Accepted Manuscript

Improvement in Gastrointestinal Symptoms After Cognitive Behavior Therapy for Refractory Irritable Bowel Syndrome

Jeffrey M. Lackner, PsyD, James Jaccard, PhD, Laurie Keefer, PhD, Darren Brenner, MD, Rebecca Firth, MHA, Gregory D. Gudleski, PhD, Frank Hamilton, MD, Leonard A. Katz, MD, Susan S. Krasner, PhD, Chang-Xing Ma, PhD, Christopher Radziwon, PhD, Michael D. Sitrin, MD

PII: S0016-5085(18)30406-2
DOI: 10.1053/j.gastro.2018.03.063
Reference: YGAST 61819

To appear in: *Gastroenterology*
Accepted Date: 30 March 2018

Please cite this article as: Lackner JM, Jaccard J, Keefer L, Brenner D, Firth R, Gudleski GD, Hamilton F, Katz LA, Krasner SS, Ma C-X, Radziwon C, Sitrin MD, Improvement in Gastrointestinal Symptoms After Cognitive Behavior Therapy for Refractory Irritable Bowel Syndrome, *Gastroenterology* (2018), doi: 10.1053/j.gastro.2018.03.063.

Improvement in Gastrointestinal Symptoms After Cognitive Behavior Therapy for Refractory Irritable Bowel Syndrome

Jeffrey M. Lackner, PsyD[1], James Jaccard, PhD[2], Laurie Keefer, PhD[3], Darren Brenner, MD[4] , Rebecca Firth, MHA[1], Gregory D. Gudleski, PhD[1], Frank Hamilton, MD[5], Leonard A. Katz, MD[1], Susan S. Krasner, PhD[1, 6], Chang-Xing Ma, PhD[7], Christopher Radziwon, PhD[1], and Michael D. Sitrin, MD[1]

[1] Division of Gastroenterology, Department of Medicine, Jacobs School of Medicine, University at Buffalo, Buffalo, NY; [2]School of Social Work, New York University, New York, NY; [3] Division of Gastroenterology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; [4]Division of Gastroenterology, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL; [5]Division of Digestive Disease and Nutrition, NIDDK, Bethesda, MD; [6]Department of Anesthesiology, Jacobs School of Medicine, University at Buffalo, Buffalo, NY [7]Department of Biostatistics, University at Buffalo, SUNY, Buffalo, NY

Corresponding Author: Jeffrey M. Lackner, Psy.D., Behavioral Medicine Clinic, Department of Medicine, Jacobs School of Medicine, University at Buffalo, ECMC 462 Grider Street, Buffalo, NY 14215. Telephone: 716-898-5671; Fax: 716-898-3040; Email: lackner@buffalo.edu

Grant Support and Disclaimer: Research reported in this manuscript was supported by the NIH/NIDDK Grant 77738 (Dr. Lackner). The content is solely the responsibility of the authors and does not necessarily represent the official views of NIH.

Conflict of interest: None reported.

Author Contributions: Dr. Lackner and Dr. Jaccard had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Lackner, Firth, Jaccard, Gudleski, Katz, Krasner, Keefer, Brenner, Sitrin, Hamilton
Acquisition, analysis, or interpretation of data: All authors
Drafting of the manuscript: Lackner, Jaccard
Critical revision of the manuscript for important intellectual content: All authors
Statistical analysis: Jaccard
Obtained funding: Lackner, Jaccard, Firth, Keefer, Sitrin
Administrative, technical, or material support: All authors
Study supervision: Lackner, Firth, Jaccard, Keefer, Brenner, Hamilton, Ma

Short Title: Brief Cognitive Behavior Therapy for IBS

Role of the Funder/Sponsor: NIDDK scientists (Drs Frank Hamilton and Patricia Robuck) contributed to the design and conduct of the study, which included the collection and management of data. The project scientist from the NIDDK served as a member of the IBSOS steering committee. The decision to publish was made by the IBSOS steering committee in consultation with all authors, with no restrictions imposed by the sponsor. As a coauthor, the NIDDK scientist contributed to the interpretation of the data and the preparation, review, and approval of the manuscript

ACKNLOWEDGEMENTS: The investigators would like to thank the volunteers who enrolled in the IBSOS. We gratefully acknowledge the following individuals for their instrumental roles in the design and conduct of the IBSOS:

NIDDK: Sherry R. Hall, M.S., Patricia Robuck, Ph.D., MPH (past Project Scientist), Rebecca Torrance, R.N., M.S.N., Aynur Unalp-Arida, MD, MSc, Ph.D (Program Officer), Rebekah Van Raaphorst

Data and Safety Monitoring Board: Jennifer A. Haythornthwaite, Ph.D., Brian E. Lacy, MD, Ph.D. (Chair), Donald B. Penzien, Ph.D., Catherine Spino, D.Sc., Arnold Wald, MD.

Data Coordinating Center: Mark Byroads, Kenneth Wood (Frontier Science).

Study Sites: *University at Buffalo:* Deana Bervoets, Adam Booth, Alicia Brasel, Abbey Braun, Ann Marie Carosella, Ph.D., Ray Dannenhoffer, Ph.D., Paul Dressel, Gary Iacabucci, Justin Kimber, Pat Klinck, Jessica Perkins, Cathrine Powell, Tatyana Raby, Mark Schneggenberger, Camille Simonetti, Amanda Smith, Emily Smith, Christopher Sova, Travis Stewart, Andrew Wurl and the staff of the UB Clinical and Translational Research Center. *Northwestern:* Caroline E. Artz, Sarah K. Ballou, Ph.D., Jason R. Bratten, MBA, Beth Doerfler, RD, Kate Eident, Sarah Kinsinger, Ph.D., Sarah E. Quinton, PsyD, Tiffany Taft, PsyD.,

Collaborators: Kathleen Carroll, Ph.D. (Yale University); Mel C. Wilcox, MD, MSPH (University of Alabama); Bruce Naliboff, Ph.D., Emeran Mayer, MD (UCLA); Nancy Norton (International Foundation for Functional GI Disorders)

Abbreviations

IBSOS	Irritable Bowel Syndrome Outcome Study
IBS	Irritable Bowel Syndrome
CBT	Cognitive Behavior Therapy
S-CBT	Standard-Cognitive Behavior Therapy
MC-CBT	Minimal Contact-Cognitive Behavior Therapy
EDU	Education condition
CGI	Clinical Global Impressions Scale
CGI-I	Clinical Global Impressions-Improvement Scale
IBS-SSS	Irritable Bowel Syndrome Symptom Severity Scale
CSQ	Client Satisfaction Questionnaire
PP	Per-protocol
ITT	Intent-to-treat
df	degrees of freedom
ESS	Effect size sensitivity
TOST	Two One-Sided Test

ABSTRACT

Background & Aims: There is an urgent need for safe treatments for irritable bowel syndrome (IBS) that relieve treatment-refractory symptoms and their societal and economic burden. Cognitive behavior therapy (CBT) is an effective treatment that has not been broadly adopted into routine clinical practice. We performed a randomized controlled trial to assess clinical responses to home-based CBT compared with clinic-based CBT and patient education.

Methods: We performed a prospective study of 436 patients with IBS, based on Rome III criteria, at 2 tertiary centers from August 23, 2010 through October 21, 2016. Subjects (41.4±14.8 y old; 80% female) were randomly assigned groups that received: standard CBT (S-CBT, n=146, comprising 10 weekly, 60-min sessions that emphasized the provision of information about brain–gut interactions; self-monitoring of symptoms, their triggers, and consequences; muscle relaxation; worry control; flexible problem solving; and relapse prevention training), or 4 sessions of primarily home-based CBT requiring minimal therapist contact (MC-CBT, n=145), in which patients received home-study materials covering same procedures as S-CBT), or 4 sessions of IBS education (EDU, n=145) that provided support and information about IBS and the role of lifestyle factors such as stress, diet, exercise. The primary outcome was global improvement of IBS symptoms, based on the IBS-version of the Clinical Global Impressions-Improvement Scale. Ratings were performed by patients and board-certified gastroenterologists blinded to treatment allocation. Efficacy data were collected 2 weeks, 3 months, and 6 months after treatment completion.

Results: A higher proportion of patients receiving MC-CBT reported moderate to substantial improvement in gastrointestinal symptoms 2 weeks after treatment (61.0% based on ratings by patients and 55.7% based on ratings by gastroenterologists) than those receiving EDU (43.5% based on ratings patients and 40.4% based on ratings by gastroenterologists) (P<.05). Gastrointestinal symptom improvement, rated by gastroenterologists, 6 months after the end of treatment also differed significantly between the MC-CBT (58.4%) and EDU groups (44.8%) (P= .05). Formal equivalence testing applied across multiple contrasts indicated that MC-CBT is at least as effective as S-CBT in improving IBS symptoms. Patients tended to be more satisfied with CBT vs EDU (P<.05) based on immediate post-treatment responses to the client satisfaction questionnaire. Symptom improvement was not significantly related to concomitant use of medications.

