

Study design considerations for irritable bowel syndrome clinical trials

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Abstract

Clinical trials of therapies intended to alleviate symptoms of irritable bowel syndrome (IBS) are prevalent. However, the ideal study design remains elusive since there is no obvious pathophysiological target and no universally accepted endpoint to assess symptom improvement in IBS. The purpose of this paper is to identify and discuss the most problematic issues in the design of clinical trials intended to evaluate the effectiveness of treatments for IBS symptoms. Lack of standardized diagnostic criteria, symptom variability, heterogeneous subject characteristics, large placebo effects, lack of statistical power, inappropriate endpoint selection, and poorly selected study design are the most critical issues that may confound study outcomes in IBS clinical trials.

Keywords Clinical trial, irritable bowel syndrome, study design

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Introduction

Irritable bowel syndrome (IBS) is a chronic, relapsing functional gastrointestinal disorder that affects 11% of the global population [1]. The cardinal symptoms of IBS include bloating and abdominal pain/discomfort associated with changes in bowel habits [2,3], although tremendous variability exists among patients [4]. IBS symptoms have a significant negative impact on daily living and result in lower quality of life, interfere with social interactions, and lead to high health care costs [5,6].

A number of risk factors for IBS have been identified including female gender, psychological problems, stress, food intolerance, and bacterial overgrowth of the small intestine [2,7-9]. However, the cause of this disorder is unknown and likely multifactorial. Consequently, identification of effective IBS treatments remains a challenge.

Initial management of IBS symptoms focuses on lifestyle and dietary habits as possible culprits. IBS symptoms may be exacerbated by sedentary lifestyle, lack or excess of dietary fiber intake, high caffeine consumption, high lactose intake, and/or nutritional deficiencies. If lifestyle modifications are unsuccessful in alleviating symptoms, probiotics or medications may be prescribed based on the dominant symptoms. Unfortunately, heterogeneity in the design and conduct of IBS clinical trials hinders the ability to systematically compare

studies and, consequently, to draw firm conclusions regarding the safety and efficacy of therapeutic options [10-12]. There is much uncertainty regarding the ideal design and conduct of such clinical trials since there is no obvious pathophysiological process in IBS and, consequently, no universally accepted methodology or endpoint to assess symptom improvement. The fact that the syndrome may manifest with predominant constipation (IBS-C), predominant diarrhea (IBS-D), a combination of the two (IBS-M, or "mixed"), or undefined (IBS-U) further complicates development of standardized clinical trial designs. Numerous factors must be considered in the development of such studies in order to ensure a rigorous, yet practically feasible, evaluation of an investigational product. The purpose of this paper is to identify and discuss critical areas in the design of IBS clinical trials that pose common problems to researchers.

Study design considerations for IBS trial

Diagnostic criteria

IBS is diagnosed solely on the basis of patient-reported symptoms when obvious biochemical and anatomic pathology have been excluded since no biomarkers have been identified to date. Despite numerous efforts to standardize the definition of IBS [13-16], various diagnostic criteria are used in practice. Trials of IBS have historically been confounded by enrolling subjects who self-reported IBS or by using one of several diagnostic criteria, which complicates comparisons among trials. The use of recognized diagnostic criteria does allow for a certain degree of standardization in patient characteristics and Rome II [16] and Rome III [14] are useful resources for

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this purpose. In the US, the Food and Drug Administration has published guidance stating “prospective IBS clinical trials should enroll patients who meet the subtype-specific Rome III IBS diagnostic criteria” [17]. However, the Rome criteria have been met with wide criticism [18-21]. While some authors have reported that the Rome III criteria accurately identify patients labeled with IBS in primary care [22], most argue that the Rome III criteria are not well validated [23], are rarely used in clinical practice [23], and have only modest ability in accurately classifying IBS patients [24,25]. Nonetheless, the Rome criteria remain the best accepted tools for standardized IBS diagnosis [14,16].

