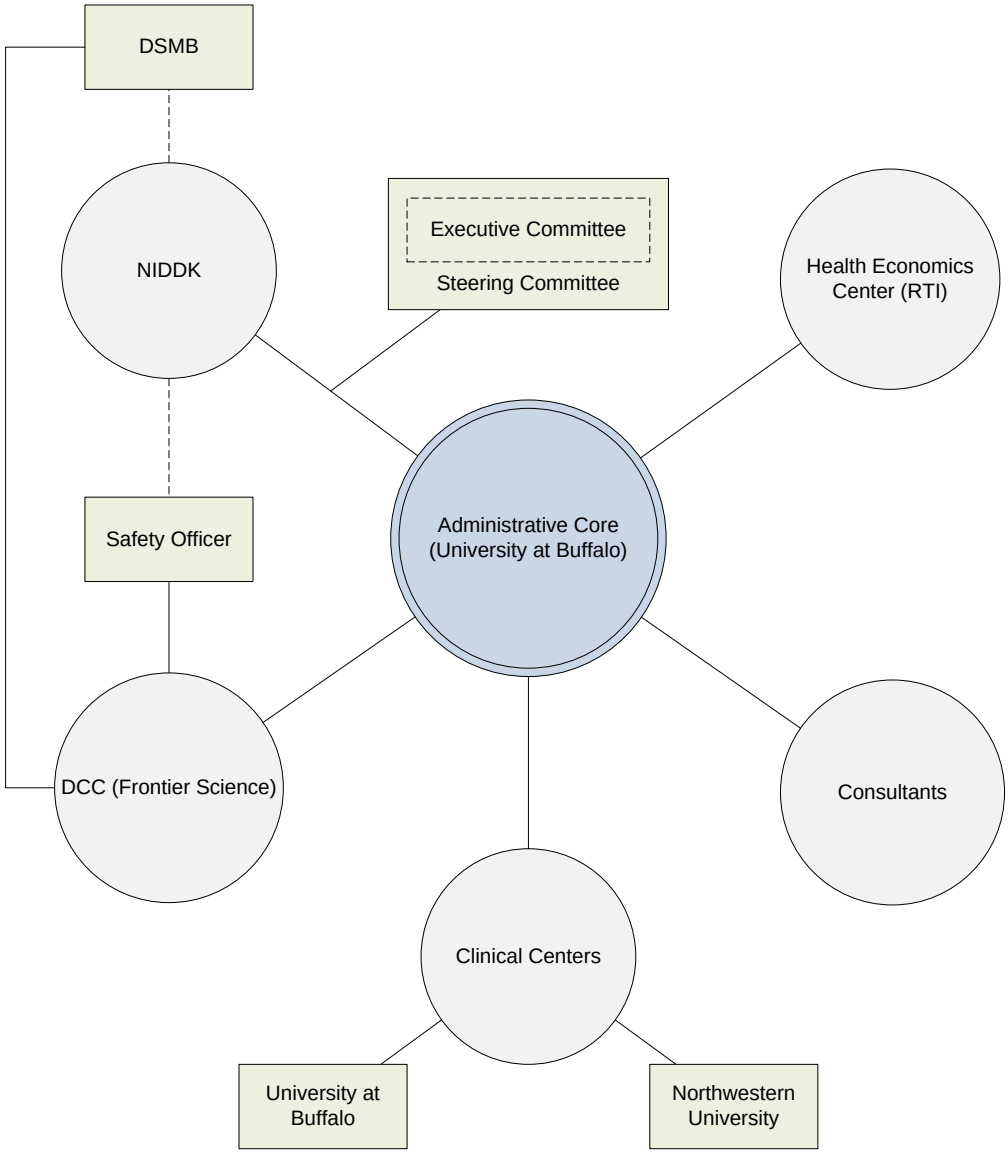


Figure 2: Trial Governance Structure

Note. DCC: Data Coordinating Center

Administrative Core

The Administrative Core, under the leadership of Project PI Lackner, has primary responsibility for developing mechanisms for ensuring quality control and execution of the scientific goals of the study are carried out by the administrative core, clinical centers, Data Coordinating Center, and consultants as dictated by 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 interventionists, data coordinators and other clinical center personnel, and monitoring clinic performance
- 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

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" included as an Appendix to this document.

Steering Committee

The Steering Committee (SC) is the governing body that provides main leadership for IBSOS, is responsible for the overall direction of the trial, and establishes scientific and administrative policy for the study. The SC oversees all aspects of the design, execution, and publication of the study. The SC will be 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
- Creating, making appointments to, and disbanding subcommittees
- Allocating resources based on competing study demands
- 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, Lead Project Coordinators (Rebecca Firth and Jason Bratten), Data Coordinating Center Chair, and NIDDK Project Scientist (Dr. Pat Robuck). Each member of the SC will have one vote. All major scientific decisions will be determined by majority vote of the SC. The SC for IBSOS has a Chair (Project PI) and a Co-Chair, chosen from among the SC members. Committees appointed by the Executive Committee (EC), comprised of investigators and staff from the clinical centers and Administrative Core, will be involved in design of the protocol and manual of operations and in ongoing functions of the trial (e.g. review of ancillary studies and preparation of publications). Committees may also seek the input of consultants on an ad hoc basis to address issues beyond the immediate scope of expertise of DSMB.

Executive Committee

An Executive Committee (EC) is comprised of the IBSOS Chair (Dr. Lackner) and Vice Chair (Dr Keefer), Project Coordinators (Rebecca Firth and Jason Bratten), and the NIDDK Project Scientist (Dr. Pat Robuck). The EC is convened to manage the day-to-day operations of the study between SC meetings. It develops the agenda for and prepares recommendations for the SC meetings. The EC reports its actions to the SC on a regular basis. Meetings of the EC will generally be held by conference call

according to a regular schedule. 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) will be appointed by the NIDDK Director to review periodically the progress of the IBSOS trial. The charter for the DSMB is included as an appendix. (Note: the draft charter will be included until the DSMB approves the charter and it becomes final.)

Safety Officer

The safety officer (Dr. Loraine Collins) 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 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. This change could be across the study or a change in the AE profile at a specific site. Procedures for forwarding all adverse events to the Safety Officer in a timely manner should be clearly delineated in the Manual of Procedures. The frequency of safety data review and reports should also be delineated.

Funding Mechanism

Funding for the IBSOS is granted by the NIH through the NIDDK. Support to the participating centers will be provided through the NIDDK using the mechanism of the Cooperative Agreement (U01). Unlike the R01 grant mechanism, the U01 is a Cooperative Agreement mechanism that entails substantial federal scientific or programmatic involvement. The details of the relationship between the NIDDK and the IBSOS are included in the “Terms and Conditions for Large Scale Research Project Applications” included as an Appendix to this document.

Trial Communication Plan

Importance of Trial-Wide Communications

Maintaining lines of good communication is important to the successful operation of a long-term collaborative clinical trial. During the course of the IBSOS study the Administrative Core will be responsible for the following tasks that depend heavily on effective communication channels and skills:

- Arranging orientation and initial training of clinical center personnel
- Monitoring project adherence
- Reporting to the NIDDK, committees, and DSMB
- Responding to clinical center and NIDDK requests,
- Staffing trial committees, including logistic arrangements and distribution of meeting minutes

The tools of communications for IBSOS include: regular meetings of the SC and its subcommittees, conference calls, website and site workstation posting of study documents, e-mail, sequential memos, telephone calls, data analyses, edit reports, and routine trial updates.

This section summarizes the principles for IBSOS communications and describes the procedures for sending communications between participating institutions.

Principles of IBSOS Communications

Electronic Communications:

A key component of the IBSOS communications protocol is that wherever possible, documents will be delivered electronically. *The Administrative Core will use e-mail and the IBSOS web site as the preferred delivery method for all study materials.*

Direct Delivery of Urgent Items:

Urgent communications (faxes and express mail) are normally sent directly to the recipient, rather than the contact person, to avoid any delays in delivery. However, if a staff member is out of town, the staff member must notify the Administrative Core and s/he must coordinate with the contact person to ensure that the mail and incoming faxes are checked and re-routed if necessary. To minimize delays related to fax delivery, we encourage project investigators, staff, and external advisors to scan paper-based materials and send the PDF files to recipients by e-mail whenever possible.

It is important that all project staff have an email address. If project staff do not have reliable e-mail access for an extended period of time, urgent information will be sent to them via fax or express mail.

Central Contact Person for Non-Urgent Items:

For non-urgent documents and materials for project-wide distribution (e.g. recruitment materials, continuing education materials, etc.) each participating institution should identify a single person to serve as the contact person for that site. The project coordinator typically assumes the role of contact person. It is not recommended that a part-time student or part-time staff member serve as contact person because their schedules may interfere with timely dissemination of materials. IBSOS communications directed to several people at a site should be sent to the contact person, who is then responsible for forwarding copies of the document as appropriate. In the event that this individual is not available, backup coverage should be arranged at the clinical site so that someone else checks for incoming correspondence on a daily basis.

Rapid Turnaround of Minutes:

Especially during the initial planning stages of a trial, the work of the trial is done by committees who meet to design the trial and work out the various procedures. For this process to proceed smoothly it is critical that accurate minutes of committee meetings be taken and that they be distributed in a timely manner. One of the lead PCs (R. Firth, J. Bratten) or his/her designee takes notes during all IBSOS committee meetings and key conference calls. If non-Administrative Core staff takes minutes for a meeting, it is his/her responsibility to forward the minutes to the either lead PCs. Meeting minutes are posted weekly on the IBSOS website.

Rapid Turnaround of Queries:

All participating institutions in the trial shall make every effort to promptly respond to queries. Phone messages, e-mail messages, or written queries should be answered in a timely manner. We expect that routine correspondences should be addressed within 48 hours, although more complicated issues can and should be addressed within a maximum of five working days. It is the expectation of NIDDK and IBSOS leadership that all staff will respond to queries in a timely manner.

Elements of Communications Network

The Administrative Core uses a variety of tools to facilitate study communications.

Internal Web Site:

The Administrative Core will use the IBSOS website as the primary study communications tool. This allows maximum access to all study materials by all key project staff, regardless of geographic location. While most of the documents on the site originate with the Administrative Core, committee chairs can also submit documents to be posted on the website. The password-protected website is secured so that only project staff will have access it and its materials.

Fax and Mail Delivery:

For informal communications, and all documents that cannot be posted to the website, the Administrative Core and sites use a combination of fax, e-mail, express mail, and regular mail to send written study communications and materials.

Selection of Communication Method

The Administrative Core maintains a detailed document, the "Communications Flow sheet," that describes which methods should be used for each type of communication. This ensures consistent, reliable, and efficient communications with all project staff.

The appropriate communication method is selected based on the information to be communicated, its format, the urgency of the message, the amount of information to be sent, and the location of the recipient.

The following table is a summarized version of the Communications Flow Sheet:

Table 2: Communications Flow Sheet

Communication Method	When To Use
E-Mail*	Informal communication, notifications of web postings, notifications of revisions to study documents on web/workstations
Phone	Informal communications
Web Site*	Minutes; packets of materials for committees to review; draft and final MOP chapters; forms; protocol; staff directory; conference call schedule; analysis guide; paper proposal and manuscript review materials/ ballots
Fax	Short memos, short trial monitoring reports
Express Mail	Long memos, long trial monitoring reports, urgent supplies/ materials, urgent bound reports/ documents
US Mail	Non-urgent supplies/ materials, non-urgent bound reports/ documents
Site Workstation Posting	Final MOP chapters, forms, protocol, staff directory

**Note: express mail or fax delivery may be used in cases of e-mail failure, or inability to access website.*

Introduction

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[3]. 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. [4]. 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 [5, 6]. IBS accounts for 40% of the referrals made to gastroenterologists (GE) and is the 7th leading diagnosis made by primary care physicians in the U.S. [6]. IBS is also costly in terms of medical treatments and diagnostic procedures [7], time lost from work [8], and non-monetary costs such as diminished quality of life [8, 9] and activity limitations [10]. A conservative estimate of the combined social and economics costs of IBS is $20 billion annually [11, 12]. It is believed that the lack of a satisfactory medical treatment partly drives these costs[13].

There is therefore a demand among primary care physicians, gastroenterologists, health insurance providers, participants[14, 15] 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-control condition that adequately controls for the non-specific effects of CBT; (b) identification of baseline patient characteristics, psychosocial variables, and extra-intestinal medical problems that may predict or moderate patient 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-control conditions, and e) clarifying the long-term durability of treatment effects.

Conventional Medical Options

In an effort to obtain relief, participants often switch from one drug class to another or use several drugs concomitantly, thereby increasing the likelihood of drug-related adverse effects for which more medications are sought [16]. Current therapeutic choices include a range of drugs aimed at normalizing bowel habits, reducing pain or treating comorbid psychological symptoms. However, this individual symptom-targeted approach remains "largely unsatisfactory in terms of global symptom relief and patient satisfaction"[17]. There is therefore a demand among primary care physicians, gastroenterologists, health insurance providers, participants[14, 15] 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 healthcare resources.

Biopsychosocial Model of IBS

As a functional disorder, IBS lacks a reliable biomarker and is therefore best understood from a biopsychosocial perspective [3]. At the heart of the biopsychosocial model is recognition that IBS involves dysregulation in the coordination of the brain-gut axis [18]. Although alterations at any level of the neuroenteric system may influence motility, visceral sensation, and intestinal secretion [19], multiple lines of evidence underscore the role of CNS activity in modulating IBS symptoms, particularly in more severely affected participants. These include (a) high rates of psychiatric comorbidity [20-22]; (b) the therapeutic value of centrally acting agents (e.g. antidepressants) for specific symptoms (e.g. pain)[23]; (c) disappearance of IBS symptoms or small intestinal dysmotility during sleep when the CNS is less active [24]; (d) high comorbidity with benign, extraintestinal problems (e.g. fibromyalgia, headache)[25] consistent with a central hyperalgesic state; (e) the lack of correspondence between pain intensity and gut motility [26]; (f) neuroimaging data documenting a perceptual bias to visceral stimuli among IBS participants [27]; and (g) the effect of psychosocial factors on the expression and outcome of IBS [28].

One measure of the importance of psychosocial factors on IBS comes from outcome research supporting the efficacy of psychosocial therapies. Their efficacy was recently summarized in rigorous systematic review and meta-analysis conducted to date [29]. Data suggest that psychological treatments are at least moderately effective in reducing IBS symptoms. Although there were too few trials to establish statistically the relative superiority of any one type of psychological treatment, 14 of 17 trials whose data were suitable for analysis featured a specific treatment called cognitive behavior therapy (CBT).

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 and (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 [29], 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 [9], and psychological distress [29]. Less impressive, albeit statistically significant, results have emerged from the few trials [30, 31] that have pitted CBT against an active control (attention control) condition that controls for nonspecific therapy effects. These data underscore the importance of adding an attention control arm to determine whether CBT's effects are due to particular techniques specified by cognitive behavioral theory (i.e. social learning theory [32]) or to nonspecific therapy effects.

CBT has practical limitations restricting its clinical utility. Assuming an hourly charge per 50-minute session of $90 [33], a 12-week regimen of individual CBT [30] costs $1,090. The average wholesale price of a 12-week regimen [30] of desipramine, one of the more efficacious pharmacological agents [30], is $221.76 per patient [34]. 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 [35]), high level of demand and limited availability of adequately trained therapists [36], 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.

Minimal-Contact CBT

In a minimal-contact (MC) treatment (e.g.[37]), 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 [38]; greater patient involvement; a reduction in patient 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 subject 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 [39]. 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 patient 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 [39, 40].

These findings provide a data-based rationale for performing tests of the feasibility of a brief CBT for IBS. To this end, we conducted a small-scale randomized clinical trial [41, 42] funded under NIDDK's R03 mechanism. A major goal was to determine if the effects of MC-CBT would be sufficiently strong to warrant a larger, multi-center trial. To this end, 76 Rome II diagnosed adults (18-70 years of age) were recruited from primary and tertiary care centers and randomized to one of three 10-week conditions after a 4-week baseline period:

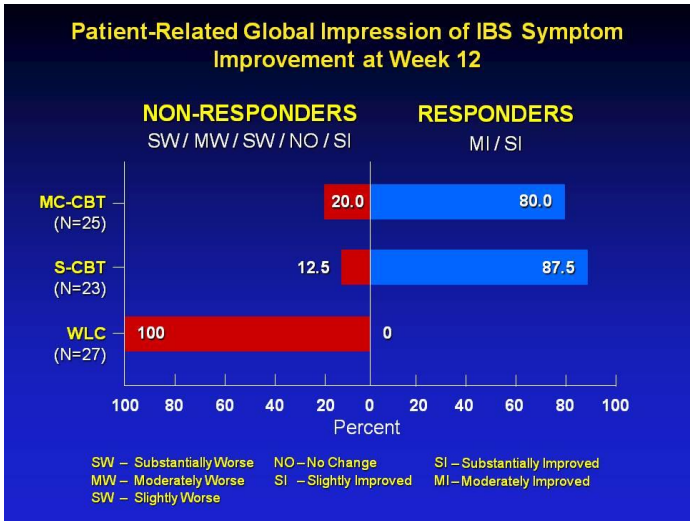
(1) 10 one-hour sessions of manualized CBT (Standard or S-CBT);
(2) four one-hour sessions; or
(3) wait list delayed condition.

Participants randomly assigned to the wait list condition received no treatment during a 10-week waiting period after which they were crossed over to one of the two active treatments.

The primary efficacy variables were overall improvement in IBS symptoms (CGI-I) and adequate relief of IBS symptoms [43]. Secondary efficacy variables included quality of life, IBS symptom severity, emotional distress, cost efficiency, and patient satisfaction. Assessments were completed at baseline, midtreatment, post acute (week 12), and 3 months post treatment termination. Responder status was defined [44-47] *a priori* by a score of 1 (very much improved) or 2 (much improved) on the CGI Improvement scale [48], an affirmative response to 2 adequate symptom (pain, bowel problems) relief scales, and a pre/post treatment reduction in symptom severity scores (IBS-Symptom Severity Scale, IBS-SS) of ≥50 points [49].

At week 12, both CBT versions were significantly ($p < .05$) superior to WL in the percentage of participants reporting adequate relief (e.g. MC-CBT = 72%, S-CBT = 60.9%, WL = 7.4%) and improvement of symptoms. Compared to WL participants, CBT-treated participants reported significantly improved quality of life and IBS symptom severity but not psychological distress ($p < .0001$). In general, these data lent preliminary empirical support to a brief, patient-administered CBT regimen capable of providing short-term relief from IBS symptoms largely unresponsive to conventional therapies.

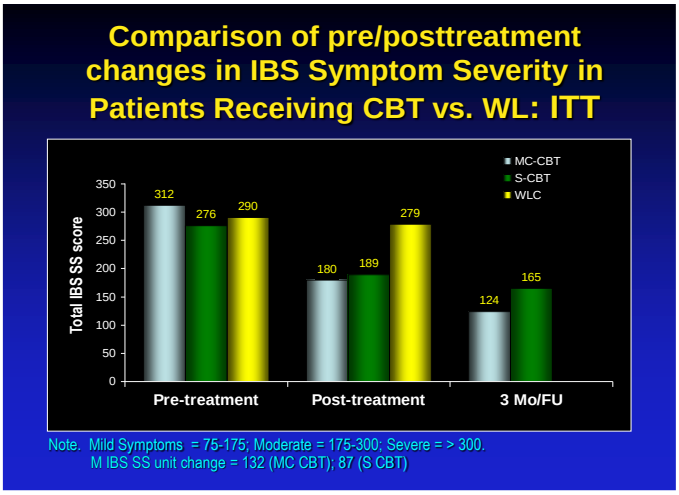
GI Symptom Relief



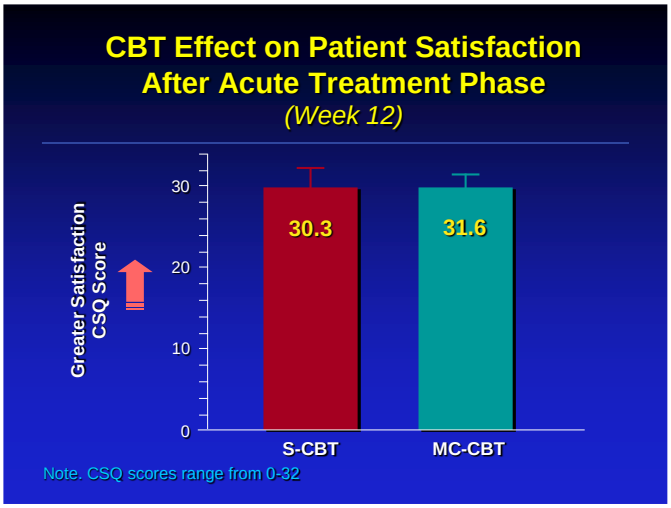
At two-week post-treatment evaluation (week 12), both CBT conditions were associated with marked positive response and performed significantly better than the waiting list condition in terms of the % of participants whose symptoms improved "much" to "very much" (80%, MC-CBT; 87.5%, S-CBT; 0%, WL), the % of participants who reported adequate relief from pain in the dose response analysis (90%, MC-CBT; 82.4%, S-CBT; 9.1%, WL) as well as the intent to treat analysis (72%, MC-CBT; 60.9%, S-CBT; 7.4% WL) and the % of participants who achieved adequate relief from GI symptoms in both the DR (75%, MC; 81.3%, S-CBT; 0%, WL) and ITT (60%, MC-CBT; 60.9%, S-CBT; 0%, WL). Waiting list control participants did not improve on either efficacy variable.

Significance of Symptom Relief

In IBS efficacy research, clinically significant improvement is operationalized as a reduction of ≥ 50 points on the IBS Symptom Severity Scale (IBS-SS) (Francis, Morris et al. 1997). The average reduction in IBS-SS scores was 149.7 points for MC-CBT and 124.8 points for S-CBT partici-pants. No statistically significant differences were found between the two treatment conditions.



Acceptability / Tolerability



The acceptability and tolerability of the 2 CBT treatments, as gauged by dropout rates, was excellent. Of the 76 randomized participants who completed week 12 assessment, 6 dropped out from S-CBT (26%); 5 from MC-CBT (20%) and 5 from WLC (19%), yielding an overall treatment dropout rate of 22%. Attrition analysis revealed no differences between participants completing only the baseline and those completing follow-up assessments on dimensions of experimental condition, treatment credibility, demographic characteristics, or outcome measures indicative of a systematic attrition bias. Further, CBT-treated participants were uniformly satisfied with the care they received as evidenced by their close-to-maximum possible scores (MC-CBT M = 31.6; S-CBT M = 30.3) on the Client Satisfaction Scale (range = 8 to 32).

Cost-Efficiency

We approximated the relative cost efficiency of MC-CBT by calculating the percent change of symptom severity (IBS-SS) divided by mean minutes of time spent performing administrative and therapist activities required to coordinate and render interventions (e.g. scheduling, sending information, performing assessments, delivering CBT sessions for each patient), excluding from analyses administrative and clinical staff time spent performing tasks specific to administering the research component of the study. The % change/patient encounter time formula is a widely used measure to estimate the relative cost efficiency of self-administered treatments [39, 50-52]. The average patient encounter time was estimated at 11.97 hr and 6.90 hr for participants in S-CBT and MC-CBT, respectively. This yielded a cost efficiency index of 0.030 and 0.080 for the S-CBT and MC-CBT conditions, respectively. These data indicate that MC-CBT is delivered 2.67 times more efficiently than S-CBT with 42% less staff/therapist time.

The findings above provide evidence that both MC-CBT and S-CBT are superior to a waiting list control condition in increasing the percentage of participants reporting overall improvement in IBS symptoms (CGI-I) and adequate relief of IBS symptoms. Indeed, there was a tendency for M-CBT, compared to S-CBT, to produce clinically significant improvements in IBS symptoms in a larger percentage of participants. This group difference may not have attained statistical significance due to the relatively low statistical power associated with random assignment of 76 participants to 3 treatment conditions. Moreover, MC-CBT produced improvement on the primary outcome measures that were comparable to those associated with S-CBT with substantially greater efficiency.

STUDY OBJECTIVES

The major objectives of the IBSOS clinical trial are:

Primary Objective

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 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**.**

Table 3: Primary Objective; Aim 1

Secondary Objectives

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 describe the cost and cost effectiveness of MC-CBT, S-CBT and attention control 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. **Hypothesis 2**: MC-CBT will prove cost effective relative to either S-CBT or attention control.

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 control through quarterly follow-up periods extending to 12 months after treatment completion.

Table 4: Secondary Objectives

Overview of Study Design

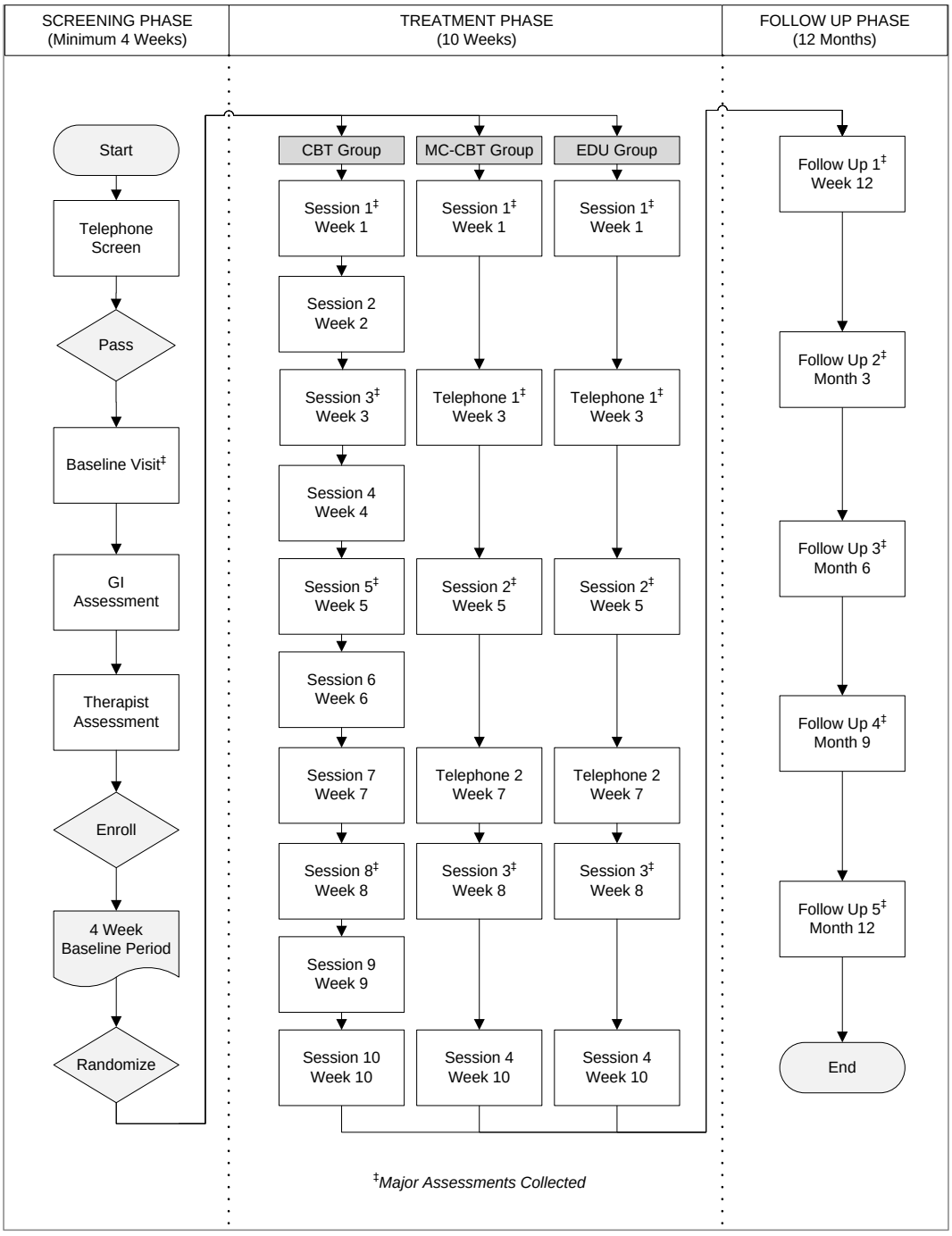
IBSOS is a prospective, randomized, multi-site clinical trial comparing 3 types of psychotherapy delivered in an individual format for severely affected adults with IBS. The study population will consist of 480 Rome III diagnosed IBS participants between the ages of 18 and 70. Participants will be drawn from 2 tertiary care sites over a 48-month period. The trial will evaluate the effect of two versions of CBT, with reference to an attention control, on the primary outcome of global IBS symptom improvement. Additional outcome measures include health care utilization, patient satisfaction, psychological functioning, quality of life, distress, changes in stool frequency and severity of IBS symptoms. Process measures will include personal control beliefs (e.g. self efficacy, locus of control), motivation, therapeutic alliance and treatment expectation.

After a four-week baseline data collection period, participants will be randomly assigned to receive either 4-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 2 weeks after treatment ends (week 12) and 3, 6, 9, and 12 months after the end of treatment. At each follow-up phase, participants will 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, etc. Interim assessment will be designed to clarify the mechanism of change attributed to active treatments (e.g. quality of patient-therapist relationship, changes in perceptions of control over IBS, reduced fear of arousal/visceral sensations).

IBSOS Work Flow

NIDDK U01 DK0077738



Page 1

Figure 3: IBSOS Participant Flow

STUDY POPULATION

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,. 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.

There are two non-clinical sites that have been enlisted to support key aims of the study:

- Frontier Science
- RTI

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 2 weeks after their assigned treatment ends (week 12) and at quarterly intervals (three, sic, nine, 12 months) out to 12 months. Follow-up of all participants will continue until the last patient randomized has completed 12 months of follow-up.

INFORMED CONSENT

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.

ASSIGNMENT TO TREATMENT GROUPS

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.

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 [53]. 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 [54] at the conclusion of Session 1.

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.

IBSOS INCLUSION / EXCLUSION CRITERIA

Table 5: Inclusion / Exclusion 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.
▪ The participant demonstrates an ability to speak, read, and understand English at the sixth grade level or higher.
▪ 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

ROME III DIAGNOSTIC CRITERIA FOR IBS

1. 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:

    1. Improvement in pain/discomfort with defecation
    2. Onset of pain/discomfort associated with a change in stool frequency
    3. 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.

Table 6: Rome III Diagnostic Criteria for IBS

CLASSIFICATION OF IBS SUBTYPES

Rome III irritable bowel syndrome subgroup schema by percentage of stool consistency

IBS subgroup	Hard or lumpy stools (%)[a, c]	Loose (mushy) or watery stools (%)[b,c]
IBS with constipation (IBS-C)	≥25	<25
IBS with diarrhea (IBS-D)	<25	≥25
Mixed IBS (IBS-M)	≥25	≥25
Unsubtyped IBS	Insufficient abnormality of stool consistency to meet criteria for IBS-C, D, or M	Insufficient abnormality of stool consistency to meet criteria for IBS-C, D, or M

[a] Correlates to types 1-2 on the Bristol Stool Form Scale (separate hard lumps like nuts [difficult to pass] or sausage shaped but lumpy).
[b] Correlates to types 6-7 on the Bristol Stool Form Scale (fluffy pieces with ragged edges, a mushy or watery stool, no solid pieces, entirely liquid).
[c] When antidiarrheals or laxatives are not being used.

Table 7: Classification of IBS Subtypes

Rationale for Participant Inclusion / Exclusion Criteria

Three considerations guide the choice of inclusion / exclusion criteria: generalizability of study results, the preservation of the integrity of data, and patient safety. Because of the high rate of medical comorbidity among IBS participants, we included adults with extraintestinal disorders to ensure that enrolled participants were as similar as possible to the general population of treatment seeking adults with IBS. Individuals were excluded if they had medical conditions that would interfere with participation in or completion of the protocol, or that have a confounding effect on the primary outcomes of the study. For example, we will exclude participants who are at realistic risk for harm to themselves or others. When a patient is exhibiting behavior that is potentially and imminently dangerous to self, good clinical practice dictates that treatment intervention should first be directed at amelioration of the dangerous behavior. By the same token, we will also exclude participants who are not medically stable because of their pressing need for immediate acute care. Such individuals could be re-evaluated once medically stabilized providing stabilization is brief.

Participants with comorbid GI disease (e. g. IBD) whose symptoms mimic IBS symptoms will be excluded if their symptoms are better represented by a structural or biochemical abnormality that obscures the interpretability of treatment effects. A comorbid GI disease does not, however, necessarily render a volunteer ineligible for participation. For example, participants who have been diagnosed by a physician with lactose intolerance will be eligible for participation if they continue to experience

moderate to severe GI symptoms after an appropriate interventional trial (e.g. lactose avoidance, Lactaid supplementation), provided the trial occurs prior to completion of the pre-treatment baseline. In these instances where residual symptoms are characteristic of and more attributable to IBS than the co-morbid condition, the study leadership believes that excluding these participants would conflict with an important aim of the IBSOS; namely, to assess the negative prognostic impact of comorbid medical illness on treatment outcome. Further, there is no reason to believe that volunteers with comorbid medical disease of any type will be disproportionally assigned to one of the three conditions (randomization will control for between group differences). Participants with major psychiatric disorders which in the opinion of clinic staff would impede the conduct of the IBSOS are excluded.

Participants who are unwilling and unable to participate fully in the protocol (e.g. to accept assignment to a particular treatment condition; to allow their treatment sessions to be taped for fidelity/process assessment and supervision; to provide sufficient locator information for follow-up data; to be receptive to instruction) are excluded because these behaviors are likely to affect the conduct of the trial. To reduce the impact of carry-over effects, participants who are receiving *targeted* CBT for IBS are excluded because involvement in outside psychological treatment directed toward IBS may obscure the interpretation of treatment effects ascribed to the study treatment. It is unethical to randomize suicidal participants to treatment and therefore participants who represent a risk to themselves are excluded.

Ethnic and Gender Issues

Every effort will be made to recruit a broad spectrum of participants representing all racial groups and both genders. The study protocol will be developed according to the principles of the Declaration of Helsinki.