Conclusions: In a randomized controlled trial, we found that a primarily home-based version of CBT produced significant and long-term gastrointestinal symptom improvement for patients with IBS compared to education. Clinicaltrials.gov no. clinicaltrials.gov/ct2/show/NCT00738920

KEY WORDS: functional gastrointestinal disorder, disease management, value-based healthcare, brain-gut interactions

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder that affects up to 15% percent of adults worldwide[1]. While only 10% of IBS sufferers seek medical attention[2], it is one of the commonest diseases gastroenterologists and primary care physicians treat. There is neither a reliable biomarker nor a uniformly effective medical treatment for the full range of IBS symptoms (abdominal pain/discomfort, constipation and/or diarrhea). The development of effective pharmacotherapies has been impeded by withdrawal of several FDA-approved IBS drugs due to safety concerns. There is an urgent need for effective treatments that relieve IBS symptoms and their societal and economic burden estimated at $US28 billion annually[3].

Various practice guidelines support the efficacy of a cognitive behavior therapy (CBT)[4-6], a specific psychological intervention that targets putative factors maintaining IBS. Despite comparatively strong levels of empirical support of clinic-based CBT[7], only a small fraction of people receive it in accordance with practice guidelines. Barriers to adoption include cost, limited therapist availability beyond select metropolitan areas, stigma, and logistical challenges such as transportation and time. In a value-based healthcare environment, there is a demand for treatments that retain the efficacy profile of "gold standard" therapies but are more efficient to implement and disseminate. One strategy for achieving this goal is decreasing therapist contact time through the use of primarily self-administered or "home-based" treatments[8].

The immediate and sustained efficacy of a primarily home-based CBT was investigated in the context of a multicenter randomized trial addressing methodological shortcomings (e.g., small-scale studies from single investigative teams, inadequate blinding) of prior trials. Patients with moderate-to-severe IBS symptoms were assigned to clinic-based CBT (Standard-CBT), a home-based version of CBT requiring minimal therapist contact (Minimal Contact-CBT), or an active comparator (EDU) that emphasized IBS education but excluded CBT techniques. The aim was to assess clinical response of CBT-treated patients 2 weeks, 3 months, and 6 months after a 10-week treatment phase. Based on our pilot work[8], our primary hypothesis was that Minimal -Contact-CBT would deliver a comparable clinical response to Standard-CBT and superior response to IBS Education on a primary endpoint of global symptom improvement featured in previous NIH and industry-funded FGID trials.

METHODS

Study Design and Participants

As shown in Figure 1. the IBSOS is a randomized controlled, parallel group trial that allocated patients into one of three conditions at two sites (University at Buffalo, Northwestern University). Additional details regarding the rationale and methodology of the Irritable Bowel Syndrome Outcome Study (IBSOS) protocol are detailed elsewhere[9]. Patients were recruited from referrals from health care professionals, advertising and word of mouth (first assessment: 8/23/2010-12/30/2015; last follow-up: 10/21/2016). Recruitment ended when accrual goals were met. This study presents immediate post-treatment, 3- and 6-month follow-up data. All authors had access to these data and reviewed and approved final manuscript.

Adults (18-70 years) suffering from IBS as defined by Rome III criteria[10] were included provided GI symptoms were at least moderately severe (i.e., they occurred at least twice weekly and caused some life interference). IBS diagnosis was established by study gastroenterologists at baseline assessment. Patients were excluded if they presented evidence of current structural/biochemical abnormalities or other primary GI disease that better explained gastrointestinal symptoms; had been diagnosed with a malignancy other than localized basal or squamous cell carcinomas of the skin in the past 5 years; were undergoing IBS-targeted psychotherapy; could not commit to completing all scheduled follow up visits; had an unstable extraintestinal condition or a major psychiatric disorder (e.g., depression with severe suicidality, psychotic disorder); reported a current gastrointestinal infection or an infection within 2 weeks before evaluation; used a gut-sensitive antibiotic during the 12 weeks prior to baseline assessment.

Study Oversight

Institutional Review Boards at each site approved the protocol. An independent Data Safety Monitoring Board the NIDDK Project Scientist appointed monitored the trial on a bi-annual basis for participant safety, study conduct, and progress. Bi-annual external quality assurance audits verified the trial was conducted in accordance with protocol.

Randomization and Masking

Simple randomization without constraints was performed using a centralized web-based

allocation scheme (1:1:1) overseen by a study coordinator without patient care responsibilities. Study gastroenterologists masked to treatment assignment functioned as independent evaluators of improvement at immediate and 6 month follow-ups. Participants were blind to treatment assignment through pretreatment baseline period. Patient-reported expectation of IBS symptom improvement[11] by end of treatment was 60.2% across conditions

Treatments

Standard-CBT (S-CBT[8]) involves 10 weekly, 60-minute face-to-face sessions and emphasizes the provision of information regarding brain-gut interactions; self-monitoring of GI symptoms, their antecedents and consequences; muscle relaxation to dampen physiological arousal and increase control over GI symptoms; worry control to challenge and dispute negatively skewed thinking patterns; flexible problem solving to aid in the deployment of more effective ways of managing realistic stressors; and relapse prevention training. As a learning-based program, CBT assigns home exercises to facilitate acquisition of symptom self-management skills introduced in session through didactic instruction. Because Minimal Contact-CBT (MC-CBT[8]) requires only four clinic visits over the 10 week period, it relies more extensively on home study materials[12] to cover the same procedures S-CBT introduces at each session. Figure 2 describes the structure and format of CBT of IBS. The education condition (EDU[9]) was equivalent to MC-CBT in time, attention and receipt of home study materials[13]. EDU sessions were structured around education, support and reflection. Content included information about IBS, its clinical features, epidemiology, diagnostic criteria, medical tests, and treatment options as well as the role of stress in IBS, diet and physical activity. Clinicians were prohibited from prescribing relevant behavior changes (e.g., stress management skills). To mimic receipt of the workbook MC-CBT patients, EDU patients received a copy of *IBS: Learn to Take Charge* Of It [13] which emphasizes the "empowering" value of patient education. All content referencing CBT strategies were extracted through a special printing of the book. As such, the EDU condition represents a viable treatment protocol in its own right and whose procedures did not overlap with those deemed critical to CBT for IBS. This design allowed rigorous evaluation of the incremental value of the technical features of CBT over and above the contribution of state-of-the art educational protocols. It creates a much higher standard of comparison than designs that feature wait-list control or active controls with clinically inert activities such as receiving attention from

someone. By emphasizing education and support, EDU incorporated lifestyle recommendations that are regarded as "of great importance in the management of patients with …IBS"[14] and featured in practice guidelines [15] and was therefore more clinically robust and ecologically valid than attention control conditions whose main goal is to control for nonspecific factors (attention, expectancy)

Outcomes

Consistent with recommendations for efficacy assessment for functional gastrointestinal and chronic pain trials[16,17], the *a priori* primary endpoint was global IBS symptom improvement based on the IBS version[8] of the Clinical Global Impressions-Improvement Scale (CGI-I)[18]: "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 = substantially worse, 2 = moderately worse 3, slightly worse, 4= no change, 5 = slightly improved, 6 = moderately improved, 7 = substantially improved). We adopted the practice of classifying patients whose symptoms were rated as "substantially improved" or "moderately improved" as treatment responders. Study gastroenterologists completed a physician-version of the CGI[19]. Use of "blind" physician ratings is advantageous because they are not subject to patient reporting bias and they represent judgments by trained professionals with extensive experience in IBS. Data source triangulation (using evidence about an endpoint from different data sources) is a notable study strength because it lends verification and validity to outcome data. The IBS Symptom Severity Scale (IBS-SSS[20]) served as a secondary index of efficacy (0-500 scale, ≥300 = Severe). Quality of care was measured at immediate post-treatment with the 8-item Client Satisfaction Questionnaire (CSQ[21], range = 8-32, higher scores signifying greater patient satisfaction with treatment).

Quality Assurance

To ensure treatment fidelity, therapists received extensive training in the components of each treatment under expert supervision before assigned study patients. Delivery was optimized by treatment manuals that provided detailed session-by-session guidance to standardize intervention among therapists, the completion of checklists for session protocols after each session; and regularly scheduled supervision with senior clinicians. Sessions were audio taped 20% of which were randomly selected per patient and rated for protocol adherence (1= ineffective, 5 = extremely effective). Overall therapist adherence ratings were 4.45 (SD = .50). Clinicians rated weekly patient adherence to home exercises

using a 6-point scale ranging from 1 (0%) to 6 (>100%): MC-CBT, 68%, S-CBT, 57%, EDU, 71%

Statistical Analyses

Because both per-protocol (PP) and intent-to-treat (ITT) frameworks provide unique perspectives on efficacy profiles of treatments[22,23], both were applied as specified *a priori* in the statistical analysis plan approved by the sponsor and DSMB prior to unblinding. ITT data included all randomized patients who completed 4-week baseline period. Given the disease chronicity (17 years) of our sample, ITT patients who dropped out during treatment (9%) were assigned a score of no improvement (CGI =4; IBS-SSS = baseline score) at posttest and two follow-ups. Small normally-distributed random perturbances were added to the imputed scores (including the IBS-SSS imputed values) to remove downward bias of within-condition variability (in sensitivity analyses, different residual distributional forms were explored and did not affect conclusions). Attrition was negligible (see below). For treatment completers with missing data at a given follow-up, two strategies were explored for purposes of sensitivity analysis. The first used multiple imputatons with chained equations and the second used listwise deletion, which was justified given the small amount of missing data and the lack of any evidence for systematic missing data bias across a very wide range of covariates. Each approach makes assumptions that can be questioned, so sensitivity analyses are called for[24,25]. Core conclusions for the two methods were comparable, with the few exceptions noted.[26]

Primary analyses focused on within-time single degree of freedom (df) contrasts between the three treatment conditions. For dichotomous outcomes, between-group comparisons used a modified linear probability model with Huber-White robust estimators[27]; for between-group mean comparisons, single df contrasts used Huber-White robust estimators. These analyses included site as a covariate as well as covariates representing medication status (patient using medication for abdominal pain, bowel symptoms, or for multiple IBS symptoms versus not), and patient ethnicity (White versus non-White, see below). For dichotomous outcomes, contrasts were replicated using logistic regression for sensitivity analyses. All such contrasts were between-subjects in nature, not repeated measure based. For posttest/follow-up versus baseline analyses, contrasts used difference scores with non-pooled error terms. Marginal probabilities instead of odds ratios are reported in the interest of interpretability. 95% confidence intervals are reported as margins of error, i.e., the maximum absolute half width for the lower

versus upper confidence limit relative to the parameter estimate.