Symptom variability

IBS presents as a constellation of gastrointestinal symptoms that recur on an episodic basis and vary widely among patients. A study of 249 IBS patients demonstrated that 39% had predominant symptoms of IBS-D, 31% with IBS-C, 6% with IBS-M, and 24% with IBS-U [26]. A recent meeting of international experts on IBS concluded that bloating was the most troublesome symptom in IBS patients, not abdominal pain as previously thought [3]. Therefore, clinical trials should be designed to account for fluctuations in symptoms and the potential for wide variations in bowel habits. A run-in period of 1 to 3 weeks has been advocated to monitor placebo responses before randomization [27,28]. Subjects who demonstrate significant symptom improvements or who demonstrate lack of compliance during this period may be excluded from further study participation although the validity of this practice is debatable [29]. Studies that measure only pre- to post-treatment effects may miss important data trends in the interim periods. Subject diaries that record frequency and severity of daily symptoms may be used to ensure that symptom severity fluctuations are identified and taken into account during data analysis. Area under the curve analyses, as proposed by Matthews and coworkers, are ideal for reporting such data [30].

Subject characteristics

A female predominance should be anticipated in most IBS clinical trials. Women present with IBS more commonly than men with a ratio of 2:1 ratio [31]. Furthermore, IBS-C is more common in women while IBS-D is slightly more common in men [32,33]. The age range of eligible subjects should span a wide range since IBS prevalence peaks at ages of 25 to 35 years in women and at 30 to 50 years in men [34]. Ethnicity is an important consideration in the design of IBS trials with wide ethnic variation in IBS prevalence and subclassification [35]. Additional factors that influence IBS symptoms include comorbid conditions, diet, and mental health status. These items should be considered as stratification factors or covariates to control for potential confounding effects [36-39]. For example, depression is reported in 30%

of IBS patients compared to 18% of the general population. Similarly, 16% of IBS patients report anxiety versus 6% of the general population [38]. Obviously, patients with psychological issues represent a fair proportion of the IBS population and controls should be put in place to minimize the influence of changes in medication, uncontrolled psychological disorders, or inaccuracies related to self-reported diagnoses. Use of periodic dietary recalls during the study provides objective data that may be used to determine if dietary habits may have influenced clinical trial outcomes given the known relationship of changes in fiber, fat, and carbohydrate intake on symptom severity [37,40]. Exercise can influence IBS symptoms [41] and, therefore, quantification of physical activity habits using simple tools [42] is encouraged. Women report increased IBS symptom severity during menses [32] and, therefore, consideration of timing of enrollment and/or recording of menses timing in the study database as a covariate should be considered. Finally, the use of multiple enrolling sites is strongly encouraged in order to maximize external validity and to minimize the confounding influence of regional variations in diet, exercise habits, and ethnicity.

Placebo effects

The use of a placebo comparator in IBS trials is crucial. There are typically no ethical dilemmas to be encountered by administering placebo since no consistently effective treatments for IBS are available. The placebo effect is a common phenomenon in clinical research in which subjects allocated to a blinded placebo unexplainably experience symptom amelioration. The placebo effect has been attributed to several possible factors including the quality of the patient-physician interaction, the belief that one is assigned to the active product, and natural history [43]. Others have suggested that since there is a strong positive relationship between treatment effects and the risk of adverse events (AEs) with active treatments, that the mere presence or absence of an AE may inadvertently unmask the treatment assignment [44]. Even inconspicuous components of the clinical trial process such as informed consent language have been shown to influence patient perception of treatment benefit [45].

A review of 25 randomized controlled studies of various therapeutic agents for IBS reported a median placebo response of 47% [12]. This finding was corroborated in a review of 19 randomized controlled studies of complementary and alternative medicines for IBS treatment that reported an overall placebo response of 43%, with higher placebo responses associated with longer duration of treatment and a greater number of office visits [46]. Others have similarly reported that the placebo response initially increases, stabilizes over a period of 2 to 5 weeks, peaks at 8-12 weeks, and then decreases steadily thereafter [12,47]. Therefore, IBS trials of less than 5 weeks duration are not recommended due to unstable placebo group estimates while trials of 5 to 12 weeks duration must account for a considerable placebo effect with concomitant increases in sample size during the planning phase of the trial. From

a study design perspective, it appears that a trial of longer duration with less frequent follow-up visits may help minimize the placebo effect and, consequently, improve statistical power.