Caseness Panel Mechanism

To make sure that study-eligible participants are not excluded and to guarantee cross-site uniformity by establishing a series of common precedents, we will implement a Caseness Panel mechanism to review exclusions that call for clinical judgment. The composition of the panel should be made up of at least one board-certified gastroenterologist, one licensed health psychologist, the Project PI or study co-chair (Dr. Keefer), and Project Scientist. Specifically, sites will ask the Caseness Panel to review a participant eligibility that is ambiguous and requires expert clinical judgment. This panel will convene either through telephone conference or email exchange as needed. A member of the site who has requested review should recues him or herself from review process. Because clarification of caseness bears on the efficiency of recruitment, it is expected that the panel will convene and resolve the issue in question within 48 hours (work days) of the eligibility issue being identified.

Study Endpoints

Primary Efficacy Endpoints

The primary efficacy endpoint is as follows:

- Patient-rated global improvement of IBS symptoms. A patient 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.

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 patient 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 patient is regarded as a weekly responder on the basis of prospective improvement (pre – post-treatment reduction during acute phase) in pain intensity *and* stool frequency

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)

Stool Frequency Responder

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

Pain Intensity Responder

- Decrease in weekly average amount of "worst abdominal pain in past 24 hours" score of $\geq$ 30% based on the 11 point NRS

Stool Consistency Responder

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

Participant Discontinuation Criteria

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.

Steps to Take Before Concluding a Participants's Whereabouts Are Unknown

Every effort should be made to maintain contact with each participant randomized in the IBSOS. At enrollment, the participant should provide the names and contact information for two people who can be reliably contacted in case of emergency or if the participant appears lost to follow-up (see "Patient Locator Information Form"). Each contact person's address, email, telephone numbers (home, work. mobile/cell), and relationship to the participant should be obtained with the clear understanding that strict participant confidentiality will always be maintained in the event that study personnel contact these individuals.

When a participant cannot be located or contacted directly – for example, scheduled visits have been missed and Site staff cannot reach the participant by phone after 3 attempts – the Project Coordinator and/or PI (or designee such as Co I) should try to locate the participant through the people named as contacts, without indicating that the participant has volunteered in a research study. If the persons are located but are unwilling to provide the participant's location, ask them to ask the participant to contact the Site.

Other IRB approved methods may be used to determine a participant's whereabouts, depending on the Site's participant population. Some potential methods are:

- Mailing a registered letter to the participant's last known address, requesting that s/he contact the Project Coordinator by telephone, calling collect if the call is long-distance

- Contacting neighbors at the participant's last known address (A reverse telephone directory is helpful for this purpose: (http://www.whitepages.com/reverse-lookup)
- Contacting the Department of Motor Vehicles
- Contacting the participant's place of employment

These are only to be treated as **sources of information** about the participant's whereabouts (vs. sources of information regarding participant's health status). Study personnel must protect the participant's confidentiality and should **never provide** information about participants to these or other sources. **We will use these sources of information with methods that are in accord with HIPAA guidelines and approved by the Institutional Review Boards at all participating sites**.

The Project Coordinator should record each step taken to locate a participant, to avoid duplicating effort and annoying contacts who might otherwise be willing to help.

If the participant is contacted but refuses further participation in the IBSOS Study, a withdrawal form should be completed to document withdrawal of consent. Use Off-Study Form.

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.

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 patient 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 patient 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 patient fully disclosed information regarding health status at the time eligibility was determined.

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).

Steps to Minimize Withdrawal

IBSOS will implement specific compliance enhancement strategies to minimize withdrawal. These and other techniques are proven effective in yielding a withdrawal rate of less than 10%. These techniques are more fully elaborated in the chapter on treatment adherence.

Withdrawal minimization effort will include but are not in any way limited to:

- Identifying and troubleshooting barriers (e.g. by addressing parking and other transportation issues, providing easy-to-follow directions, flexible clinic hours, financial compensation for time and travel required to undergo regularly scheduled follow-up visits) that would offset the value participants attach to the benefits of study participation at the time they decided to enroll.

- Incorporating a variety of "customer service" practices to promote contact with all participants. The goal will be to maintain some form of regularly scheduled contact (e.g. phone, email) with all participants and cultivate a warm, friendly, and supportive environment that conveys frequent messages that participants are key ingredients to the success of an important landmark research study.

- Providing all staff and investigators who have contact with IBSOS

participants with training and regular re-training in motivational enhancement techniques.

- Ensuring that participants' concerns are identified and addressed before they express a desire to reduce their involvement in the study.

- Regular updating of the locator form that elicits the address and telephone number of each participant. These forms will be obtained at the screening visit and updated at post treatment and at each follow-up visit. Alternative contact information for friends or family members will be collected and updated on a regular basis. This information may be used by study site staff to notify a participant of upcoming visits as well as locate a participant who has missed a scheduled visit.

- Ensuring that each participant is treated cordially when s/he arrives for each clinic encounter.

- Minimizing waiting time, and attending to participants' discomfort during waiting times. Accommodate the need for brief breaks, food or drink, or need to make a phone call.

- Rescheduling appointments, when necessary, in ample time so that the participant can revise his/her own schedule.

- Prompt follow-up on all missed appointments. In some cases, a phone call from the project coordinator stressing the need for a follow-up appointment may be sufficient. Some participants will respond more favorably if they are called by the PI or Co-I.

- Recognizing the importance of the participant's needs and feelings. Saying that a person has to schedule an appointment because "the study protocol requires it" should never be given as a reason because it suggests that the participant's needs are secondary to adhering to research protocol. Staff should emphasize the personally relevant advantages of ongoing participation to the volunteer.

- While some withdrawal is to be expected in any long term trial, the use of outside services for locating participants lost to follow-up can minimize these occurrences. The last known address and telephone number of many persons can be obtained through a locator service such as the URL www.555-1212.com. Staff should update information on participant contacts using this service.

- Remind participants that their continued commitment represents an important contribution to science and that the ability of this project to tell the treatment field which treatment works depends on their participation.

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.

Elimination of Participants

Participants who meet all inclusion/exclusion criteria and are prematurely withdrawn from the study post randomization will not be replaced by an equal number of newly enrolled participants. It is not uncommon for a participant to fail to disclose the presence of exclusion criteria that would have rendered him or her ineligible prior to randomization. This may occur when, for example, the individual participant does not disclose the presence of an exclusionary criterion (e.g. undergoing concurrent targeted psychotherapy for IBS at the time of screening, unstable medical disease or psychiatric disorder that is likely to impede the conduct of IBSOS, excessive alcoholic intake, inability to comply with monitoring during 4-week pre-treatment baseline period, etc.) that would have rendered him/her ineligible for randomization. It is important to document the nature of these protocol violations so that outcome analyses with and without these patients. For intent to treat purposes, all randomized participants, including those who are terminated early, are followed at post treatment and at 3, 6, 9 and 12 months.

Handling "False Starts"

The IBSOS should strive to have patients adhere to their treatment schedules they are given shortly after they have been randomized to a treatment arm. In

our experience, this is not a problem. It is conceivable that situations may arise that forces patients to suspend treatment indefinitely. However, the participant may express interest in re-enrolling in the study at a more convenient time. Study personnel should discuss potential future enrollment and gauge interest. When a study participant experiences a false start (i.e. if the patient has only completed one MC CBT, one EDU or three S CBT sessions) s/he can resume treatment provided the participant first undergoes a four-week baseline assessment. The participant will be re-enrolled in the same treatment arm that s/he was initially randomly assigned to. The 1st session (MC CBT or EDU) or sessions 1 to 3 (S CBT) should be reviewed to maintain consistency in treatment. Participants who are unable to complete the study due to outside demands after the 2nd session (MC CBT or EDU) or the 4th session (S CBT) should not be considered false starts. Rather these should be handled using the study protocol for drop-outs.

Assessment Procedures

ASSESSMENT DEFINITION

An **assessment** is a standard interview or self-report that a patient or research staff member completes to characterize or describe the current status of the patient's characteristics (e.g. severity of GI symptoms, mental status, quality of life, etc). Assessments are also referred to as "instruments" or "measures" or "CRFs" (case report forms). Good clinical practice defines CRFs as printed, optical, or electronic documents designed to record all of the protocol-required information that will be reported for each trial participant. The following measures are designed to gauge the relative magnitude of treatment effects across multiple domains of patient-reported outcomes. This section reviews the types of data that will be collected by the clinical center, stored in the central data base, and analyzed to meet the scientific goals of the study.

OUTCOME MEASURES AND DATA COLLECTION

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 (2-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.

STANDARDIZED ASSESSMENTS

Reliability and Validity

Standardized assessment such as the Beck Depression Inventory, State Trait Anxiety Inventory, Brief Symptom Inventory, etc., have gone through a series of rigorous tests to ascertain that the results are reliable and valid. *Reliability* is a term that describes whether tests results are consistent. This is usually evaluated by administering the assessment over different time points or under different conditions (e.g. by different interviewers). *Validity* is a term that describes whether an assessment evaluates what it claims to evaluate. This is tested in several ways. One measure of validity is that a new test should have the same interpretative results on a similar standardized test's results already shown to be reliable and valid. This type of validity is referred to as *concurrent validity*. A brief description of the structure, content, and basic psychometric properties of each measure forming the IBSOS testing battery is found in the Appendix.

Instructions/Manuals

Standardized tests usually come with a specific set of instructions and, in the case of an interview, a manual. The instructions on a self-report form should be readable to the patient ("in the past week…"). Manuals associated with standardized instruments should be read prior to administration of the first interview to develop a full appreciation of the intention or spirit of the assessment as well as the individual items that make up an instrument. Additionally, manuals should be used as a tool for ongoing search for appropriate categorization of response.

ASSESSMENT PHASES

Screening/Eligibility

To determine a prospective patient's possible eligibility for participation, a "quick" (7-15 minute) screening interview is conducted by the project/research coordinator or research assistant. The pre-screen is designed as a fast, relatively inexpensive, and efficient means of identifying obviously ineligible (e.g. previously diagnosed GI disease) volunteers and to include potentially viable volunteers prior to scheduling a formal, more labor- and time-intensive evaluation. While the pre-screening is typically conducted on the phone, it can be conducted face to face if needed. The pre-screening includes a brief questionnaire regarding major exclusion criteria, collection of key demographic

variable including age, duration of symptoms, referral source, as well as a general description of the trial. Individuals who complete screening are either excluded from further participation or are scheduled for a formal evaluation with the study GE and health psychologist. The reason for screen failure should be clearly and immediately identified on the screening log.

A secondary goal of the telephone pre-screen is to gauge the effectiveness of recruitment initiatives. The data from the screening question will be analyzed regularly throughout the accrual period in order to guide decisions regarding effective recruitment strategies and the characteristics of persons who refuse and/or agree to participate in study procedures. Therefore it is important that the screening form collect information about how the caller heard about the study (e.g. physician, newspaper ad, radio, word of mouth, etc.).

If the preliminary screen disqualifies the participant from further consideration (e.g. the caller is too young) a list of referring organizations or possible treatment settings can, upon request, be provided, including the site clinic and other available site or community-specific services. However, it is important to remember that the IBSOS should not assume responsibility for prescribing or directing follow-up care of callers.

Pre-Treatment Baseline Assessment

Volunteers who “pass” the telephone screening will be scheduled by the project / research coordinator as soon as is feasible for a formal evaluation with a health psychologist and the study GE. This evaluation takes about two hours to complete and ideally should be scheduled at the conclusion of the telephone screen. This evaluation should be scheduled for a date as soon as possible. **The research staff should strive to schedule the evaluation no more than 5-21 days after the telephone screening.**

Multiple studies show that scheduling evaluations with minimal delay significantly reduces the attrition rate between initial contact and the assessment. It is important to remember that participants are prompted to seek help when their symptoms have become exceedingly bothersome, disabling, and/or uncomfortable. For many participants, their phone call amounts to a desperate cry for help. Excessive delays in returning participants’ calls, administering screening, and scheduling evaluations runs the risk of closing the window of opportunity to help participants and denying them care their symptoms warrant. Administratively, such delays increase recruitment burden.

Evaluation

The purpose of the evaluation is (1) to explain the entire study protocol to the participants, answer questions about what is required of them, review the consent form, and obtain written informed consent from interested individuals; (2) to formally confirm eligibility criteria and diagnosis (e.g. Rome III); (3) to obtain baseline levels of functioning against which the immediate and long-term effects

of treatment can be gauged; and (4) to explain and distribute symptom diaries to be completed on a daily basis for 4 weeks from the date of evaluation. In addition to establishing baseline level of severity of individual GI symptoms (pain, bloating, urgency, etc.), the purpose of daily diaries is to ensure both that the severity of IBS symptoms is sufficiently stable at moderate to severe levels at the time that treatment begins and that participants have sufficient motivation and resources (ability to drive to the clinic, etc.) to participate in the study.

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

All potentially eligible participants will undergo an initial telephone screen. If s/he passes the telephone screen, the volunteer will be referred to a board-certified gastroenterologist acting at one of the two participating clinical sites for a non-

invasive medical examination to confirm Rome III diagnosis of IBS. To facilitate patient flow through the study, this examination should be scheduled within 5-21 days of the screening call.

At this visit the gastroenterologist will be responsible for the completion of the following tasks:

1. Confirmation of the diagnosis of IBS based on Rome III Criteria
2. Confirmation that the patient has moderate/severe symptoms (frequency ≥ two days/week)
3. Completion of the "Exclusion/Inclusion Criteria for IBS Study" survey
4. Determination whether the patient requires further testing prior to enrollment to rule out structural disease that may better account for presenting symptoms
5. Communication of results of this evaluation back to the institutional project coordinator recommending either performance of the baseline assessment or suspension/conclusion of the screening process

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 **IBS-SSS** 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-SSS at baseline, and at each of the 5 follow-up assessments. Because the psychometric properties of the IBS-SSS 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 http://pmbcii.psy.cmu.edu/core_c/social_environmental_burdens_and_resources.html#Social_Support) 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 (α = 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 (http://pmbcii.psy.cmu.edu/core_c/behavioral_pathways.html#Restorative_Activities) 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.

Adverse Events Monitoring Form

To ensure patient safety and to evaluate the tolerability of treatments, IBSOS will require careful monitoring of (1) adverse events and (2) concomitant medications (this form is described in more detail in the AE section of this manual).

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). A detailed assessment schedule is located in the Appendix.

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.

To determine dates for the follow-up assessments, add three months, six months, nine months or 12 months, respectively, to the date of the last active treatment session. Add and subtract two weeks around that date to obtain the one-month window in which to perform the follow-up assessments. For example, if the date of the last active treatment is 8/7, then the three-month assessment date should be 11/7. Two weeks on either side leave a one-month window of 10/24 - 11/21.

PREVENTING DROPOUTS AND MISSED VISITS

It is important to collect complete data on as many randomized participants as possible. Missing information can bias the results of the study. Although occasional missed visits due to illness or work cannot be prevented, study data could be rendered invalid if there are too many missed visits (e.g. if numerous participants drop out and are lost to follow-up). When data are incomplete, it is difficult to predict the direction of any bias resulting from the incompleteness.

The only way to deal with missing data is not to have any. Although it is inevitable that a few participants will drop out or be lost, it is expected that each clinical site will lose no more than 7% of randomized participants to follow-up.

Dropout Prevention Methods

To achieve a 93% retention goal across all sites, it is important to adopt and consistently implement a number of administrative practices to locate and re-interview randomized participants at each of the five major follow-up periods. See Adherence and Retention Section.

PROCEDURES FOR ADMINISTRATION OF SELF-REPORT QUESTIONNAIRES

With the exception of the IBS Economic Form, MINI and the PRO-IBS, the majority of testing instruments are self-report questionnaires. This section outlines the specific procedures to be used for all “pen and pencil” questionnaires.

Demeanor and Manner of Administration

Administration of all psychosocial measures requires establishing a positive rapport with the patient. It is important that the clinical and administrative staff maintain a professional and friendly manner at every contact with the patient and make the patient feel confident in the interviewer and understand that his or her responses are important.

Except for administration of semi-structured instruments noted, which depend upon the interviewer's flexibility and ability to improvise in order to elicit and clarify patient responses, a critical aspect of the IBSOS staff member’s demeanor when administering the pen and pencil measures is to maintain *neutrality and objectivity*. Assessors should never improvise when clarifying questions or probing for responses.

This neutral, standardized manner of assessment helps ensure that the IBSOS staff member's presence does not influence the patient's perception of, or response to, a question. When introducing a questionnaire or answering questions, the assessor should be careful to avoid any statements that could influence the patient's responses. Some participants may ask for clarification of the meaning of some symptoms included in our self-report measures of distress. Although several of these symptoms occur infrequently, the assessor should not provide verbal cues regarding the frequency with which any symptoms are present in the general population.

The assessor should also convey a sense of impartiality toward each participant, and should be gracious and adaptable to all participants regardless of whether or not their dress, ethnic or racial identity, appearance, style of speech or personal preferences are consistent with the interviewer's values and preferences.

- The demeanor of the assessor should be casual, yet professional.
- Staff should be very familiar with the questionnaire and procedures prior to administering the first questionnaire to a patient.
- Interviewers should take sufficient time to cultivate rapport with respondents before administering questionnaires.
- Staff should convey a pleasant and friendly demeanor and a sympathetic and understanding attitude.

The respondent should be made to feel that there are no correct answers, that what s/he thinks or experiences is really what counts, and that his/her opinion can never be wrong. Many test items inquire about negative characteristics, (e.g. anxiety, bowel habits, depression, trauma history, etc.), and some people are reluctant to admit to having these characteristics because they regard them as signs of weakness. Moreover, people who desire to look good in the eyes of the examiner may endorse more positively to neutral and positively skewed test items than they actually feel.

To deal with such test-taking attitudes, the examiner needs to establish a trusting relationship with participants by sincerely communicating that their honest and candid responses will enable the therapist to be more helpful and effective. Similarly, participants generally respond more objectively and accurately if they are informed that their responses will be kept confidential, and especially if they are given some feedback about their test results to the extent possible. Clinical and research findings suggest that distorting effects of adverse test-taking attitudes are not a serious problem if sufficient care on the part of the staff is taken to obtain the cooperation and trust of the respondent at the time the questionnaires are administered.

However, the interviewer should avoid long explanations of the study and should not invent or improvise explanations of the study or of specific questions. S/he should use the standard responses and introductory material provided below. Similarly, the assessor should never try to justify or defend what s/he is doing; should not try to explain procedures or question wording; should never suggest an answer; never agree or disagree with an answer; and never interpret the meaning of a question. If the patient does not understand a question, just repeat the question slowly, exactly as written.

Introducing the Self-Administered Items

The following script can be used when introducing the self-administered items:

> *“We would like to better understand how you feel and how you are doing. To help us better understand these things about you, please complete this questionnaire about your health-related information.*
>
> *“Be sure to read the instructions carefully. Remember, this is not a test and there are no right or wrong answers. Choose the response that best represents the way you feel. Your responses to these questions are completely confidential — you are identified only by a code number, not by a name. I will briefly look over the questionnaires when you are done just to make sure that all the items have been completed.*

“You should answer these questions by yourself. Spouses or other family members should not assist you in completing the questionnaire.

“Please fill out the questionnaire now. I will be nearby in case you want to ask me any questions. Return the questionnaire to me when you have completed it.”

Administering and Completing the Self-Administered Items

Provide a pen or pencil and solid writing surface such as a clipboard or table top.

Special attention should be paid to maintaining the privacy of the participant to the greatest extent possible. If feasible, administration should be in a private setting or room where distractions are minimized. If administration is in a clinic or office setting, you should assist the patient in finding a comfortable, quiet place to complete the questionnaire. If this place is not in the immediate clinic area, it is important that you take responsibility for making sure the patient is returned to familiar surroundings once the questionnaires are completed.

The patient should complete the questionnaires without the help of a spouse or friend, and you should discourage others from staying with the patient while s/he is completing questionnaires. This may not always be possible; however, you should reinforce the value of the patient's response.

As the assessor, you should make it clear to the patient that you are easily available if the patient has any difficulty with the questions. If necessary, the assessor should stay in the room while the first page or so of a questionnaire is filled out, and should say something like: "I'll wait with you while you get started to be sure it is clear to you what is being asked.” When the participant finishes the first page, the assessor should indicate how he or she can be located should any questions arise. It is advisable for the assessor to periodically check back with the patient while he or she is completing assessments to ensure there are no problems or questions.

Educational level should be considered before self-completion. This can be done by asking participants what grade level they have completed or by administering a short reading comprehension test such as the WRAT. Persons with low literacy or diverse language skills should always be provided interviewer assistance.

Respondent Questions and Problems

The assessor should be very familiar with all questions and their meaning. This means that the investigator should not only be familiar with the content of the questionnaires but their manual, etc. It is the responsibility of the examiner to access these materials. If the participants asks for clarification, the examiner should re-read the question exactly as it appears, stressing by your voice intonation references to time, place, and question intent — for facts or feelings.

Do not ad-lib an explanation of the question “on the fly.” It is important to stay with the literal expression of the questions because this is the best way to assure standardization of psychosocial assessment across centers.

Always Take the Blame for Problems with the Questionnaire

If the respondent complains of particular wording or redundancy or length of the questionnaire, say you don't know why it was done as it was, but it is important for the respondent to answer as best s/he can. Should you encounter difficulties with questionnaire wording or procedures that you have serious concerns about or cannot otherwise resolve yourself, check with your Principal Investigator or site Co-Investigator who is responsible for supervising the study.

Closing and Review of Questionnaire

When the patient returns the questionnaires, the assessor should ask the patient if any of the questions were unclear. Then the assessor should check to see that all answers have been completed. Among the things to note:

- Are the answers clearly marked?
- Are any answers left out or double-marked?
- Is there a systematic response bias (e.g. patient responds yes to everything)?

This review should be done immediately while the patient is in the room so any problems can be addressed right away. If any response is incomplete, illegible, or has multiple responses, ask the respondent whether s/he had any difficulty completing it. Where the patient had difficulty with an item, use the methods described below to clarify the question or probe for a response. If the patient indicates the omission was purposeful, simply record this on the Evaluation form and continue reviewing the questionnaire. **It is within the patient's right to decline to answer any particular question**. If the incomplete answer or omission was not purposeful (e.g. an inadvertently missed page or item), ask the patient if s/he would complete the unanswered question(s). If there are ambiguous responses, such as double markings or unclear erasures, ask for clarification.

Finally, thank the respondent using the following exit script:

> *“Thank you for taking the time to complete this survey. It is possible you will be asked to complete the questionnaire again at a later date.”*

Probing for Responses

The psychosocial measures used in IBSOS have been designed to minimize open-ended responses. However, even with closed-response questions, probing is sometimes required. Probing is a critical technique to master as it is an easy place to fall prey to directing responses or altering the meaning of a question. Thus, probes must be as uniform as possible within and across centers.

If the patient provides an inappropriate response to a question (e.g. uses the wrong response category), repeat the question and the response categories. For example, if the interviewer asks a question that requires a patient to provide his or her degree of agreement and, instead, the patient says, “That's true,” the interviewer responds, “Would you say you strongly agree, agree," etc.

If a patient provides an ambiguous response to a question, then the interviewer must obtain a clarification without directing the response. The following can be used:

- Pausing — sometimes just waiting expectantly or giving the respondent time to think may be helpful.
- Rereading the question focuses the respondent on the questionnaire task especially if there is distraction or possible misunderstanding. Say, *“I'm going to reread the question,”* then reread the question exactly as written. Do not paraphrase.
- When necessary you may ask for more information in a neutral way: *“Can you tell me more?”*
- Stress generality — *“Usually / mainly / overall which answer comes closest?”*
- Stress subjectivity — *“Your opinion / your best estimation / your recollection”*
- When zeroing in, keep it neutral, don't suggest any specific response (e.g. *“Can you remember who?"* not *"Was it your son?"*)

Concomitant Treatment

For practical (e.g. ease of patient recruitment) and methodological (e.g. generalizability of results) reasons, the IBSOS permits concomitant therapies provided they are instituted either before or after pre-treatment baseline period and are systematically tracked through the acute treatment phase and at follow-up phases. Concurrent medications and non-drug therapies will be recorded in the participants' records at the initial screening/evaluation. If the participant is randomized, the information will be transcribed in the Case Report Forms (CRF). An up-to-date record of all concurrent therapies will be maintained at each visit. In IBSOS, relatively few restrictions are placed on involvement in other forms of treatment during the 10-week intervention period. Use of the following treatments is NOT allowed after eligibility is established and pre-treatment baseline monitoring begins:

Psychological therapy targeted explicitly at IBS and unwillingness or inability to stop treatment for the duration of the study

Participants receiving concomitant medications are eligible provided their medication regimen can be stabilized safely during the four-week baseline period.

At the time of the initial evaluation, the patient will be asked to use the Intake form to identify all medications and significant non-drug therapies (e.g. physical therapy, massage therapy, chiropractic care) on the Concomitant Medication Log. The interviewer will use this sheet to elicit information regarding duration of each of the current medications or therapies. The investigators should instruct the patient to notify the study site about changes to current medications (i.e. those that were reported at initial evaluation) or the addition of any new medications (names, dosages, etc.) s/he takes after treatment begins and through the follow-up phase.

All medications and significant non-drug therapies (e.g. physical therapy, massage therapy, chiropractic care) must be listed on the Concomitant medications Log. This form will be used in all subsequent visits so that the patient can review the medications previously recorded, look for errors, and list any changes and/or updates since the previous visit. This method of patient review should increase the patient's awareness of changes and attentiveness to detail regarding their medication.

Participants who are undergoing psychological therapy targeted explicitly at IBS and who are unwilling or unable to stop treatment for the duration of the study should be discontinued from the study (not randomized).

It is important that therapists assume a neutral stance toward participants' participation in concurrent therapies. Medications and other treatment options are neither encouraged nor discouraged. If therapists have difficulty with this requirement, they should discuss their concerns at once with their PI, supervisor, or training staff. If participants express interest in other forms of psychotherapy for IBS, they are urged to postpone them if possible until at least the acute treatment phase is completed.

Therapy and Supervision: Clinical Staff

INTRODUCTION TO TREATMENT PROTOCOL

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, patient-administered CBT
- Attention Control Condition

The Attention Control Condition represents a credible psychological 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:

Standard CBT (S-CBT) is a skills-based training program [130] 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.

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 one-hour clinic visits, MC-

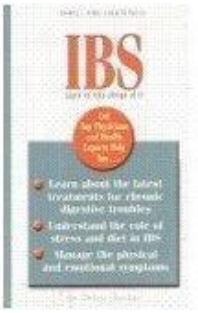
CBT meets for only four, one-hour clinic visits over a 10-week period.

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.

The Attention Control Condition (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 [30, 131, 132] to control for nonspecific therapeutic influences inherent in CBT. The attention control 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 [133].

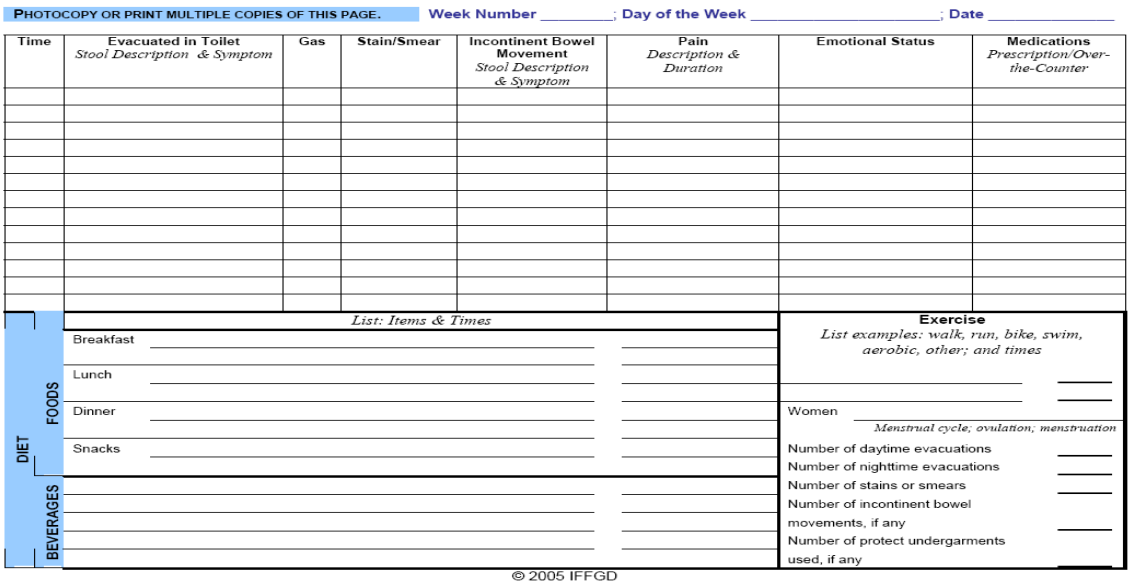
The format of the attention control condition parallels the MC-CBT condition (four monthly sessions with two 10-minute phone calls and self-study materials). Previous studies demonstrate that an education/supportive psychotherapy condition whether administered in group, individual, brief or extended format produces evaluations of credibility and outcome expectations similar to those generated by CBT [132, 134-136]. It is recognized as a best available psychological placebo control condition for IBS and other comparable disorders [135, 137-139].



To control for receipt of self-help materials, participants will receive a copy of *IBS: Learn to Take Charge of It* [140], an

evidence-based 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.

ACC participants will complete responses to weekly handouts which serve as a basis for discussion with the therapist. Participants will also maintain a daily diary of bowel habits, pain, food, and emotions using the **Personal Daily Diary** (Fig. 5) developed by the International Foundation of Functional GI Disorders, an IBS advocacy group.



PHOTOCOPY OR PRINT MULTIPLE COPIES OF THIS PAGE. Week Number _____; Day of the Week _____; Date _____

Time	Evacuated in Toilet *Stool Description & Symptom*	Gas	Stain/Smear	Incontinent Bowel Movement *Stool Description & Symptom*	Pain *Description & Duration*	Emotional Status	Medications *Prescription/Over-the-Counter*

DIET

FOODS — *List: Items & Times*

Breakfast _____

Lunch _____

Dinner _____

Snacks _____

BEVERAGES

_____

_____

_____

_____

Exercise

List examples: walk, run, bike, swim, aerobic, other; and times

_____ _____

_____ _____

Women _____

Menstrual cycle; ovulation; menstruation

Number of daytime evacuations _____

Number of nighttime evacuations _____

Number of stains or smears _____

Number of incontinent bowel movements, if any _____

Number of protect undergarments used, if any _____

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Figure 4: Personal Daily Diary (IFFGD)

THERAPIST SELECTION

Quality control of treatment delivery as intended is assured through the identification, training, and maintenance of qualified therapists. With appropriate training and supervision, a diverse range of therapists can learn to effectively implement CBT for IBS. However, because IBSOS focuses on specific psychotherapeutic techniques, certain minimum requirements are recommended:

- Doctoral or master's degree in psychology, counseling, social work or a closely related field
- Experience in cognitive behavioral therapy and other therapeutic modalities (e.g. supportive counseling, psychoeducation)
- At least three years of clinical experience
- Sufficient knowledge of basic gastrointestinal physiology and medical procedures/terminology concerning functional GI disease

In addition, therapists, regardless of treatment condition, must be:

a) Willing to be randomized to the treatment they will deliver

b) Willing to learn a manualized version of treatments and follow manual guidelines for the duration of the protocol

c) Willing to be participate in any initial and "refresher" training sessions

d) Willing to have their sessions audio-recorded for review by clinical supervisor and adherence/competence raters, attend regular supervision sessions and complete process ratings (e.g. ratings of the therapeutic alliance and techniques used during sessions)

e) Approved by the IBSOS administrative/supervisory staff as appropriate for the study (e.g. sufficiently reliable, performs clinical and administrative duties competently)

f) Willingness to accommodate the scheduling needs of participants (e.g. occasional sessions to approximately 7 p.m.)

THERAPIST TRAINING

Use of Treatment Manuals to Guide Treatment Delivery

In addition to regularly scheduled supervision with a master clinician, treatment adherence among therapists is accomplished primarily through the use of treatment manuals which describe the goals of each session as well the procedures by which these goals are achieved. A written checklist is used to track clinician adherence to treatment protocol. Each treatment manual specifies and describes the therapy and provides guidelines for implementing these treatments.

Therapists often have a variety of misconceptions about the use of treatment manuals. Rather than viewing manuals as detailed “blueprints” which define a treatment and guide a therapist through the context of treatment, therapists sometimes perceive them as therapeutic straight jackets or scripts from which they cannot deviate. Good manuals attempt to directly confront this misconception by stressing the need for therapist adherence to the manual to be balanced with competence and judgment. For example, no supervisor would encourage a therapist to plunge ahead with difficult therapeutic tasks without first establishing rapport, formulating the case, agreeing on treatment goals, and building a working relationship with the patient. However, few manuals explicitly point out the importance of these more fundamental tasks of treatment as a prerequisite for moving ahead to other, treatment specific tasks. While it is easier to teach or describe *technique* than *competence* in manuals, the central importance of competence and nonspecific elements of therapy should not be ignored in treatment manuals.

Each treatment manual defines the theoretical underpinnings, goals, and difference among treatments. In addition, the manual describes the strategies the therapists use to reach the treatment goals and articulates guidelines that direct the therapist through the treatment process. Finally, treatment manuals also define behavior prescribed and proscribed while conducting treatment.

The use of treatment manuals is designed to achieve many purposes:

- Provide a means for objective comparison of different therapies
- Set standards for the training and evaluation of therapies
- Establish clear treatment goals and clinical care standards
- Foster replication for clinical trials in other setting
- Reduce clinician allegiance to single treatments by facilitating clinicians’ familiarity with and training in alternative approaches
- Provide a means for identifying effective components of particular treatments and link treatment process to outcome
- Reduce variability in treatment delivery
- Disseminate specialized therapies among non-expert clinicians

Didactic Seminar

Each therapist will participate in a didactic training seminar. The didactic seminar usually lasts 16 hours over two days and is organized by the project coordinator with the assistance of clinical sites. Each therapist travels to Buffalo for a two- to three-day intensive training seminar which is led by a senior therapist. The seminar includes review of background and rationale of IBSOS, basic cognitive behavioral theory and technique, extensive review of the treatment manuals, review of taped examples of therapists implementing the treatment, several role-play and practice exercises, discussion of case examples, and rehearsal of strategies for difficult or challenging cases. Each therapist then returns to their clinical site and is assigned a minimum of two training cases which are conducted following the treatment manuals. Ongoing training should be provided in clinical supervision. However, the trainer providing the training should periodically offer refresher or booster training to all staff delivering the model.