Power analyses used an alpha of 0.05, two-tailed test, and a desired power of 0.80. The effect size sensitivity (ESS) for a between-condition contrast for a sample size of 145 per condition yields a Cohen ESS of d = 0.33. For between-group differences in proportions where one proportion is set to 0.50, the ESS is 0.16 (i.e., a group difference of 16%). For posttest/follow-up versus baseline contrasts, the ESS assuming a correlation of 0.40 between measures yields Cohen's d = 0.26. For a within-time, across-condition proportions, ESS is 0.12 (or 12%), assuming a 0.40 phi coefficient.

A study goal was to evaluate the comparability of the 4-session MC-CBT versus the 10-session S-CBT. Supplemental analyses used Two One-Sided Test (TOST) equivalence tests between these conditions requiring 95% confidence intervals of condition differences to be fully contained within *a priori* defined equivalence intervals. For dichotomous outcomes, the *a priori* equivalence interval was set at plus or minus 10%. For the IBS-SSS, the accepted equivalence threshold is ±50 points[20]. Because no guidelines for defining equivalence thresholds for CGI means exist, we conducted preliminary analyses (blind to and collapsing across treatment condition) and determined a reasonable interval was ± 0.50.

RESULTS

As Table 1 shows, of 652 individuals assessed for eligibility, 436 (66%) completed 4-week baseline and were randomized to S-CBT (N=146); MC-CBT (N=145), or EDU (N=145). Table 1 presents self-reported sociodemographic characteristics for the sample. All baseline characteristics were comparable across treatment groups. Mean (SD) age was 41.4 years (14.8). Participants were predominantly female (80.3%) and non-Hispanic White (89.4%). GI symptoms were generally severe, longstanding, disruptive, and unresponsive to conventional medical therapies (i.e. treatment refractory[4]). Medication use was common. While medication use was unrelated to outcome, it was included as a covariate in all analyses.

Attrition

Nine percent of patients dropped out during treatment (no statistically significant percent differences between conditions). Dropout was unrelated to a range of demographic, psychological, and IBS-related variables measured at baseline, with one exception: an 8% treatment dropout rate for Whites versus a 22% rate for non-Whites ($p < 0.05$). Non-whites represented only 10% of the sample. This

difference did not vary significantly by treatment condition. Eighty-nine percent of the sample received a minimally sufficient dosage of their assigned treatment, defined *a priori* as completion of 8 of 10 for S-CBT sessions and 3 of 4 for MC-CBT and EDU. This percent did not vary significantly by condition. Attrition between posttest and 3-month follow-up was 5.1%. Attrition between 3- and 6-month follow-ups was 4.1%. None of these rates varied significantly by condition. There were no statistically significant differences between those lost to attrition versus those retained on multiple demographic and clinical variables assessed at baseline, nor as a function of outcome variables at immediate posttest.

Analyses of Outcomes

Table 2 presents per protocol and intent-to-treat results for the percent of treatment responders for the CGI as reported by patients and study gastroenterologists. Table 3 presents comparable data based on mean CGIs. Table 4 presents data for the IBS-SSS and CSQ.

MC-CBT produced a statistically significantly larger percent of treatment responders than IBS education (EDU) at immediate posttest for the patient reports (per-protocol (PP) = 68.1% versus 46.7%. ITT = 61.0% versus 43.5%) and for gastroenterologist assessments (PP = 63.0% versus 43.6%, ITT = 55.7% versus 40.4%). ITT data are graphically represented in Figure 3. Gastroenterologist-reported CGI differences retained significance at 6 months for both PP and ITT analyses and this also was true for the patient reported analyses using chained equation imputation for the PP analysis but not the ITT analyses (thought a trend was evident).

There was a tendency for mean values of the CGI to be more positive in the MC-CBT condition than the EDU condition, although patterns of statistical significance were less consistent beyond two-week follow up. Table 4 shows, substantial change in the IBS-SSS from baseline to posttest and follow-ups (>80 points where 50 points is clinically significant) for all conditions but no statistically significant differences between the three groups at any time point. The magnitude of changes on the secondary endpoint (IBS-SSS) for all conditions corresponded to a Cohen's d ≥ 3.5 (large). Both CBT dosages yielded significantly higher patient satisfaction than EDU (Cohen's d for MC-CBT= 0.53).

For equivalence tests for the parameter MC-CBT minus S-CBT, the critical result is whether confidence interval limits are completely within the equivalence interval (or, for the present study, if the CI lower limit of the difference is larger than the lower limit of the equivalence interval, to affirm S-CBT is not

superior to MC-CBT). This generally was the case, suggesting that MC-CBT is, at minimum, as efficacious as S-CBT.

Adverse events

One patient reported an adverse event (suicide attempt) but it was unrelated to treatment protocol and resolved

Discussion

In this multisite study, a brief, primarily home-based version of CBT yielded comparable results to the "gold standard" clinic-based version of CBT in improving chronic, severe, and treatment-refractory GI symptoms of IBS. Within-CBT gains were clinically meaningful and substantial with negligible erosion (~5%) 6 months after treatment ended. A 10-session, clinic-based version of CBT does not appear to confer incremental advantage over a 4-session, home-based version, even though the latter required 60% less clinician delivery time. Symptomatic improvement was achieved without risk of safety to patients which is notable given reported adverse effects of most medical therapies for IBS[28]

While both CBT conditions outperformed IBS education on the primary measure of symptomatic improvement at immediate follow up, we found no significant between-group differences on the IBS-SSS. All 3 conditions yielded significant IBS symptom severity reductions that persisted over time. The discrepancy between CGI and IBS-SSS outcome data may relate to the nature of the IBS-SSS, which is heavily weighted by sensory (e.g., pain, bloating) symptoms[29]. Because the CGI requires patients to rate any symptomatic improvement on the basis of both sensory and defecatory symptoms, it may be a more sensitive IBS endpoint.

CBT improvement rates post treatment are among the highest in the IBS outcome literature when examined on an absolute level. To put these data in context, treatment response of FDA-approved pharmacological agents using global IBS symptom improvement scales range from 17-40%[30,31]. CBT improvement rates compare favorably to the immediate and sustained efficacy profile of available medical or dietary therapy from over 100 trials. A less robust but still important effect is evident when comparing the degree of therapeutic gain (absolute % benefit increase) of CBT. At immediate follow-up, the magnitude of therapeutic gain of CBT over an active education/support comparator met or exceeded (11-21%) the threshold (10-15%) for defining clinical significance of novel pharmacotherapies in placebo-

controlled trials[32]. Because these contrasts isolate treatment effects attributable to therapeutic ingredients specific to CBT rather than the overall effect that also includes the influence of factors common across all therapies such as the formation of a collaborative doctor-patient relationship, the somewhat diminished effect size is expected.

CBT appears to improve IBS symptoms in a way that cannot be explained solely by nonspecific factors such as placebo, patient support, or education. First, CBT response far exceeded the 30-40% placebo response rate reported in IBS trials[33,34]. Second, unlike a placebo response, CBT gains generally persisted with negligible erosion after treatment cessation through 6 month follow ups[35]. Third, the overall pattern of response on primary outcome did not appreciably differ when reported by patients or blind assessors whose ratings were immune from bias from any expectation or allegiance favoring a specific condition. Fourth, while education/support leads to symptomatic improvement in a sizable minority of patients, it falls short of the response rate of the two CBT conditions particularly at immediate post-treatment which represents the critical follow up period for gauging efficacy of a Phase II trial. Patient education and support may be insufficient for some patients to achieve more immediate symptomatic improvement. For these patients, optimizing treatment response may involve learning strategies to correct faulty threat appraisals that can dysregulate brain-gut interactions[36].

While response rate for CBT is generally strong, it is by no means complete. At immediate follow up, less than half (42%) of CBT-treated patients who reported symptomatic improvement (28%, EDU) met remission criteria as defined by having no to mild IBS symptoms on the gastroenterologist-administered CGI-Illness Severity Scale[19]. Combination treatments of CBT and medical therapies that target both central and peripheral mechanisms of IBS may have therapeutic advantage over monotherapies for patients whose symptoms do not improve or whose improvement falls short of registering as clinically meaningful. Effectively reducing the societal and economic burden of IBS, however, calls for more than clinically proven treatments regardless of how they are configured or how well they work. Innovative direct-to-patient delivery systems are needed to transport evidence-based learning content key to symptom self-management to a broader number of individuals than more time-intensive, face-to-face encounters with specially trained professionals in select clinical settings reach. This study is a step in this direction.