Effect to detect

Formal power analyses should be conducted with appropriate assumptions for treatment effect and placebo response derived from previous relevant studies. For example, if the anticipated treatment effect of a product (i.e. magnitude of benefit with product over the placebo) were anticipated to be 20% with a 10% placebo response, the required sample size for a trial would be 156 subjects (78 per group), assuming $\alpha=0.05$, statistical power of 80%, and anticipated attrition of 20%. However, given these parameters, if the anticipated treatment effect of the product remained 20% but there was a 30% placebo response, the sample size would be 234 subjects (117 per group). Put simply, even if the anticipated treatment effect of a therapy remains static, greater placebo effects mandate a greater sample size. The use of continuous endpoints allows greater reporting detail and frequently offers greater statistical power versus dichotomous (i.e. yes/no) outcomes, although this choice must be balanced by the clinical relevance of the chosen endpoint.

Clinical endpoints

Abdominal pain was historically believed to be the hallmark feature of IBS [48] though newer research suggests that bloating is the predominant complaint of patients [3]. Although bowel symptoms are another hallmark of this condition, bowel-related symptoms differ among patients such that no single endpoint is appropriate. In fact, patient presentation varies so widely among patients with IBS-C and IBS-D that these subjects are frequently studied in separate clinical trials [49]. For example, stool consistency assessed with the Bristol Stool Form (BSF) would be a poor endpoint for the entire cohort in an IBS trial since clinical improvement in those with predominant symptoms of constipation is characterized by higher BSF scores while clinical improvement in those with diarrhea would yield lower BSF scores resulting in a neutralizing of the overall treatment effect. Stratification of subject enrollment by predominant symptom and clearly defining clinical success according to these strata may help to differentiate clinical improvements by specific symptoms.

Numerous relevant endpoints may be considered for a clinical trial of IBS. Use of well-accepted instruments to measure each endpoint is crucial to obtaining valid and reproducible results. Several endpoints, and available instruments with which to measure them, are considered below:

Adequate relief

Historically, binary global assessment questionnaires have been used as primary endpoints in a number of IBS

trials with pharmacological agents [50]. Perhaps the most commonly used global assessment of IBS symptoms is IBS-Adequate Relief (IBS-AR), which simply asks the following question, "In the last 7 days, have you had adequate relief of your IBS symptoms?". This endpoint has numerous advantages. The IBS-AR is easy to administer, easy to understand, responsive, reproducible, and correlates well with IBS symptoms [51]. Furthermore, the FDA, Rome III, and other investigators have encouraged the use of IBS-AR in IBS clinical trials [52-55].

However, the IBS-AR suffers from serious limitations. First, as IBS encompasses a constellation of symptoms that vary from subject to subject, a binary endpoint does not effectively capture the treatment response of a product on critical individual symptoms. Second, the sample size required to detect statistically significant differences between groups is largest when the outcome is binary (i.e. yes/no). A considerable increase in power, with a concomitant reduction in sample size, may be obtained if a continuous or ordinal endpoint can be used. For example, Table 1 details the exponential increase in required sample size with progressively smaller treatment effects, assuming $\alpha=0.05$, statistical power of 80%, and estimated attrition of 20%, while Table 2 shows the required sample size for means and standard deviations of continuous outcomes. This is an important consideration since the effect size of IBS treatments on clinical symptom improvement is often small to moderate.