Certification of Therapists

After reviewing the treatment manuals and receiving the didactic training and supervised training cases, a therapist must be certified prior to treating study participants. Certification of therapists helps ensure that the therapies are being delivered as outlined in the treatment manuals. Therapists are certified, or approved, to implement the treatment at lower levels of supervision when the attending supervisor determines that they have completed an adequate number of training cases successfully.

An objective approach to certification requires the therapist to tape therapy sessions and have them rated by a clinical supervisor on clear, discrete, and objective psychotherapeutic dimensions. The **Therapist Skillfulness Scale** (TSS; Figure 6) has been developed to aid in the tape review and the clinical supervision process. The TSS assesses a therapist's working alliance, adherence to the manual, and competence in the treatment being delivered. The IBSOS supervisor can use the TSS to determine whether interventions used in session consistently reflected the protocol. The TSS consists of Likert-type items that cover a range of skills from non-specific basic therapy skills to CBT-specific technical skills. This scale is used to provide direction and constructive feedback in supervision. Consistent ratings of four and five on the TSS and a demonstration by the therapist that s/he is implementing the treatment interventions in a competent and consistent manner are necessary for certification.

The use of a structured rating scale fulfills the following goals:

- It provides structured feedback to the therapist and forms the basis of supervision.
- It provides a method of determining whether a therapist in training is ready to be certified to deliver the treatment.

- When used with ongoing supervision, it enables the supervisor to monitor and correct therapist "drift" in implementing the treatment.
- For therapists who have trouble adhering adequately to manual guidelines, but who maintain that they do follow it, pointing out discrepancies between the scale and the checklist is a useful strategy for enhancing adherence.

SUPERVISOR RATINGS OF THERAPIST SKILLFULNESS

Supervisor's Name: Therapist Name:
ID #: ID#
Subject ID: Session Date: Session Number:

Please rate the therapist on the following items.	Not at all	A little	Somewhat	Considerable	Extensive	Not Observed	Comments
1. To what extent did the therapist follow the session format?	1	2	3	4	5		
2. To what extent did the therapist use language and interventions consistent with the treatment type?	1	2	3	4	5		
3. To what extent were the treatment goals consistent with the treatment type?	1	2	3	4	5		
4. To what extent did the therapist demonstrate expertise, and competence?	1	2	3	4	5		
5. To what extent did the therapist engage the client?	1	2	3	4	5		
6. To what extent did the therapist use interventions at appropriate times (interventions not missed when appeared to be needed, interventions not made too early)?	1	2	3	4	5		
7. To what extent did the therapist use inappropriate self-disclosure?	**5**	**4**	**3**	**2**	**1**		
8. To what extent did the therapist use an appropriate level of activity/directiveness?	1	2	3	4	5		
9. To what extent did the therapist maintain session focus?	1	2	3	4	5		
10. To what extent did the therapist set appropriate tone and structure for the session?	1	2	3	4	5		
11. To what extent did the therapist demonstrate, warmth and sensitivity, and genuine concern?	1	2	3	4	5		
12. To what extent did the therapist understand and express patient's feelings and concerns?	1	2	3	4	5		

TSS0499.pdf April 19, 1999

Figure 5: Therapist Skillfulness Scale (TSS)

Supervised Training Cases

Supervised training cases offer an opportunity for therapists to apply treatment approaches featured in IBSOS and learn to adapt their usual approach to conform to manual guidelines. The number of training cases varies according to the experience and skill level of the therapist. Generally, more experienced therapists require only two training cases to achieve high levels of competence. Less experienced therapists generally require three to four supervised cases.

Each session should be taped and forwarded to the supervisor, who should:

- Review each session.
- Complete a rating form (Figure 7) to evaluate therapist's adherence to CBT guidelines and competence in implementing treatment that session.
- Provide one hour of individual supervision to the therapist. Supervision sessions are structured around ratings of adherence to CBT and competence in delivering the treatment, with the supervisor noting when the therapist delivered the treatment effectively as well as areas in need of improvement.

SESSION 1

1	2	3	4	5	
Absent or Ineffective	**Somewhat Effective**		**Reasonably Effective**	**Extremely Effective**	
Part	**Component**				**Score** *To what extent did therapist attempt and succeed at:*
1	**Introduction**				
	To receive a rating of 5, the therapist should: Briefly ask patient about their IBS, symptoms and quality of life. Therapist avoids spending too much time on these details and assigns "expert status" to patient.				
2	**Psychoeducation**				
2.1	**Review IBS pathophysiology** To receive a rating of 5, the therapist should communicate that: IBS is a functional disorder (nothing wrong with the physical structure of the bowels but rather a problem with how the bowels work). "Irritable" suggests that the nerves controlling muscle contractions in the bowel are extra sensitive to certain foods, hormones and stressors. A brain gut dysregulation is at the foci of this disturbance.				
2.2	**Provide information on stress & stress response** To receive a rating of 5, the therapist should communicate that: IBS is not caused by stress, but stress is a controllable trigger for symptoms. The stress response is normal and a condition of modern living. Stress has 3 components which interact with each other—physical, mental and behavioral.				
2.3	**Provide treatment rationale** To receive a rating of 5, the therapist should communicate that: The role of behavioral treatment is to teach skills to manage each of the systems (recognizing and reducing tension, learning more realistic ways of thinking, learning new ways of responding).				
3	**Self-Monitoring**				
	To receive a rating of 5, therapist should make appropriate efforts to: Review the importance, value and goals of symptom monitoring and teach the patient how to complete the daily stress log, emphasizing the focus on *modifiable* variables at a level consistent with the client's sophistication and motivation.				
4	**Introduce relaxation skills—controlled breathing**				
	To receive a rating of 5, therapist should make appropriate efforts to: Provide rationale for using controlled breathing to target physiological aspect of stress-ibs connection, describes abdominal breathing and concentration components, provide instructions for practice and help client troubleshoot potential difficulties.				
5	**Assign Homework**				
	To receive a rating of 5, the therapist should clearly explain the assignment for the upcoming week and check to assure the client understands what is being asked and troubleshoot any difficulties that can be anticipated regarding completion of the assignment. HW: Practice/Record Relaxation 2X/day, continue monitoring, read Ch 1-3 before next visit				

Figure 6: Supervisor Checklist

THERAPIST SUPERVISION GOALS

The goals of supervision and monitoring of interventions are to ensure a baseline of quality care and minimize cross site differences in the delivery of featured interventions.

Structure and Process of Supervision

The initial stages of supervision concentrate on establishing an open, honest, approachable, and helpful alliance. Supervision should provide a forum for therapists to develop her/his skills and grow. It is very hard for a therapist to do so if s/he is intimidated. A positive approach to supervision is also a form of modeling IBSOS treatment. Once a positive working alliance has been established, the process of supervision is much more productive.

The IBSOS supervisor functions as a teacher, skill developer, resource person, coach, team captain, and motivator. He or she must have skill and knowledge in basic counseling skills and IBSOS procedure and be able to convey that knowledge to others. At the same time, the supervisor should be open to the importance of receiving supervision herself. It is unrealistic to believe that even the most experienced therapists could not benefit from periodic peer supervision to avoid therapist drift. To this end, senior therapists/supervisors will meet quarterly to discuss their experiences with cases and with supervisees with the goal of obtaining corrective feedback and ensuring that there is continuity across sites.

Individual supervision should take place at least one day per week for a minimum of 60 minutes. During this time, numerous activities could occur depending on the needs of the therapist. Typically this weekly meeting with the therapist begins with a brief overview of his or her cases. The case review is one means of providing the supervisor and therapist with information that can be used to decide how best to use remaining supervision time for the week. Other information that helps highlight supervision needs includes the supervisors' review of therapy tapes and accompanying checklists. The therapist is also involved in setting the content and agenda for the clinical supervisor sessions to ensure their relevance to his or her needs.

The most common focus during a supervision session is discussing the best approaches for addressing clinical cases presented by the study patient and helping therapists improve their skills in the delivery of IBSOS procedures. Typical supervisory activities include reviewing tapes, providing corrective feedback, role-playing exercises, modeling, providing training or instruction, and problem solving.

Supervision Guidelines

Supervision is most effective under the following circumstances:

- It is conducted at a consistent place, date, and time.
- The goals of the supervision are clear and both participants' roles are defined.
- The procedures that will be used for evaluation of the therapist are clear.
- Feedback to the therapist is focused and concrete.

> *"When you were describing the goals and steps of problem solving, I thought you did not correctly employ the 'goodness of fit' approach. For example, the patient reported her problem was that she had to ride in a car with her boss for 60 minutes next week. You were able to get her to define the problem ('I may have bowel urgency on the way and have to ask my boss to stop') and come up with some reasonable solutions ('I could wear a sanitary pad').*
>
> *"However, you allowed her to make the assumption that she had more control over whether or not she would have an IBS attack on the ride than she does. An alternative approach would have been to help her feel confident in her ability to manage the attack if it were to occur using coping phrases like 'nobody dies of embarrassment,' 'uncomfortable situations are time limited,' 'my boss would understand if the worst case scenario occurred'.*
>
> *"Stress arises when there is poor goodness of fit — even if your patient had come up with a million ways to 'ward off' or reduce the likelihood of an attack, there is no guarantee that she wouldn't have to deal with her IBS. Setting up the goal of not having a problem on the car ride actually increases stress (uncontrollable outcome) and may actually increase the likelihood that a problem would occur."*

Video Tapes and/or Audiotape Reviews

Supervisor and therapist reviews of tapes from actual sessions provide important information for supervision. Therapists often initially feel threatened by having their sessions taped, but tapes provide the greatest opportunity for improving their skills. Audio- or videotaping also leads to self-supervision; the tape may speak for itself with little need for comments by the supervisor. The therapist has the opportunity to experience feelings and thoughts from the session while listening to the tape, instead of relying on his or her perception of what transpired in the session. The supervisor and therapist can stop a tape frequently to focus on the therapist's behavior and thought process. Tape reviews provide an opportunity for corrective feedback or for problem solving, with the therapist considering what else could have been tried or done at a particular point in the session. The supervisor may choose to model a procedure or ask the therapist to

role play a procedure so that he or she has the opportunity to improve his or her techniques.

When a supervisor reviews a tape, either alone or with a therapist, it is important to look for a number of behaviors. First, it is important to notice and provide feedback on what the therapist does well. The supervisor can also point out appropriate procedure options within a session that might have been overlooked by the therapist. It is also important that the supervisor review tapes with an eye toward the most common problems found in implementing IBSOS treatment. If problems are noticed during the tape review, the supervisor can provide feedback to the therapist and model what the therapist might have said in any given situation.

Common problems implementing manualized treatments in the IBSOS include:

- **Overly strict conformance to the manual**
  - — Failure to select interventions appropriate to client
  - — Giving the impression that the manual, rather than the client, determines the course of therapy

- **Failure to adapt treatment to client**
  - — Use of inappropriate language or terms
  - — Failure to attend to client concerns

- **Looseness in conforming to the manual**
  - — Covering manual material only at end of session
  - — Failure to fully cover core interventions

- **Contamination**
  - — Using proscribed techniques from other treatments
  - — Using language and terms associated with other treatments

Practicing Role-Plays

Intensive and extensive role-plays are excellent skill builders. During supervision, it is important not only to talk about how procedures should be done but also to practice them. Role-plays provide the therapist the opportunity to practice procedures in the safety of a training situation and provide the supervisor the opportunity to give feedback on the therapist's performance. Just like the therapist participants, therapists may be embarrassed or reluctant to practice role-playing. It is important that the supervisor does not convey the expectation of perfection but instead provides support and encouragement. The supervisor can verbally reinforce (e.g. praise) the therapist for any effort he or she made. Because an IBSOS supervisor functions as coach and motivator, it is not appropriate to be negative and critical. Because the therapist is expected to use a positive approach with therapy participants, the approach is modeled during supervision well.

COMMON PROBLEMS ENCOUNTERED BY THERAPISTS IN SESSION

Balance

The structure of CBT sessions (and the 20/20/20 rule) is intended to integrate skills training with effective, supportive therapy that meets the needs of each patient as an individual. Novice therapists, particularly those with little experience in treating IBS or who are unaccustomed to a high level of structure in treatment, often let sessions become unfocused, without clear goals, and do not make the transitions needed to deliver skills training effectively. Such therapists often wait to introduce skills training until the last few minutes of the session. This results in rushing through important points, failing to use patient examples or get patient feedback, and neglecting review of the practice exercise — all of which gives the impression that skills training is not very important.

Other therapists allow themselves to become overwhelmed by the patient's report of weekly symptoms and fail to focus on skills training or use it as an effective strategy to help the patient learn to manage symptoms. Falling into a symptom-driven approach tends to increase, rather than decrease, patient anxiety and to undermine self-efficacy.

Maintaining a relatively consistent session routine and balancing the patient-driven discussion of current concerns with a focus on skills and strategies are also means by which the therapist can model effective coping and problem solving.

Conversely, some therapists become overly fixed and inflexible in their application of skills training and adherence to the manual. Anxious to get it right, they present the material in the manual more or less verbatim and fail to adapt it to the specific needs, coping style, and readiness of the particular patient. For example, even though skills training requires considerable activity and commitment from the patient, some therapists launch into it with participants who are still highly ambivalent or even resistant to treatment. It is important to remind such therapists that the manual is not a script but rather a blueprint or set of guidelines that provides a clear set of goals and overall structure for the treatment. This often requires considerable familiarity with the didactic material so that therapists can alter the material for each patient and present it in a way that sounds fresh and dynamic. Participants should never think that the therapist is blindly following a manual.

Speeding through the Material

Many of the skills-training concepts, while seemingly straightforward and based on common sense, are quite complex, particularly for participants who have cognitive inflexibility, poor problem solving skills or low baseline levels of coping

skills. A common error made by many therapists is to fail to check back with participants to make sure they understand the material and how it might be applied to their current concerns. When this occurs, it often takes the form of a lecture rather than a dialog between the patient and therapist. Ideally, for each concept presented, therapists should stop and ask participants to provide an example or to describe the idea in their own words.

Blaming the Patient

It is tempting to blame the patient for unsatisfactory outcome when treatment falls short of expectations. Participants often do not seem to appreciate efforts to help them. They can be seen as unmotivated, disengaged, etc., in responding to therapists' offers of assistance. Certainly, outcome is influenced by many factors including those specific to participants (e.g. ability to learn and practice skills, motivation, psychological mindedness, etc). Therapist factors are an important piece of a larger puzzle of variables that influence treatment outcome. However, it is very important for the IBSOS therapist to refrain from the knee-jerk temptation to blame the patient and instead to examine outcome in light of the possible contribution of one's own behavior and actions before assigning blame. Such introspection will not only improve the quality of treatment delivery for future participants but enhance professional development of the therapist.

Overwhelming the Patient

Some therapists try to present to each patient all of the coping strategies in the order given in the manual. For many participants, this is overwhelming. Learning and feeling comfortable with one or two coping strategies is preferable to having only a surface understanding of several strategies. Similarly, if too much material is presented, the time available for practice is limited. A good general tactic is to start by presenting one of the coping strategies the patient already uses and is familiar with, and then to introduce one or two more that are consistent with the patient's coping style. Also, new coping strategies can be introduced over two sessions.

Unclear Strategies

Therapists should attempt to teach general coping strategies using specific examples. However, some therapists use the coping strategies during the session but do not effectively communicate the basic underlying strategy. For example, they may effectively apply problem solving strategies to participants' problems but fail to make the problem solving steps explicit or ensure that participants understand the concepts. It is essential that therapists use examples to teach the general, underlying strategy, but it is equally important that the general strategy be made clear.

Non-Specific Examples

Just as some therapists do not effectively communicate underlying principles, others fail to make the coping skills "come alive" through specific examples.

Skillful therapists make the transition from the patient's report of current concerns to the skill-focused section of the session by using specific examples, either from the patient or from the therapists' own experiences working with participants:

> *"I like how you were able to identify some of your thoughts about having abdominal pain during your church retreat. Perhaps we could spend some more time flushing those out a little more and seeing whether we can identify a core belief using the downward arrow technique we just discussed."*

Again, skills training should be presented as a dialog between the patient and therapist, with the therapist attempting to convey the message, "Here is how skills training can help you with the issue you are struggling with *right now*."

Downplaying Practice Exercises

Although most participants do their homework, and those who practice their skills outside of sessions have better outcomes, a number of therapists do not sufficiently attend to the homework in session. This tendency can take the form of a cursory review of homework completion in the beginning of sessions, rushing through the homework instructions at the end of sessions, not making homework assignments relevant, and/or failing to provide corrective feedback or address resistance when homework is done incompletely or incorrectly. A review of the assignment provides some structure to the first part of the session and sends the message that outside practice is important. Generally, therapists who expect their participants to practice outside of sessions have participants who do so.

Abandoning the Manual with Difficult Participants

Many participants present with a range of complex and non-IBS related problems (i.e. personality disorder, chaotic home life). Therapists may become overwhelmed by concurrent problems and drift from use of the manual in an attempt to address all the patient's problems. In such cases, therapists often take a less structured approach rather than the greater structure needed by the patient. Generally, if the patient is sufficiently stable for outpatient therapy, the treatment described in the manual is adequate, even for participants with clinical levels of distress.

ONGOING MONITORING OF TREATMENT DELIVERY

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 on the degree to which the therapist delivers the treatment in adherence with manual guidelines and on the skills with which the treatment is delivered. Reviews of taped treatment sessions can be particularly useful for highlighting situations in which important clinical process issues arose and 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 while adhering to a specific treatment protocol.

This information can help extend the therapists’ skills and repertoire and keep the treatment “fresh” throughout the trial. Treatment delivery ratings are sent regularly to the SI to alert local supervisors to therapist drift. Therapists whose performance deviates in quality or adherence to the manual are “redlined” by the CC and the frequency of sessions monitored and supervision is increased until the therapist’s performance returns to acceptable limits.

Recording Participant Feedback

Participants may provide feedback regarding treatment, including treatment logs, assessment measures, or other aspects of the study that will provide important information about their study experience. As these data may be valuable to understanding implementation and feasibility, study personnel at each site will record this information in the **Participant Feedback Log** (Figure 8).

This document should contain the following information:

- Participant ID
- Site
- Therapist
- Treatment Arm
- Session
- Specific feedback

This information will be periodically reviewed across sites to identify any common themes or issues that may be reported by participants.

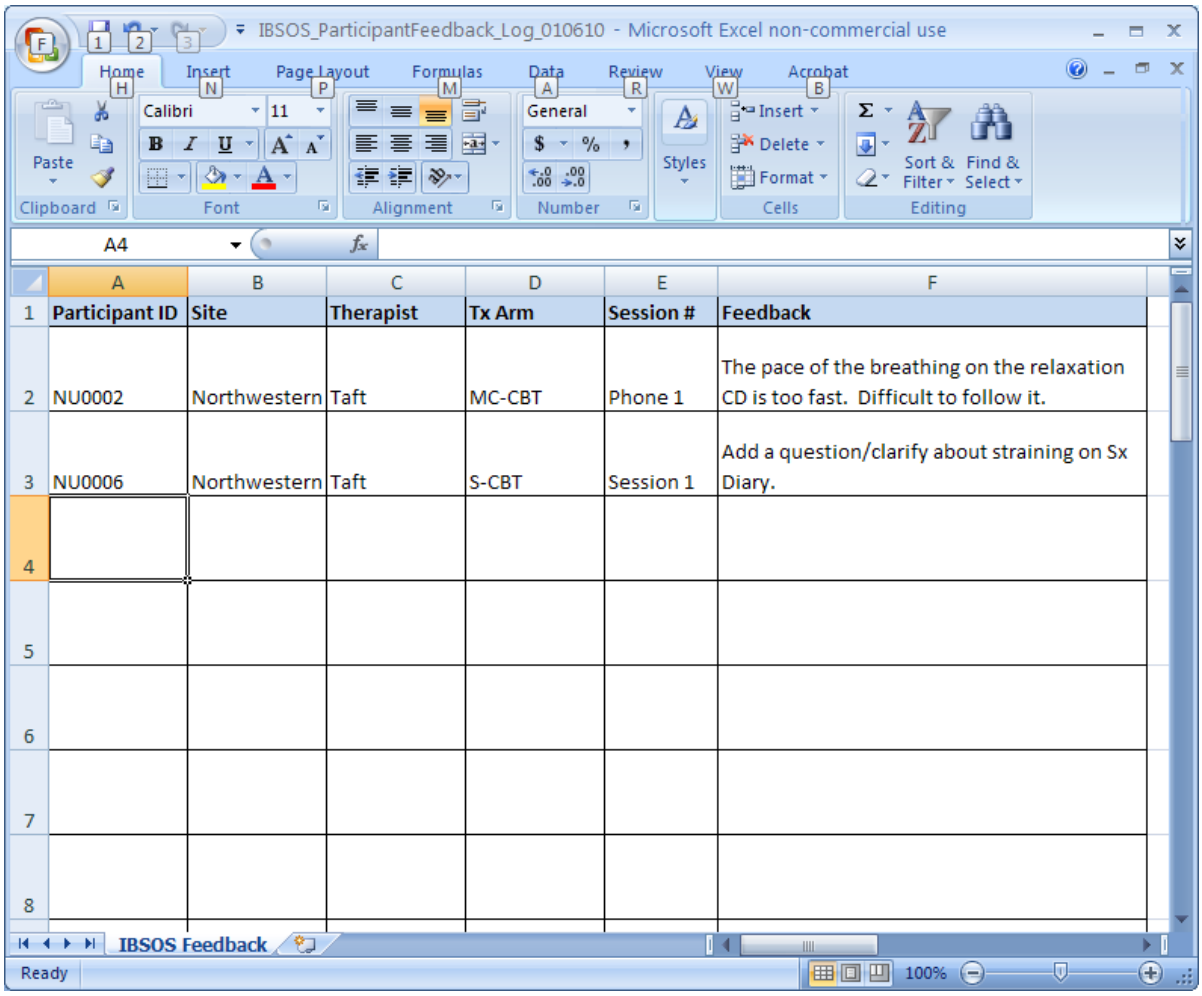
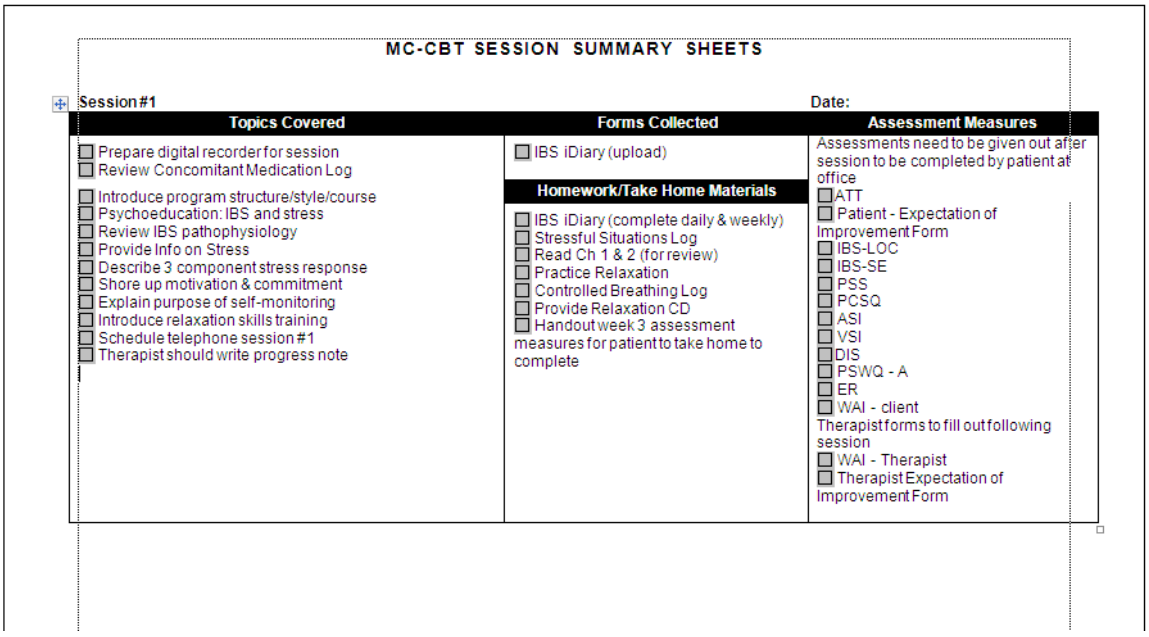


Figure 7: Participant Feedback Log

Session-by-Session Checklists

It is critical that the guidelines in the treatment manual be strictly adhered to. Significant deviations will add “noise” to the study. One way to help therapists adhere to protocol guidelines and prevent therapy drift is to use session-by-session checklists (figure 9) of clinician adherence to protocol. These checklists will ensure that key ingredients from each session are included, that homework is correctly assigned and that study procedures are followed. Therapists will be asked to initial and date each checklist at the end of each session attesting to the completion of the session as intended and to ensure that any outstanding issues can be addressed prior to the next session (i.e. failure to provide new symptom monitoring forms).



MC-CBT SESSION SUMMARY SHEETS

Session #1 Date:

Topics Covered	Forms Collected	Assessment Measures
☐ Prepare digital recorder for session ☐ Review Concomitant Medication Log ☐ Introduce program structure/style/course ☐ Psychoeducation: IBS and stress ☐ Review IBS pathophysiology ☐ Provide Info on Stress ☐ Describe 3 component stress response ☐ Shore up motivation & commitment ☐ Explain purpose of self-monitoring ☐ Introduce relaxation skills training ☐ Schedule telephone session #1 ☐ Therapist should write progress note	☐ IBS iDiary (upload) **Homework/Take Home Materials** ☐ IBS iDiary (complete daily & weekly) ☐ Stressful Situations Log ☐ Read Ch 1 & 2 (for review) ☐ Practice Relaxation ☐ Controlled Breathing Log ☐ Provide Relaxation CD ☐ Handout week 3 assessment measures for patient to take home to complete	Assessments need to be given out after session to be completed by patient at office ☐ ATT ☐ Patient - Expectation of Improvement Form ☐ IBS-LOC ☐ IBS-SE ☐ PSS ☐ PCSQ ☐ ASI ☐ VSI ☐ DIS ☐ PSWQ - A ☐ ER ☐ WAI - client Therapist forms to fill out following session ☐ WAI - Therapist ☐ Therapist Expectation of Improvement Form

Figure 9: Session Checklist

ADMINISTRATION OF STUDY THERAPIES

Randomization

Treatment assignments will be generated using an existing web-based participant registration and randomization system. This system uses protocol-specific specifications files that 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 will work with the Principal Investigators 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.

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 (Lackner et al, 2004). To the extent that blinding seeks to control differential expectations and consequent demand characteristics they may generate, then we will adopt the 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 [54] at the conclusion of session 1.

PROCEDURES TO MINIMIZE POTENTIAL BIASES IN ADMINISTRATION OF THERAPIES

(See also adherence and retention section)

Accommodation of Patient Schedules in Randomization Process

It is often necessary to pair participants with therapists and therapies based on their availability. For example, a patient who travels for work may be best suited to one of the four-session therapies or to a therapist who provides treatment in the early morning or late evening. Occasionally, it may be necessary to be flexible with a patient to maintain his or her commitment to the study. However, excessive accommodation of patient schedules in the randomization process will introduce bias into the administration of therapies over time and should be avoided at all costs.

For this reason, all therapists need to understand the importance of flexible scheduling and a willingness to see participants during the day and late afternoon/early evening hours. In our previous R03, very few participants required appointments that that began after 5 p.m. Of course, therapists who have late appointments should adjust their schedule so they start the work day later. All therapists regardless of seniority need to maintain flexible schedules and no one therapist is expected to assume responsibility for all off-hour participants. We request that all therapists commit to this requirement prior to joining the study.

Accommodation of Patient Schedules in Treatment Process

There is a fundamental difference in a therapy that is administered over three months vs. six months, regardless of the intervention. Participants may need to cancel periodically, prolonging their treatment schedule. Therapists should make every effort to complete therapy within the proscribed period of time (12 weeks), even if it means that they need to offer a different session time in the same week or double up sessions in the following week. In cases where this cannot be

accommodated, the therapist should make every attempt to complete the participants' treatment within two weeks of the proscribed follow-up date.

PROCEDURES TO MINIMIZE ATTRITION AND NON-ADHERENCE

Minimizing attrition and enhancing adherence in a clinical trial are difficult but achievable goals toward which the IBSOS must strive. Accomplishing treatment goals is essential to fulfill the aims of the IBSOS and begins with the assumption that the responsibility and capability for change lies with the patient under the guidance of a skilled therapist and administrative team. Your task — as a member of the clinical research staff, either as student, project coordinator, physician, physician, or therapist — is to create a set of conditions that will enhance the patient's own motivation and commitment to change. A therapist's sensitivity to the complexity of motivation will seek to mobilize the patient's own change resources as well as those inherent in the client's relationship with his or her therapist (Table 8: Adherence Enhancement Strategies in Clinical Research).

Table 8: Adherence Enhancement Strategies in Clinical Research

Recruitment	Spend adequate time providing informed consent and getting to know participant
	Explain IBSOS, its protocol, and treatment conditions
	Explain participants' roles, need for and importance of randomization, confidentiality, and adherence
	Explore motivation, expectations, views of research, tolerance of randomization, history of research participation, history of discipline in self-care
	Set clear, mutually accepted goals and assess understanding
	Balance recruitment objectives to enroll the largest number of participants possible but also limit enrollment to those with reasonable likelihood of adhering to the protocol
Social Aspects	Promote positive, collaborative relationships between participants and members of research team
	Maintain frequent phone contact, email, and clinic visits
	Provide positive feedback for regimen and follow-up adherence
	Mutual goal setting: Develop clear and realistic expectations
Regimen Characteristics	Ensure materials are readable, culturally sensitive, and engaging
	Tailoring: Develop regimen that can be realistically integrated with participants' other daily activities
	Ensure the regimen is not too complex or difficult to comprehend
	Schedule appointments at convenient times and in convenient locations; minimize waiting times

Logistical Support	Provide free parking
	Feasible scheduling of appointments around work schedule
	Provide reminders of regimen and importance of sustaining adherence throughout treatment
	Incorporate staff and consultants with expertise in adherence
Adherence	Educate all staff on how to negotiating adherence and understand the types of non-adherence as well as ethical issues in research and adherence
	Devise adherence plan as part of study design, including protocol for addressing non-adherence
	Promote collaboration between participants and research staff
	Provided feedback about how well participants are adhering to protocol or achieving target goals whenever possible
	Promote candid, non-judgmental discussion of adherence, including barriers, facilitators, and personal challenges
	Anticipate adherence challenges and address them proactively (teach skills necessary to organize behaviors that underlie adherence and time management)
	Monitor adherence (e.g. homework)
	Incorporate behavioral techniques and problem-solving to enhance adherence (i.e. reminders)
	Provide positive reinforcement (i.e. social reinforcement, incentives) for good adherence whenever possible
	Model adherence behavior (i.e. demonstrate timeliness for appointments and phone contacts)
	Intervene early and as often as necessary when adherence problems emerge (i.e. call immediately if an appointment is missed)
	Discuss barriers to adherence with patient
	Promote the development of a therapeutic relationship (i.e. listen empathically, provide support and encouragement, display genuine concern, respond to patient concerns, address disagreements promptly, provide clarification and explanations, engender trust)
	Clinical staff should attend to cues of non-adherence during screening visits (e.g. rescheduling, lateness to visits, difficulty reaching participants by phone, participants' grimaces when staff describe study expectations, and hesitancies)
	Provide reminders
	Educate participants about treatment benefits
	Use written or verbal contracts
	Clinical staff should avoid strategies that may elicit resistance (i.e., aggressive confrontation, excessive questioning, a condescending attitude, interrupting the patient, or arguing with the patient)

Adapted from Robiner, W. N. (2005). Enhancing adherence in clinical research. *Contemporary Clinical Trials, 26*, 59-77.

Careful Screening and Enrollment

The most efficient way to address poor adherence and retention problems in a randomized controlled trial is to prevent their occurrence. Strategies to minimize the number of participants enrolled who are potential risks for poor retention and adherence are essential to the success and impact of a randomized controlled trial. This means that enhancing adherence starts with the selection and training of research staff that can effectively communicate with participants and help them navigate through the study process. Staff and investigators who interact with potential participants must fully appreciate the importance of adherence and retention, have sensitivity to potential cues signifying adherence problems, have an ability to deploy strategies for addressing problems, and have a collaborative style that fosters easy and direct communication with other staff members regarding potential adherence problems.

"If in doubt, screen out" is a phrase often bandied by experienced randomized controlled trial staff. The phrase reflects the assumption that non-compliant volunteers display salient cues or behaviors early that are relatively reliable predictors of poor adherence in the future. Attending to these cues will permit staff to make appropriate choices about who they should or should not enroll in a given study. In fact, there is very little empirical evidence to indicate that a clinical research staff can reliably predict future nonadherence. However, there do appear to be cues to nonadherence to which investigators and staff should attend during the enrollment phase of the study.

Many of these cues surface during the evaluation and consenting period of the study and include:

- Known history of non-compliance/adherence
- Socially unstable
- Expressed difficulty with, and numerous objections to, protocol requirements (e.g. completion of questionnaires, self-monitoring, forgetfulness)
- Cavalier attitude toward protocol

If possible, clinical research team members should try to ascertain the participants' prior history with treatment interventions that emphasize lifestyle change (e.g. weight management, parenting classes, smoking, etc.) and their successes or failures with these behaviors. The best predictor of future adherence behavior is past adherence behavior, and potential participants are often candid about their former experiences with, for example, diets, medication regimens, and exercise programs. Weak compliance should not necessarily render a participant ineligible but should heighten awareness of potential factors that threaten the administration of treatments, and help staff plan ways to work around obstacles.