While the primary aim of the IBSOS was to characterize short-term efficacy of CBT, data speak to durability of treatment effects of which there are two vantage points. Using a within-condition perspective, the percent of symptom responders for the patient- reported CGI for the M-CBT at the immediate posttest was 61% and at 6 months it was 57%, suggesting treatment durability. For the (blinded) physician assessments, the corresponding percents were 56% and 58%, also suggesting durability. Neither of these changes in percents between the immediate posttest and FU6 were statistically significant. For the IBS-SSS, the mean change at 6 months was about -99 units, which is substantial relative to standards in the field (a 50-point pre-post change is considered clinically significant) and did not degrade from prior levels of change (see Table 4) From a between-condition peprspective, the MC-CBT versus EDU comparisons focused not so much on the durability of the overall treatments and all that they entail but rather the durability of improvement attributed to the technical components of CBT. For the physician assessments, the increment in the percent responders in M-CBT over and above EDU was 17% at the immediate posttest and 14% ar the 6 month follow-up. Both increments were statistically significantly different from EDU. For the patient reports, the incremental percent of responders at the immediate posttest in M-CBT beyond EDU was 18% and at the 6-month follow-up it was 10%. This change in incremental rates over time was not statistically significant, but the latter 10% increment by M-CBT over EDU was the one durability comparison that was not statistically significant (although it trended in the expected direction). It is possible that CBT has a more powerful catalytic effect on initiating rather than maintaining GI symptom relief. However, the broad pattern of the above data suggest that CBT has a relatively durable effect particularly in comparison to medical therapies whose efficacy diminishes with treatment withdrawal. Nonetheless, we suggest that further efforts be devoted to determine how to optimize CBT's maintenance effects, perhaps through brief, phone-based booster sessions to keep CBT skills salient and help patients troubleshoot around difficulties they previously had in relieving GI symptoms

Study limitations include relatively few male patients for examining gender differences. Reliance on volunteers most of whom were White females may limit generalizability. Supplemental analyses such as those based on machine learning principles using targeted maximum likelihood for purposes of sensitivity analyses might be of value.[37,38] While an inert placebo comparator may have enhanced the

interpretability of findings, this was neither feasible nor ethical given study demands extending months after treatment discontinuation to characterize maintenance effects. Like all patient-reported outcomes, the global endpoint approach we adopted at the recommendation of the Rome Foundation[16] is subjective and vulnerable to potential biases of self-report. Such biases should, however, operate equally across treatments, rendering any observed between-group differences as clinical meaningful. Further, blind ratings not subject to the same biases yielded results comparable to patient-reported ratings, suggesting findings are robust across data source. A focus on dichotomous improvement judgments also has inherent limitations, although this is a standard metric for gauging efficacy in the field. Strengths of the design include extended follow-up assessments, methodologically rigorous trial architecture that minimized risk of multiple biases that obscures study findings and supports their reproducibility, negligible attrition and missing data, and a relatively large, well-characterized sample from two sites that rendered comparable data.

In conclusion, a primarily home-based version of CBT produced substantial gains in the percent of patients reporting moderate to substantial improvement of GI symptoms . GI symptom improvement is not explained away by nonspecific effects such as support, patient education, or attention.

References

1. Hungin APS, Chang L, Locke GR, Dennis EH, Barghout V. Irritable bowel syndrome in the United States: prevalence, symptom patterns and impact. *Aliment Pharm Ther.* 2005;21(11):1365-1375.
2. Camilleri M, Choi MG. Review article: irritable bowel syndrome. *Aliment Pharmacol Ther.* 1997;11(1):3-15.
3. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part II: lower gastrointestinal diseases. *Gastroenterology.* 2009;136(3):741-754.
4. Ford AC, Lacy BE, Talley NJ. Irritable Bowel Syndrome. *N Engl J Med.* 2017;376(26):2566-2578.
5. Mayer EA. Clinical practice. Irritable bowel syndrome. *N Engl J Med.* 2008;358(16):1692-1699.
6. Ford AC, Quigley EMM, Lacy BE, et al. Effect of Antidepressants and Psychological Therapies, Including Hypnotherapy, in Irritable Bowel Syndrome: Systematic Review and Meta-Analysis. *Am J Gastroenterol.* 2014;109(9):1350-1365.
7. Laird KT, Tanner-Smith EE, Russell AC, Hollon SD, Walker LS. Short-term and Long-term Efficacy of Psychological Therapies for Irritable Bowel Syndrome: A Systematic Review and Meta-analysis. *Clin Gastroenterol H.* 2016;14(7):937-947.e934.
8. Lackner JM, Jaccard J, Krasner SS, Katz LA, Gudleski GD, Holroyd K. Self-administered cognitive behavior therapy for moderate to severe irritable bowel syndrome: clinical efficacy, tolerability, feasibility. *Clin Gastroenterol Hepatol.* 2008;6(8):899-906.
9. Lackner JM, Keefer L, Jaccard J, et al. The Irritable Bowel Syndrome Outcome Study (IBSOS): rationale and design of a randomized, placebo-controlled trial with 12 month follow up of self- versus clinician-administered CBT for moderate to severe irritable bowel syndrome. *Contemp Clin Trials.* 2012;33(6):1293-1310.
10. Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead W. *Rome III. The functional gastrointestinal disorders: Diagnosis, pathophysiology and treatment: A multinational consensus,.* 2 ed. ed. McLean, VA:: Degnon Associates; 2006.
11. Deviliya GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. *J Behav Ther Exp Psychiatry.* 2000;31(2):73-86.
12. Lackner JM, Holroyd KA. *Breaking the bonds of IBS: A step-by-step guide.* 2nd edition ed. Buffalo, NY: University at Buffalo, SUNY; 2010.
13. Gordon D. *IBS: Learn to take charge of it.* New York: Barnes & Noble; 2004.
14. Ringstrom G, Storsrud S, Posserud I, Lundqvist S, Westman B, Simren M. Structured patient education is superior to written information in the management of patients with irritable bowel syndrome: a randomized controlled study. *Eur J Gastroenterol Hepatol.* 2010;22(4):420-428.
15. Ford AC, Moayyedi P, Lacy BE, et al. American College of Gastroenterology Monograph on the Management of Irritable Bowel Syndrome and Chronic Idiopathic Constipation. *The American Journal Of Gastroenterology.* 2014;109:S2.
16. Irvine EJ, Whitehead WE, Chey WD, et al. Design of Treatment Trials for Functional Gastrointestinal Disorders. *Gastroenterology.* 2006;130(5):1538-1551.
17. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain.* 2005;113(1-2):9-19.
18. Klein KB. Assessment of treatment outcome in the functional gastrointestinal disorders. In: Corazziari E, ed. *Approach to the patient with chronic gastrointestinal disorders.* Milano, Italy: Messaggi; 1999.
19. Guy W. ECDEU Assessment Manual for Psychopharmacology. In: US Department of Heath E, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration, ed. Rockville, MD1976. .
20. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. *Aliment Pharmacol Ther.* 1997;11(2):395-402.
21. Larsen DL, Attkisson CC, Hargreaves WA, Nguyen TD. Assessment of client/patient satisfaction: development of a general scale. *Evaluation and program planning.* 1979;2(3):197-207.
22. Feinman RD. Intention-to-treat. What is the question? *Nutrition & Metabolism.* 2009;6:1-1.
23. Mallinckrodt C, Molenberghs G, Rathmann S. Choosing estimands in clinical trials with missing data. *Pharmaceutical statistics.* 2017;16(1):29-36.

24. Allison PD. Multiple Imputation for Missing Data: A Cautionary Tale. *Sociological Methods & Research.* 2000;28(3):301-309.
25. Cheema J. Some general guidelines for choosing missing data handling methods in educational research. *Journal of Modern Applied Statistical Methods.* 2014;13(53-75).
26. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Statistical Methods in Medical Research.* 2007;16(3):219-242.
27. Angrist J, Pischke J. *Mostly harmless econometrics: An empiricist's companion. .* Princeton, NJ: Princeton University Press; 2009.
28. Shah E, Kim S, Chong K, Lembo A, Pimentel M. Evaluation of Harm in the Pharmacotherapy of Irritable Bowel Syndrome. *The American Journal of Medicine.*125(4):381-393.
29. Lackner JM, Jaccard J, Baum C, et al. Patient-Reported Outcomes for Irritable Bowel Syndrome Are Associated With Patients' Severity Ratings of Gastrointestinal Symptoms and Psychological Factors. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2011;9(11):957-964.e951.
30. Pimentel M, Park S, Mirocha J, Kane SV, Kong Y. The Effect of a Nonabsorbed Oral Antibiotic (Rifaximin) on the Symptoms of the Irritable Bowel Syndrome. *Annals of Internal Medicine.* 2006;145(8):557-563.
31. Drossman DA, Chey WD, Johanson JF, et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome--results of two randomized, placebo-controlled studies. *Aliment Pharmacol Ther.* 2009;29(3):329-341.
32. Corazziari E, Bytzer P, Delvaux M, et al. Clinical trial guidelines for pharmacological treatment of irritable bowel syndrome. *Aliment Pharm Ther.* 2003;18(6):569-580.
33. Ford AC, Moayyedi P. Meta-analysis: factors affecting placebo response rate in the irritable bowel syndrome. *Aliment Pharm Ther.* 2010;32(2):144-158.
34. Elsenbruch S, Enck P. Placebo effects and their determinants in gastrointestinal disorders. *Nat Rev Gastro Hepat.* 2015;12(8):472-485.
35. Jones J, Boorman J, Cann P, et al. British Society of Gastroenterology guidelines for the management of the irritable bowel syndrome. *Gut.* 2000;47(suppl 2):ii1-ii19.
36. Mayer EA, Labus JS, Tillisch K, Cole SW, Baldi P. Towards a systems view of IBS. *Nat Rev Gastroenterol Hepatol.* 2015;12(10):592-605.
37. Moore KL, van der Laan MJ. Covariate adjustment in randomized trials with binary outcomes: targeted maximum likelihood estimation. *Stat Med.* 2009;28(1):39-64.
38. van der Laan MJ, Gruber S. Collaborative double robust targeted maximum likelihood estimation. *The international journal of biostatistics.* 2010;6(1):Article 17.