Table 1 Sample size required for varying magnitudes of adequate relief of symptoms

Adequate relief (%) [*]		Total sample size required [†]
Active product	Placebo	
75	50	145
70	50	233
65	50	423
60	50	968

^{*}Percentage of subjects who report adequate relief of symptoms; [†]Assuming a parallel-group, two-arm study with 1:1 treatment allocation, $\alpha=0.05$, power=80%, and 20% attrition

Table 2 Sample size required for varying magnitudes of improvement in symptom severity measured on a continuous scale

Mean symptom score		Common standard deviation	Total sample size required [*]
Active product	Placebo		
2.5	5.0	2.5	44
3.0	5.0	2.5	66
3.5	5.0	2.5	114
4.0	5.0	2.5	250

^{*}Assuming a parallel-group, two-arm study with 1:1 treatment allocation, $\alpha=0.05$, power=80%, and 20% attrition

Abdominal pain

Abdominal pain is typically measured with a visual analogue scale (VAS), in which subjects make a mark along a 10-cm line indicating their level of discomfort, or with a Likert scale, which presents ordered categories from which the subject must choose. Subjects use a VAS or Likert scale to rate their worst abdominal pain over the past 24 h on a daily basis (typically using a diary). Improvements in abdominal pain of at least 30% compared to baseline have been proposed as clinically meaningful changes [54].

Stool consistency

Stool consistency is rated with the BSF [56]. Subjects rate the consistency of each bowel movement in a daily diary as follows: 1 = separate hard lumps like nuts, difficult to pass; 2 = sausage shaped but lumpy; 3 = like a sausage but with cracks on surface; 4=like a sausage or snake, smooth and soft; 5 = soft blobs with clear-cut edges; 6 = fluffy pieces with ragged edges, a mushy stool; and 7 = watery, no solid pieces, entirely liquid. Stool consistency, but not stool frequency, correlates with colonic transit time and may be a better indicator of bowel function [57]. The stool consistency entry criterion for IBS-D patients has been proposed to be a BSF score of 5 or higher [54]. An improvement of ≥ 1 in the weekly BSF average may be used as the threshold for identifying a responder in IBS-D patients [54].

Stool frequency

Stool frequency is assessed by the number of complete spontaneous bowel movements (CSBMs) per day, recorded in a subject diary [54]. A CSBM is defined as a spontaneous bowel movement that is accompanied by the subject self-reporting a feeling of complete emptying of the bowel. The stool frequency entry criterion for IBS-C patients may be defined as less than 3 weekly CSBMs [54]. An increase of 1 CSBM per week compared to baseline is proposed as a clinically meaningful improvement in IBS-C patients [54].

Colonic transit time

Colonic transit time (CTT) assesses the time required for stool to pass through the colon. Although several measurement methods exist, the most common utilize the classic single film estimate [58] where subjects ingest radiopaque markers each day for 3 to 6 consecutive days prior to abdominal x-rays taken at pre- and post-treatment. The number of markers present in the right, left, and rectosigmoid colon are summed to yield a total marker count and standard algorithms are used to estimate CTT [59,60]. Wireless motility capsules that measure pH, pressure and temperature have been utilized for CTT measurement with increasing frequency over the last several years [61,62]. This technique is advantageous in that patient compliance is not a concern and there is no radiation exposure from x-rays as with radiopaque markers. The main disadvantage of wireless motility capsules is that the cost is significantly higher than that of radiopaque markers.

IBS global assessment of improvement scale (IBS-GAI)

The IBS-GAI asks a single question, "Compared to the way you felt before you entered the study, have your IBS symptoms over the past 7 days been: 1)"Substantially Worse"; 2)"Moderately Worse"; 3) Slightly Worse; 4)"No Change"; 5) Slightly Improved"; 6) Moderately Improved"; or 7) Substantially Improved" [63]. Subjects who report "moderately improved" or "substantially improved" are often considered responders to treatment [64].

IBS symptom severity scale (IBS-SSS)

The IBS-SSS is a 5-question survey that asks the severity of abdominal pain, frequency of abdominal pain, severity of abdominal distention, dissatisfaction with bowel habits, and interference with quality of life over the past 10 days. Subjects respond to each question on a 100-point visual analogue scale [65]. Scores on the IBS-SSS can range from 0 to 500 with higher scores indicating more severe symptoms. Subjects can be categorized as having mild (75-175), moderate (175-300), or severe (>300) IBS. A decrease of 50 points is associated with a clinically meaningful improvement [65].