The four-week monitoring phase also provides a useful window of time to assess the ability of the participant to comply with study regimen. Volunteers who do not

comply with the monitoring assignment do not meet eligibility criteria and therefore are deemed ineligible for the IBSOS even if they have been provisionally assigned a treatment condition for the sake of efficiency. Investigators should also attend to subtle and not-so-subtle cues during screening visits (e.g. rescheduling, lateness to visits, difficulty reaching participants by phone, participants' grimaces when staff describes study expectations and hesitancies). Clinical staff can and should maintain close communication with administrative staff who are best informed about these issues based on their frequent communications with participants concerning scheduling, etc. (Table 9: Factors that Contribute to Non-Adherence)

Table 9: Factors that Contribute to Non-Adherence

Characteristics of the Patient	Type and severity of diagnosis
	Vision or hearing problems
	Altered mental states (i.e. forgetfulness, stress, depression, substance abuse)
	Competing sociocultural or ethnic folk concepts of disease and treatment
	Apathy and pessimism
	Failure to recognize that one is ill or in need of medication
	History of nonadherence
	Erroneous health beliefs
	Erroneous expectations about treatment
	Dissatisfaction with health provider or treatment
	Lack of social support
	Family instability
	Residential instability/ unstable living circumstances
	Nonsupportive environment
	Competing or conflicting demands (unemployment or poverty)
	Lack of transportation, money, or time
Characteristics of the Disease or Disorder	Unstable medical condition
	Symptomatology no longer clinically meaningful to patient
	Cognitive impairment (i.e. confusion, visual problems)
Characteristics of the Treatment	Location or transportation problems
	Poor continuity of care
	Long waiting time
	More than eight days delay between referral and appointment
	Timing of referral
	Lack of cohesion in the treatment delivery system

	Inefficient or unfriendly office personnel
	Clinical staff or facility with a poor reputation
	Complex or long treatment regimen
	Regimen requiring many complex lifestyle changes
	Inaccurate diagnosis of patient's problems
	Vague instructions (i.e. daily diary)
	Lack of follow up from therapist on treatment recommendations (i.e. homework)
	Adverse reactions or side effects
	Inadequate communication
Characteristics of the Patient-Therapist Relationship	Poor rapport
	Verbal or nonverbal attitudinal and behavioral problems by physician or patient
	Failure by therapist to elicit negative feedback about the treatment
	Providers are untrained, overworked, or inadequately supervised
	Lack of connection to patient's support systems (i.e. spouse)

Adapted from Meichenbaum D, **Turk** DC. Facilitating Treatment Adherence: A Practitioner's Guidebook. New York, NY: Plenum Press; 1987

Patient-Therapist Relationship

In the IBSOS, the therapeutic alliance is at the core of treatment and a positive working alliance lays a foundation for skills building, support, etc. A positive relationship is regarded in the IBS literature as a critical mechanism of change. Even though IBSOS treatments are brief, the quality of the relationship is important and a major ingredient of psychological interventions. Moreover, if the relationship with the therapist and the rest of the study/treatment staff is positive, compliance and retention are more likely. Thus, the staff should strive to promote the therapeutic relationship throughout treatment through empathic listening, providing support and encouragement, displaying genuine concern for the patient and his/her welfare, responding to patient concerns and addressing disagreements when they occur, and providing needed clarifications and explanations throughout treatment.

The importance of cultivating a quality therapeutic relationship begins as early as the first time the patient calls for information about the study and undergoes a telephone screen. In other words, establishing a strong therapeutic alliance is the responsibility of all IBSOS staff. IBSOS staff should avoid strategies that may elicit resistance, including aggressive confrontation, excessive questioning, condescending attitude, interrupting the patient, or arguing with the patient. In sessions, the therapist should respond to client concerns and complaints while providing consistent, reliable, and predictable structure for the sessions. Participants who may have never participated in therapy or psychosocial

treatments may need extra guidance about the process of treatment to foster therapeutic engagement.

Engender trust.

One way to enhance the quality of the therapeutic alliance is if participants learn to trust the therapist and the rest of the clinical staff. This is not automatic but must be earned to some extent. Developing the necessary degree of trust requires a satisfactory working relationship with participants. Only then may participants be willing to divulge personal material in therapy, follow through on scheduled appointments, and complete assignments.

The primary goal is to foster a sense of active participation and shared responsibility between therapist and client. Specific techniques include probing for the client's worries and concerns, attending to and reflecting what the client is saying, exploring the client's expectations about treatment, and discussing potential adherence problems openly with the client. Therapists should use a friendly, empathic, nontechnical communication style, and encourage participants to express any doubts or misgivings they may have, particularly those that may interfere with their ability to derive maximum benefit.

Express empathy.

Clinician style is an important element for establishing rapport and building a trusting relationship with participants. The importance of connecting with and understanding your client's perspective and personal values as opposed to yours cannot be overstated. Accurate empathy has been well described and tested in clinical research. Empathy involves seeing the world through the patient's eyes, thinking about things as the client thinks about them, feeling things as the client feels them, sharing in the patient's experiences. Expression of empathy is critical to enhancing motivation and adherence to trial demands. When participants feel that they are understood, they are more able to open up to their own experiences, share those experiences with others, and commit to research activities. Having participants share their experiences with you allows you to assess when and where they need support, and what potential pitfalls may need to be focused on in the treatment process. Importantly, when participants perceive empathy on a therapist's part, they become more receptive to gentle challenges by the therapist about taking steps to control IBS. In short, the therapist's accurate and genuine understanding of the patient's experience lays a firm foundation for behavior change to occur.

Empathy occurs when the therapist listens carefully and accurately reflects what the individual is feeling and experiencing. Persuasion is gentle, subtle, and always with the assumption that change is up to the patient. To engage in a sound therapeutic relationship, participants must perceive their therapists as a person who deeply understands their circumstances. A client's sense of acceptance can facilitate change. Skillful reflective listening (i.e., responding to what the client says in a way that conveys understanding of the client's feelings

or the meaning of the client's statements) by the therapist is fundamental to behavior change and preventing premature termination.

Participants will confide in you if they feel comfortable and safe within the treatment setting. Their natural reactions may depend on their gender, age, ethnic identity, and life experiences. For example, ethnic minorities may bring a reticence to research settings that are based on historical events. Initially for these participants and others who have experienced life adversity (e.g. trauma), safety in a treatment setting is a particularly important issue.

Aim and Strategies for Expressing Empathy in Motivational Interviewing

Aim:

To understand the client's world

Clinical Strategies:

Practice active listening behaviors:

- Good eye contact
- Responsive facial expression
- Body oriented toward the client
- Verbal and nonverbal "encouragers" (e.g. head nods, saying "I see")
- Use reflective listening (i.e. paraphrasing the client)
- Ask clarifying questions

Avoid:

- Challenging the client
- Expressing doubt
- Passing judgment
- Giving unsolicited advice

Orient the patient to the demands of an RCT.

Early on in the research program, the research staff spends time describing the treatment, session structure and format, and answering questions. Tell your participants explicitly what treatment involves, what is expected of them (and you), and the procedures of the study. Use language the client can understand. Also be sure to encourage questions and provide clarifications of anything that seems perplexing or not straightforward. Some will not understand what it means to participate in treatment, why they have to be monitored for four weeks before treatment, why they need to return two weeks after treatment ends, and general information about the program such as the day, time, location of session, the duration of treatment, the names of staff, etc.

The provision of this type of information is similar to what Orne and Wender [141] describes as anticipatory socialization for therapy. The assumption is that participants who understand the process and "rules of the game" are likely to succeed in therapy. Role indication by itself is not likely to prevent premature termination, but it does clarify what is expected from the clinical site's perspective and strengthens participants' sense of control [142].

Role induction extends through treatment sessions when therapists provide an overview at the beginning of each session, and provide a few minutes at the end summarizing the topics addressed to help the patient develop a framework for sessions and retain material that was discussed. Do not assume that the patients, many of whom have never undergone psychosocial treatments, are familiar with the therapeutic process. Again, anything you can do to familiarize participants with the process will enhance sense of control and commitment to treatment.

Staff members should also discuss confidentiality, randomization and other procedural issues during the screening phase. Fully informing participants about the meaning of a randomized clinical trial is critical. Participants must realize that they may end up in either the control group or the treatment group. Volunteers are often prompted to participate in an RCT because of their desire for treatment. Thus, during the consenting process, it is important that the meaning and consequences of randomization be clearly explained; simply relying on the "coin toss" analogy may not be sufficiently informative for all volunteers. Study staff should fully explore the participants' understanding of randomization and staff should attempt to gauge if a potential participant is oriented against IBSOS treatments [143]. Strong, inflexible preferences are viewed as warning signs for future adherence and retention problems if participants do not "win" their first choice.

The patient may be unfamiliar with the confidentiality of information disclosed in treatment. Participants who understand that research staff will maintain confidentiality are more likely to comply with research protocols. It is important that participants trust you to protect their privacy, and your credibility (as well as the treatment you administer or represent) rests on your continually earning your participant's trust. He or she may need updated information on new rules such as the Health Insurance Portability and Accountability Act (HIPAA). Although the patient will have signed an informed consent, staff members should not assume that the patient understands the issues surrounding confidentiality, and it is good clinical practice to discuss them. This not only has important ethical value for volunteers to a research trial but it also goes a long way in enhancing participants' sense of control over study participation, strengthening commitment to project, and minimizing the chance of premature dropout.

Support self-efficacy.

Self-efficacy refers to the patient's confidence in his or her ability to achieve a specific goal [144, 145]. In the content of the IBSOS, self-efficacy refers to patients' perceived judgment that they can adopt behavioral skills or strategies to control IBS symptoms. Many participants entering the IBSOS trial do not believe they can control IBS symptoms on their own. A person who understands that s/he has a serious problem may still not move toward believing they can change and that such change is beneficial. ***Individuals who do not believe that they have problems that need changing (or that cannot be changed), and are placed in a treatment that they do not believe will help, are susceptible to adherence problems.***

Strengthening self-efficacy requires supporting hope, optimism, and firm commitment underscoring the feasibility of accomplishing change. A patient's belief that change is possible is an important motivator to succeeding in making change called for in managing IBS symptoms. As participants are held responsible for choosing and carrying out actions to change, therapists focus their efforts on helping the participants stay motivated. Supporting participants' sense of self-efficacy is a great way to do that. If a patient has little hope that things could change, there is little reason to face the problem in the context of a behavioral clinical trial like the IBSOS.

The client can be helped to develop a belief that he or she can make a change, and this belief is strengthened by (a) reviewing past experiences or (b) through the experience of immediate, small successes. For example, the clinician might inquire about other behavior changes the client has made in his or her life, highlighting skills the client already has. Sharing brief clinical examples of other, similar participants' successes at changing the same habit or problem can sometimes be helpful. The client can be helped to undertake less daunting challenges and let success build upon success rather than have to cope with the pressure of making wholesale changes first, or changing much of one's entire behavioral repertoire at one time.

Aim and Strategies for Supporting Self-Efficacy in Motivational Interviewing

Aim:

To foster hope in the client that s/he can achieve desired changes

Clinical Strategies:

Express optimism that change is possible:

- Review example of the client's achievements in other areas
- Reframe prior "failures" as examples of the client's personal strengths in coping with such problems as:
    — Family health problems

    - — Medical illnesses
    - — Financial pressures/job loss
    - — Marital discord
- Use reflective listening
- Acknowledge past frustrations, while remaining positive about the prospects of change

Help the patient to identify and build on past successes

Encourage patient responsibility for change.

Although the patient may not be responsible for acquiring IBS symptoms, s/he needs to take responsibility for participating in treatment. Social learning theory (the conceptual model upon which IBSOS research is based) requires active participation by the individual client as well as her/his assumption of responsibility of learning the necessary skills/ information to control IBS symptoms. Through active participation in a behavioral training program in which new skills and cognitive strategies are acquired, an individual's maladaptive habits can be replaced with more adaptive ones governed by cognitive processes involving awareness and self-regulation.

The interested reader should turn to Brickman [146] for an extensive discussion of the distinction between attribution of responsibility for the development of a problem and attribution of responsibility for a solution. Therapists should be prepared to discuss this distinction. The therapist can empathize with the client over her/his difficult history and instill hope for the future by suggesting that regardless of how s/he acquired IBS symptoms (food poisoning, life adversity, surgery, genetic vulnerability, etc.), it is never too late to learn how to take control of symptoms. This can be accomplished by learning self-management skills that have either been lost or never adequately learned.

Explore patient expectancies and determine discrepancies.

One of the first things to discuss with new participants is their expectations about the treatment process, including past experience, and whether there are discrepancies with the reality of their treatment. Ask participants to elaborate on their expectations about treatment and what are their initial impressions, hopes, and concerns. Acknowledging a list of concerns other treatment participants have had can help them feel more comfortable expressing their own concerns. Some of these concerns can be addressed through the following:

Aim and Strategies for Developing Discrepancy in Motivational Interviewing

Aim:
To help the client see that his or her personal goals are inconsistent with current behavior, and thus to motivate the client to work on new behaviors

Clinical Strategies:

- Highlight the discrepancy between the patient's present behaviors and expressed priorities, values and goals
- Use the Socratic method to help the client reach his or her own conclusions
- Break large, long-term goals into smaller, more manageable steps
- Use questions to explore with the client how IBS may interfere with achieving personal goals

Destigmatize treatments.

Because treatment is psychological, its focus is often viewed as the resolution of emotional difficulties not physical symptoms. Participants will often times believe that because treatments are not physical, the therapist believes symptoms are not real or a psychological construction. It is important to convey to the patient that the goal of treatment is reducing physical symptoms through behavioral solutions much like other disease management approaches (e.g. lifestyle change for hypertension, diabetes management, etc.).

Many participants will have negative expectations based on previous and usually unsuccessful treatment episodes. A motivational approach can elicit a client's concerns without being judgmental. Each client needs an opportunity to vent apprehension or negative reactions to the treatment process and have these concerns validated — not punished for them, but addressed therapeutically.

Unrealistic hopes about what treatment can accomplish — particularly without much work by the client — are equally dangerous and seductive but have to be flushed out. The client may feel that the therapist will "fix" or "cure" her symptoms. Be honest about what the program can do and what it cannot do. Remember you are working for the patient and are accountable to some extent for the objectives you define early on. It is important that you reach understanding with the client about positive and negative expectancies before beginning the "meat" of treatment.

An important motivational enhancement strategy is helping participants perceive a discrepancy between where they are now and where they want to be. The therapist elicits the discrepancy from the client, rather than placing words in the patient's mouth. "Motivation for change occurs when people perceive a discrepancy between where they are and where they want to be" [147]. Motivationally sensitive therapists work to develop this situation by helping participants examine the discrepancies between their current behavior (e.g. avoidance of restaurants, worrying about having an accident) and future goals (improving social life). This can be achieved by raising the patient's awareness of the personal consequences of her/his current health situation. In other cases, the process of developing discrepancy may involve clarifying and resolving the patient's ambivalence by strengthening his/her motivation for change while diminishing motivation to accept the status quo.

The therapist's feedback of personal information, when properly presented, can enhance the patient's perceived importance of change. As a result the patient may be more willing to consider change options to reduce the discrepancy. When participants perceive that their current behaviors are not leading toward some important future goal, they become more motivated to make important life changes. Of course, the therapist gently and gradually helps participants to see how some of their current ways of acting and thinking (e.g. avoidance, intense worry) may lead them away from, rather than toward, their eventual goals.

Avoid argumentation and "roll with the resistance."

In the IBSOS, emphasis is placed on avoiding disagreements with participants about the severity of their IBS problem, or tugs of war over homework assignments, etc. Argumentation is counterproductive to the change process and defending positions may breed client defensiveness. Rather, disagreements are met by empathically reflecting the participants' negative reactions to the treatment situation. Heavy-handed efforts to persuade participants about the severity of their problems, or persuade them on the value of IBSOS treatments are not utilized. This approach is bound to escalate resistance.

We conceptualize resistance as an observable behavior or statement that occurs during a treatment session. Behavior such as arguing, repeatedly forgetting homework, interrupting, denying, and ignoring indicate resistance from a patient — or therapist! Resistance behaviors are often responses to the style of an interaction. Ensuring that you avoid evoking or strengthening resistance to change in the individual is critical to enhancing compliance and maximizing the therapeutic value of treatment procedures featured in the IBSOS.

Motivation to enter treatment or to change is not always apparent. Treatment receptivity and motivation vary across participants. Resistance is normal. "Resistant" behaviors are barriers to successful treatment implementation and they point to important processes for therapeutic focus.

The skilled therapist does not fight client resistance, but "rolls" with it and uses it as a signal to change or shift strategies. Rolling with resistance means:

- Acknowledging that a disagreement exists
- Acknowledging limitations of existing case formulation
- Emphasizing client responsibility for choices and change
- Encouraging consideration of goals relative to status quo
- Redirection toward behavioral change techniques

Statements demonstrating resistance are not aggressively challenged. Instead the therapists use the client's "momentum" to further explore the client's views. Using this approach, resistance tends to be decreased rather than increased, as

participants are not reinforced for becoming argumentative and playing "devil's advocate" to the counselor's suggestions.

By rolling with resistance, the therapist encourages participants to develop their own solutions to the problems that they themselves have defined. Thus, there is no real hierarchy in the patient-therapist relationship for the client to fight against. In exploring client concerns, therapists may invite participants to examine new perspectives, but therapists do not impose new ways of thinking on participants.

Aim and Strategies for Rolling with Resistance

Aim:
To overcome the client's resistance to adopting symptom self-management behaviors by acknowledging and dealing with resistance, but avoiding direct confrontation

Clinical Strategies:

- Don't over apologize resistance — it's normal
- Rather than opposing resistance, explore it
- Identify and problem-solve the client's specific concerns about achieving symptom self-management behaviors
- Express the disadvantages of change to get the client to own the side of change
- Use simple reflective listening or amplified reflection

It is the therapist's job to actively re-engage the client rather than wait for the client to get back in contact. First, try to reach the client by telephone. The client may immediately apologize or express regret for the missed appointment and ask to reschedule. If so, reschedule and briefly review any possible barriers to the patient's attendance at the rescheduled appointment. When the client repeatedly cancels appointments, misses a rescheduled appointment, or shows reluctance to reschedule, it is essential to do more troubleshooting by phone.

Cover the following points:

- Clarify the reasons for the missed appointment
- Affirm the client for prior attendance
- Express your eagerness to see the client again
- Briefly mention important concerns that emerged (change talk) and your appreciation (as appropriate) that the client is exploring these
- Express your optimism about the prospects for change
- Reschedule the appointment

If possible, conduct a brief functional analysis of the missed appointment. If the client offers no reasonable explanation for missing the appointment, explore with the client whether the missed appointment might reflect any of the following:

- Uncertainty about whether there is a need for treatment (e.g. “My IBS symptoms aren’t so bad that I need treatment”)
- Ambivalence about making behavior change or about specific aspects of treatment (e.g. “I am not sure whether this is the right time for me”)
- Frustration or anger about having to participate in the treatment (e.g. “Monitoring is a pain”)
- Logistical issues (e.g. illness, lack of transportation, child care)

Handle such concerns in a motivational interviewing style. Encouraging the participants to voice their concerns directly may help to reduce the possibility of their expressing them indirectly by missing future appointments. Affirm the client for being willing to discuss concerns. Summarize what you have discussed, add your own optimism about the prospects for positive change, and obtain recommitment to treatment. Then, reschedule the appointment. When a patient returns to treatment after a missed session, the therapist should show appreciation (verbally reinforce patient for returning).

Ambivalence

Ambivalence about change is normal, and yet it represents a key motivational barrier to change. Ambivalence may be recognized by conflicting statements, or actions that conflict with one’s stated commitment to a particular course of action. For example:

- *“I keep promising myself I’m going to do my worry records, but I just don’t seem to get around to it.”*
- *“This might work, but it’s too hard — I can’t stick with it more than a couple of days and then I feel I’m going through the motions.”*
- *“I know I agreed to research follow-up, but I’m tired of answering all those questions. What good is it?”*

When faced with ambivalent or resistant statements, it is tempting to respond with persuasion regarding the importance of change, reassurance to shore up the patient’s confidence for change, or information to correct the patient’s apparent misconceptions. This “righting” makes intuitive sense, and occasionally works, but more often, the patient responds with more resistance.

Therapist: *Most people find it helpful to choose a regular time each day for relaxation.*

Client: *I know, but I don’t even have 10 minutes to spare. I’m too busy getting the kids up and out in the morning, and then I have to help*

my mother. She can't manage on her own anymore. And then it's car pools and homework and dinner, and then the day is gone.

Therapist: *You know, you'll be much better help to others when you take care of yourself properly.*

Client: *Maybe, but what am I supposed to stop doing? I already can't do everything I need to do every day.*

Studies have shown that the more we argue for a particular viewpoint, the more we tend to believe it. Therefore, it is especially unproductive to find ourselves arguing for change while the patient argues for staying the same. In a motivational enhancement approach, the goal is for the patient to make the argument for change. Therefore, rather than persuade or cajole the patient, the clinician seeks to elicit "change talk" while minimizing resistance.

"Change talk" consist of statements made by the patient that indicate increased motivation or commitment to a course of action.

Change talk has been categorized as:

- **D**esire for change
- **A**bility to change
- **R**easons for change
- **N**eed for change
- **C**ommitment for change, and
- **T**aking steps toward change

The guidelines create the acronym **DARN-CT**. Alternatively, it may be helpful to think of change talk in terms of the following beliefs:

1) *"It is important for me to change."*
2) *"I am confident that I can change."*
3) *"I am going to make a change."*

If the patient is reluctant to commit to making a change in behavior, the therapist should not push too hard. If the patient commits to a change s/he is not ready to make, the patient may drop out of treatment rather than renege on an agreement. Premature commitment is likely to develop resistance and undermine the therapeutic process.

The therapist should not assume that ambivalence has been completely resolved and commitment is firm and everlasting. It is safer to assume that the patient is still ambivalent and continue using motivation building and commitment strengthening strategies.

The therapist should reflect and explore the patient's expressions of uncertainty and ambivalence. It can be helpful to "normalize" ambivalence and concerns, for example:

> **"***What you are feeling is common, especially in the early stage of treatment. It's easy to understand why you are feeling mixed. You have gone through so many promising treatments that did not work and this may seem like just one of many that are destined for disappointment. Further, you are thinking about changing a set of behaviors that have developed over many years; give yourself both time and an opportunity to succeed. The changes you and I are going to work on will take a bit of work in the short term but in the long-term we believe they will be worth it."*

The therapist should reinforce any self-motivational statements (i.e. those s/he hears arguing FOR change) why change would be important now, an indication of willingness to change, and provide reassurance that people can and do change, often with only a few treatment sessions, and when they do change they achieve improvements in symptoms that have eluded them. The patient may consider resistance to change after accepting the fact that the therapist understands his or her reasons for being hesitant to change. Alternatively, pushing the patient may result in a treatment dropout.

Tailor Program to Participants' Needs

It is crucial that participants perceive the treatment they are receiving as personally relevant to the major issues they are confronting. Therapy manuals employed in clinical research studies often require that the focus of sessions be limited to prescribed topics. However, if therapists ignore the real-life problems that participants are experiencing and probably want to talk about, they risk having participants view treatment as peripheral or even irrelevant to their current needs.

A compromise is therefore necessary between the demands of the protocol and being responsive to participants' perceived needs. A limited amount of time can usually be allocated at the start of each session for setting an agenda and determining how current problems can be addressed in light of treatment procedures.

The general rule is that these discussions be structured in a way that preserves the integrity of the therapeutic protocols to which the patient has been assigned.

> *"Our topic for the session is continuing to work on relaxation skills. I hear that you want to talk about the phone call from your mother earlier this afternoon. How about if we take this opportunity to practice using relaxation skills to deal with stress and then discuss what happened?"*

"I appreciate your coming in today even while you have your hands full dealing with your daughter's illness. Let me ask you — are you up to focusing on new material from the workbook today or would it be more helpful to review some of what we've already covered?"

It may become necessary to inform participants with multiple issues that, given the limitations imposed by the treatment protocol, not all problems can be dealt with fully. Participants with issues that require interventions beyond the study treatment can be given referrals for additional therapy.

Another potential relevance issue is the presentation of didactic material. If therapists present new information by reading from a manual, they may give the appearance of being more concerned with following a protocol than meeting the needs of their participants. Therefore, when presenting new material, therapists should paraphrase major points in their own words and use illustrative examples derived from what they have learned about their participants' particular problems or needs.

When appropriate, consider exploring the participants' prior knowledge of, or theories about, the topic you are about to discuss, before presenting new information. After ensuring that you understand the participants' ideas, then decide how much additional content you need to present. Present the new information simply, using short sentences and non-technical language.

Therapists should check for client understanding and reactions during the course of any presentation they make. In motivational interviewing parlance, this process of information exchange is referred to as: Elicit (the client's knowledge or ideas) — Provide (additional information) — Elicit (the client's reaction).

Enhancing Adherence to "Homework" Assignments

"Homework" is an essential component of IBSOS treatments, utilizing real-life situations for out-of-group practice. This offers the distinct advantage of practice in actual problem situations, enhancing the likelihood that these behaviors will be repeated in similar situations (generalization). A preplanned homework exercise is planned for every session of treatment for all three protocols.

Their importance reflects our conceptualization that more severely affected IBS participants have specific educational or skills deficits and that symptom relief comes about by remediating these deficits, which requires learning compensatory skills. Homework is not just an assignment; it is a means by which participants remediate skills deficits.

Compliance with homework is occasionally a problem. Whenever possible, the therapist should encourage the patient to complete between-session practice exercises. The therapist should provide rationale and description of exercises, give specific instructions, and explain how the tasks relate to treatment goals.

The therapist ensures that the patient understands each practice exercise, follows up on between-session exercises during the next session, and examines any obstacles around understanding and completing homework. When the therapist ignores noncompliance with the exercises, early dropout may follow.

Participants are asked to identify a specific time they can set aside to work on the homework assignment. Therapists review the preceding session's homework exercises at the beginning of each session, making an effort to praise all approximations to compliance with the assignment. Although problems that the participants have with the exercises should be discussed, the main emphasis is on reinforcing the positive aspects of performance. While it important for participants to do the assignments as prescribed, it is still important to solicit suggestions to ensure compliance with the next assignment.

Remember: what the client does outside the session in cognitive-behavioral skills training is at least as important as what goes on in sessions.

Based on her work on Project Match, Dr Kathleen Carroll of Yale University (IBSOS Consultant) has provided a checklist for enhancing adherence to between-session therapy assignments and for monitoring and following-through on completion of assignments:

- Provide a rationale and a clear description of the assignment, balancing the need for detail with the need for clarity and simplicity
- Explore any fears about, or attitudes toward, the assignment
- Elicit participants' thoughts and feelings about the assignment, and troubleshoot as needed

  "You've told me you understand the reasoning behind self-monitoring, and you say it won't be too hard to do, yet you're not sure you are willing to do it. Help me understand your reaction."

- Include review of homework toward the start of each session
- Reinforce adherence by praising all approximations to adherence
- Discuss problems participants may have had with the homework, but keep the main emphasis on the positive aspects of performance

  "I'm glad to hear that the relaxation exercises were relaxing! How did you make sure you got it done as often as you did? What was different on the days that you didn't do it?"

- For those who did not do an assignment, ask what they could do to ensure that they will complete the next assignment.

"What do you think you need to do in order to practice relaxation every day, and also fill out the worksheets?"

- Emphasize that adherence to assignments is up to the individual

  "I only want to help you get what you want."

- Keep the discussion of homework compliance within the bounds of the treatment protocol

Therapist Response to Missed Appointments

When a client misses a scheduled appointment, the therapist should respond immediately. The therapist should attempt immediately attempt to phone a patient who does not show up for a scheduled therapy session to find out why the session was missed. Participants sometimes miss because they had flare-ups and are embarrassed to admit their difficulty progressing through treatment to the therapist or are ambivalent about making behavior changes. Careful inquiry by the therapist reveals which situation is the case.

Treatment Dissatisfaction

A patient may say that treatment is not going to help or may want a different treatment. The therapist should first reinforce the patient's honesty. The therapist should confirm that the patient has a right to quit treatment at any time, seek help elsewhere, or decide to work on the problem in another way. The therapist should explore the patient's feelings further. Concerns that arise in the first session are probably reservations about an approach that the patient has not tried. No one can guarantee that a particular treatment will work, but the therapist can encourage the patient to try it for the planned period. In other words, encourage the patient to suspend judgment and give her/himself an opportunity to succeed.

Guidelines for Study Gastroenterologists

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OVERVIEW OF IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is the most common disorder seen in gastroenterology (GI) practice [148]. Its prevalence in the general population is estimated between 10-20% in the United States and 7-10% in the world. It is characterized by abdominal discomfort associated with altered bowel habits. The diagnostic criteria have undergone multiple revisions, with the Rome III criteria being the current standard. Whereas the diagnosis of many functional gastrointestinal disorders must be made by exclusion, multiple studies and the most recent American College of Gastroenterology guidelines have argued that the **diagnosis of IBS can be made with confidence and without significant diagnostic testing if one meets Rome III criteria**.

These recommendations are supported by multiple lines of evidence. In a prospective study, Tolliver et al. [149] enrolled 196 participants who met clinical criteria for IBS and subjected them to a battery of serologic, radiologic and endoscopic testing. Of these participants, 99% had negative diagnostic workups and were diagnosed with IBS. In a subsequent study, Vanner et al. [150] demonstrated that Rome I criteria combined with the exclusion of red flag symptoms yielded a specificity and positive predictive value of 100% for the diagnosis of IBS. A meta-analysis of six studies also revealed that participants who met symptom-based criteria for IBS had a probability of less than 1% of receiving an alternative diagnosis [151]. Two studies have also validated the longevity of an IBS diagnosis, with a follow-up period of three to greater than 20 years yielding a change in diagnosis in less than 1% of cases [152, 153].

ROME III DIAGNOSTIC CRITERIA FOR IBS

Table 10: Rome III Diagnostic Criteria for 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:

- Improvement in pain/discomfort with defecation
- Onset of pain/discomfort associated with a change in stool frequency
- 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.

It is important to note that a few alterations were made to the Rome criteria when the most recent criteria were released. Because the vast majority of IBS participants do not obtain complete *relief* of their pain/discomfort with defecation, the Rome III committee adjusted the requirement to include *improvement* in pain/discomfort with defecation. The time intervals necessary to make a diagnosis of IBS were also modified. Participants now meet criteria if they have experienced symptoms three days a month for the past three months with symptom onset greater than six months prior to making the diagnosis.

CLASSIFICATION OF IBS SUBTYPES

Table 11: Classification of IBS Subtypes

a. **IBS with diarrhea (IBS-D):** Loose or watery bowel movements >/= 25% of the time with hard or lumpy bowel movements < 25% of the time.

b. **IBS with constipation (IBS-C):** Hard or lumpy bowel movements >/= 25% of the time with loose or watery bowel movements < 25% of the time.

c. **Mixed IBS (IBS-M):** Loose or watery stools >/= 25 of the time AND

hard or lumpy stools >/= 25% of the time.

d. **Unsubtyped IBS (IBS-U):** Insufficient changes in stool consistency to meet criteria for #s 1-3.

Adapted from Longstreth et al.,1

Furthermore, updated evidence indicates that the best manner for subcategorizing IBS participants is stool form as opposed to bowel frequency. Therefore, participants are now classified into one of four subcategories:

- IBS with diarrhea (IBS-D)
- IBS with constipation (IBS-C)
- IBS mixed subtype (IBS-M)
- IBS unsubtyped (IBS-U)

TRIAL DESIGN AND THE GASTROENTEROLOGIST'S ROLE IN THE IBSOS PROJECT

The responsibilities of gastroenterologists acting as site investigators/co-investigators for the IBSOS are as highlighted (in yellow) and bolded on the flow chart below (Figure 10: GE Responsibilities). All potentially eligible participants will undergo an initial telephone screen. If s/he passes the telephone screen, s/he will be referred within 5-21 days to a gastroenterologist acting as an investigator/co-investigator at one of the participating clinical sites. An exception to this policy will be allowed at Northwestern University where practicing academic gastroenterologists, pre-determined at the discretion of the Northwestern University investigator/co-investigator, will be allowed to perform the initial investigator screen.

The **sole purpose of this evaluation is to confirm or exclude the diagnosis of IBS** and to assure that the patient meets inclusion/exclusion criteria for the IBSOS trial. This visit is not meant to serve as a tertiary referral consultation, and the participating gastroenterologist is discouraged from making any specific recommendations regarding supplemental and/or alternative therapies. For these inquiries, the patient should be referred back to their primary gastroenterologist.

Screening Phase

At baseline (screening phase) the gastroenterologist will be responsible for the completion of the following tasks:

Table 12: Gastroenterologist Responsibilities – Screening Phase

1. Confirmation of the diagnosis of IBS based on Rome III Criteria
2. Confirmation that the patient has moderate/severe symptoms (>/= 2 days/week)
3. Completion of the MD Rating Form
4. Determination whether the patient requires further testing prior to enrollment
5. Communication of results of this evaluation back to the institutional project coordinator recommending either performance of the baseline assessment or suspension/conclusion of the screening process
6. Correspondence with referring gastroenterologist regarding participants' eligibility and enrollment in the trial.