Table 1. Baseline Sociodemographic and Clinical Characteristics by Treatment Condition

Characteristic	Overall (n = 436)	MC-CBT (n = 145)	S-CBT (n = 146)	EDU (n = 145)
Age, mean (SD)	41.4 (14.8)	40.9 (14.6)	41.1 (14.4)	42.2 (15.4)
Women, N (%)	350 (80.3%)	124 (85.5%)	112 (76.7%)	114 (79.2%)
Race/ethnicity N (%)				
Non-Hispanic white	390 (89.4%)	133 (91.7%)	128 (87.7%)	129 (89.0%)
African-American	28 (6.4%)	8 (5.5%)	9 (6.2%)	11 (7.6%)
Other or missing	18 (4.2%)	4 (2.8%)	9 (6.2%)	5 (3.5%)
Marital status, N (%)				
Never married	185 (42.4%)	61 (44.1%)	60 (41.1%)	64 (44.1%)
Married	185 (42.4%)	68 (46.9%)	58 (39.7%)	59 (40.7%)
Separated/Divorced	57 (13.1%)	11 (7.6%)	26 (17.8%)	20 (13.8%)
Widowed	9 (2.1%)	5 (3.4%)	2 (1.4%)	2 (1.4%)
Income ($), mean (SD)	74.0 (54.2)	77.9 (56.4)	73.1 (52.2)	71.3 (54.0)
Education, N(%)				
High school or less	99 (22.7%)	31 (21.4%)	30 (20.5%)	38 (26.2%)
Associate or Vo-tech	65 (14.9%)	25 (17.2%)	22 (15.1%)	18 (12.4%)
College degree	142 (32.6%)	54 (37.2%)	41 (28.1%)	47 (33.1%)
Post-grad degree	127 (29.1%)	35 (24.1%)	52 (35.6%)	40 (27.6%)
Missing	3 (0.7%)	0	1 (0.7%)	2 (1.4%)
Employment status, N (%)				
Employed full- or part-time	277 (63.5%)	92 (63.4%)	91 (62.3%)	94 (64.8%)
Unemployed	109 (25.0%)	38 (26.2%)	40 (27.4%)	31 (21.4%)
Homemaker	13 (3.0%)	4 (2.8%)	5 (3.4%)	4 (2.8%)
Retired	33 (7.6%)	9 (6.2%)	9 (6.2%)	15 (10.3%)
Missing	4 (0.9%)	2 (1.4%)	1 (0.7%)	1 (0.7%)
Predominant bowel type, N (%)				
Constipation	130 (29.8%)	43 (29.7%)	40 (27.4%)	47 (32.4%)
Diarrhea	188 (43.1%)	59 (40.7%)	67 (45.9%)	62 (42.8%)
Mixed	98 (22.5%)	33 (22.8%)	35 (24.0%)	30 (20.7%)
Undifferentiated	20 (4.6%)	10 (6.9%)	4 (2.7%)	6 (4.1%)
Years with IBS, mean (SD)	17.1 (14.4)	15.7 (13.3)	17.7 (13.3)	17.7 (16.4)
Received medical care for IBS (lifetime), N (%)	328 (75.2%)	107 (73.8%)	116 (79.5%)	105 (72.4%)
IBS treatment-naïve, N (%)	10 (2.2%)	4 (2.6%)	3 (1.9%)	3 (1.9%)

Table 1. (Continued)

Assessment scores, mean (SD)				
IBS Symptom Severity Scale[a]	281.9 (72.1)	278.0 (68.6)	285.1 (76.7)	282.4 (71.0)
Brief Symptom Inventory[35,a]				
Anxiety	4.50 (4.50)	4.22 (4.26)	4.27 (4.41)	5.02 (4.81)
Depression	3.97 (4.29)	4.07 (4.47)	3.82 (4.33)	4.03 (4.09)
Somatization	4.22 (3.93)	4.16 (4.31)	4.00 (3.56)	4.54 (3.91)
Global Severity Index	12.7 (11.0)	12.4 (11.6)	12.1 (10.5)	13.6 (10.8)
Medical comorbidities[36], #	4.6 (4.9)	4.8 (5.2)	4.3 (4.7)	4.8 (5.0)
Psychiatric comorbidities[37], #	1.2 (1.6)	1.1 (1.5)	1.3 (1.7)	1.2 (1.7)
Medication use for IBS symptoms, (N, %)	292 (67.0%)	94 (64.8%)	95 (65.1%)	103 (71.0%)
Pain medication	35 (8.0%)	9 (6.2%)	13 (8.9%)	13 (9.0%)
Bowel medication	271 (62.2%)	86 (59.3%)	87 (59.6%)	98 (67.6%)
Multi-symptom medication	20 (4.6%)	6 (4.1%)	7 (4.8%)	7 (4.8%)
Psychiatric medication	26 (6.0%)	8 (5.5%)	12 (8.2%)	6 (4.1%)

(notes: [a] = Higher scores indicate more severe symptoms; IBS-SSS ≥300 = Severe)

Table 2: Percent of Responders on CGI as Reported by Patients and Physicians

	Per Protocol			Intent-To-Treat		
Condition	Immediate	3 Month	6 Month	Immediate	3 Month	6 Month
Patient-Report CGI						
MC-CBT	68.1% ± 8.1	64.0% ± 8.8	63.9% ± 8.8	61.0% ± 8.0	57.0% ± 8.4	56.6% ± 8.4
S-CBT	64.6% ± 8.9	64.6% ± 9.3	58.1% ± 9.4	54.5% ± 8.4	53.3% ± 8.6	48.1% ± 8.6
EDU	46.7% ± 8.8	49.5% ± 9.3	51.0% ± 9.6	43.5% ± 8.4	45.8% ± 9.0	47.0% ± 9.2
MC-CBT – S-CBT	3.5% ± 12.0	<1% ± 12.7	5.9% ± 12.9	6.5% ± 11.6	3.7% ± 12.0	8.5% ± 12.0
MC-CBT – EDU	21.5% ± 12.0**	14.5% ± 12.8*	12.9% ± 13.0[a,b]	17.6% ± 11.6**	11.2% ± 12.3[a,b]	9.6% ± 12.5
S-CBT – EDU	18.1% ± 12.5**	15.0% ± 13.1*	7.1% ± 13.4	11.1% ± 11.9[a,b]	7.5% ± 12.2	1.1% ± 12.6
MC-CBT – S-CBT CI	-8.5% to 15.5%	-13.2% to 12.5%	-7.0% to 18.7%	-5.1% to 18.0%	-8.3% to 15.8%	-3.6% to 20.5%
Physician-Rated CGI						
MC-CBT	63.0% ± 9.0	-	66.4% ± 9.1	55.7% ± 8.6	-	58.4% ± 8.9
S-CBT	61.0% ± 9.4	-	64.0% ± 9.9	50.6% ± 8.7	-	51.6% ± 9.2
EDU	43.6% ± 9.2	-	49.6% ± 10.5	40.4% ± 8.8	-	44.8% ± 10.0
MC-CBT – S-CBT	2.0% ± 13.0	-	2.4% ± 13.5	5.1% ± 12.2	-	6.8% ± 12.8
MC-CBT – EDU	19.4% ± 12.9**	-	16.8% ± 13.9*	15.2% ± 12.3**	-	13.7% ± 13.4*
S-CBT – EDU	17.4% ± 13.1*	-	14.4% ± 14.5[a,b]	10.1% ± 12.4	-	6.8% ± 13.6
MC-CBT – S-CBT CI	-10.0% to 15.0%	-	-11.1% to 15.9%	-7.1% to 17.3%	-	-5.9% to 19.6 %

(notes: * = $p < 0.05$, ** = $p < 0.01$, [a] = $p < 0.08$; [b] = trend p value using listwise deletion is $p < 0.05$ for chained equation missing data algorithm; MC-CBT - S-CBT CI = 95% CI for difference; numbers after ± are margins of error (half widths of 95% CIs); IBSOS was not designed to collect blind ratings at 3 month follow up)