IBS quality of life (IBS-QOL)

The IBS-QOL is a 34-item questionnaire that assesses the degree to which IBS interfered with quality of life for a subject over the past 30 days. Each item is rated on a 1 to 5 Likert scale, with higher values indicating a lower quality of life [66]. Scores are summed to comprise eight subscales including a total score with a range of 34 to 170. A decrease of 10 points or more is considered a clinically meaningful improvement [64].

Gastrointestinal symptom rating scale (GSRS)

The GSRS questionnaire was originally developed for dyspeptic patients but was later validated in patients with IBS [67]. The GSRS is a 15-item instrument designed to assess common gastrointestinal symptoms. The questionnaire has five subscales (reflux, diarrhea, constipation, indigestion, and abdominal pain) with subscale scores ranging from 1 (no discomfort) to 7 (severe discomfort). Higher scores represent higher symptom burden.

Functional bowel disorder severity index (FBDSI)

The FBDSI is comprised of three key items including severity of current pain measured on a VAS, diagnosis of chronic functional abdominal pain, and number of physician visits over the past 6 months. Patients can be classified with mild (<37), moderate 37-110, or severe (>110) disease [68].

AEs

A thorough evaluation of AEs, regardless of their relationship to the experimental product, should be an integral component of all IBS clinical trials. The harms associated with IBS treatments have been well documented [44,69] and must be accurately recorded in order to clarify the benefit: risk profile of novel therapies. The Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug

Dictionary (WHODRUG) are useful tools for standardized collection of AEs in clinical trials [70]. In the absence of one of these medical dictionaries, customized AE code lists may be utilized. In general, AEs are classified by type, seriousness, severity, and relationship to the investigational product. Case report forms that merely ask the investigator to describe the AE in a text field are to be avoided.

Additional endpoints

Importantly, there are no identifiable biochemical or anatomical manifestations of IBS. Therefore, clinical outcomes in IBS patients are generally limited to self-reported symptoms. Other endpoints that further characterize the utility of therapies such as cost effectiveness [71] or functional net value [72] may be considered although their use is not widespread. Given the multifactorial presentation of IBS and the lack of a single appropriate endpoint for the measurement of product effectiveness, multiple endpoints are encouraged. In fact, the FDA has proposed that abdominal pain and stool consistency should be used as co-primary endpoints in clinical trials of IBS therapies [54]. Importantly, primary and secondary endpoints should be specified *a priori* with an appropriately conducted power analysis that accounts for multiplicity and possible confounder variables.

Study design

The double-blind, randomized, placebo-controlled, parallel group trial is the most commonly utilized study design in IBS trials. While we advocate that double-blinding, randomization, and placebo controls should always be utilized in such studies, several study design options exist that may prove fruitful in limiting placebo effects, reducing sample size, and encouraging subject recruitment.

Run-in period

Run-in periods are integral design components of IBS trials that are intended to exclude potential subjects who meet initial eligibility requirements but lack the symptom severity or frequency required to meet IBS diagnostic criteria in the post-screening follow-up period. Since about 75% of IBS patients with moderate pain report a symptom frequency of at least 2 days per week, this has been proposed as the minimum symptom frequency in order for a potential study subject to successfully complete the run-in period [73,74]. The exclusion of potential subjects who report adequate relief of symptoms at the screening visit has also been proposed [64].

On balance, the use of a run-in period is controversial. Although excluding high placebo responders and subjects with lack of symptoms may initially appear to be an attractive option, this creates an artificially biased cohort of subjects that will more than likely experience regression to the mean (i.e. improvements in symptom severity) with or without treatment. Run-in periods are also inappropriate in short-term trials designed to resolve a brief period of IBS symptom

exacerbation since spontaneous symptom resolution is often observed when patients are followed for longer periods.

Cross-over design

The randomized, controlled, parallel-group clinical trial is the most common design in that each group of subjects is exposed to only one study treatment. However, the parallel design has a main limitation, which is the requirement for a relatively large sample size. In certain trials, the cross-over design, where subjects are exposed to both treatments in random order separated by a washout period, may be considered since this design results in a much smaller sample size compared to the parallel design because variability is reduced with each subject serving as his or her own control. For example, in a clinical trial assuming a moderate effect size of 0.5, $\alpha = 0.05$, statistical power of 80%, and estimated attrition of 20%, the total required sample size is 160 subjects (80 per group) in a parallel design. However, with the crossover design, the sample size is only 43 subjects. A limitation of the crossover design is that subjects must complete both intervention periods. For this reason, the sample size must be adjusted to allow for higher attrition vs. parallel-group studies.