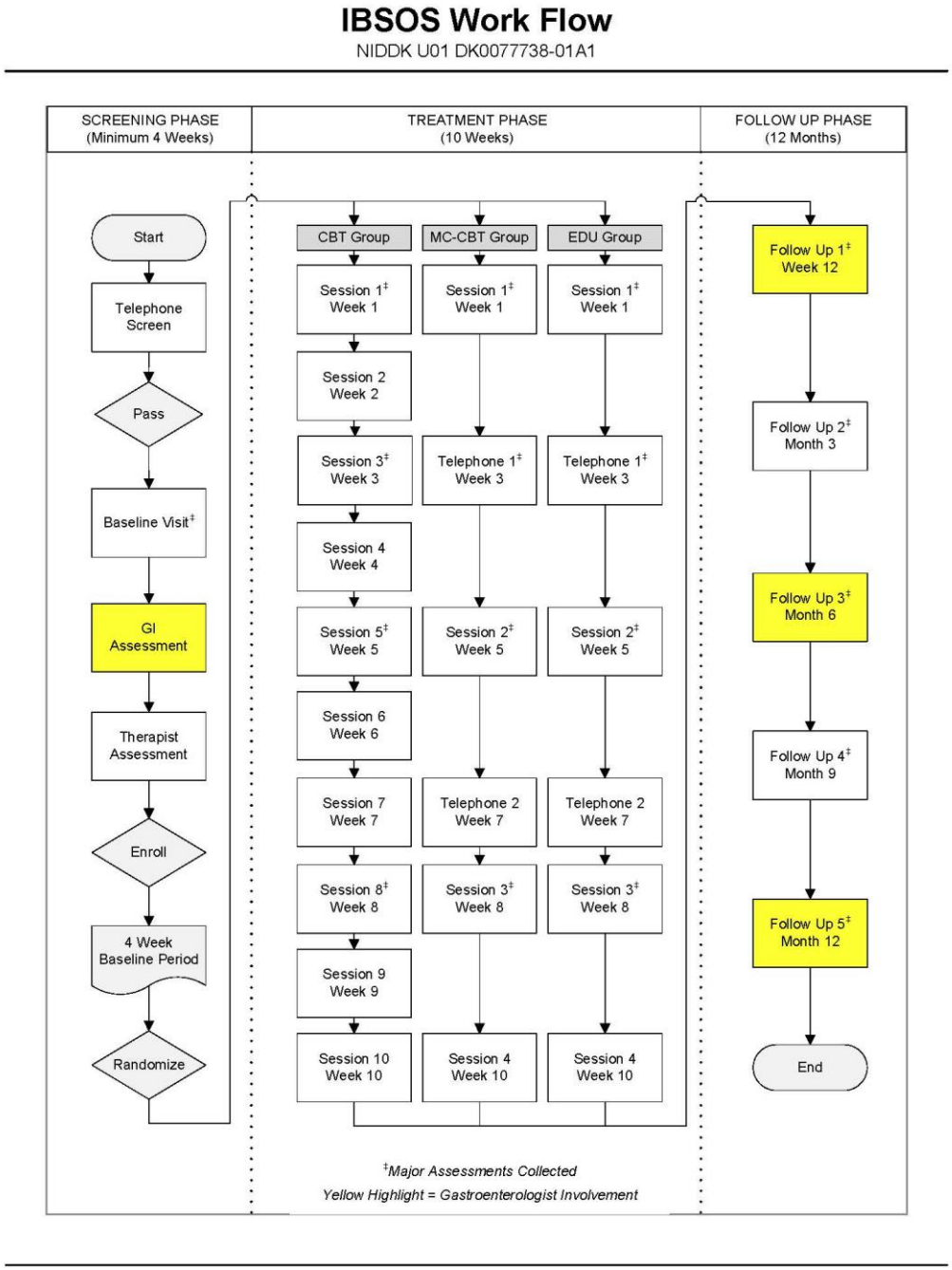


Figure 10: GE Responsibilities

Treatment Phase

Participating gastroenterologists will be blinded to the arm of the trial to which participants are enrolled. That is, they will not be informed of the treatment to which participants will be assigned, nor should they elicit information that would reveal treatment assignment. This would of course compromise their objectivity.

Follow-Up Phase

Study doctors will be asked to complete the "Clinicians Rating Form," a nine-point visual analog scale reflecting their estimation of the severity of the patient's IBS symptoms at baseline and at the 12-week and six-, and 12-month follow-up visits. In this scale, the gastroenterologist should use his or her *best estimate* of the patient's *current* degree of distress and disability associated with IBS, taking into account the patient's ability to work, maintain relationships, engage in social activities, and the presence/severity of any depression or anxiety associated with IBS. No one symptom (e.g. pain) should be used as a general index of IBS symptom severity because the goal is to obtain a global estimation of the severity of all IBS symptoms in general. The clinician should also take into account the degree of IBS-specific distress and disability the patient presents within the context of other patient's the clinician has seen with similar symptoms. Because of logistical issues, study gastroenterologists may not necessarily follow these participants through trial.

FREQUENTLY ASKED QUESTIONS

How do I approach a patient who most likely has IBS but for whom there is some evidence of "alarm signals" that require additional workup?

If the study physician believes that alarm signs are present, this information should be relayed to the project coordinator as well as to the referring gastroenterologist. This does not preclude enrollment in the trial if the symptom in question is appropriately evaluated and a non-exclusionary diagnosis made. Alarm symptoms are not to be regarded as "rule outs" but as signs and symptoms of possible organic pathology which warrants additional clinical evaluation.

What special considerations, if any, should be given to a patient who has gastrointestinal comorbidities (dyspepsia, pelvic floor dysfunction, etc.)?

It is common for participants with functional disorders to have overlapping conditions. Up to 35% of participants with dyspepsia also meet Rome criteria for IBS, for example. The goal of the GE evaluation is to establish that the patient meets Rome III and inclusion/exclusion criteria for this trial regardless of most other medical comorbidities. As long as the patient meets these criteria and has symptoms which are at least moderate in severity (i.e. symptoms ≥ 2 days/week) then the patient can be enrolled in IBSOS.

What special considerations, if any, should be given a patient who has other nonpsychiatric medical comorbidities (fibromyalgia, chronic fatigue syndrome, PCOS, endometriosis, etc.)?

There is no special approach which needs to be taken for these participants. As with comorbid functional disorders, participants should be enrolled if they meet Rome III criteria for IBS with moderate severity. Nonpsychiatric comorbid medical disease does not preclude participation in the IBSOS, provided the volunteer's medical illnesses do not interfere with study demands. Obviously, a patient who requires frequent hospitalizations for a comorbid medical disease may be unable to make regularly scheduled appointment and would therefore not meet eligibility criteria for the IBSOS

Are there restrictions on treatment of these participants when they are enrolled in the study?

Participants enrolled in this trial are asked to remain on stable doses of IBS medications during the four-week baseline period. They are not restricted from receiving new pharmaceuticals during the trial; however, they should contact their project coordinator immediately with the name, dose and frequency of consumption of the medication. They should also contact their project coordinator with any changes in the dosage or frequency of these medications or medications prescribed prior to trial enrollment.

Does the IBSOS trial require that participants undergo a routine of diagnostic testing to confirm a diagnosis of IBS?

NO. Because the symptoms of IBS are common to a number of other GI conditions, IBS was long considered a "diagnosis of exclusion" leading to excessive testing of participants with characteristic symptoms. Advances in research have led to the development of a symptom-based approach aimed at standardizing IBS patient subgroups [154]. The development of consensus guidelines advocates making a diagnosis of IBS based primarily on the pattern and nature of symptoms. It is not the practice of the IBSOS to require routine diagnostic testing to confirm a diagnosis of IBS. However, one should look for "red flags" or alarm symptoms that may be detected in a careful history and physical exam. Participants with symptoms of IBS and coexistent alarm symptoms should undergo appropriate additional diagnostic testing (i.e. colonoscopy in those with rectal bleeding and age older than 50 years, sprue antibody tests in younger participants with weight loss, diarrhea, and a first-degree relative with a history of celiac disease).

In the unlikely event that additional diagnostic testing is called for prior to enrollment in IBSOS, this information should be relayed promptly by the study gastroenterologist to the referring physician. The study gastroenterologist should not perform any routine or specialized diagnostic testing. However, a positive diagnosis of IBS can be routinely established without diagnostic testing.

Who manages the patient's day-to-day IBS symptoms throughout the course of the trial?

Throughout the entirety of the trial inclusive of the observation, active treatment and post-treatment follow-up periods, the patient's medical treatment for his/her IBS symptoms remains with the referring physician.

How should the IBSOS GE respond when a volunteer asks for specific treatment recommendations?

The role of the IBSOS GE is to confirm the Rome III diagnosis for IBS, rate the overall severity of IBS symptoms at the pre-treatment visit, conduct "blind observer" follow-up assessments, and characterize the apparent improvement in symptoms at follow-up appointments. GEs are strongly discouraged from providing advice, recommendations, or prescriptive behaviors on how to manage IBS symptoms. Such information would compromise the "objective" status of the GE. It is highly possible that a patient may solicit specific recommendations on drugs, diet, etc. The GE should respond by asserting that, as study gastroenterologist, s/he is not in a position to give specific treatment recommendations. At the same time, it is totally appropriate for the GE to convey a sense of hope, optimism, and positive treatment expectancy consistent with the established efficacy of treatments featured in the IBSOS.

How should I respond to a volunteer who does not meet Rome criteria and wants to participate in the IBSOS?

If the patient does not meet Rome III criteria, s/he is not eligible to enroll in the IBSOS trial. Whether or not you "feel" the patient has IBS should not a factor in establishing IBS diagnosis. Kindly thank the participant for his or her time and effort and refer them back to their primary gastroenterologist.

If the patient still wishes to receive CBT for their underlying condition, you may wish to recommend that they address this with the site PI, their PMD, or primary gastroenterologist who can subsequently arrange a referral outside the scope of the IBSOS trial.

I have a patient who meets Rome criteria but reports uncertainty about how often her symptoms occur. Technically, s/he does not meet eligibility criteria, but I am not sure how I should proceed.

This information can be clarified through daily monitoring over a two-week period. If daily monitoring reveals a pattern of symptoms that renders him or her eligible, s/he would qualify for IBSOS participation. Of course, a brief period of monitoring may also verify that her symptoms occur too infrequently to qualify for IBSOS. IBSOS research team should take advantage of the monitoring phase to gain clinically important information that bears on eligibility issues (severity, motivation, etc.).

There are a variety of ways to determine predominant bowel habits. What approach has the IBSOS adopted?

The IBSOS has adopted the sub-stratification design recommended by the Rome III Committee. This sub-classification scheme stresses stool characteristics over stool frequency using the following cut-offs:

1. **IBS with diarrhea (IBS-D):** Loose or watery bowel movements >/= 25% of the time with hard or lumpy bowel movements < 25% of the time.
2. **IBS with constipation (IBS-C):** Hard or lumpy bowel movements >/= 25% of the time with loose or watery bowel movements < 25% of the time.
3. **Mixed IBS (IBS-M):** Loose or watery stools >/= 25 of the time AND hard or lumpy stools >/= 25% of the time.
4. **Unsubtyped IBS (IBS-U):** Insufficient changes in stool consistency to meet criteria for #s 1-3.

Adapted from Longstreth et al.,1

Two major diagnostic issues need to be considered when arriving at predominant bowel habit. First, participants commonly transition between these subgroups and therefore it is important to establish predominant bowel habit at the time of the GE examination. Second, the symptoms of diarrhea and constipation are commonly misinterpreted in IBS participants. Thus, many IBS participants who complain of “diarrhea” are referring to the frequent passage of formed stools and, in the same patient population, “constipation” may refer to any one of a variety of complaints associated with the attempted act of defecation and not simply to infrequent bowel movements. For this reason, predominant bowel habit should not be based non-standardized terms such as “diarrhea” or “constipation.”

Practical Strategies for Enhancing Client Motivation to Participate in Research

RESEARCH AND CLINICAL STAFF

ROLE OF RESEARCH STAFF

Initial contact

The initial contact with the treatment site will often be over the phone; this is your first opportunity to engage potential participants. Typically in research studies, a staff member conducts an initial screening to determine whether the caller is likely to be eligible for the study, provides a referral to alternate treatment for ineligible callers, and sets up a consent and assessment appointment for eligible callers. Use a friendly, welcoming, and professional phone manner. Make it easy for participants to reach someone who is knowledgeable about the study.

Considerations for the Initial Contact:

Employ rapid response.

- Participants may be most motivated for treatment at the time of their first call to the program.
- To increase the likelihood that clients will actually enter treatment, schedule the initial appointment while they are on the phone with you. Ideally, the person will be able to come in to the center for their baseline assessment within 7-10 days of screening.
- Timely scheduling of the initial appointment is facilitated by having several staff members available to do interviews and by providing evening and/or weekend hours for appointments to increase flexibility.
- Project / research coordinators should maintain staff schedules and make every attempt to "fill" them regularly so that staff does not make alternative arrangements during those times. For example, if Dr. X sets aside Wednesday mornings for assessment, the coordinator should make every effort to schedule participants during that time each week.
- Project/ research coordinators should gently encourage participants to take the "next available" appointment slot; i.e. *"Our next available opening is with Dr. X on Monday, October 3rd at 9 a.m. Can I go ahead and schedule that for you?"*

Provide adequate information about the program.

A. Provide a brief description of the program, including the main points on the IBSOS User's Guide. Include a basic outline of the research and clinical aspects of the program so that the client will not be surprised by the more detailed information that will be provided at the informed consent meeting.

B. Make sure you underscore the time commitment involved in the study, stressing that the time commitment is to their advantage. "Our team is really interested in your progress over time and therefore will be in touch with you for at least one year after treatment."

C. Invite and respond to questions. If you don't know the answer, offer to transfer the call to someone who does know, or find out the information and call the client back promptly.

Describe pre-treatment meetings in detail.

A. When the first appointment is made, fully inform participants about the reason for the meeting and what to expect. This includes who they will see, how long the meeting will last, the procedures that will be followed, and the kinds of information they will be asked to provide.

B. If final eligibility for the study will be determined at the initial meeting, be sure participants are aware of the possibility that they may not qualify for the study when they come in.

C. Anticipate common logistical problems, such as transportation, parking, meals, and child care, and offer appropriate solutions. Keep in mind that participants with IBS may tend to be anxious. Calmly work with participants to minimize the stress of their first visit to the clinic. For example, maps prepared in advance with printed directions can be emailed or mailed to participants on the same day of their telephone screening to ensure arrival before the appointment.

RESEARCH COORDINATOR ROLES AND RESPONSIBILITIES

Pre-treatment Meetings

Study Environment

Create a welcoming environment for participants. Provide a pleasant waiting area. Greet the participants upon entry to the treatment site and let them know how long

they will wait to be seen. Offer beverages and/or snacks and point out the restroom. Above all, maintain a pleasant, affirming, and respectful attitude. Participants may be more likely to remain committed to the study if they feel that they receive “VIP” treatment” because they are in the study. Remember, participants aren’t here to be in a “study” — they are here to see an expert in their condition that they would not otherwise have access to.

Administrative Staff Oversight/Training

Often, the first person encountered by a potential participant upon arrival is the clinic receptionist, not a member of the research project staff. This initial introduction to the research project is an essential first step in creating a welcoming environment, yet is often overlooked during the planning of research studies. Research participants are not typically registered in the patient scheduling system, which can cause confusion for administrative staff and a sense of “does anyone know what is going on here?” for the participant. Personnel will require both proper training and advanced notices for scheduling participants.

The following steps will be taken to ensure department receptionists are well informed and prepared to provide participants with the appropriate level of service:

1. **Weekly Appointment List**: Project Coordinator will provide a list of client appointments at the beginning of each week to receptionists and the office manager. Lists will be in paper form for receptionists and emailed to management. This list will include names and times as well as the appropriate contact information for research staff.

2. **Receptionist Training**: The PI and Project Coordinator will meet with both receptionists and management to provide an overview of client scheduling procedures for the study. To help ensure proper buy-in, the importance of team work will be emphasized. Receptionists will know they are an integral part of the project.

Informed Consent

Common barriers to research and treatment participation include: distrust of research, doctors, or psychotherapy; misunderstanding of procedures; concern about random assignment and/or skepticism about one of the treatment conditions; concerns regarding loss of privacy; and logistical barriers. The informed consent process, when conducted skillfully, can serve as an opportunity to build trust and rapport, and to avert common barriers to treatment and research participation. The consent form will include information about study procedures, and the risks and benefits associated with participating. **It is your responsibility to ensure that participants have enough information to make a fully informed decision about participation.** Follow standard procedures and don’t try to “sell” the

program. For ethical reasons, it is essential that participants not feel coerced into research participation.

Special Considerations

Some special considerations when preparing participants for treatment within a research study:

- **Review the differences between research and treatment phases of the study.** Give participants a clear timeline that provides an overview of the different phases over time.

- **Note that timelines are tentative.** A more definitive timeline will be given to the client at the first treatment visit (visit 2), as this date will determine the succeeding visits.

- **Review staff roles during all study phases**. Indicate project staff to call in case of emergency.

- **Review differences between study treatment and other non-research treatments potentially available.**

- **Review how eligibility will be determined,** because not all who give consent for assessment will turn out to be eligible.

- **Review informed consent procedures**, and give participants a copy of the form. Include review of:

    i. Confidentiality
    ii. Procedures for assessment
    iii. Random assignment to treatment. Be realistically optimistic about the participants' chances for success in each of the treatment conditions.
    iv. Client obligations during treatment. Describe possible problems that may occur, and how the project handles them.
    v. Procedures and payment for follow-up assessments. Remind participants that even if they choose to withdraw from treatment prematurely, you will still contact them to complete follow-up assessments. This represents a substantial commitment to the client, and participants should be encouraged to think through their

commitment to participating in the entire study.

- **Invite and respond to questions**. Normalize participants' concerns with statements such as: *"Many participants ask about…"* or *"That's a good question."* Remember, *you* may have consented many participants, but this is the first time *the client* has been through the process.

- **Review potential barriers to full participation**. Ask open questions, such as: *"What might get in the way of following through on your commitment to completing the study?"* Listen carefully, and address any second thoughts participants may be having regarding random assignment to treatment or use of personal information. In addition, ask about such common logistical problems as transportation, child care, and scheduling conflicts. Invite participants to think through what would be needed for them to attend all their sessions. Be prepared to offer available solutions participants may not be aware of; for example, flexible scheduling of appointments, travel reimbursement, or onsite child care. Be careful not to be overly accommodating, however. Oftentimes, participants who require a great deal of accommodation are truly unable to commit to the study in any event.

- While this may not be available at the first visit due to randomization processes, **the project / research coordinator will prepare a handout for each individual client** that identifies: the treatment to which they have been assigned; the therapist; session location; starting and ending dates and times; and expectations regarding attendance, directions to the center, parking facilities or local landmarks (if they come from a distance).

- All participants should be provided with **a handout listing follow-up dates and their primary research contact person**. Introduce participants to their follow-up person if it will be someone different than at baseline.

Project / Research Coordinator Checklist

The information to cover at time of consent is included in the following **Visit Checklist** (figure 11).

VISIT CHECKLIST
IRRITABLE BOWEL SYNDROME OUTCOME STUDY

Subject Number: Date of Visit:

PRE-TREATMENT VISIT(S)

Topics covered at this visit:	Patient Completed Measures & Forms:	
Introduction: ☐ Welcome client ☐ Provide overview of program ☐ Review time commitment and timeline of study ☐ Answer any questions client may have ☐ Review Informed Consent Form and obtain signature (provide client with signed copy before they leave) Inclusion/Exclusion Criteria: ☐ Confirm inclusion/exclusion criteria ☐ Record past and present medical health, surgeries, and medication/non-drug therapies Dispense Assessment Measures: ☐ Explain measures, procedures for completing, and answer any questions ☐ Confirm completeness of all measures by the subject (first step in data QA) Enroll/Randomize: ☐ Assign PID (Patient Identifier) ☐ Enter Subject Enrollment System (SES) and complete Eligibility Checklist ☐ Confirm SID (Study Identifier) on Enrollment Confirmation Scheduling (procedures may vary per site): ☐ Schedule client for 1st treatment session ☐ Provide client with Treatment Schedule Closing: ☐ Provide client with GI symptom diaries and review instructions for completing ☐ Confirm appointment for 1st treatment session ☐ Thank client for participating Post-Visit Items: ☐ Confirm subject is scheduled in calendar for 1st treatment session ☐ Organize CRF, chart, and measures according to Data Management Plan	INTAKE	☐ Signed Informed Consent ☐ IBSOS Intake Form
	MEDIATORS	☐ Frankfort Monitoring & Blunting Scale ☐ ASI [1] ☐ VSI [1] ☐ IBS Locus of Control [1] ☐ IBS Self-Efficacy [1] ☐ PSWQ [1] ☐ PSS [1] ☐ Pain Coping Strategies ☐ Emotional Regulation
	CLINICAL ENDPOINTS	☐ BDI-II [1] ☐ EQ-5D [1] [QLW2] ☐ IBS-QOL [1] ☐ Survey on Health & Well-Being [QLW4] ☐ IBS-SSS [QLW3] ☐ McGill Pain Inventory-Short Form [1] ☐ BSI [1] ☐ SF--12 [1] ☐ STAI-Short Form [1] ☐ GSRS-IBS [1] ☐ Restorative Activities
	MODIFIERS	☐ K-ESS ☐ IIP [1] ☐ Life Events Scale ☐ Negative Interaction Scale ☐ NPMC-IBS ☐ TSRQ-A [1]
	Staff Completed Forms:	
		☐ Concomitant Med Log [F0408] ☐ Emergency Contact Form ☐ MINI [3] ☐ Economic Form [3] [QLW6] ☐ Comprehensive Interview [3] ☐ MD Screening Form [4] ☐ Eligibility Checklist on SES System
	Patient Take Home Materials:	
		☐ IBSOS Daily Diary [LGW1] ☐ Welcome Packet ☐ Copy of signed consent form ☐ Treatment Schedule

[1] Scantron form; [2] PRN; [3] Therapist; [4] MD; * Mailed prior to visit

Figure 11: Coordinator Visit Checklist

Provide Support and Advocacy

Sometimes participants are more likely to continue attending treatment if they can contact the staff to share concerns about the treatment. In most cases, rather than intervene directly, staff will encourage participants who are dissatisfied with treatment to bring up their concerns with their therapist, while expressing confidence that the therapist will welcome hearing whatever the client has to say.

In some cases, staff may be able to assist with solving site-specific logistical problems. Encouraging participants to share concerns about their treatment may also serve to alert the research team to problems with access to or delivery of treatment "as advertised" in the protocol.

Front-line research staff without counseling training will usually involve a supervisor in responding to a patient's complaint.

> *"Before you leave, let me make sure I validate your parking ticket so you don't have to pay for parking. I'll make sure our project manager knows that our parking passes aren't being honored so she can follow-up on it and spare you any trouble."*

Red Flag Behaviors Suggestive of Possible Attrition

Personnel will want to identify and address "red flag" behaviors as soon as they occur in order to minimize attrition. Below are examples of client patterns which staff should be proactive in recognizing and addressing:

The newly unreliable client

This pattern reflects the research participant who was previously engaged, reliable and consistent in their attendance, follow-up and timeliness. When participants like this begin to miss visits, become difficult to reach by phone, and/or fail to return calls or emails in a timely manner, research staff should appeal to the participants' initial good intentions by listening carefully to their concerns and doing their best to address concerns or problems. If necessary and appropriate, research staff may want to arrange study requirements so they are less burdensome. Direct involvement from the site PI may also be useful.

The scatterbrain

Individuals who reschedule more than once for a single visit are at risk for attrition. Either they have difficulty committing to the study or their lives are chaotic enough that they are unable to manage their schedules. Staff should make an effort in these cases to schedule reminder calls and generally let them know that we appreciate their time and are aware of how difficult it is for them to commit to something on a regular basis. Occasionally, clinicians may want to provide participants with the feedback that the goal of this program is to improve their self-care by making it a priority for the participant.

The "real deal"

Lost adherence is commonly associated with serious life circumstances and may be a temporary concern. Study personnel should use their clinical judgment to determine whether it is appropriate to check-in with the client or whether it would be better to leave them alone to deal with their issue with the expectation that they will re-engage when their stressor is over.

The bitter participant: changing attitudes about the study

If staff begins to note complaints about visits, impatience with visits, quiet or withdrawn behavior during visits, or lack of concern about the study or treatment, it is possible that the participant needs help re-engaging. Routine contact by the research team during the treatment phase of the study provides an excellent opportunity to help participants re-engage in treatment.

The dropout

Participants who verbalize their intention to discontinue the study should be handled very carefully. Good communication between clinical and research staff can help in this effort — clinical staff need to know who has dropped out in order to initially attempt to help them reengage. Simply asking treatment dropouts if they would like for the researcher to make a "termination" appointment with the clinician may yield results. If participants offer objections, the researcher may be able to help with logistical issues. However, participants must feel free to "vote with their feet" regarding treatment, and the research team's primary concern is collecting complete data from participants, regardless of whether they are in treatment. **Don't pressure treatment dropouts so much that they end up dropping out of research follow-up, too!** Remember, even if a patient prematurely withdraws from treatment, our goal is to obtain follow-up data through one year.

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.

Locating missing participants

Staff should do their best to maintain current locator information on their participants to avoid mislocating participants who are willing to follow-up. After confirmation has been made that the client has moved or changed his or her contact information, staff may decide to make contact the person through their emergency contact person or place of work. If so, staff should be very discrete about why they are calling but still indicate that it is very important that the participant return your call. Other potential locator techniques include registered mail, Google or other online searches. (See **PARTICIPANT DISCONTINUATION CRITERIA**)

Dealing with client unavailability

Remember that collection of the follow-up data is critical to the study and that staff should go to great lengths to obtain this. If participants prefer to complete their assessments over the phone, online or via mail due to unavailability, this should be accommodated. Further, even if participants miss one assessment, this should not preclude the staff from attempting to collect follow-up data at the next time point. Remember that many times non-adherence is temporary due to

life circumstance. Stress the importance of follow-up to the patient including that it helps us answer the question regarding durability/sustainability of treatment.

Change of staff or study environment

Whenever something about the study environment changes, participants may feel disconnected from the project. It is important that changes are clearly communicated and "transitions" are handled well, especially with respect to introducing new personnel.

Reluctant participants

If appropriate selection, informed consent, and locator procedures are followed, most participants will readily participate in follow-up assessments. However, some will be reluctant to continue in the study. "Reluctant" participants are those who repeatedly cancel appointments, repeatedly do not show up for appointments, repeatedly indicate that now is "not a good time," screen calls and do not respond to messages.

Dropout recovery

Begin "dropout recovery" efforts, described below, as soon as there is any indication that the client is becoming reluctant to return for follow-up assessments.

Dropout recovery methods have been demonstrated in clinical trials to re-engage participants who have become inactive when applied systematically [155]. While not originally conceptualized in this manner, this approach incorporates the use of good reflective-listening and directive skills to elicit barriers to participation from participants. This information is then used to problem-solve with participants for methods to overcome the identified participation barriers. Finally, an essential component of dropout recovery is the application of selected motivational interviewing techniques in an attempt to further elicit and clarify participants' personal reason for continued participation.

The general approach to re-engaging reluctant participants and dropout recovery will involve the following steps:

- Contact the patient.
- Identify barriers to participation or reasons for withdrawal.
- Negotiate solutions to overcome barriers.
- Apply motivational interviewing techniques in an attempt to further elicit and clarify participants' personal reason for continued participation.

Recording of Attrition

Having already established and nurtured a good working relationship with the client places you in a good position to elicit the true barriers to participation for any given client. Inquire about reasons for missed appointments or reluctance to

schedule in a caring, concerned tone. A direct approach can encourage the participant to be direct with you.

> *"You were so interested in being in this trial initially, but I sense reluctance now. What accounts for that?"*
>
> *"I sense that it is hard for you to do the things we are asking of you. What would make it easier or doable?"*

Try to understand clients' concerns from their perspective. Summarize what you've heard to be sure you've got it right, and be prepared to be changed by what you hear.

ROLE OF CLINICAL STAFF

Procedures to Minimize Attrition and Non-Adherence

Engender trust.

Successful implementation of adherence-enhancement strategies is facilitated if participants learn to trust the therapist. Developing the necessary degree of trust requires a satisfactory working relationship with participants. Only then may participants be willing to divulge personal material in therapy and complete assignments.

A number of steps can help to improve the therapeutic relationship. The primary goal is to foster a sense of active participation and shared responsibility between therapist and client. Specific techniques include probing for the patient's worries and concerns, attending to and reflecting what the client is saying, exploring the client's expectations about treatment, and discussing potential adherence problems openly with the client. Therapists should use a friendly, empathic, nontechnical communication style, and encourage participants to express any doubts or misgivings they may have.

Maintain relevance to participants' needs.

It is crucial that participants perceive the treatment they are receiving as relevant to the major issues they are confronting. Therapy manuals employed in clinical research studies often require that the focus of sessions be limited to prescribed topics. However, if therapists ignore the real-life problems that participants are experiencing and probably want to talk about, they risk having participants view treatment as peripheral or even irrelevant to their current needs.

A compromise is therefore necessary between the demands of the protocol and the need to be responsive to participants' perceived needs. A limited amount of time can usually be allocated at the start of each session for setting an agenda and determining how to address current problems. The general rule is that these

discussions need to be structured in a way that is consistent with the therapeutic protocol employed in the study.

> *"Our topic for the session is continuing to work on relaxation skills. I hear that you want to talk about the phone call from your mother earlier this afternoon. How about if we take this opportunity to practice using relaxation skills to deal with stress and then discuss what happened?"*
>
> *"I appreciate your coming in today even while you have your hands full dealing with your daughter's illness. Let me ask you — are you up to focusing on new material from the workbook today or would it be more helpful to review some of what we've already covered?"*

It may become necessary to inform participants with difficult issues that, given the limitations imposed by the treatment protocol, not all problems can be dealt with fully. Participants with issues that require interventions beyond the study treatment can be given referrals for additional therapy.

Another potential relevance issue is the presentation of didactic material. If therapists present new information by reading from a manual, they may give the appearance of being more concerned with following a protocol than meeting the needs of their participants. Therefore, when presenting new material, therapists should paraphrase major points in their own words and use illustrative examples derived from what they have learned about their participants' particular problems or needs.

When appropriate, consider exploring the participants' prior knowledge of, or theories about, the topic you are about to discuss, before presenting new information. After ensuring that you understand the participants' ideas, then decide how much additional content you need to present. Present the new information simply, using short sentences and nontechnical language. Therapists should check for client understanding and reactions during the course of any presentation they make. In motivational interviewing parlance, this process of information exchange is referred to as *Elicit* (the client's knowledge or ideas) — *Provide* (additional information) — *Elicit* (the client's reaction).

Enhance adherence to "homework" assignments.

"Homework" is an essential component of CBT for IBS. What the client does outside the session in cognitive-behavioral skills training is at least as important as what goes on in sessions. Carroll (MATCH) has provided a checklist for enhancing adherence to between-session therapy assignments:

1. Provide a rationale and a clear description of the assignment, balancing the need for detail with the need for clarity and simplicity.

2. Explore any fears about, or attitudes toward, the assignment.

3. Elicit participants' thoughts and feelings about the assignment, and troubleshoot as needed.

Therapist Techniques for "Rolling with the Resistance"

Expect ambivalence about at least some assignments, even from the most motivated participants. Use reflective listening to "roll with" resistance as needed:

1. Model and/or practice the assignment during the session.

2. Ask participants to try something once, or a limited number of times, rather than setting an expectation that they do it "from now on."

3. Encourage participants to make an appointment with themselves to do the assignment and to consider what cues may help remind them to do it.

4. Anticipate what sorts of things might get in the way of completing the assignment.

5. Anticipating obstacles will make them seem like an expected part of the overall learning process that requires application of a problem-solving approach, rather than an indication of failure on the part of treatment or the client.

6. Find out how the participants motivate themselves to do things more generally.

7. Use open questions to discover the strengths the client brings to following through on skill training.

8. Help participants anticipate the possibility of failure and how to react to it.

9. Encourage use of previously learned skills to recognize and avoid catastrophizing.

10. Ask participants to identify how they will reward themselves for completing the assignment.

11. Obtain an explicit commitment to complete the assignment. Therapists should ask whether the client intends to comply with the assignment and obtain a commitment to do so. Stating a commitment to follow through increases the likelihood that the client will do so. If the client is unwilling to make a commitment, explore this unwillingness and problem solve ways to increase commitment.

12. Be open to the possibility of needing to revise the assignment, or even needing to review the rationale for the assignment. Avoid getting into an argument about it.

    "You've told me you understand the reasoning behind self-monitoring, and you say it won't be too hard to do, yet you're not sure you are willing to do it. Help me understand your reaction."

Dr. Carroll has provided an additional checklist for monitoring and following through on completion of assignments:

- Include review of homework toward the start of each session.
- Reinforce adherence by praising all approximations to adherence.

    "You did your relaxation exercise 4 days out of 7, and completed the paperwork three times. Good job. Tell me how it went on the days that you did it."

- Discuss problems participants may have had with the homework, but keep the main emphasis on the positive aspects of performance.

    "I'm glad to hear that the relaxation exercise was relaxing! How did you make sure you got it done as often as you did? What was different on the days that you didn't do it?"

- For those who did not do an assignment, ask what they could do to ensure that they will complete the next assignment.

    "What do you think you need to do in order to practice relaxation every day, and also fill out the worksheets?"

- Emphasize that adherence to assignments is up to the individual.

    "I only want to help you get what you want."

- Keep the discussion of homework compliance within the bounds of the treatment protocol.

Therapist Response to Missed Appointments

When a client misses a scheduled appointment, respond immediately. It is the therapist's job to actively re-engage the client rather than wait for the client to get back in contact. First try to reach the client by telephone. The client may immediately apologize or express regret for the missed appointment and ask to reschedule. If so, reschedule and briefly review any possible barriers to the client's attendance at the rescheduled appointment.

When the client repeatedly cancels appointments, misses a rescheduled appointment, or shows reluctance to reschedule, it is essential to do more troubleshooting by phone.

Cover the following points:

- Clarify the reasons for the missed appointment.
- Affirm the client for prior attendance.
- Express your eagerness to see the client again.
- Briefly mention important concerns that emerged (change talk) and your appreciation (as appropriate) that the client is exploring these.
- Express your optimism about the prospects for change.
- Reschedule the appointment.

If possible, conduct a brief functional analysis of the missed appointment. If the client offers no reasonable explanation for missing the appointment, explore with the client whether the missed appointment might reflect any of the following:

- Uncertainty about whether there is a need for treatment
- Ambivalence about making a change or about specific aspects of treatment
- Frustration or anger about having to participate in treatment

Handle such concerns in a motivational interviewing style. Encouraging the participants to voice their concerns directly may help to reduce the possibility of their expressing them indirectly by missing future appointments. Affirm the client for being willing to discuss concerns. Summarize what you have discussed, add your own optimism about the prospects for positive change, and obtain a recommitment to treatment. Then, reschedule the appointment.