Table 3: Means on CGI as Reported by Patients and Physicians

	Per Protocol			Intent-To-Treat		
Condition	Immediate	3 Month	6 Month	Immediate	3 Month	6 Month
Patient-Report CGI	*					
MC-CBT	5.79 ± 0.22	5.75 ± 0.23	5.70 ± 0.25	5.61 ± 0.21	5.55 ± 0.23	5.51 ± 0.24
S-CBT	5.76 ± 0.23	5.67 ± 0.24	5.64 ± 0.23	5.49 ± 0.22	5.38 ± 0.23	5.35 ± 0.22
EDU	5.43 ± 0.21	5.36 ± 0.23	5.42 ± 0.24	5.33 ± 0.20	5.2 ± 0.22	5.31 ± 0.24
MC-CBT – S-CBT	0.03 ± 0.31	0.08± 0.34	0.05 ± 0.34	0.12 ± 0.30	0.17 ± 0.32	0.16 ± 0.32
MC-CBT – EDU	0.36 ± 0.30*	0.39 ± 0.32*	0.28 ± 0.35	0.28 ± 0.29[a,b]	0.29 ± 0.32[a,b]	0.20 ± 0.34
S-CBT – EDU	0.33 ± 0.31*	0.31 ± 0.33[a]	0.22 ± 0.34	0.16 ± 0.29	0.12 ± 0.32	0.04 ± 0.32
MC-CBT – S-CBT CI	-0.28 to 0.35	-0.26 to 0.42	-0.29 to 0.39	-0.18 to 0.43	-0.15 to 0.49	-0.17 to 0.48
Physician-Rated CGI						
MC-CBT	5.69 ± 0.19	-	5.91 ± 0.18	5.50 ± 0.19	-	5.67 ± 0.20
S-CBT	5.70 ± 0.20	-	5.70 ± 0.24	5.42 ± 0.20	-	5.37 ± 0.23
EDU	5.28 ± 0.19	-	5.38 ± 0.24	5.20 ± 0.19	-	5.26 ± 0.24
MC-CBT – S-CBT	-0.01 ± 0.28	-	0.21 ± 0.30	0.08 ± 0.28	-	0.30 ± 0.30*
MC-CBT – EDU	0.41 ± 0.27**	-	0.53 ± 0.30**	0.30 ± 0.27*	-	0.42 ± 0.31**
S-CBT – EDU	0.42 ± 0.28**	-	0.31 ± 0.34[a,b]	0.22 ± 0.27	-	0.11 ± 0.33
MC-CBT – S-CBT CI	-0.29 to 0.26	-	-0.09 to 0.51	-0.20 to 0.35	-	0.01 to 0.61

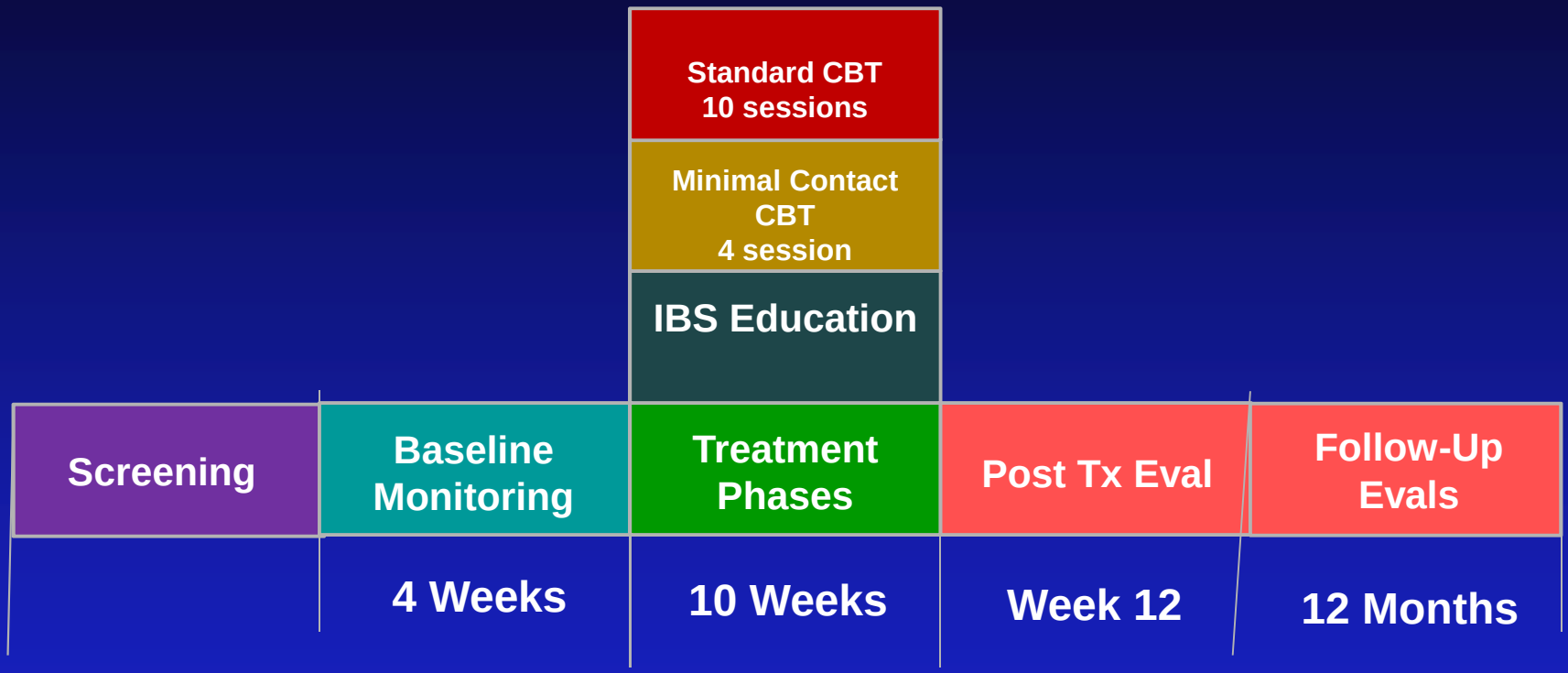
(notes: * = $p < 0.05$, ** = $p < 0.01$, [a] = $p < 0.08$; [b] = trend p value using listwise deletion is $p < 0.05$ for chained equation missing data algorithm; MC-CBT - S-CBT CI = 95% CI for difference; numbers after ± are margins of error (half widths of 95% CIs))

Table 4: Mean Change in IBS-SSS from Baseline and Patient Satisfaction

	Per Protocol			Intent-To-Treat		
Condition	Immediate	3 Month	6 Month	Immediate	3 Month	6 Month
IBS-SSS						
MC-CBT	-89.35 ±17.0	-105.9 ±17.7	-111.3 ±17.9	-80.69 ± 15.9	-95.27 ± 16.7	-99.09 ±17.0
S-CBT	-80.99 ±17.0	-103.2 ±16.4	-103.5 ±17.7	-67.57 ± 15.3	-87.10 ± 15.3	-85.16 ± 16.4
EDU	-84.43 ±14.6	-88.53 ±14.6	-97.93 ±15.4	-78.88 ± 14.3	-82.19 ± 14.2	-91.37 ± 14.9
MC-CBT – S-CBT	-8.39 ±24.0	-2.71 ±24.2	-7.74 ± 24.9	-13.11 ± 22.1	-8.16 ± 22.7	-13.93 ± 23.6
MC-CBT – EDU	-4.95 ±22.4	-17.41 ±22.9	-13.34 ±23.4	-1.81 ± 21.4	-13.08 ± 21.9	-7.72 ± 22.6
S-CBT – EDU	3.44 ±22.4	-14.70 ±22.0	-5.60 ±23.1	11.31 ± 21.0	-4.91 ± 21.0	6.21 ± 22.4
MC-CBT – S-CBT CI	-32.4 to 15.6	-26.9 to 21.5	-32.7 to 17.2	-35.2 to 9.0	-30.8 to 14.5	-38.0 to 9.7
Patient Satisfaction						
MC-CBT	28.9 ± 0.6	-	-	-	-	-
S-CBT	28.4 ± 0.7	-	-	-	-	-
EDU	26.6 ± 0.9	-	-	-	-	-
MC-CBT – S-CBT	0.70 ± 1.0	-	-	-	-	-
MC-CBT – EDU	2.27 ± 1.0**	-	-	-	-	-
S-CBT – EDU	1.79 ± 1.1**	-	-	-	-	-
MC-CBT – S-CBT CI	-0.3 to 1.6	-	-	-	-	-