There are other limitations of the crossover design. This design is not appropriate in interventions with a prolonged carry-over effect, which may result in a lingering treatment effect of the first intervention after the washout period. The duration of the washout period should always be longer than the time required for a treatment effect to diminish after discontinuing product use. Because of the importance of keeping subjects in the trial through both intervention periods, the duration of the trial should be considered; a clinical trial with a 2-week run-in period, a 12-week intervention period, and a 6-week washout period may not be appropriate in a crossover design since the total duration of subject participation would be 32 weeks (as opposed to 20 weeks in a parallel design). In IBS trials, the crossover trial likely has limited utility unless the treatment duration is short, the carryover effects of product administration are known to resolve over a short period and sample size estimates account for reasonable subject attrition rates.

Unequal treatment allocation ratio

Subjects may be unwilling to participate in clinical trials because there is a 50% chance they will be randomized to the placebo group. Although a 1:1 randomization scheme is typically utilized in randomized parallel group trials, unequal randomization strategies are valid and should strongly be considered in IBS trials or any trial in which subjects may be hesitant to participate for fear of placebo assignment [75]. There are disadvantages of unequal allocation that must be mentioned at the outset. First, one must ensure that the placebo group is of adequate size when using unequal allocation techniques. For example, in a trial of 200 subjects, the placebo group will have 100 subjects when equal allocation is used but only 50 subjects with 3:1 allocation. Second, the total sample size requirement increases slightly with unequal allocation although decreases in statistical power

Table 3 Recommendations for optimal clinical trial design in irritable bowel syndrome studies

Study design component	Clinical study recommendation	Next research steps
Diagnostic criteria	Utilize Rome II or III criteria	Develop new diagnostic criteria validated against patient symptoms typically seen in clinical practice
Symptom variability	Use patient diaries to record daily symptom fluctuations	Further develop electronic data collection tools (e.g. apps, email-based software) to enhance diary compliance
	Utilize a run-in period to ensure stability of untreated IBS symptoms	Identify factors responsible for symptom variability; develop validated questionnaires that account for day-to-day symptom fluctuations
Subject characteristics	Collect detailed information on potential confounders (e.g. diet, mental health, comorbidities) and use as stratification factor or covariate	Identify accurate and reliable biomarkers for IBS
Placebo effects	Assume significant placebo effects and incorporate methods to minimize this effect	Identify objective markers that reliably identify placebo responders
Effect to detect	Perform power calculations that consider a realistic range of plausible treatment effects, including consideration for significant placebo effects	Explore study designs such as Bayesian models or adaptive sample size re-estimation strategies that may improve trial efficiency with smaller sample sizes
Clinical endpoints	Use multiple valid and reliable tools that assess efficacy and a standardized adverse event collection database or code list	Develop validated tools that accurately and reliably assess primary complaints of typical patients seen in clinical practice
Study design	Double-blind, randomized, placebo-controlled trials provide the highest level of evidence for a therapeutic agent	Identify methods to structure clinical trials that maintain internal validity without compromising generalizability to the general population

are modest unless the active-to-placebo ratio is greater than 3:1 [76]. The main advantage of this scheme is in improved subject recruitment speed. A subject will likely be much more willing to participate in a trial if the chances of active group assignment are 67% (with 2:1 allocation) than if the chances are 50% (with 1:1 allocation). Objective data regarding the success of this scheme, however, are lacking.

Concluding remarks

We summarize our general recommendations for IBS clinical trial design and for future research in this area in Table 3. The ideal clinical trial design for assessing the effectiveness of therapies for IBS symptoms remains elusive and must be determined on an individual basis. A study design that considers enrollment of well-characterized subjects, measures specific and relevant endpoints, and controls for potential confounders is crucial to clinical trial success.

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