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.

Recruitment Plan

Site investigators will formally present their formal recruitment plan at the initial four-five day training workshop before recruitment is initiated. The sites will review their plan 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.

Recruitment Toolbox

To support recruitment efforts, the CC will produce a "recruitment toolkit" containing a variety of materials (e.g. brochures, fliers, newspaper ads, posters, physician letter template) that each clinical site can use as prototypes for their own recruitments efforts. This toolkit will include a combination of direct and indirect recruitment materials, all of which must be approved by local IRBs.

Indirect or Peer-to-Peer Approaches

Indirect or peer-to-peer approaches promote recruitment by appealing to health care professionals who are in a position to influence their prospective participants' decision to enter a clinical trial. This approach entails cultivating a network of physicians and other health care professionals (physician assistants, rehabilitation nurses, nurses) as dependable referral sources. Examples of indirect recruitment strategies include the following:

Branding

It is recommended that the investigators promote the IBSOS acronym (which is formed from the initial letters of the title **I**rritable **B**owel **S**yndrome **O**utcome **S**tudy). Abbreviated trial names serve many purposes. They are useful mnemonics that simplify reference to and facilitate recall of a study; promotes "brand" awareness, conveys a cohesive identity that links the disease focus (IBS) to a helpful treatment goal (SOS or help), and resonates with physicians who routinely use them to convey important medical information (SOAP, HIPAA, CBC, etc.).

Brochures and Posters

Provide clinicians with brochures and posters for office distribution in high-traffic areas.

Referral Letters

Send physicians referral letters which introduce them to the IBSOS trial ("Dear Colleagues"). This tool is designed to raise the level of awareness about the IBSOS among the sites' network of referral sources. Tapping into the medical community is an important recruitment source of prospective participants. However, some physicians may be reluctant to refer their participants for participation in a clinical trial. To overcome common concerns, a site should seek to assure physicians who have participants to refer that: (1) participants who are referred to the IBSOS and qualify will still be followed by the referring MD; (2) ongoing medical treatment need not be suspended or modified while their patient participates in the IBSOS; and (3) the investigator will send information on study participant at regular times (e.g. after completion of treatment) to apprise referring physician of participants' status. Open communication with referring physicians will contribute to a good working relationship, eliminate disincentive for patient referral, and facilitate opportunities for referrals.

Educational Opportunities
Provide educational opportunities ("lunch and learn," grand rounds, journal club, local medical society meetings) for potential referring physicians (GEs, PMDs) and other health care staff (NPs, PAs) who may have influence over participants and other physicians with access to IBS participants.

Announcements
Place announcements in health care-related newsletters, websites, and other community publications.

Cards
Provide laminated study reference cards with inclusion/exclusion criteria for local physicians and nurses.

Public Presentations
Conduct presentations at local GI society meetings.

Networking
Promote support from local HMOs who may be favorably disposed to a non-drug treatment program emphasizing patient self care.

Education
Educate the professional community through an external website that will provide downloadable study brochures.

Symposiums
Hold dinner symposiums for the study's site referral network of physicians and allied health providers (NPs, RNs, etc.) to raise awareness about the trial. A slide kit that provides background information about the trial and specific study details will be developed to support the investigators during presentations.

Direct Recruitment Approaches
Direct recruitment approaches use tools that are pitched directly to prospective participants. Direct methods include:

Patient Brochures
The development of well written, eye-catching brochures and fliers is widely accepted as the first-line method of advertising for clinical trials. Brochures are relatively easy and affordable to produce in bulk, and easy to distribute in areas with high patient traffic, such as the waiting room, beauty salons, laundromats, coffee shops, bookstores, places of worship, and grocery stores. The purposes of the patient brochure are to provide information about study participation, to encourage inquiries, and to provide contact information. It includes an overview of the study and basic requirements for participation. The patient brochure is designed as a guide to facilitate discussion with clinical trial staff regarding study

participation, as well as to facilitate the informed consent process. Participants may take the brochure home and use it as a reference tool for general questions about the IBSOS, and share it with family and loved ones while discussing and considering study participation.

Study Poster

The study poster will briefly introduce the study, encourage discussion about study participation and provide contact information. A useful poster will increase awareness of the IBSOS, facilitate follow-up discussion between patient and his/her MD about eligibility, or prompt a pre-screening call. The poster may be displayed in waiting areas, exam rooms, on notice boards, and in other appropriate areas with high prospective participant traffic.

Direct Mail

Direct mail is one of the oldest forms of publicity. Although labor intensive, it is highly targeted and measurable. A useful direct mail letter contains targeted messages that are designed to mobilize patents to action. Direct mail provides a simple explanation of the study and top-line inclusion/exclusion criteria of the IBSOS, and includes appropriate contact information.

Talks to Various Groups

Another excellent way to recruit participants directly involves speaking to various groups in the community. Informative talks build a raised identity of the clinical center (‘branding”), heighten awareness of the study, generate interest in study participation, and provide information in a format that audiences will understand and trust. Speaking opportunities also establish the clinical site as the “go to” site for cutting-edge care. There is a wide range of target audience groups, including patient support groups, social organizations, educational institutions, fraternal organization (e.g. Rotary Club, American Legion, Knight of Columbus, Jaycees), community centers (YMCA, JCC), and places of worship (temples, synagogues, churches). If you choose to do a series of talks, it is important to distribute materials for audience members. Distributing materials is more than putting brochures out on a display table. At meetings in which audience members receive a packet of material, include a cover letter signed by a high- profile person in your community such as study gastroenterologist, etc.

Word of Mouth

In the long run, recommendations from previous participants are viewed as probably the most reliable source of new volunteers. For this reason, it is worthwhile to send occasional announcements to former participants advising them that the IBS treatment is still being offered and asking them to consider recommending the center to friends and family with IBS who have not been previously treated.

Internet

With rising Internet usage, it's becoming more and more important that a clinical research study have a presence on the Web. The IBSOS will develop an external (public) website describing the goals and requirements of the trial, and basic eligibility criteria. Additional web-based strategies that may help recruitment include:

- Local hospitals in close proximity to clinical centers periodically can post information about IBSOS.
- Periodic announcement of trial information of the IBSOS emailed to university community using faculty list serve mailing list .
- The Center Watch Trials Listing Service on www.centerwatch.com maintains a list of research trials that includes the IBSOS.
- Social networking websites and clinical research blogs (e.g. Facebook)
- Online classifieds websites (e.g. Craigslist)
- Websites of health organization and advocacy groups (e.g. IFFGD, ibselfhelp.com; Crohn's and Colitis Foundation of America, ibdcrohns.com); see below for GI-related resources and contact information.

IBS Self Help and Support Group
P.O. Box 94074
Toronto, ON M4N 3R1
Canada
Tel: 416-932-3311
http://www.ibsgroup.org/

American Board of Colon and Rectal Surgery
20600 Eureka Road
Suite 600
Taylor, MI 48180
Tel: 734-282-9400
Fax: 734-282-9402
Email: admin@abcrs.org
http://www.abcrs.org

American Liver Foundation
75 Maiden Lane
Suite 603
New York, NY 10038
Tel: 212-668-1000
Toll-Free: 800-GO LIVER
Fax: 201-483-8179
Email: info@liverfoundation.org
http://www.liverfoundation.org

The CURE: Digestive Diseases Research Center
UCLA Building 115, Room 117
Los Angeles, CA 90073
Tel: 310-312-9284
Fax: 310-268-4963
Email: cureadmn@mednet.ucla.edu
http://www.cure.med.ucla.edu/

American Association for the Study of Liver Diseases
1729 King Street
Suite 200
Alexandria, VA 22314
Tel: 703-299-9766
Fax: 703-299-9622
Email: aasld@aasld.org
http://www.aasld.org/

Digestive Disease National Coalition
507 Capitol Court NE
Suite 200
Washington, DC 20002
Tel: 202-544-7497
Fax: 202-546-7105
Email: romano@hmcw.org
http://www.ddnc.org

International Foundation for Functional Gastrointestinal Disorders
P.O. Box 170864
Milwaukee, WI 53217-8076
Tel: 414-964-1799
Toll-Free: 888-964-2001
Fax: 414-964-7176
Email: iffgd@iffgd.org
http://www.iffgd.org

Gastro-Intestinal Research Foundation
70 East Lake Street
Suite 1015
Chicago, IL 60601-5907
Tel: 312-332-1350
Fax: 312-332-4757
Email: girf@girf.org
http://www.girf.org

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
P.O. Box 6
Flourtown, PA 19031
Tel: 215-233-0808
Fax: 215-233-3918
Email: naspghan@naspghan.org
http://www.naspghan.org

Crohn's and Colitis Foundation of America
386 Park Ave South
17th Floor
New York, NY 10016-8804
Toll-Free: 800-932-2423
Fax: 212-779-4098
Email: info@ccfa.org
http://www.ccfa.org

American College of Gastroenterology
P.O. Box 342260
Bethesda, MD 20827-2260
Tel: (301) 263-9000
http://www.acg.gi.org/

Social Networking Websites

Social networking websites have significantly increased in usage. The largest of these is Facebook (http://www.facebook.com) with over 75 million active users in the United States as of this writing. To recruit potential study participants, the IBSOS will develop a group on Facebook describing the goals and requirements of the trial, and basic eligibility criteria. Contact information for each site will be provided for interested persons to obtain further information. While the group will be open to all users to view, comments and discussion board features will be disabled for the group to prevent any unwanted communication about the study. Additionally, the IBSOS will create a fee-for-click targeted advertisement that will appear on user pages that provides basic information and links them to the study website.

Online Classified Websites

In addition to social networking websites, online classifieds have also increased in usage and provide nationwide access for recruitment of potential study participants. The most widely used online classified site is Craigslist (http://www.craigslist.com) with established markets for all IBSOS study site locations. Advertisements are free to post and are listed for 10 days. However, as part of the site's terms of service, only one ad may be posted per market per Craigslist account so each recruitment site must have its own Craigslist account. Study ads will describe the goals and requirements of the trial, basic eligibility criteria, and appropriate contact information. Ads should be posted in the "Community" category under "Volunteers" for the designated geographical area.

Study Website

Along with housing the online screening questionnaire, the study website will help anchor the patient outreach initiative for the IBSOS and provide an alternative information source that may be viewed by all interested parties, including prospective participants and their loved ones. This site will include a screening questionnaire prospective volunteers can complete and send electronically to the research site. Results of the screening questionnaire will be analyzed and communicated to research staff that will follow up with a pre-screening phone call. Provide information on how to reach someone, even after hours. Explain that the IBSOS is an NIH-funded study. Set up the website so that readers can email questions on the study.

Public Service Announcements (PSAs)

Broadcast media — radio and television — are required by the Federal Communications Commission (FCC) to serve "in the public interest." Most stations use Public Service Announcements, or PSAs, as one of the ways they meet this requirement. While broadcast media aren't required to donate a fixed percentage of air time per day to PSAs, stations do have to state in their licensing and renewal applications how much air time they plan to devote to PSAs. Most stations donate about a third of their commercial spots to non-commercial causes; in other words, if a station has 18 minutes of commercials in a given hour, six minutes of that will probably be devoted to PSAs. PSAs are short messages produced on film, video, or audiocassette and given to radio and television stations. Generally, PSAs are sent as ready-to-air

audio or video tapes, although radio stations (especially community or public stations, such as campus radio or National Public Radio affiliates) sometimes prefer a script that their announcers can read live on the air.

There are a number of advantages to PSAs:

- First, they are generally inexpensive. Because the airtime is donated, the only cost is production. Most stations will allow you to include a telephone number for more information in your PSA. PSAs tend to be really effective at encouraging the audience to take action; for example, call a phone number for more information about the IBSOS trial.

- PSAs can help long-range advocacy goals by helping maintain community awareness of the IBSOS. They represent an easy way to spread information as well.

There are limitations to PSAs, however:

- Because PSAs are done on donated time, you will often find you're not able to get them run on all the media outlets you'd like, or you may find yourself at the mercy of station staff members who may be overworked, arbitrary, or personally opposed to your group's work.

- PSAs are often run as "filler" in the middle of the night or during other times when only a few people are listening or watching.

- The competition among non-profit groups for free air time is very stiff. Depending on the market, there could be hundreds of other groups vying for time on any given station. You may not be able to count on getting a lot of air time for your PSAs.

- Stations may not track and report when your PSAs have been played, but they will do this for paid advertising.

A couple tips about using PSAs:

- First, many media outlets run community calendar segments during newsbreaks or talk programs. Call outlets and ask to insert an item in their community calendar segment. They will either take down the information over the phone or ask that you provide it in writing.

- Second, when distributing your PSA, include a letter that sums up your center's mission and why your PSA is important to your community. You can also provide the public service director at the news outlet with a press kit that include more extensive information on the IBSOS and IBS.

- PSAs are more likely to be broadcast or printed if they announce a meeting or public event.

Patient Advocacy Groups

Patient advocacy groups play an influential role in the lives of participants by helping them learn about their illnesses. These groups also provide information regarding available and investigational treatments. IBSOS sites should work hard to cultivate strong relationships with advocacy groups for IBS and those of highly comorbid medical problems (Crohn's colitis, arthritis, chronic pain). In partnering with patient groups, the clinical sites may gain exposure to a large group of prospective participants through newsletters, list serves, and other communication methods.

Orientation Meetings

Orientation meetings can be valuable because they give you the opportunity to tell people about the IBSOS and give the audience members the opportunity to have their questions answered. Orientation meetings have multiple purposes. The first task is to provide an overview of the IBSOS program and to engage audience members. A second goal is to answer questions. If you hold such a meeting, plan out in advance what you will say, which of the staff members will participate, and what questions are likely to be asked by the people who attend. Make sure you develop PowerPoint slides to convey your material. As a practical detail, holding several orientations at different times can increase attendance because fewer schedule conflicts are likely occur.

News Stories in Local Newspapers, Radio, or Television

These are an excellent way of drawing attention from the local community to the clinical trial. They provide information such as the objectives of the trial, types of participants sought, and, more importantly, the expected benefits for participants. News stories are free, but the opportunity does not come often, nor are these opportunities easily repeatable. The likelihood of a media outlet running a supportive story will increase if sites prepare a press release with a catchy “story angle.” See Examples:

IBS: America’s Hidden Health Problem

As many as 40 million Americans may suffer from IBS, yet less than one in five has been diagnosed with the disease. As a result, many are not getting the care they need. The illness can take a huge toll in terms of impairment of physical, emotional, economic and social well-being.

IBS: A Misunderstood Disease

A recent survey shows that only 66 percent of Americans have heard of “Irritable Bowel Syndrome” and only 17 percent understood what the term means. Many people still believe that IBS is a psychological or psychosomatic condition and that it is “all in the heads” of suffers, even though leading researchers say that is not the case. The confusion may lie in the fact that IBS cannot be detected by any visible marker and may be triggered or exacerbated by certain emotional issues, including stress.

IBS: Affects Men, Too

About two-thirds of IBS sufferers are women. Studies reveal that men comprise about one-third of sufferers. It is incorrect to characterize IBS as a “woman’s disease.”

IBS: Research the Brain-Gut Connection

Although IBS is characterized by symptoms including abdominal pain and altered bowel habits, scientist are focusing on much more than simply controlling diarrhea and constipation. They are looking at the brain and how its interaction with the gut causes these symptoms to manifest themselves.

Alternative Treatment for IBS

While approved drugs to treat IBS symptoms are few at present, alternative therapies including lifestyle changes, hypnosis, meditation and stress management can help. IFFGD’s IBS National Survey revealed that, among those diagnosed with IBS (or that had a family member with IBS), treatment options they were aware of included relaxation therapy (44 percent) and hypnosis (25 percent).

Coping with Economic Stress

As economic woes persist, people around the country are reporting anxiety, worry, and stress-related symptoms such as pain, diarrhea, and constipation. While the future health of the economy is unclear, there is fortunately good news about how to gain control some over the most common, disabling, and painful stomach problems.

Extraintestinal Medical Comorbidity of IBS

As many as one-third of irritable bowel syndrome (IBS) participants have a host of non-GI medical problems such as rashes, tension headaches, and muscle pains. Research has shown that as many as 60% of IBS participants also suffer from fibromyalgia syndrome (FMS). Conversely, as many as 70% of FMS participants have reported experiencing symptoms of IBS. Could there be a common cause for IBS and coexisting medical problems?

Workplace Loss of Productivity

Approximately 10 to 15 percent of the American population suffers from some degree of irritable bowel disease, according to the National Institute for Diabetes and Digestive and Kidney Disease. And while the nature and unpleasantness of IBS symptoms — pain, diarrhea, constipation — is very private, their impact has very public consequences. Indeed, IBS has been identified as second most common cause of work-related absenteeism behind the common cold.

Harnessing the Mind to Manage Irritable Bowel Syndrome

When drugs and dietary changes don't provide relief from the pain, bloating and other unpleasant gastrointestinal symptoms of irritable bowel syndrome, participants may want to try a different, clinically proven approach. Recent studies show that making changes to one's own thoughts and behaviors may help ease symptoms in ways that eludes available medications. Likewise, educating oneself about IBS can be a powerful treatment strategy, too.

Pitch Letter

A pitch letter attempts to persuade local newspapers, radio, or television stations there is a story in their community they don't want to miss. Like a cover letter with a job application, a pitch letter provides just enough information to get the interview. You provide details later. Call an editor of your local paper or a broadcast producer to discuss your topic. Be prepared to provide written background material.

Op-Ed Pieces

Opposite-Editorial (Op-Ed) pieces are opportunities to write an editorial for publication. Op-Ed pieces are usually limited to about 800 words in length. A simple phone call to a media outlet can provide you with its Op-Ed guidelines. Op-Ed pieces usually appear on the editorial pages with their own headlines and bylines. They can be effective ways to raise support and awareness of issues relevant to IBS (the silent epidemic of pain, importance of disease management for chronic illnesses for which there is no cure, etc.) by providing a leading expert's opinion.

Press Releases

Press releases are one-page write-ups that contain breaking news that media outlets can develop into print and broadcast news stories. To be effective, they should be used sparingly. Press releases are best used to announce an event, news, or other strategy that you are using to spread important information. Many media outlets receive large quantities of press releases daily, so you are facing stiff competition for media attention.

An eye-catching headline and compelling first paragraph are essential to being noticed. A trusted relationship with the media (i.e. they see you as reliable and credible) will greatly increase your chances of receiving coverage. A good press release communicates objectively about breaking news and provides background information. Opinions can be expressed using quotes from credible sources.

The press release also lists one or two knowledgeable contact people who are prepared to provide additional information. Make sure these contacts are easy to reach during normal business hours.

A good press release communicates objectively about breaking news and provides background information. Opinions can be expressed using quotes from credible sources.

Keep in mind that most media outlets are deluged with press released. For this reason, alternatives to the press release format should be considered. These include:

- Fact sheets — who, what, where, and why

- Position statements — a brief explanation of an issue and why it is important to the IBSOS

Press Releases There are some upsides to press releases:

- Provide an excellent way to tip off journalists and editors to IBSOS-relevant news

- Can be produced quickly

- Allow you to frame an issue that merits coverage

- Are easily distributed by mail, fax, or email
  Encourage credible, objective journalists to report on your work

Press releases also have their downsides:

- They require skill as well. Writing and distributing a press release isn't enough. You have to work hard to form good relationships with the media to make journalists more receptive to your press release and other efforts.

- Once you establish ties, you have to work to maintain them. Remember that the attention span of the news media is generally very short and that your story has to compete with many others for attention.

Tips for Getting Your Press Release Noticed

- **Make it newsworthy.** In the first paragraph of the release, highlight why the reporter or editor (and readers/viewers) should care. For example, tie the release to a related breaking story in the news.

- **Cover the basics.** Your press release should always include your contact information, a headline, a lead paragraph, supporting information and a summary paragraph about your organization.

- **Write creatively.** The headline and copy should be catchy to capture the attention of the reader. Use active verbs.

- **Make it easy.** Scrap the jargon and. Use words that are easy to read and understand.

- **Provide useful information.** If there's a new research report or publication related to the topic, or if you can refer readers to an informative Web site for more information, include those details in the release.

Tips for Speaking to the Media

Prior to the interview:

- **Be available.** Answering calls promptly is essential. Understand that reporters are usually working on a deadline. Call back right away. When a reporter calls you, always find out what kind of deadline he or she is facing. Give a reporter your cell phone to avoid phone tag.

- **Find out who you're talking to.** Ask for the reporter's name and the media organization for which he or she is reporting. However, it's best not to play favorites when deciding whether or not to grant an interview to a specific reporter. It may seem like a good idea in the short run, but in the long run it will damage your relationship with reporters and may come back to haunt you.

- **Get background.** When a reporter calls requesting an interview, you have a right to ask the participants of the interview and some sample questions. If you need time to collect your thoughts and the reporter's deadline allows, offer to call back later at a specific time and follow through.

- **Don't let yourself be ambushed by the media.** If a reporter shows up in your office or calls at a time when you are unprepared, reschedule the interview for a time when you feel comfortable.

- **Do your homework.** Think of two to three main talking points you would like to make about your participants. Gather facts, figures and anecdotes to support your points. Anticipate questions the reporter might ask and have responses ready.

- **Stick to facts.** Have printed materials to support your information whenever possible in order to help reporters familiarize themselves with the topic and minimize errors. If time allows, offer to send the reporter printed information in advance of the interview. An excellence source is the Reporter's Guide to IBS. Developed by IFFGD, this guide provides in-depth information about IBS, frequently asked questions, glossary of medical terms, IBS resources,

bibliography of key IBS articles and books, and reasons for writing about IBS.

- **Don’t be put off.** Be aware that reporters' schedules are determined by the "breaking" news of the day. Do not be offended if an interview gets canceled or rescheduled because a more urgent story arises.

During the interview:

- **Be prepared.** No matter how familiar you are with the topic, don’t try to wing it. This approach is bound to back fire sooner or later, and when it does it is very embarrassing. Spend time preparing for the interview. If you prepare well, you and the reporter will feel more confident in your interview.

- **Ask if you’re being recorded.** If you are being interviewed by phone, the reporter is required by law to tell you when you are being recorded. If you're not certain, you should ask.

- **Begin at a basic level.** Avoid academic or technical jargon; explain special terms if you must use them.

- **Be brief!** We live in the age of the sound bite. Television and radio stories may use only a 10-30 second cut. The shorter your comments, the less likely they are to be edited. Even print reporters are looking for short, snappy quotes.

- There are **five C's** to success:
  - Speak with ***conviction*** in a ***conversational*** manner while retaining your ***composure***.
  - Be ***confident*** — you are the expert.
  - Be ***colorful*** — tell stories and anecdotes that illustrate your point; give examples.

- **Stick to your main points** and do not allow yourself to get drawn too far off on tangents. Most people make the mistake of talking too much. Repeat your points if necessary to get back on track.

- **Speak in complete thoughts.** The reporter's question may be edited out and your response should stand on its own.

- **Don't overestimate** a reporter's knowledge of your participants. When a reporter bases a question on information you believe is incorrect, do not hesitate to set the record straight. Offer background information where necessary.

- **Ask for clarification** if you do not understand a question, rather than talking around it. If you do not have the answer, say so. Tell the reporter where to find the information, if possible.

- **Never say, “No comment.”** You are not on Law and Order. Instead, if you cannot or do not choose to answer, explain briefly. For example, you can say: "I can’t answer that because I haven't seen the research paper you are referring to."

- **Avoid saying things "off the record."** Reporters may or may not honor this, and it annoys them. If you don't want to hear it on the evening news, you had better not say it.

- **Be honest.** Don't try to conceal negative information; rather, let your interviewer know what you are doing to solve a problem.

Specifically for broadcast media:

- **Wear solid-color clothing** for television interviews. Stripes, plaids or other designs can cause problems with color TV pictures. Avoid large, jangling or reflective jewelry.

- **Look in a mirror**, if possible, just before going on camera. The reporter may not tell you that your collar is folded over or your hair is out of place.

- **Choose a location** where you can screen out extraneous noises. Hold your calls and turn off your computer, if possible. Avoid rooms with loud background hums from air conditioning or heating units.

- **Find out in advance** whether the interview is edited or "live." If you agree to a live interview, be sure you are comfortable thinking on your feet and responding off the cuff.

- **Do not answer questions too quickly** in edited interviews; pause briefly before answering. This helps the reporter get a "clean" sound bite and also has the added benefit of allowing you time to think out your answer.

- **It's O.K. to stop and start over again** in edited interviews, if you don't like the way you worded your answer.

- **Look at the reporter**, not the camera, in a TV interview. The only exception is in a satellite interview, when the reporter or anchor may not be on location. If you're uncertain where to look, ask.

- **Stay stationary** in front of radio or TV microphones and avoid sitting in a chair that rocks or spins. Wandering around or rocking in your chair can cause the recorded volume to rise and fall.

- **Be aware of and avoid nervous habits** such as pen tapping that can interfere with the interview.

After the interview:

- Ask the reporter to identify you as being affiliated with your university.

- In most instances you will not have the opportunity to check over the reporter's story before it appears. However, you can ask questions at the end of an interview to test for comprehension. For example, you might inquire, “What do you think is the main story angle here?” If the reporter sends you a draft (which they will do more often than not), take time to review it for accuracy. Do not assume that what think you said is what was either heard or transcribed.

- You may want to ask when a story will appear. The reporter may not have an answer, but if s/he does s/he'll be happy to tell you.

- If you feel after reflecting on an interview that you misspoke or gave incorrect information, call the reporter as soon as possible and let her know. Similarly, you can call with additional information if you forgot to make an important point.

- Give positive feedback to reporters, if merited, after a story appears. Like the rest of us, they usually hear only complaints and rarely get a call or note to say they've done a good job.

- If an error appears, let the reporter know right away. Sometimes a correction can be printed or aired. You also will want to prevent the incorrect information from being used as background for future stories.

- If you are unhappy with a story, share your concerns with the reporter first. Contacting his or her editor is a last resort.

- For radio and TV stories, obtain a tape of the final broadcast if possible and critique your own performance, looking for ways you might improve in the future.

- Call your university media service to let them know when you've done an interview so that they can track down clippings or tapes of your story.

- After your story runs, contact the reporter and thank them for their time and for sharing your message with the public. A simple handwritten note card or an e-mail is a very nice gesture

Mass Screenings

Community health fairs are excellent opportunities to enhance community awareness around the IBSOS and educate attendees about the problem of IBS and available treatment options. Staff can distribute study brochure and IBS screening form that is designed to solicit follow-up calls.

Clergy

Clergy are often a good source of public relations and may be willing to make a comment at the end of services or allow for staff to post flyers within the place of worship. Staff should be particularly careful in this regard to avoid being perceived as disrespectful (e.g. going to synagogue to post flyers on Friday evening).

Media Advertisements

(Radio, television, newspapers, magazines, the Internet)

Advertising is used to disseminate information about a particular clinical trial either locally or nationally. If you decide to use electronic media (e.g. radio), keep in mind that radio and TV can be very expensive so it is very important to find the right times and venues to coincide with your participants and their friends' listening habits.

Free weekly newspapers are a good way of maximizing advertisement dollars. They are giveaway papers and are widely distributed. The placement of the ad in the weekly paper can be very important.

No single strategy is successful in meeting recruitment goals. Multiple strategies are essential. Combined strategies may be used either simultaneously or sequentially, depending on the staffing of the trial and the community setting. In our experience, concurrent recruitment efforts are more likely to prompt inquiry.

When developing new recruitment material, Grant et al [156] outline several guidelines to which the IBSOS team should adhere:

Content:

- Put most important points first and last.
- Be brief and only include information pertinent for potential participants to decide if they wish to contact you and find out more about the trial.
- Use about a fifth-or sixth grade reading level.
- Pilot test material with people similar to the target population and ask what they (1) notice, (2) remember, and (3) should do? Further, ask for ways to improve these materials.
- Acknowledge the funding agency (NIH/NIDDK) on recruitment materials. This not only is required by funding agency but lends credibility to the announcement.

Patient-centered message:

- Simple explanation of the study
- Clear understanding of what's expected of volunteers
- Clear understating of what the potential benefits and risks are
- Contact person to call for further information, questions or concerns
- Knowledge that they can quit at any time

- Knowledge of results when they become available
- Reimbursement for time and effort
- Make sure your message is consistent across media
- Use the same slogans, colors, pictures, in all media so that your "brand" will be remembered. Repeated exposure to the same message has a greater chance of being remembered.

Visual design:

- Place clearly visible study logos and taglines on all recruitment materials.
- Allow ample amount of white space in margins and between blocks or text.
- Use visuals and illustrations that draw the eye to two or three key points.
- Use of institutional seals increases credibility.
- Use a 12-point or larger type ($\geq$ 13 for older adults); serif font (NIH, 2004). Serif fonts have small appendages at the top and bottom (The Internet Digest, 2003) and are easy to read.
- Do not use all capital letters, even in titles or headings. Use upper and lower case letters, larger and bolder prints, and underlining for emphasis.

Writing style:

- Use short and simple words, phrases, and sentences.
- Limit each sentence to one idea.
- A sentence structure of participants, verb, and objective is best.
- Use the active voice.
- Be positive, direct and personal, and unafraid to use the word *you*.
- Bulleted lists make it easier to scan and identify important points.
- Avoid large blocks of text.
- Minimize medical terminology and technical words (e.g. "about" rather than "approximately.")

Printing:

- Use camera-ready copy rather than photocopies.
- Black print on white or yellow is easiest to read.
- Put letters on institutional or referring agencies' letterheads with official signatures and recent dates.
- Print on 60-pound paper, or heavier, if double-sided. If using self-mailers, 65-pound paper is good.

Mailing:

- Type (if time and cost are prohibited) or handwrite address on envelopes.
- Avoid mailing to the same individual more than three times within a single recruitment blitz.

Recruitment and HIPAA

It is crucial that the research team bear in mind the implication of the **Health Insurance Portability and Accountability Act of 1996 Privacy Rules**. The law (known as HIPAA) has three main parts:

- insurance portability
- fraud enforcement (accountability), and
- administrative simplification (privacy protection).

The third component, administrative simplification, was developed to provide privacy protection for health information, and is known as the Privacy Rule. The primary objectives of this Privacy Rule are to:

1. limit the use and disclosure of health information,
2. restrict most uses and disclosures of health information to the minimum necessary to carry out the intended purpose, and
3. to give participants the right to receive a notice of Privacy Practices describing how providers and affiliates use and disclose their health information and give them the means to control this information.

Additionally, the HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes.

According to HIPAA rules, research is defined as a “systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.” Recruitment techniques must meet HIPAA standards for privacy and confidentiality. Research recruitment is neither a marketing nor a health care operations activity. Under these Rules, a covered entity is permitted to disclose protected health information to the individual who is the owner of the information, regardless of the purpose of the disclosure. Therefore, covered health care providers and participants may continue to discuss the option of enrolling in a clinical trial without patient authorization, and without an IRB or Privacy Board waiver of patient authorization. However, where a covered entity wants to disclose an individual's information to a third party for purposes of recruitment in a research study, the covered entity first must obtain either authorization from that individual or a waiver of authorization as permitted at Sec. 164.512(i) of the Privacy Rule.

See http://privacyruleandresearch.nih.gov for useful information researchers need to know.

Each site will only use recruitment methods that meet HIPAA requirements and are approved by site Institutional Review Boards. Information regarding site-specific IRB policies can be found at the following:

1. UB: Health Sciences Institutional Review Board,
2. NU: Office for the Protection of Research Subjects

Ethical Issues of Advertising

Materials used to recruit participants into research studies are viewed as an extension of the informed consent process. **IRB approval is therefore required prior to use of any materials for participant recruitment.** IRB approval of advertising is needed for the following materials prior to distribution:

- Flyers, posters, newspaper ads, press releases, bulletins
- TV and/or radio spots
- Websites/internet ads
- Electronic mailings
- Recruitment letters
- Scripts for telephone or other personal contact

Note: IRB Approval is needed for *all* advertising materials prior to distribution.

When to submit advertising and recruitment materials for approval:

IRB approval is required prior to use of any advertising or recruitment materials. When the IRB approves the materials, they will generally be stamped with an approval date. The IRB approval will continue to be valid until/unless changes are made to the document/materials. If changes are made, the materials must be resubmitted for IRB approval prior to their use.

Video or Audio Advertisements

If an advertisement will be audio- or video-taped, it is recommended that IRB approval of the message content be obtained prior to taping in order to avoid the necessity of re-taping if the IRB requires changes.

Internet Advertisements

If an ad will be posted on the Internet, the Internet address (URL), screen shots, or printed content of the web pages or Internet ad must be provided to the IRB for approval.

Content Requirements

Recruitment materials and advertisements must be consistent with information contained in the protocol and informed consent document.

All advertisements and recruitment materials must clearly state that the purpose for recruitment is research. In addition, the materials should generally contain the following elements:

a) The name of the investigator or research facility (letterhead is acceptable)

b) Title of project (optional)

c) The condition under study or the purpose of the research

d) A summary of the criteria that will be used to determine eligibility for the study (in lay terms)

e) The location where the research will be conducted

f) Time or other commitments required by the study

g) Indication whether compensation will be offered (but the actual dollar amount *may not* be included). The description of incentives should be straightforward and truthful (e.g. reimbursement for time, travel, or parking, or a no-cost health exam).

h) The person or office to contact for further information including phone number and/or email address.

i) The advertisement may not claim the safety or effectiveness of the therapy under study.

j) The advertisement may not claim that the therapy under study is equivalent or superior to any other therapy.

k) The terms “new treatment” and “new therapy” may not be used because it inappropriately implies that safety and effectiveness have been determined.

Advertisements or recruiting tools must not include the promise of “free medical treatment” when the intent is only to say the participants will not be charged for taking part in the investigation.

Recruitment “Metrics”

The effectiveness of patient recruitment initiatives can and should be systematically and regularly measured. Useful approaches to measuring the success of recruitment efforts include:

- tracking how participants heard about the study
- tracking media coverage
- reporting the number of hits to the trial website
- comparing the number of telephone calls received before rolling-out recruitment initiatives to the number received during and after
- conducting focus groups to pilot test different recruitment strategies

Methodological and Ethical Issues

Despite the general objectivity and good intentions of all members of the research team, there are a number of methodological problems that could affect the quality of the research data if therapists and research assistants do not strictly adhere to the study protocol. This section describes some of those problems and suggests how they might be avoided.