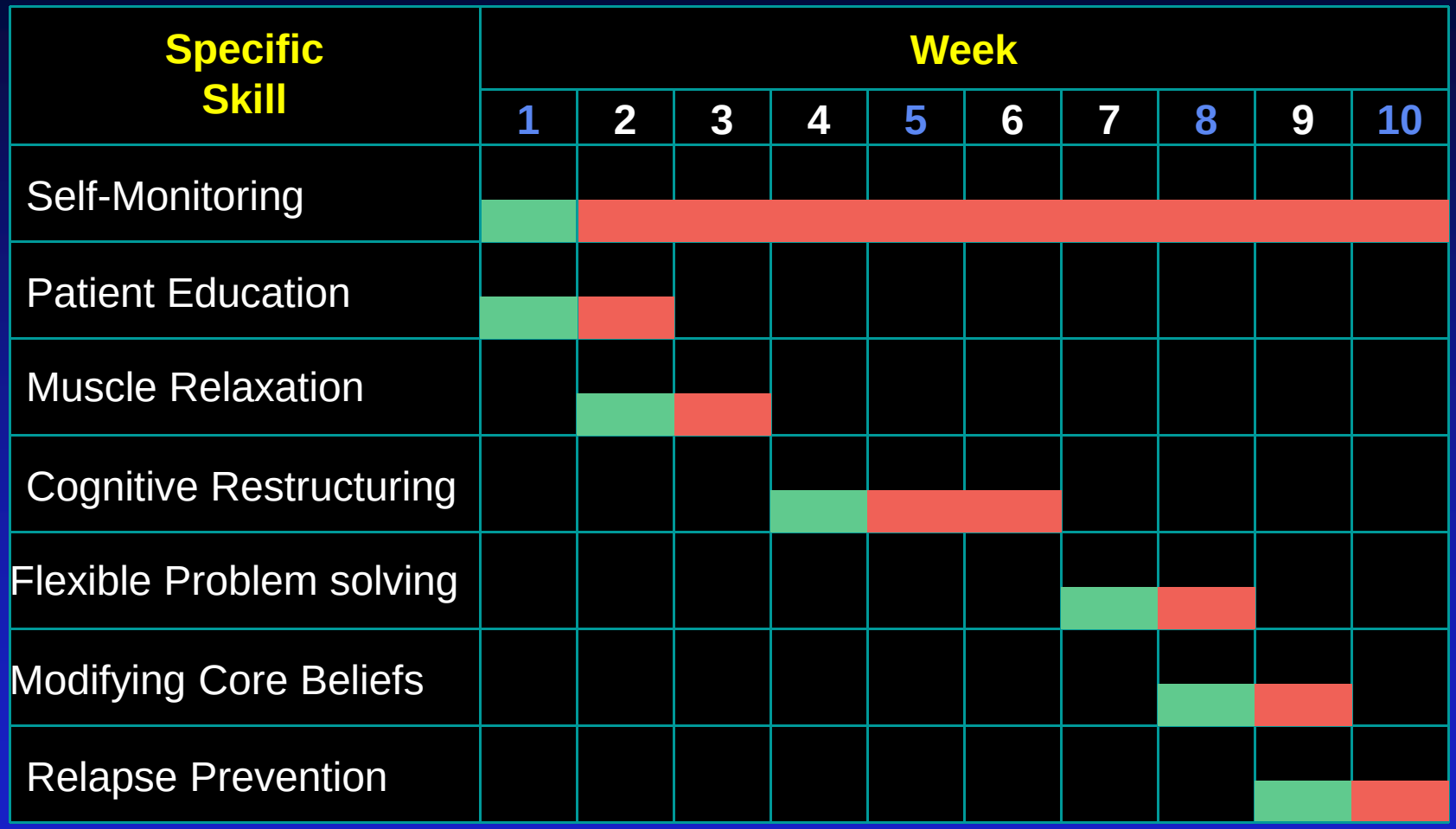
(notes: * = $p < 0.05$; mean IBS-SSS at baseline across conditions = 281.9 with a margin of error of ± 7.4; all changes from baseline are statistically significant, $p < 0.01$; Unadjusted standard deviations for IBS-SSS change scores at each time point are about 19.0, indicating substantial standardized effects (Cohen's d) relative to baseline; MC-CBT - S-CBT CI = 95% CI for difference; Cohen's d for patient satisfaction for MC-CBT- EDU = 0.53 and for S-CBT- EDU = 0.37; numbers after ± are margins of error (half widths of 95% CIs)

Study Design



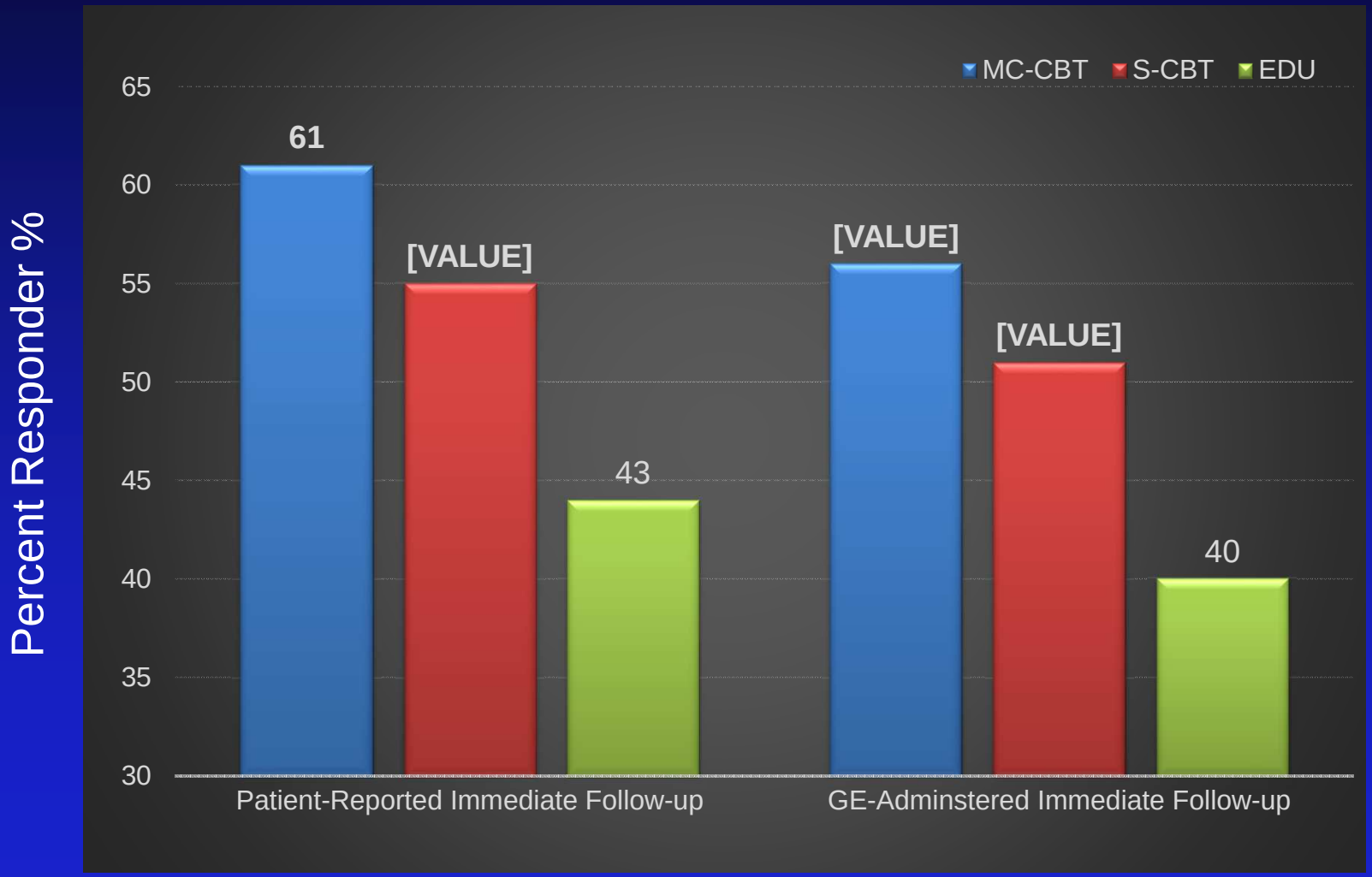
Note: Follow-up assessment done 2 weeks after treatment ends and at 3, 6, 9, and 12 month follow-ups.

Overview of CBT for IBS



Source: Lackner, Jaccard, et al, 2008

Global Improvement of IBS Symptoms at Week 12: ITT



MCCBT – EDU, $p < .01$; S-CBT- EDU, $p < .05$

IBSOS 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)

Trial Logo

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 home-based, patient-administered version of CBT compared to a clinic-based, therapist administered version of CBT and a psychological placebo condition (education/support) 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

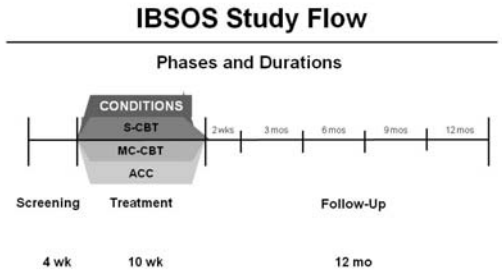
- Minimal Contact Cognitive Behavior Therapy (MC-CBT)
- Standard Cognitive Behavior Therapy (S-CBT)
- Attention Control Condition (four-session) (ACC)

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
• A minimum 6th grade reading level based on the Wide Range Achievement Test (WRAT 4) if necessary
• Participant is willing to be randomized to CBT or Support/Education to which s/he has been assigned and to adhere to protocol requirements
• Participant is willing to attend regularly scheduled therapy sessions during active phase of the trial
• Participant is willing to be contacted and scheduled for follow-up assessments at week 12 and 3, 6, 9, and 12 months after the conclusion of acute treatment phase
• Participant is able to a maintain daily symptom diary and complete questionnaires through treatment and at regularly scheduled follow ups
• Participant has access to a telephone
• Participant is willing and able to provide adequate information for locator purposes

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

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).

Target Enrollment

The study is expected to enroll (i.e., randomize to treatment) a total of 480 participants. The projected target enrollment date is 12/31/2015.