As a general introduction to the topic of research bias, it should be emphasized that the success or failure of the entire project, or the performance of an individual clinical research unit, will not be evaluated by our ability to demonstrate treatment effects. It would be a grave injustice to the people with IBS if our study reports treatment effects that are based on biased data or inadequate measurements. If participants do equally well (or poorly) in all three study treatments, these "negative findings" will still be of enormous value to the treatment field. The only way an individual site, or the study as a whole, can "fail" is if bias or random error produce a treatment effect that *should not* be there or obscure a treatment effect that *should* be there.

Bias and error can enter into the study in a variety of different ways: experimenter bias, interviewer bias, contamination of treatments, random error, and scientific misconduct.

EXPERIMENTER BIAS

Problem: Experimenter bias is the unintended influence that the expectations, hypotheses and theories of scientific investigators have on the collection and interpretation of data. Investigators who have strong preference for a given treatment or strong expectations about a given treatment matching effect may communicate this bias to therapists and research staff, who in turn modify their interviewing procedures or therapeutic practices to confirm these expectations.

Solution: While it is not feasible to "blind" therapists and research assistants to the major study hypotheses, they should do their best to "quarantine" any bias (either negative or positive) toward a given condition. Therapists and research assistants should not discuss or speculate about treatment effects in informal conversation among staff members or with the investigators. In general, there is little evidence in the treatment literature to support clear hypotheses about which types of participants will do well in IBS so there is little basis for project staff to formulate strong hypotheses about what participants will do well or will do poorly. **Project personnel should avoid speculating about treatment effects and should report any evidence of bias to the PI if they become aware of it.**
When making subjective ratings of participants' behavior, cooperation, treatment response, motivation or other characteristics, always keep in mind that objective data are more important than "proving" that a particular theory is correct.

INTERVIEWER BIAS

Problem: Both the research assistants and therapists will perform numerous interviews with participants. In performing these interviews it is important not to allow personal preferences or biases to affect the accuracy of the data collection. For example, a research assistant may learn that a particular patient has been receiving a particularly "good" study treatment or has a therapist who is believed to be superior to the other treatments' therapists. This could influence the way the research assistant asks questions or records answers.

Solution: Interviewers should avoid asking "leading questions" or otherwise influencing the client's response when research data are being collected. Therapists should not discuss their participants with research assistants, and research assistants should avoid exchanging assessment information with therapists.

CONTAMINATION

Problem: The treatment approaches being provided in IBSOS were selected in part because they were separate and distinct from one another. Each therapy of this trial is not designed to be delivered by separate groups of therapists. Instead, all therapists will deliver each of the three treatment arms. This creates a potential for contamination in the event that a unique aspect of one treatment (e.g. skills building) is carried over to a conceptually distinct treatment (e.g. ES). To avoid contamination, it will be very important for therapists to familiarize themselves with the treatment manuals of each of the three therapies. If therapists are not keenly familiar with the procedural components of each treatment, contamination may occur which could adversely affect our ability to detect treatment effects.

Another form of contamination is the sharing of research data collected from participants with therapists. Sharing of data with the therapist, particularly when the patient is still undergoing treatment could adversely affect the delivery of both forms of CBT treatment as well as the ES treatments. Sharing of any preliminary results or trends in the data could also affect the delivery of treatments.

Solution: Research assistants and therapists are expected to minimize contamination across treatment conditions in the following ways:

1. Therapists should familiarize themselves with each treatment manual, be well versed in prescribed and proscribed procedures, and adhere to session by session checklists for each treatment.

2. Therapists and research assistants should avoid discussing details of the treatments.

3. Research assistants should not discuss individual participants with therapists, except when it directly involves the patient's safety or the performance of routine project tasks.

4. Research assistants should not discuss preliminary findings or data trends with therapists.

RANDOM ERROR

Problem: Random error is the "noise" that enters into the data collection process because of unreliable measurement or mistakes made in the processing of data. This can be caused by intoxicated, tired, or unmotivated participants, and by sloppiness on the part of the research assistant or therapist.

Solution: Research assistants should constantly by aware of the need for accurate recording of data, and careful filing of forms.

SCIENTIFIC MISCONDUCT

Problem: Scientific fraud has become a major concern in recent years to both government funding agencies and the scientific community. It can manifest itself in many different ways, from the deliberate fabrication or modification of research data by an investigator, to the subtle substitution of a response for a question that an interviewer forgot to ask.

Solution: Research assistants and therapists have a strict obligation to avoid any manipulation or alteration of research data. Any mistake or omissions should be reported to the Project Coordinator. In most cases, missing data caused by faulty forms, patient omissions, or failure to administer the appropriate form at the right time can be accommodated in the statistical analyses. In some cases the patient can complete the form at a later time or by mail.

To the extent that mistakes, missing data or a client's uncooperativeness may be a symptom of a structural problem in the assessment procedures or methodology, it is incumbent upon Research Assistants and Project Coordinators to bring these to the attention of their own PIs and the Administrative Core.

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.

INFORMED CONSENT

All potential candidates for the study will be given a current copy of the Informed Consent Form to read at the initial assessment appointment. The investigator or sub-investigators will explain all aspects of the study in lay language and answer all of the candidate's questions regarding the study. If the candidate chooses to participate in the study, s/he will be asked to sign the Informed Consent. No study procedure will be performed prior to signing Informed Consent. Participants who refuse to participate or who withdraw from the study will be treated without prejudice.

CLINICAL MONITORING

There will be a minimum of one site visit per year to monitor the progress of study recruitment, the quality and integrity of data collected in the research records, the accuracy of the data submitted and to determine that all process and /or regulatory requirements are being met.

All investigators will allow representatives of NIDDK to periodically monitor, at mutually convenient times during and after the study, all CRFs and corresponding source documents for each participant. These monitoring visits provide the opportunity to evaluate the progress of the study and to inform NIDDK of potential problems at the study sites. The monitors will assure that submitted data are accurate and in agreement with source documentation; verify that study treatments are properly provided; verify that participants' consent for study participation has been properly obtained and documented; and confirm that research participants entered into the study meet inclusion and exclusion criteria.

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.

Adverse Events Reporting

DEFINITIONS AND DESCRIPTIONS

To ensure patient safety and to evaluate the tolerability of treatment, the IBSOS will require careful monitoring of adverse events. This section of the IBSOS MOP has been developed to delineate and standardize procedures for **Adverse Events Monitoring** that will be necessary to address those clinical crises and concerns that inevitably will arise in the course of treatment during the IBSOS. To balance feasibility with our need to gather important information, IBSOS stays carefully centered between the FDA regulatory approach (i.e. weekly patient interviews and recording of all untoward medical occurrences) and the need to minimize participant and investigator burden.

Definitions

An ***adverse event*** is defined as any unfavorable medical change that occurs during or after beginning the study that may or may not be related to or caused by active or non-specific treatments featured in the IBSOS. A *medical event* is defined as a clinically significant change in physical and/or mental health status.

Adverse events include the following**:**

1. Any medical event that causes clinically significant interference with physical or mental health functioning (e.g. an injury at work that causes work absence or otherwise leads to clinically significant activity restriction).

2. Any event that requires medical attention (e.g. a URI with visit to a doctor, regardless of whether or not the event causes clinically significant interference with physical or mental health functioning).

Adverse events ***do not*** include the following:

- Any medical event that induces the participants to take a concomitant medication (e.g. URI that causes the participants to take an over-the-counter decongestant), unless that event also satisfies AE criterion 1 or 2 above. For example, an episode of back pain for which the participant took an NSAID would not be defined as an AE unless it also prompted him or her to miss work or seek medical attention.

- AE reporting does NOT include pre-existing conditions or illnesses that do not significantly worsen or increase in frequency during the study period.

- Behavior change, such as simple withdrawal from usual social activities that is not directly attributable to a change in mental health, e.g. avoidance secondary to pre-existing panic disorder, rather than a change in mental health such as onset of panic disorder.

- AE reporting does not include doctor visits for routine medical care, prescription renewals, immunizations or routine dental or other preventive health care.

- AE reporting does not include patient dissatisfaction with magnitude of clinical improvement unless this is associated with significantly increased interference with physical or mental health function. For example, increased severity of depressive symptoms or increased work absence that either (a) the patient attributes to lack of improvement or (b) follows the patient's reports of distress regarding lack of improvement.

Serious adverse events include any untoward medical occurrence that at any "dose" of the administered therapy**:**

- results in death
- is life-threatening
- requires hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- leads to a congenital anomaly/birth defect
- is a medically important condition that requires intervention to prevent permanent impairment or damage

The demands of the clinical trial must always be weighed in light of broader mental or physical health needs of participants. Any physical or mental problem that bears on the safety and security of the participant takes priority over specific demands of the IBSOS. While the IBSOS staff does not assume responsibility for managing the health care needs of the participant, good clinical practice dictates that staff encourage patient to receive immediate and appropriate health care. If a clinician, in consultation with the site PI, judges that a participant suffers from a medical problem that requires immediate medical attention that would interfere with the demands of the IBSOS, trial participation will be suspended. Consistent with the ITT principle, all patients will be followed up at each of the four post-treatment follow-up sessions. The reason for dropout will be documented. Below is a verbatim script that conveys the important message noted above:

> *"We understand that you have (X, Y, or Z medical/mental health condition) and that you need to obtain appropriate health care right now. We understand that your treatment may interfere with the demands of the IBSOS. Please know that our main focus is your health and safety. We will continue to monitor you and see how you are feeling. We plan to include you in follow assessments. We appreciate the time and effort that you have put into this study and wish the best for you in dealing with (the condition)."*

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) the date of onset of the AE and, if the AE has been resolved, the 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 patient/event outcome or action criteria usually associated with events that pose a threat to the patient’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.

ADVERSE EVENT REPORTING DEADLINES

Completing AE CRF Forms

- All AEs will be recorded in the CRF regardless of the seriousness and expectedness of the AE or the suspected causal relationship between the AE and treatment condition.

- All AEs and SAEs should be reported from the time the participant has signed the informed consent through the completion of the final follow-up assessment.

- AEs that do not meet criteria for an SAE should be recorded in the CRF as soon as possible, but no longer than 10 working days (14 calendar days) after the clinician becomes aware of the event.

- All SAEs should be recorded in the CRF within 24 hours after the clinician becomes aware of the event.

SERIOUS ADVERSE EVENT REPORTING

Overview

After completing the ratings described above, the clinician must determine whether or not the AE meets criteria for a Serious Adverse Event (SAE).

We present again the criteria for identifying SAEs and information that must be presented on the AE CRF that are unique to SAEs:

Criteria for Serious Adverse Event

Any event temporally associated with a participant's involvement in research that meets any of the following criteria:

Death

Report a sudden unexplained death with no known cause. It should be noted that the absence of an explanation or cause of death is the only circumstance under which death may be indicated as an SAE. In all other situations, death is recorded as an outcome of an SAE.

Life-Threatening

Report if the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the therapy would result in the patient's death.

> Examples: Pacemaker failure; gastrointestinal hemorrhage; bone marrow suppression; infusion pump failure which permits uncontrolled free flow resulting in excessive drug dosing

Hospitalization (initial or prolonged)

Report if admission to the hospital or prolongation of a hospital stay results because of the adverse event.

> Examples: Anaphylaxis; pseudomembranous colitis; or bleeding causing or prolonging hospitalization

This SAE criterion does *not* include hospitalizations for normal childbirth, hospitalization for planned surgical procedures, and hospitalization for pre-existing or non life-threatening medical conditions that are unrelated to therapy administration use.

Persistent or Significant Disability or Incapacity

Report if the adverse event resulted in a clinically significant, severe, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical or mental health function (including activities of daily living), or quality of life.

> Examples: Cerebrovascular accident due to drug-induced hypercoagulability; toxicity; peripheral neuropathy

Congenital Anomaly or Birth Defect

Report if there are suspicions that exposure to a treatment prior to conception or during pregnancy resulted in an adverse outcome in the child.

> Examples: Vaginal cancer in female offspring from diethylstilbestrol during pregnancy; malformation in the offspring caused by thalidomide

Medically Important Condition that Requires Intervention to Prevent Permanent Impairment or Damage

Report if you suspect that the participation in treatment resulted in a condition that required medical or surgical intervention to preclude severe and permanent damage, impairment, disability or death to a patient.

> Examples: Acetaminophen overdose-induced hepatotoxicity requiring treatment with acetylcysteine to prevent permanent damage; burns from radiation equipment requiring drug therapy; breakage of a screw requiring replacement of hardware to prevent malunion of a fractured long bone

SAE notes:

A. The term "life-threatening" in the definition of "serious" refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

B. Hospitalization for convenience does not constitute an SAE.

C. Medically important conditions that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Final Outcome

Check the appropriate box to indicate the outcome at time of resolution of SAE or at completion of study if SAE is ongoing:

a. **Resolved**: with no sequelae (lasting problems or complications)

b. **Resolved, with sequelae**: Specify the sequelae that occurs even after the AE was resolved.

c. **Ongoing:** Check if event is unresolved and still ongoing at time of report

d. **Death**: If the participant died, record the date of death under the Final Outcome Date and Time

Other Information

Provide any additional information about the SAE that is deemed important.

Principal Investigator's Signature and Date

Be sure to obtain the signature of the study PI within the box, followed by the date.

Note: If the PI is not on site, the AE CRF can be sent in initially without a signature and then re-sent once the signature is obtained. Finally, please ensure the PI signs and dates each box where SAE details have been recorded.

At the time of the ongoing review by the Data and Safety Monitoring Board, investigators will be asked to summarize the unexpected and related or possibly related AEs that have occurred since initiation of the project, with special attention paid to events that occurred since the most recent report.

Completing AE CRF Forms

- All AEs will be recorded in the CRF regardless of the seriousness and expectedness of the AE or the suspected causal relationship between the AE and treatment condition.

- All AEs and SAEs should be reported from the time the participant has signed the informed consent through the completion of the final follow-up assessment.

- AEs that do not meet criteria for an SAE should be recorded in the CRF as soon as possible, but no longer than 10 working days (14 calendar days) after the clinician becomes aware of the event.

- All SAEs should be recorded in the CRF within 24 hours after the clinician becomes aware of the event.

At the time of the continuing review by the Data and Safety Monitoring Board, investigators will be asked to summarize the unexpected and related or possibly related AEs that have occurred since initiation of the project with special attention paid to events that occurred since the most recent report.

Crisis Intervention

In certain circumstances, an IBSOS volunteer may contact staff members in a condition of crisis. In many cases, you will be able to handle the situation by telephone.

If at any time, in your opinion, the immediate welfare and safety of the client or another person is in jeopardy (e.g. client is acutely suicidal or violent), consult with the senior clinician or your supervisor about the best way to intervene for the protection of those involved. If a client's urgent needs require more treatment than is provided, make a referral.

Below are some standard counseling procedures used in crisis intervention that can serve as guidelines during emergency sessions:

- *Listen*. Rely on reflective listening to gain and understanding of what has happened and how the parties are reacting.

- *Assess.* What is needed? Are there immediate safety issues to address? Is there danger of suicide or other violence? What additional information is needed?

- *Help with understanding.* Help the parties understand what is happening to them. Make the situation comprehensible. As appropriate, normalize events and reactions.

- *Focus on problem*-solving. After listening, assessing, and helping with understanding, focus on practical problem-solving. What needs to be done first? How can the immediate crisis be abated? Develop a specific plan to address short-term and long-term problems.

- *Mobilize social support.* Who can offer practical and emotional support for the client? What health care workers (e.g. PMD), family or community resources are available to provide additional support? Encourage the volunteer to connect with these sources of support. Remember, none of the IBSOS clinical centers are traditional mental health facilitates designed to field or process crisis intervention problems.

Staff members should never feel like they have to singlehandedly "solve" a crisis on their own but should instead inform their supervisor or senior clinician for further evaluation and consultation, particularly when crises involve suicidal thoughts, violence, etc. The senior clinician will determine what action is warranted based on his/her own evaluation and defined procedures of the study. Options include referring to primary care physician, mental health professional or facility for further evaluation. It is important to remember that none of the IBSOS clinical centers are full-service mental health facilities that are designed to resolve crises intervention issues. Your empathy and sensitivity to the volunteer's troublesome life circumstances does not make the IBSOS any more effective in serving as a formal crisis intervention facility.

Imminent Suicide Risk

Crises intervention may involve volunteer reports of suicidal ideation. Suicidal ideation is a common symptom of depression and chronic pain conditions, so it is possible that some participants who volunteer for IBSOS may report suicidal thoughts. Although interviewers should always be duly concerned about suicidal ideation, they should not assume that it always portends suicidal behavior. Indeed, relatively few cases of attempted or completed suicide have been reported in the literature on depressed medically ill participants. However, major depression has been implicated as a contributing factor in between 40 and 60% of all suicides [157, 158].

Because a sizable, albeit minority, proportion of IBSOS participants will be clinically depressed, a small number of these participants screened for participation may be at risk for suicide and therefore their risk of suicide should be formally assessed.

Within the context of eligibility screening, the objective of suicide risk assessment is to identify imminent or emergent suicide risk [159, 160]. The IBSOS has developed a checklist of key suicide assessment risk factors (Table 13: Clinical Tips for Suicide Assessment), interviewing topics, and sample questions that can guide clinical decision making.

Participants who are identified as possibly or definitely being at imminent risk of attempting suicide or otherwise harming themselves must be excluded from participation and referred immediately for appropriate treatment.

Suicidal ideation will be routinely assessed as part of the psychological testing (both the MINI and Beck Depression Inventory include suicidal ideation items). If a patient reports any suicidal ideation, the interviewer will probe to determine frequency, chronicity, and content of the ideation. Following guidelines delineated by Clark and Fawcett [159], the identification of active thoughts of suicide will be followed up by assessing the mental status of the individual:

- Is the participant passively thinking about harming himself or herself or someone else, or is there a clear intention and, if so, why?
- Does the participant have a plan?
- Does the participant have the means to carry out this plan?
- Has the participant ever tried to harm him/herself or someone else?
- Does the participant have outside resources to help him or herself through the crisis?

Table 13: Clinical Tips for Suicide Assessment

1. Identify risk factors associated with suicide that fit your client		
	Specific Risk Factors/Clinical Tips	**Sample Questions**
Vulnerable group due to demographic characteristics	Females more likely to make suicide attempts, while males more likely to succeed at attempt. Caucasians, homosexuals (additional stressors/limited social support), teens and those over 45 y.o .at higher risk. Type of occupation? For example police officer, farmer (access to guns), health care professional (access to drugs)	
Previous attempt	Number and lethality of attempts. A past history of suicide attempts is one of the strongest risk factors for death by suicide	*Have you ever tried to hurt yourself before? If yes, was it planned and deliberate?* *What kind of method did you previously use?* *What happened after? Did someone find you and take you to the hospital?* *After you were revived what was your reaction? How did you feel about the fact that you were still alive?*
Alcohol/drug abuse		
Presence of psychiatric disorder	Delusions, auditory hallucinations commanding death, confusion, even if no formal diagnosis apparent	
Unemployment/Financial pressures		
Unmarried/alone	Divorced, widowed, separated, withdrawal from others; isolation; living alone; child custody issues	
Physical health conditions	Chronic pain, recent childbirth (post natal depression), progressive illness	
Significant personal loss	Loss of ability, possessions, resources, status/self esteem, or social support network; upcoming anniversary of loss	
2a. Evaluate for depression		
	Specific Risk Factors/Clinical Tips	**Sample Questions**
Depression present?		*How would you describe your mood?* *What feelings would you say you experience most often during the course of the day?* *Have you felt particularly guilty, sad or hopeless as if you are trapped and there is no way out)?* *Rate your depression today on a scale of 1 to 10:* *1 means you are so depressed you would just as soon die, and 10 means you feel the best anyone could ever feel … Has there been a time when you would have given yourself a lower rating?*
2b. Evaluate for risk factors associated with suicidal behavior among depressed participants		
	Specific Risk Factors/Clinical Tips	**Sample Questions**
Panic attacks		
Psychic anxiety	Tension, intense, worry, anxious mood, restlessness	
Lack of interest or pleasure in usually pleasurable activities		
Alcohol abuse increase during affective episode		
Diminished concentration		
Global insomnia	Difficulty falling asleep, intermittent awakening, and early morning awakening	

Table 13: Clinical Tips for Suicide Assessment (cont'd)

3. Evaluate for hopelessness, helplessness, or excessive guilt		
	Specific Risk Factors/Clinical Tips	**Sample Questions**
At least one of the above is present	Persistence and intensity of the feelings ("Would you describe your mood as blue or black?")	*Do you believe a time will come when you feel better?* *How do you suppose you'll be feeling a week (month, year) from now?* *Sometimes people who are feeling down also feel guilty…is there anything you're feeling guilty about now?* *Is there anything you think you deserve to be punished for?*
4. Evaluate characteristics of suicide ideation		
	Specific Risk Factors/Clinical Tips	**Sample Questions**
Frequency		*You certainly seem to feel extremely depressed. Feeling this miserable, have you thought of ways that you might hurt yourself?* *Do you think of hurting yourself all the time or just in certain situations?*
Intensity		
Duration		
5. Evaluate suicide plans		
	Specific Risk Factors/Clinical Tips	**Sample Questions**
		You have talked about how you sometimes think it would be better for everyone if you were dead. Have you planned how you would kill yourself if you decide to follow through on your thoughts? *Many people who think about suicide have had passing thoughts about how they might do it. What thoughts have you had about how you would commit suicide if you decided to do so?*
Specificity of the plan; extensiveness of plan	How far as the suicide planning process proceeded? Has the person set a time and place? Is the chosen plan irreversible (for example, shooting, jumping); How long has person had the plans? How often does the person about the plans? How realistic are the plans?	*Do you think you might try to hurt yourself today?*
Lethality of the means/method defined	Weapons more lethal than poisoning, slashing wrists	*Have you thought of ways that you might hurt yourself?*
Availability or access of proposed method	Does the person have access to lethal means.? Is thee a firearm available? Are there poisons in the house or shed? Are there lethal medications such as insulin, cardiovascular medications or TCA available to the person?	*Do you have pills/guns(or other method) in the house (near your house)?*
Proximity of social or helping resources	Withdrawing from family, roommates, friends, neighbors, church, general practitioner	*How likely is your attempt to be interrupted?*

Table 13: Clinical Tips for Suicide Assessment (cont'd)

6. Evaluate patient level of self-control		
	Specific Risk Factors/Clinical Tips	**Sample Questions**
		Sometimes, have you been afraid that in spite of yourself, in one of your really down periods, you might go ahead and commit suicide? *When you had suicidal thoughts before, what helped you maintain control? What would deter your suicide now?*
Self-report of self-control		
History of impulsive behavior	Previous verbal outbursts, risky/unthinking activities (reckless driving, hanging out on rooftops/cliffs, promiscuity), physical altercation, and destructive substance use all indicate impulsive behavior and lack of self-control	
History of over-controlled behavior		
7. Assess level of suicidal intent		
	Specific Risk Factors/Clinical Tips	**Sample Questions**
- Absent	No suicide ideation	
- Low	Suicidal ideation but no specific or concrete plans; few risk factors are present	
- Moderate	Suicide ideation and a general plan exists; self-control is intact and there are several "reasons to live", such as religious beliefs, children, etc.	
- High	Ideation is frequent and intense; method is specific, lethal and available; many risk factors present, including lack of nearby helping resources; self-control is questionable Check "High" if there is history of suicide attempt	

Adapted from Sommers-Flanagan, J. and R. Sommers-Flanagan (1995). Intake interviewing with suicidal participants: A systematic approach. Professional Psychology: Research and Practice 26(1): 41-47.

Participants who report these features will be considered to be at imminent risk for suicide and will be excluded from IBSOS. In such cases, participants will be provided contact information for the nearest available crises center to ensure that they receive appropriate treatment and follow-up at a facility that is equipped to respond efficiently to crises. Therapists should keep supervisors informed of any changes related to suicidal status. **Any time therapist feels uncomfortable about a patient's level of risk, the patient should be referred to an appropriate service** (see table 14).

Table 14: Suicide Risk

Issue	High Risk	Medium Risk	Low Risk
'At risk' Mental State - depressed - psychotic - hopelessness, despair - guilt, shame, anger, agitation - impulsivity	Eg. Severe depression; Command hallucinations or delusions about dying; Preoccupied with hopelessness, despair, feelings of worthlessness; Severe anger, hostility.	Eg. Moderate depression; Some sadness; Some symptoms of psychosis, Some feelings of hopelessness; Moderate anger, hostility.	Eg. Minimal or mild depression, sadness; No psychotic symptoms; Feels hopeful about the future; None/mild anger, hostility.
Suicide attempt or suicidal thoughts - intentionality - lethality - access to means - previous suicide attempt/s	Eg. Continual / specific thoughts; Evidence of clear intention; An attempt with high lethality (ever).	Eg. Frequent thoughts; Multiple attempts of low lethality; Repeated threats.	Eg. Minimal or vague thoughts; No recent attempt or 1 recent attempt of low lethality and low intentionality.
Substance disorder - current misuse of alcohol and other drugs	Current substance intoxication, abuse, or dependence.	Risk of substance intoxication, abuse, or dependence.	Minimal or infrequent use of substances.
Corroborative History - family, carers - medical records - other service - providers/sources	Eg. Unable to access information, unable to verify information, or there is a conflicting account of events to that of those of the person at risk.	Eg. Access to some information; Some doubts to plausibility of person's account of events.	Eg. Able to access information / verify information and account of events of person at risk (logic, plausibility).
Strengths and Supports (coping & connectedness) - expressed communication - availability of supports - willingness / capacity of support person/s - safety of person & others	Eg. Patient is refusing help; Lack of supportive relationships / hostile relationships; Not available or unwilling / unable to help.	Eg. Patient is ambivalent; Moderate connectedness; few relationships; Available but unwilling / unable to help consistently.	Eg. Patient is accepting help; Therapeutic alliance forming; Highly connected / good relationships and supports; Willing and able to help consistently.
Reflective practice - level and quality of engagement - changeability of risk level - assessment confidence in risk level.	Low assessment confidence or high changeability or no rapport, poor engagement.		High assessment confidence / low changeability; Good rapport; engagement.
No (foreseeable) risk: Following comprehensive suicide risk assessment, there is no evidence of current risk to the person. No thoughts of suicide or history of attempts, has a good social support network.			

Is this person's risk level changeable?

High Changeable **Yes □ No □**

Guidance for Situations Which May Involve Suicidal Ideation

In evaluating a patient for IBSOS, the objective of suicide risk assessment is to classify him or her or her as (1) possibly or definitely at imminent risk of attempting suicide or otherwise harming him/herself (a psychiatric emergency); (2) not at imminent risk, but possibly or definitely at elevated risk of attempting suicide within the next few weeks or months (not an emergency, but a serious situation nevertheless); or (3) not at elevated risk for attempting suicide.

The information upon which to base this classification is to be obtained from the BDI - II, the Sheehan Suicidality Tracking Scale included in the Mini International Neuropsychiatric Interview (MINI) Structured Diagnostic Interview for DSM-IV, and when applicable, from collateral sources (the patient's medical chart, partner, spouse, caregivers, etc.).

Beck Depression Inventory II: The BDI includes 21 items that assess the severity of depression and is oriented toward the symptoms of depression as described in Diagnostic and Statistical Manual for Mental Disorders – Fourth Edition/Text Revision (DSM-IV). The BDI includes a single item (item 9) that directly assesses suicidal ideation. Respondents are asked to decide which of the following best describes the way they have been feeling: (0) I don't have any thoughts of killing myself," (1) "I have thoughts of killing myself, but I would not carry them out," (2) "I would like to kill myself," and, (3) "I would kill myself if I had the chance."

A **score of 1** on the BDI Item #9 indicates that the patient has recently had some thoughts about suicide but that he or she "would not carry them out." This suggests (but does not guarantee) that the patient is not at imminent risk, and that his or her longer-term risk is only mildly elevated, if at all. If this is an isolated finding (e.g., no other suicidal feature are detected), the designated senior project staff member(s) should be informed, but it is not necessary to notify the patient's physicians or to take any other actions unless so directed by the senior project staff.

A **score of 2** on the BDI Item #9 suggests the presence of suicidal ideation that may be more significant.

A **score of 3** is a fairly clear warning sign of suicidal intent. Even if this is an isolated finding (i.e., no other suicidal feature are detected), the designated senior project staff member(s) should be informed and the patient's physician(s) should be notified in a timely manner.

Because the BDI is only a questionnaire rather than a more in-depth psychodiagnostic interview, it does not provide sufficient information to judge whether there is any real risk for suicide. Nevertheless, whenever the BDI is administered at baseline, during the acute treatment phase, or at follow-up, it yields important information which, combined with clinical judgment, can be used to ascertain whether the patient reports any suicidal ideation.

Sheehan Suicidality Tracking Scale: The Sheehan Suicidality Tracking Scale (Sheehan-STS) is a prospective rating scale that tracks both treatment-emergent suicidal ideation and behavior. The Sheehan-STS is an eight-item scale that can be administered either by a clinician or through participant self report (see Figure 1). Each item in the Sheehan-STS is scored on a 5-point Likert scale (0=not at all, 1=a little, 2=moderate, 3=very, and 4=extremely). Data from the Sheehan-STS can be analyzed as individual item score, suicidal ideation subscale score (sum of scores from items 2,3, and 4, plus score form item 5 ≤1), suicidal behavior subscale scale (sum of scores from items 6,7a, and 8, plus score from item 5 if>1), and total score. The Sheehan-STS was adapted from the Suicidality Module of the Mini International Neuropsychiatric Interview (MINI) Structured Diagnostic Interview for DSM-IV. The MINI is one of the most cited diagnostic tools with extensive reliability and validity testing.

SUICIDALITY TRACKING SCALE (STS)

RATING INSTRUCTIONS:

PLEASE ENSURE THAT ALL DIMENSIONS OF THE QUESTION ARE TAKEN INTO ACCOUNT IN CHOOSING THE APPROPRIATE RESPONSE (FOR EXAMPLE, TIME FRAME, FREQUENCY AND SEVERITY AND EACH PART OF EACH QUESTION)

1. **Over the past week did you suffer any accident?** ☐ NO ☐ YES
   (this includes taking too much of your medication accidentally).

   IF NO, SKIP TO QUESTION 2.
   IF YES, ASK:

	Not at all	A little	Moderately	Very	Extremely
1a. to what extent did you plan or intend to hurt yourself in that accident (either passively or actively)?	0	1	2	3	4

   IF THE ANSWER TO QUESTION 1a IS 0, SKIP TO QUESTION 2.
   IF IT IS SCORED ≥1, ASK:

1b. Did you intend to die as a result of this accident? ☐ NO ☐ YES

Over the past week, how seriously did you:

	Not at all	A little	Moderately	Very	Extremely
2. think that you would be better off dead or wish you were dead?	0	1	2	3	4
3. want to harm yourself or to hurt or to injure yourself?	0	1	2	3	4
4. think about suicide?	0	1	2	3	4
5. plan for a suicide?	0	1	2	3	4
6. take active steps to prepare for a suicide attempt in which you expected or intended to die?	0	1	2	3	4

7. Over the past week, did you injure yourself on purpose? ☐ NO ☐ YES

IF NO, SKIP TO QUESTION 8.
IF YES, ASK:

Over the past week, how seriously did you:

	Not at all	A little	Moderately	Very	Extremely
7a. deliberately injure yourself without intending to kill yourself?	0	1	2	3	4
8. attempt suicide?	0	1	2	3	4

TOTAL ☐

FIGURE 1. Suicidality Tracking Scale (STS)

The individual administering these measures should be a qualified, clinically trained clinician, or be closely advised by someone with the proper qualifications and training and available while participants are being administered the measure. If the person administering the measures does not have appropriate clinical training, he or she should immediately contact a designated, qualified clinician to administer a thorough risk assessment for any participants endorsing suicidal ideation. The IRB should be notified within 48 hours in cases where imminent risk of harm is determined, or if the rate of depression and/or suicidality is higher than would reasonably be expected in the studied population. **Three general principles must apply to suicide assessing: (1) the study participant's safety is the paramount consideration; (2) continuing IBSOS treatment is only appropriate if it contributes in a meaningful way to the participants clinical care and does not conflict with other necessary interventions; and (3), other interventions within or outside the IBSOS protocol must be implemented if clinically appropriate.**

Determining Imminent Suicide Risk

Following guidelines delineated by Clark and Fawcett [1], the identification of active thoughts of suicide is to be followed up to determine whether (1) the patient has considered and/or has access to any specific method(s) of suicide; (2) the patient wants to or intends to or is planning to attempt suicide in the near future, and if so why; (3) the patient has rehearsed or made preparations to carry out the plan; (4) the patient has a past history of suicide attempt(s); and (5) there are any additional circumstances that may add to the risk of attempting or completing suicide (e.g., current alcohol abuse, social isolation, hopelessness, or crisis such as job loss). If one or more of these features are detected, the interviewer must attempt to determine whether the patient is at imminent risk (i.e., in immediate danger of attempting suicide or otherwise harming him/herself).

If the interviewer believes that the risk may be or definitely is imminent, the situation is to be treated as a psychiatric emergency. In such situations, the research staff should act quickly to protect the safety of the subject. This may mean taking steps to ensure that the study participant should not be left alone until risk is further evaluated. When appropriate, a supportive and responsible family member(s) should be informed of the urgency of limiting access to any means of suicide (firearm, medications). An additional action is to maintain or increase contact, treatment, and support intensity when suicide risk is imminent and high. It is often recommended that clinicians develop a "no-suicide contract" to minimize risk for suicidality. Although there is no empirical evidence that such contracts reduce risk for suicidal behavior (or liability risk for therapists), the components of a contract are consistent with recommended treatments for suicidal patients and include: a) providing the opportunity for both research participant and therapist to commit to actions that decrease suicidality, and not being ambivalent about this goal; b) defining the thoughts and behaviors that precede suicidal behaviors, as well as defining the suicidal thoughts and behaviors themselves, which may help the research participant and his or her support network to better monitor downward trends; c) identifying possible steps to take to reduce these thoughts and behaviors; d) informing the

research participant and his/her support network how to access crisis care, including the treating professional.

For any results less than imminent risk, research clinicians should be available to assist in developing a plan for safety with the subject. The plan for safety will depend on the level of risk and available resources. It may include contacting the person's personal physician, making sure the subject has appropriate referrals with a plan to contact subjects as a means to evaluate the subject following through with the referrals, encouraging the person to talk to trusted family members or other community support resources, or giving the subject suicide hotline information. For example, the clinician decides that although the subject has endorsed suicide ideation, there is no intent or plan, nor history of suicide attempts, but the subject does have bouts of depression. The clinician or clinician representative may provide the subject with referrals for treatment and the Suicide Prevention Hotline number, or discuss contacting the subject's primary physician or trusted family member to garner support or assistance. Documentation of the assessment and procedures ultimately followed would be important.

Patients need not be excluded from participation in IBSOS simply because of a low-probability, long-term risk of suicide or because of transient or passive suicidal ideation. Furthermore, the interviewer's duty to protect the patient's confidentiality outweighs any potential need to notify the patient's physician or other caregivers when the participant engages in passive suicidal ideation. As an example, consider the participant whose only evidence of any suicidality comes from her statement that, "Once in a while, I wonder what I would do it things got a lot worse that they are now. I might think about killing myself but I'd never do that. It's just plain wrong, and I couldn't do that to my family anyway." In such a case where suicide ideation does not extend beyond ideas or verbalizations of a plan for suicide, the interviewer would have no need, no responsibility, and no right to disclose this information to the patient's physician or other caregivers.

Verification of Qualifications

Verify the person responsible for making the assessment regarding suicide risk is qualified (education/experience) to conduct a proper assessment.

Assessment of Suicide Risk

Assessment of extent of suicidal ideas. The first step is to obtain information on the frequency, intensity, and duration of suicidal thoughts. Occasional or passing thoughts about one's death are less serious than frequent thoughts of death over an extended period of time.

- When did you begin to have suicidal thoughts?
- Did any event (stressor) precipitate the suicidal thoughts?
- How often do you think about suicide? Do you feel as if you're a burden? Or that life isn't worth living?

- What makes you feel better (e.g., contact with family, use of substances)?
- What makes you feel worse (e.g., being alone)?
- What stops you from killing yourself (e.g., family, religious)?
- Have you imagined your funeral and how people will react to your death?

Assessment of intent. Having ideas of death or killing oneself is more common than acting on these ideas. The second step in assessment is to determine whether or not the individual has an intention to harm him/herself.

- Do you have a plan to end your life?
- How likely are you to pull this plan into action?
- Have you changed you will or life insurance policy or given away your possessions?

Specificity of plans. The next step is to determine whether or not the individual has a specific plan for harming himself/herself.

- What would you do to kill yourself?
- When and where would you do this?
- Probe for specific about methods of suicide (gun, pills, cutting, hanging, etc).
- Have you "practiced" your suicide? (e.g., put the gun to your head or held the medications in your hand)?

Access to lethal means. If the person has a plan, the next step is to determine whether he/she has access to resources necessary to have a lethal outcome including a gun, pills, poison, carbon monoxide, etc.

- Do you have access to a gun, pills, etc.?
- Where do you keep this?
- Assessment of other risk factors. The single most important risk factor for suicide is a prior unsuccessful attempt.
    - Have you ever tried to harm yourself before?
    - When was this and what happened?

Routine Monitoring for Suicidality

At every office and phone visit during the acute treatment phase of the IBSOS, it is expected that the responsible clinician will formally assess suicide potential in high risk participants using the BDI and STS. If item #9 (sociality) is endorsed at a level of 3 (indicating ideation and/or intent) on the BDI, the PI or his/her designee will be notified immediately. Any participant who endorses a response of "I would like to kill myself" or "I would kill myself if I had the chance" on the BDI item #9 is contacted the same day by phone or email, regardless of their total score on the BDI. Additional information can be gleaned from the Suicide Tracking Scale. IBSOS clinical staff should construe item 5 on STS ("plan for suicide") as not going beyond ideas or

verbalizations of a plan for suicide. If actual behaviors occur (i.e., buying a gun or taking other steps), the event should be regarded as “preparatory behavior” and be treated as a psychiatric emergency.

Further determinations should be made by individuals who are clinically qualified to assess these conditions. Should there be signs of imminent risk in subsequent emails or phone contact, a verbal contract to not hurt oneself would be made and directions to the mental health resources must be given. If the individual does not agree to a verbal contract, the police would be informed to provide more direct contact with the high-risk individual. The IRB should be informed in cases where imminent risk of harm is discovered.

Routine Monitoring for Clinical Depression and Anxiety

Psychiatric comorbidity studies indicate that 40-60% of treatment seeking IBS patients have a comorbid psychiatric disorder with anxiety disorders being the most common. As treatment progresses and at follow-up visits, comorbid levels of anxiety, depression, and possible adverse effects of the experimental treatment will be assessed. Patients with clinical levels of depression and or anxiety are neither deemed ineligible to participate in the IBSOS nor necessarily resistant to treatments featured in IBSOS and. However, therapists should be aware of pre-treatment baseline levels of distress based on psychological testing (e.g., Beck Depression Inventory, Brief Symptom Inventory – 18 (BSI-18), State Trait Anxiety Inventory (STAI)), the notion that distress may signal more serious coping deficits (e.g. suicidality), and the value of ongoing monitoring of mental health status among patients with high levels of distress through the acute treatment phase. Therapists should consider administering appropriate psychological testing instrument at each clinic visit, if necessary, to characterize levels of distress in patients even if their administration falls outside of IBSOS testing schedule. For patients whose distress is an increasingly important source of impairment in life domains and interferes with their ability to undergo IBSOS treatments, the study investigator may, at his/her discretion, refer the participant for additional follow-up, additional therapy, and/or assessment for psychopharmacological intervention. Depending on the situation, the changes may be temporary or continue throughout the study. In rare cases the experimental treatment may need to be discontinued, however participant would continue to be followed per Intent to Treat. Any decision to triage volunteer to another treatment facility should be communicated expeditiously to the referring MD and PMD within the constraints of HIPPA regulations. All sites have assembled a list of local mental health facilities to which patients can be referred for mood stabilization or other mental health problems that are beyond the scope of the IBSOS treatments.

Staffing and Training

Each IBSOS study site should have a designated individual with appropriate clinical training who can be contracted by staff in order to review an evaluation or plan and support research staff. It is advisable to designate a backup clinician who can provide assistance in case the primary clinical cannot be contacted. Staff should be trained regarding assessment and intervention protocols. Training may include role playing how to respond to a patient who screens positive for suicidal ideation.

Potential Risk

Participants may experience mild, temporary discomfort from answering certain personal questions that are asked in the structured interview or psychological testing. However, more than 500 participants have completed this evaluation at the University at Buffalo and hundreds of others have completed similar evaluations at other settings without complaint; to the contrary, participants appear to appreciate the detailed information obtained during the evaluation of their GI disorder. The medical evaluation offers no more risk than any other routine, non-invasive visit with a physician.

A notable risk in this project is that the participant will not experience substantial relief of GI symptoms. In general, less than 3% of participants receiving cognitive behavior therapy for IBS report a statistical worsening of GI symptoms at post-treatment. Most of these individuals, however, do not perceive themselves as noticeably worse. A small minority of participants may experience a brief sense of drowsiness with muscle relaxation training. Paperwork may be burdensome for some participants.

Risk vs. Benefit Analysis

The risks to participants are minimal. Data gathering can be burdensome, albeit tolerable. Benefits to treatment include free assessment, which would cost about $500 if obtained privately, and free treatment that would cost $1,000 if obtained privately. Moreover, there is a reasonable likelihood that participants' GI symptoms and/or psychological well-being will improve.

Participants who are randomized to treatment after completing a four-week baseline phase will be paid up to $200 for completed data collected at post-acute and three-, five-, nine- and 12-month follow-up assessments. Financial compensation ***pending local IRB approval*** will be provided either in the form of a check or gift card (e.g. Target, Wegmans, Tops, Dominick's, Kroger, Piggly Wiggly, Wal-Mart, etc.).

An additional benefit includes the satisfaction participants may experience from increasing understanding about the efficacy of IBS treatments that may lead to knowledge that may help others. We believe the potential direct therapeutic benefits to participants and the new scientific information gained in the proposed study far outweighs the risks involved. Participants selected for participations will be monitored closely for adverse events.

Data Analysis

GENERAL ISSUES

Missing Data and Intent-to-Treat Analysis

Missing Data Points

In some analyses, there may be missing data due to a respondent electing not to answer a question. In general, this occurs infrequently and should not be problematic, but occasions may arise where missing data must be dealt with and the choice of method for doing so can be consequential. In instances of minimal missing data, values will be imputed using the Expectation-Maximization method with importance re-sampling as described in King, Honaker et al [161]. If missing data are more substantial (e.g. greater than 12% of the cases on a single variable or more than 15% of the cases have at least one missing value), a multiple imputation approach will be used with five imputation data sets. The imputations will be performed using the computer program Amelia[162]. Parameter estimates and standard errors across the imputed data sets will be estimated using the formulas in King et al. [161]. Missing data bias will be assessed by computing a dummy variable reflecting the presence or absence of missing data for each variable in the model and then this dummy variable will be correlated with all other variables in the model as well as an array of demographic variables.

Attrition

An important potential source of missing data bias is attrition. There will be some attrition due to our inability to track some respondents over time or because of refusal to participate in the study at later assessments. We do not expect sizeable nor systematic attrition bias in this regard. We will create dummy variables for attrition at a given wave (1 = dropped out, 0 = did not drop out) and use data from previous assessments to determine if there is bias based on earlier assessments (i.e. we will test for predictors of attrition). We plan on following up all respondents initially enrolled in the study independent of whether they complete treatment so that we can perform both dosage-response (DR) as well as intent-to-treat (ITT) analyses. **Dosage response** analyses focus evaluation only on those individuals who complete treatment. The logic is that to evaluate the effectiveness of a treatment protocol, analyses should be conducted on those who received a “full dose” of the treatment. By contrast, **intent-to-treat** analyses place greater emphasis on external validity and focuses on the real-world impact of the treatment, taking into account that individuals may chose to drop out of treatment because of the nature of the treatment itself. In ITT analyses, all respondents who are initially randomly assigned to the various experimental conditions are analyzed at the post tests (see the methods in Little & Yau [163] and Houck et al [164]), whereas in DR analyses, only those who complete the treatment protocol are analyzed. Both forms of analyses are informative and we will approach the data from each perspective.

Assumption Violations

Many traditional tests 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. For many cases where this occurs, some form of bootstrapping is useful. Wilcox [165-167]describes robust methods that can be used effectively in limited information estimation frameworks. For structural equation models, the computer program M Plus offers algorithms for robust statistical analyses as well as bootstrapping. In general, we will be sensitive to possible assumption violations and explore data using both robust and traditional methods of analysis.

Outliers

We will be sensitive to outliers in all analyses. We will apply standard methods for outlier detection (e.g. analysis of leverage statistics and dfBetas) and use graphical approaches as well. If outliers are problematic, we will analyze data using outlier resistant methods [165-167] .

Multiple Items, Multiple Variables, and Multiple Contrasts

For all of our multi-item measures, we will evaluate the coefficient alphas and factor structures of the measures to ensure that they are behaving in a way that one would expect based on their psychometric histories. We will routinely examine the intercorrelations of variables and, coupled with substantive criteria and the results of exploratory or confirmatory factor analyses, make decisions about combining indices or introducing latent constructs into the analysis. At times, we will conduct multiple significance tests and there will be concern for inflated experiment-wise error rates based on how the family of contrasts is defined. We will compare the robustness of our conclusions both with and without statistical corrections for multiple tests (using the strategy discussed in Jaccard & Guilamo-Ramos[168]). In general, we will use a Holm adjusted modified Bonferonni method [169] for controlling experiment-wise error rates, which is more powerful than traditional Bonferroni or Scheffe methods.

Specification Error

We will be sensitive to issues of specification error, being careful to explore a range of model diagnostics to protect against gross model misspecification. Of particular interest will be to ensure that the presumed relationships are reasonably linear rather than non-linear in form. If we detect the presence of non-linear functions between variables, then this will be modeled using either polynomial regression, spline regression, or some other non-linear method that captures the appropriate functional form of the relationship.

Measurement Error

We recognize that measurement error can bias some of our parameter estimates. Where possible, we will adopt analytic strategies that explicitly model measurement error, such as SEM with the use of multiple indicators. For single indicator structural equation models, measurement error can be modeled by fixing error variances of measures at *a priori* specified values that map onto the reliability of these measures

suggested by previous research or other psychometric based analyses (see see [170] for a description of this approach). Or, if it is a multi-item measure, we can create multiple indicators using split-half methods, as described in Jaccard & Wan [171]. If we are unable to take measurement error into account, we will take care to recognize the biasing effects of measurement error when interpreting the results of statistical analyses.

Clustering

The data will be collected at multiple sites, so there is a potential for clustering effects due to site. Clustering can affect standard errors and significance tests. 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 we will take the effects into account when estimating standard errors using the algorithms in the M Plus computer program.

Sample Size and Statistical Power

We discuss statistical power below in the context of specific analytic methods. Unless otherwise stated, the power analyses are based on an alpha level of 0.05 and a two-tailed test. Because we will invoke structural equation modeling (SEM) for some of our analyses, sample size considerations also are relevant for the use of asymptotic theory and the stability of the covariance matrices. Simulation studies suggest that sample sizes of 100 to 125 often yield adequate results for asymptotic theory for a wide range of latent variable models, given that reasonably reliable measures are used with well-defined factor structures[172] [171]. The sample size in our study exceeds this standard.

Covariates

Although random assignment should eliminate confounds, we will include covariates to increase statistical power, as appropriate. One set of covariates will focus on dummy variable representing concomitant therapies. These will be defined using the WHO Drug Reference List which employs the Anatomic Therapeutic Chemical (ATC) classification system (http://www.whocc.no/atcddd/). All concomitant therapies taken by a patient through the course of the trial will be listed along with the coded ATC class. We will prepare frequency tables of patient counts of ATC class by treatment group for concomitant therapies. We will produce a similar table for prior medications by treatment group. Covariates to control for these variables will be introduced, as appropriate.

SPECIFIC APPROACHES FOR SPECIFIC AIMS

Aim 1 and Aim 5

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

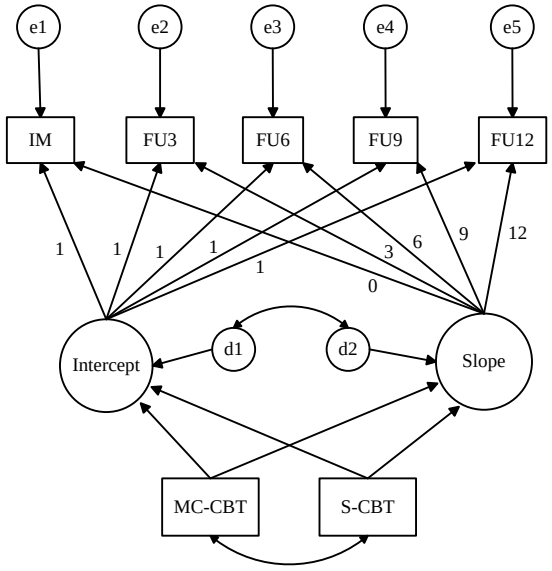
groups (MC-CBT, S-CBT and the active comparison control (attention control)). The traditional analysis for a given outcome variable is a two-way analysis of covariance using the three groups as a between-subjects factor, time as a within-subjects factor (IM, FU3, FU6, FU9 and FU12) and the baseline score 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 12. 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 [2, 173]. 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 [174], 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 12: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 [1]. 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[49]. 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 [175]. 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 [176, 177].

Aims 2 and 3

Aims 2 and 3 emphasize identifying baseline patient 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 [178] and [179] and which was implemented in [180] and [181] for costing of methadone treatment services and in [181] 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 [178, 179]; 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 patient. Few studies consider the patient's perspective in estimating costs and cost-effectiveness even though these costs may have a substantial impact on a patient'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 [182]. 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 patient 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 patient during the intervention, and taking the mean across participants in a given intervention yields the mean per-patient 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[178, 183, 184] and that has been implemented in [181, 185, 186] 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 [178, 187]. 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 [188, 189]. 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 [181, 190, 191].)

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.

Publications / Presentations and Ancillary Study Guidelines for IBSOS

Introduction

This document provides the policy for publications and presentations of the IBSOS project. The Steering Committee of the IBSOS project will implement the policy to promote publications and ensure the scientific quality and timeliness of IBSOS publications.

GENERAL PRINCIPLES FOR PUBLICATIONS / PRESENTATIONS

In publishing and/or presenting talks from the data acquired in the IBSOS project, we propose that the following principles guide our efforts:

- Our primary objectives in preparing manuscripts and talks should be to address the study's specific aims as identified in the U01 DK077738 proposal and in scheduled meetings of the Executive Committee in Buffalo as well as in teleconference/virtual meetings of this committee during the course of the project. This includes protecting the scientific integrity of the study supported by the Cooperative Agreement U01 DK077738 noted above.

- Our secondary objectives should be to offer additional contributions to the field from this rich data set.

- We wish to ensure that IBSOS investigators are able to publish in a timely manner the outcomes of study that address the approved aims and goals outlined in Cooperative Agreement (U01 DK077738).This includes promoting fairness and equity, balance across sites, and sharing of both opportunities and responsibilities in these efforts. We also will facilitate, within a reasonable timeframe, the publication of secondary analyses of our database by non-IBSOS investigators in accord with NIH guidelines.

- Each of our publications and presentations should appropriately acknowledge contributions made by members of our group.

- Members of the Executive Committee and other investigators, trainees and staff associated with the IBSOS should support one another in the process of developing ideas for and completing dissemination of projects.

- Our procedures for manuscript, abstract, poster, and oral presentations (generating ideas, conducting data analyses, writing, submitting for peer review) should be guided by the aim of effectively informing both the biomedical and behavioral health disciplines of the findings of our work in a timely manner and

with sufficient internal review to ensure merit.

- We consider it essential to effectively inform full- and part-time clinicians (i.e., practitioners) as well as full- and part-time investigators in the biomedical and behavioral health disciplines.

DEFINITIONS OF PUBLICATIONS / PRESENTATIONS

- Empirical articles, methodological or literature review papers, monographs, book chapters and other materials related to or derived from the IBSOS database that are submitted for peer review/publication in scientific or clinical journals and other scholarly literature.

- Oral and poster presentations at scientific meetings related to or derived from the IBSOS database. Specific material includes PowerPoint slides for oral presentations and PowerPoint posters.

- Publications of IBSOS-related materials (e.g. books, monographs, training manuals, therapist manuals, summaries of study protocol and trial progress reports).

- Publications also include other products of the IBSOS project, including written or graphic (e.g., PowerPoint, JPEG) descriptions of IBSOS methodology, descriptive material and other know-how or information regardless of format (e.g. research instruments, computer software, video and audio taped materials) that are produced from IBSOS activities. These also include written or graphic material used to inform colleagues or professional audiences of the IBSOS structure, purpose, or clinical trial design.

- Material not considered publications do not require review and approval by the Executive Committee. However, these materials should provide proper reference to the initial paper or presentation. These materials include:

  - Review papers or presentations by project investigators that do not present data derived from or related to IBSOS.

  - Papers or presentations that only include IBSOS data that previously have been reviewed and approved by the Executive Committee or have been previously published or presented by IBSOS investigators.

  - Materials (e.g. posters, flyers or handouts, recruitment cards) or presentations used solely to promote enrollment or inform colleagues or professional audiences of the IBSOS structure, purpose, or clinical trial design. For example, recruitment flyers that are provided to physicians and placed in the outpatient clinics at our two study sites for the purpose of recruiting participants for the trial are not considered publications.

- **Materials used for patient recruitment must be approved by the Institutional Review Boards (IRBs) at each study site.** Although the Executive Committee will attempt to develop standard recruitment materials for all sites, we recognize that each IRB may require changes in wording or other revisions that may prevent complete standardization across sites. These recruitment materials, which do not reveal previously unpublished data or current study findings, are not considered IBSOS publications or presentations. Nevertheless, the Executive Committee will review all revisions in standardized recruitment materials requested by the University IRB's and assist study personnel in responding to the IRB requests and revising the recruitment materials.

- Press releases are typically produced by University Media Relations divisions for two purposes. These purposes are: (1) enhancement of study participants' recruitment in the local community and (2) providing information to the local community regarding research-based advances in clinical care available at the university medical center. NIDDK will provide the Executive Committee with its current policy and procedures for press releases. The Executive Committee will work with study personnel at each site to produce press releases for both recruitment and community education. We will strive to ensure standardization in these press releases across the two study sites. However, since there may be minor differences in the press releases produced by University Media Relations across sites related to local recruitment demands or local community needs, press releases developed at each site must be reviewed and approved by the Executive Committee before they are provided to the local community or submitted to IRB review boards.

PUBLICATION PROCEDURES

A. During the first six months of Year 1, the Steering Committee of the IBSOS project will develop a publication plan that will include proposed paper topics, abstracts, and symposium proposals, as well as lead authors and symposium speakers for the remainder of Year 1. The Executive Committee will take into account potential overlap among proposed publications and priority for preparation in developing the publication plan.

B. During Years 2-7, the Executive Committee will develop a publication plan every six months if needed. Any project investigator (including post-doctoral trainees and graduate students who contribute effort to the IBSOS project) may propose publications, abstracts, or symposium presentations. Each proposal should include the members of the writing team (or symposium panel), hypotheses, data analysis plan, publication outlet, timeline for completion, and order of authorship (manuscripts and abstracts).

   - Authors should participate in the writing of publications in accord with guidelines of the International Committee of Medical Journal Editors [192]. Those who participated in conception and design, analysis, and interpretation of data,

drafting the manuscript, critical revision of the manuscript relating to important intellectual content, and final approval of the manuscript should be included as authors. Expertise (e.g. statistical, outcome assessment) that relates directly to the conduct of the study is additional criterion for authorship.

- Provision of study material or participants; data collection and administrative, technical, or logistic support; and obtaining funding do not necessarily merit authorship but should be considered on a case-by-case basis, especially when other contributions are included. In general, presentations and publications regarding the primary and secondary aims of the NIH application will include one author from each clinical site and the data Administrative Core.

C. The Executive Committee will review the proposal using the criteria described below (section E) and provide written feedback to the investigator. We expect that as the project matures, the Executive Committee also will assess the extent to which proposed publications overlap with previous publications. That is, it will be necessary to evaluate the extent to which proposed publications present new findings related to the aims of the IBSOS project or findings that further explicate findings previously reported by IBSOS investigators or help clarify interpretive or methodological issues discussed in previous publications.

D. Executive Committee members also will submit their proposals for review but will not participate in Committee discussions of their proposals.

E. The main criteria used for manuscript evaluations will be: (a) conventional standards of scientific merit and concern for human subjects; (b) extent to which the findings and conclusions advance cost-effective management of IBS and understanding of the factors that mediate or moderate cost-effective management; (c) integration of each manuscript's results and conclusions with those of other publications from the IBSOS project; and (d) the extent to which the proposed writing team and order of authorship reflects each member’s participation in the IBSOS project and effort to be devoted to data analyses and interpretation as well as to manuscript preparation. As noted above, as the IBSOS project matures, proposals also will be reviewed with respect to potential overlap with previous publications.

F. The Executive Committee will monitor progress on completion of approved publications. Progress will be monitored during conference calls/meetings of the Executive Committee with the lead author(s) and other writing team members.

G. Before submission to journals or conference review committees, the lead author will send the manuscript to the Executive Committee for review. The Executive Committee will provide a written evaluation to the lead author and writing team of each manuscript, including recommendations for modifications. The Executive Committee may recommend: (a) submission; (b) submission with revisions; (c) revisions and re-review; or (d) rejection.

H. We anticipate that most or all empirical manuscripts will receive reviews from journal editors that require revisions and resubmissions. The Executive Committee will assist investigators in responding to the reviews of their manuscripts and performing new data analyses that are required.

REQUESTS FOR USAGE OF THE IBSOS DATA SET

A. As the IBSOS project progresses, we anticipate that investigators who are not associated with the project will request permission to use the database to test hypotheses. The Executive Committee will develop a standard application form for these external investigators to complete and submit for review. The Executive Committee will review the completed applications using the same criteria noted above in Section E. The Executive Committee will conference regarding appropriate responses to applications that fail to meet one or more of the review criteria described in Section E.

B. The Executive Committee also will develop a standard procedure for providing external investigators with access to the IBSOS project database and managing applications to the University of Buffalo IRB for project proposals developed by external investigators. In accord with NIH guidelines, after baseline data are collected and the database is cleaned, there will be a one-year period during which IBSOS investigators will have exclusive use of the database for analysis and presentation/publication of baseline data. Following the one-year period, non-IBSOS investigators may access the database for secondary analyses in accord with the guidelines above. Similarly, after all post-treatment and follow-up data are collected and the database is cleaned, there will be a one-year period during which IBSOS investigators will have exclusive use of the database for analysis and presentation/publication of post-treatment and follow-up data. Following the one-year period, non-IBSOS investigators may access the database for secondary analyses in accord with the guidelines above. It should be noted that all publications/presentations generated by non-IBSOS investigators will provide appropriate credit to the IBSOS investigators and the Cooperative Agreement U01 DK077738.

C. Given that many requests from external investigators are likely to be submitted after the IBSOS project is completed, it will be necessary to maintain an Executive Committee structure after the project is complete. We will encourage all members of the Steering Committee to remain on the committee after the project is terminated. The Executive Committee will develop guidelines for replacing committee members who choose to leave the Committee following project termination.

ACKNOWLEDGEMENTS

A. Publications resulting from data produced by the IBSOS project should include appropriate acknowledgements. All or part of the following might be useful:

The Irritable Bowel Syndrome Outcome Study (IBSOS) is an NIDDK funded Cooperative Agreement (Grant # U01 DK077738) involving two clinical sites, an Administrative Core, and IBSOS staff.

ANCILLARY STUDIES POLICY

IBSOS may create opportunities for ancillary studies that leverage the main study's participants, population or dataset. The objectives of the IBSOS policy on ancillary studies are:

- To encourage ancillary studies that enhance the main study's value;
- To provide an orderly approval process for ancillary studies; and
- To assure that ancillary studies are scientifically sound and do not interfere with the conduct of the main study or jeopardize the main study's goals.

The specific policies are as follows:

1. Proposals for ancillary studies will be submitted in writing to the Steering Committee (SC) and in some cases, the full DCC for review. The proposer must be identified.

2. Proposals will be considered for two types of ancillary studies:
   i) **Data Analysis** studies requiring additional analytical resources beyond those already available in the main grant, and
   ii) **New Data Acquisition** studies requiring data collection beyond that collected for the main study.

3. Upon approval by the Steering Committee, and update to the DSMB, the study may commence.

4. Ancillary studies enhancing the value of the IBSOS study are encouraged but must not interfere with the conduct of the main study or in any way jeopardize the main study's goals. Funding may be needed and is the responsibility of the proposer. The SC is charged with evaluating the desirability of ancillary study results and with assessing the acceptability of additional demands on staff and participants, adequacy of estimates of funds and their likelihood of availability, risk to the participants and to the primary study goals, and the overall chances for success

5. The principal proposer of an approved ancillary study will serve as the lead member of the writing group for papers based on that ancillary study. The proposer will notify the SC of the intent to prepare papers or presentations on the ancillary study.

6. Selection of a writing group, preparation and submission of papers, and submission of abstracts will follow the guidelines for other IBSOS papers.

Protection of Human Subjects
1. Recruitment and Consent Procedures
2. Potential Risk
3. Potential Benefits

ANCILLARY STUDIES PROTOCOL

Definition

In IBSOS, an **ancillary study** is defined as one that derives support from sources other than the cooperative agreement grant funds awarded by NIH for support of the main trial. An ancillary study's objectives are not duplicative of and do not interfere with the IBSOS study but use IBSOS participants, samples, or data collected by IBSOS.

IBSOS represents a large and uniquely well-characterized population sample of severely affected IBS participants. To make the best possible use of this extraordinary resource, IBSOS encourages investigators to develop ancillary studies in conjunction with the trial and to involve other investigators, within and outside of IBSOS, in this process. An ancillary study may involve data collection from one or more IBSOS Centers for one or more cohorts.

Role of Sub-Studies and Ancillary Studies (SAS) Committee

The Steering Committee must approve all ancillary studies to ensure that they do not impose an unacceptable burden to staff or participants or conflict with the aims of IBSOS. Data collection may not proceed without the approval of the SAS Committee. The Steering Committee designates the SAS Committee to conduct a preliminary review of all proposed ancillary studies.

Ancillary Study Review

The Sub studies and Ancillary Studies (SAS) Committee will conduct preliminary review and provide recommendations to the Steering Committee for approval of ancillary studies concepts through the process described in this chapter. Proposals will be assessed to evaluate whether they would interfere with other parts of the protocol, would hamper continued recruitment or participation in IBSOS, or would be inconsistent with the IBSOS aim of facilitating a broad range of research.

Highest priority will be given to studies which:

- have the highest scientific merit,
- do not interfere with or duplicate the main IBSOS objectives,
- produce the least burden on IBSOS participants,
- produce the least demand on IBSOS resources such as blood samples,
- require the unique characteristics of the IBSOS cohort, and
- contribute to the aim of examining a broad range of research questions.

If a change occurs in the design or concept of the ancillary study after it has been approved, the SAS committee should be notified. The Steering Committee will be asked

to approve the alterations, based on the recommendation of the SAS Committee. The Data and Safety Monitoring Board (DSMB) may also be asked to judge the demands the proposed study places on participants and the priority in relation to IBSOS objectives.

Outside Funding Required for Ancillary Studies

Investigators proposing ancillary studies must seek funding from outside sources to conduct their research. Examples include funding obtained through investigator-initiated NIH research grant awards (R01s), grants from academic institutions, or private sources (e.g. drug companies, nonprofit health organizations).

In assessing the acceptability of an ancillary study proposal, the Steering Committee will be concerned with both the explicit and the hidden costs to IBSOS entailed by the proposal (e.g. costs to the Administrative Core or clinical center for coordinating and administering additional data collection). The ancillary study's PI should provide evidence that adequate support for carrying out these functions is available at his/her institution; if not, the Administrative Core will conduct the activities required using resources that must be included in the ancillary study budget.

Scientific Review of Ancillary Studies

For proposals submitted to the NIH, either in response to an RFA or as investigator-initiated R01 applications, scientific review is through the regular NIH peer review system. For other proposals, if no other acceptable peer review has taken place, the scientific merit of a proposal will be reviewed by the SAS, supplemented with additional experts as necessary.

IRB Approval

All ancillary studies must receive necessary approvals from IRBs at the individual institutions involved. Documentation of IRB approval is required to be submitted to the IBSOS Administrative Core before an ancillary study can be initiated in conjunction with IBSOS.

Confidentiality

Confidentiality of individually identifiable data about IBSOS participants must be assured. IBSOS provides no assurances that ancillary studies will be able to identify and contact participants in the future, particularly after IBSOS ends.

Industry-Sponsored Ancillary Studies

Proposals for industry-sponsored ancillary studies are evaluated in accordance with the procedures described above. In addition, it is the responsibility of the PI to obtain agreement with the industry sponsor through an appropriate contractual mechanism that all data relevant to the IBSOS ancillary study will be shared with the Administrative Core and the Steering Committee. Conduct of industry-sponsored ancillary studies also must comply with all existing IBSOS and NIH policies and guidelines.

Procedure for Proposing an Ancillary Study in Conjunction with IBSOS

Each ancillary study must include an IBSOS Principal Investigator or Co-investigator on the proposal and must have the approval of the Principal Investigator at each IBSOS site proposed. The Principal Investigator of the ancillary study is responsible for submitting the study proposal to the SAS Committee, monitoring the study to ensure continuing compatibility with IBSOS, and serving as a liaison to the IBSOS Steering Committee, including attendance as requested at SAS and Steering Committee meetings. The appended form, "Preliminary Proposal for IBSOS Ancillary Study," must be submitted to the IBSOS Administrative Core to propose an ancillary study. This form is also available on the IBSOS website. The form may be submitted online, by mail or fax. To assess the proposal, the SAS and Steering Committees need to know what additional information will be collected at any of the IBSOS clinic visits, the expected burden to participants, and the amount of time needed to complete the measurement. If IBSOS core data, staff, and/or analyses are needed for the ancillary study, this information should be provided. The SAS and the Steering Committee will consider the following questions, which should be addressed in completing the form:

1. What, if any, measurements (questionnaires, biologic samples, physical measures) are needed and when will they be collected?

2. What is the additional burden to staff and participants from the proposed measurements?

3. Which IBSOS centers have agreed to participate? Have the collaborating investigators approved the proposal? Is collaboration with investigators from additional IBSOS sites desired or planned?

4. What is the sample to be studied in terms of the number and characteristics of the participants? Justify the sample size.

5. How will the ancillary study be funded? Would any additional unreimbursed work or personnel time be expected of IBSOS?

6. Where will the data analyses be conducted? What is the estimated burden to the Administrative Core?

7. How will the confidentiality and other aspects of protection of human subjects be maintained?

The Preliminary Proposal for IBSOS Ancillary Studies form should be filled out before submitting an application for funding to a funded entity. Administrative Core staff is available to assist the investigator in the preparation and processing of the form. The Preliminary Proposal form describing the concept will generally be discussed by the SAS Committee on a conference call two to four weeks after receipt. Sufficient time should be allowed for this process. The investigator may be asked to make him/herself available at the time of the call to address questions that may arise. The SAS

Committee will provide a letter to the investigator shortly after the call, indicating whether the proposal is potentially acceptable.

Publications and Presentations

Proposals must be submitted for all publications, presentations and abstracts from an ancillary study for review and approval by Steering Committe prior to submission or presentation, in accordance with the general rules for publications and presentations.

Each manuscript and abstract is generally expected to include an IBSOS investigator as co-author, except under circumstances that should be stated and justified as part of the original submission to the SAS Committee.

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Index of Terms