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), a 12-week follow-up (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. 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 12W FU 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 mediators of response to treatment. For mediation analyses, both mediators and outcomes are measured at baseline as well as 12W FU, 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 12W FU. 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 12W FU. A recency mediation model states that the level of IBS self-efficacy at the last treatment session (W12) is the primary mediator of acute 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 12W FU (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 12W FU outcome is used as the criterion. All three sources of influences will be parameterized and modeled as predictors of change at 12W FU as well as the decay functions characterizing change from 12W FU 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. The primary means of analysis is intent to treat.

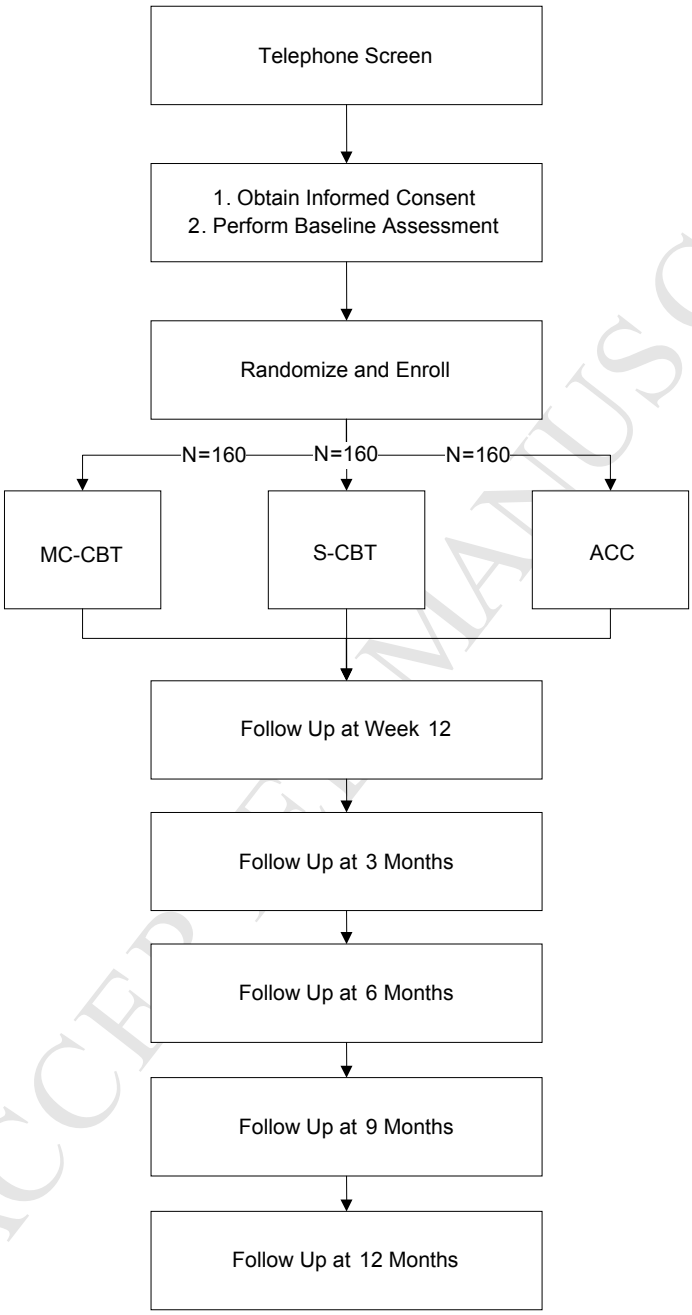


Figure 1: IBSOS Study Flow

IBSOS Organization and Personnel

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.

Key Personnel

Study Chair / Project PI:
Jeffrey M. Lackner, PsyD‡
University at Buffalo

Co-Investigator:
Laurie Keefer, PhD‡
Northwestern University

NIH/NIDDK Project Scientist:
Frank A. Hamilton, M.D., M.P.H.‡

Data Coordinating Center, Chair:
Kenneth Wood, Frontier Science

Study Gastroenterologists:
Darren Brenner, MD (Lead)
Northwestern University

Leonard Katz, MD
Michael Sitrin, MD
University at Buffalo

Project Coordinators:
Rebecca Firth, MHA‡
University at Buffalo

Jason Bratten, BS, PMP‡
Northwestern University

Statisticians:
James Jaccard, PhD
New York University

Chang-Xing Ma, PhD
University at Buffalo

Safety Officer:
Loraine Collins, PhD
University at Buffalo

‡Executive Committee Member

IBSOS Organizational Structure

NIDDK U01 DK0077738

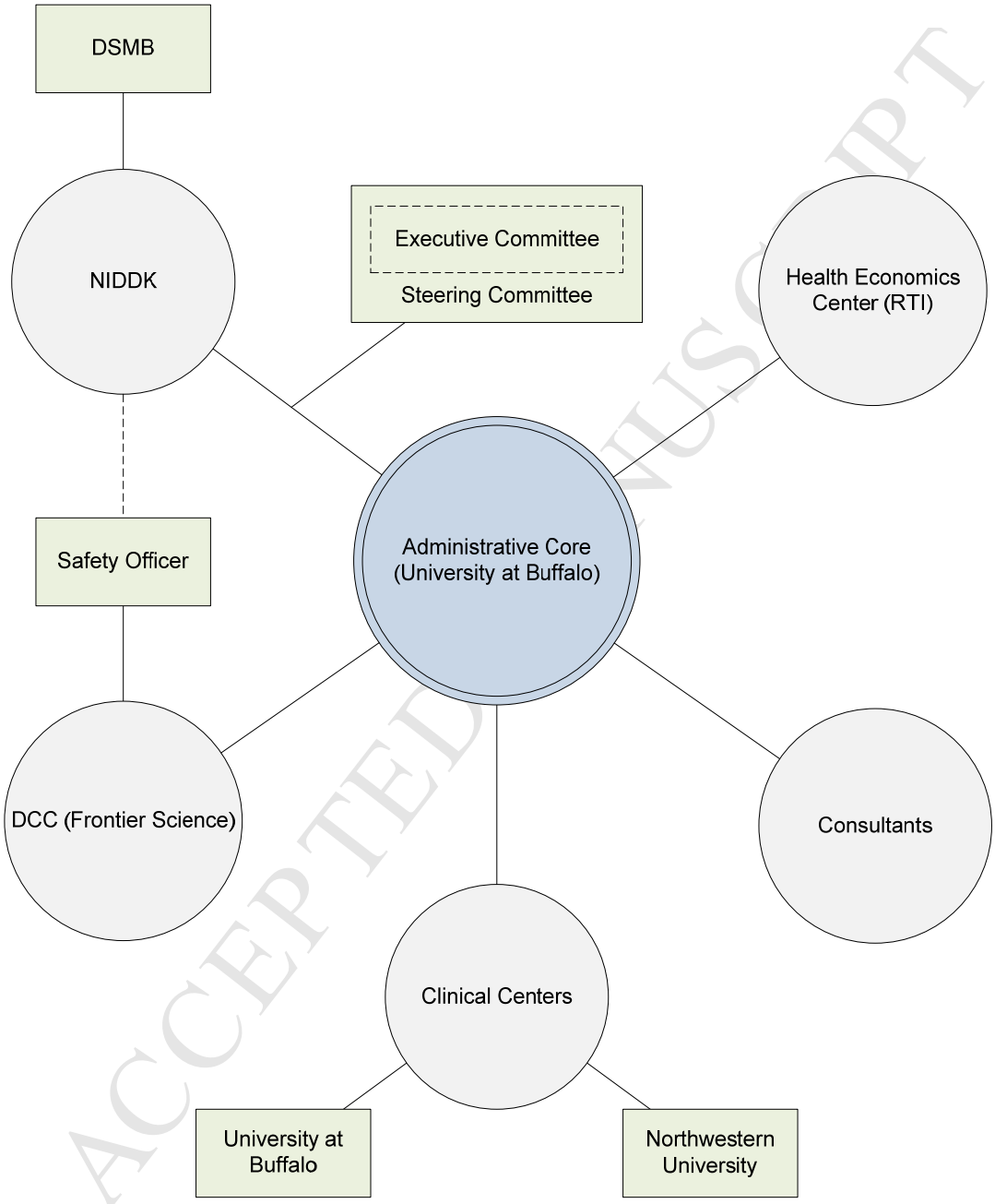


Figure 2: IBSOS Organizational Structure

Grant Year	Dates	Planned
Year 1	5/1/08 - 4/30/09	Planning / ARRA application
Year 2	5/1/09 - 4/30/10	Planning/ ARRA resubmission/ loss of a site
Year 3	5/1/10 - 4/30/11	2 sites / enrollment at 60/site/year 120
Year 4	5/1/11 - 10/31/11 11/1/11- 4/30/12	2 sites / enrollment at 60/site/year 120 2 sites / UB 60 & NU 40
Year 5	5/1/12 - 4/30/13	2 sites / UB 60 & NU 40
Year 6	5/1/13 - 4/30/14	2 sites / UB 60 & NU 40
Year 7	5/1/14 - 4/30/15	2 sites / UB 60 & NU shifts to f/u phase
Year 8	5/1/15 - 4/30/16	UB enrolls remaining subjects (12/31/15) and finishes tx phase NU finishes remaining 20+ f/u assessments and site close out
Year 9	5/1/16 - 4/30/17	UB completes remaining f/u assessments Shift focus to data analysis and study close out

Table 1: IBSOS New Timeline