CLINICAL INVESTIGATION

What should be the primary end point in irritable bowel syndrome?

Irritable bowel syndrome, one of the most common gastrointestinal disorders, is characterized by abdominal pain/discomfort and disturbances in bowel functions. Choosing the correct primary end point in irritable bowel syndrome clinical trials has a profound impact on whether a novel therapeutic may be advanced to the next stage of clinical development. During the past decade, both the US FDA and the European Medicines Agency have issued guidance documents recommending primary end points for irritable bowel syndrome studies. Currently these guidance documents are not harmonized, and some of the recommended end points have not gone through a validation process. The current perspective provides the author's recommendation for what should be the primary end point in irritable bowel syndrome clinical trials.

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Irritable bowel syndrome (IBS) is a chronic, episodic disorder characterized by abdominal pain and/or discomfort and associated disordered bowel functions. The bowel abnormalities may manifest as constipation, diarrhea, or an alternation between constipation and diarrhea; these bowel patterns define the subtypes of IBS as constipation-predominant (C-IBS), diarrhea-predominant (D-IBS) or mixed or alternating IBS (M- or A-IBS), respectively. In most cultures, IBS is a female-predominant disorder with prevalence estimates of 6–12% [1–4]. In routine clinical practice, the diagnosis of IBS is made when a patient reports a constellation of clinical symptoms in the absence of a definable organic pathology [5–6].

IBS is associated with significant morbidity and healthcare expenditures [3,4,7–22]. It is estimated that 70–75% of IBS patients are not medical consulters at any point in time, but IBS still accounts for over 10% of the patients seen in primary care and approximately a third of those seen by gastroenterologists [1]. IBS patients miss work more often than non-IBS patients, and have increased healthcare expenditures and more physician visits. Health-related quality of life is markedly reduced in patients with IBS [7,9–12,19,22]. Over the years, the absence of an identifiable organic pathology has led some to question whether IBS represents a 'real disease' versus a psychosomatic condition characterized by abdominal pain. Due to the the lack of a definable biopsy, serology or radiographic finding in diagnosing IBS in clinical trials, robust trial design is of paramount importance for evaluation of novel therapeutic agents.

Selection of the primary end point in clinical trials is a critical design feature. The statistical and clinical significance of a study's primary end point determines whether the study is considered positive for efficacy. Evaluation of the effects of treatments on the primary end point allows conclusions with respect to differentiation of an active treatment versus placebo or a comparator agent. Both the US FDA [101] and the European Medicine Agency [102,103] have published guidance documents

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relating to study design features of IBS trials, including appropriate primary end points. The author was invited to write a review on their opinion of "what should be the primary end point in IBS?"

FDA & European Medicine Agency recommendations

■ FDA

The FDA IBS Guidance outlines study entry criteria and contains components for both baseline pain and bowel function [101]. For C-IBS, the recommendation for abdominal pain at baseline is "*the weekly average of worst daily (in the past 24 h) abdominal pain score of ≥3.0 on a 0–10 point scale.*" For C-IBS, the stool-parameter entry criterion is "*fewer than three complete spontaneous bowel movements (CSBMs) per week.*" For evaluation of responders to treatment for C-IBS, criteria refer to pain and stool frequency. Specifically, "*an abdominal pain intensity weekly responder is defined as a patient who experiences a decrease in the weekly average of worst abdominal pain in the past 24 h score (measured daily) of at least 30% compared with baseline weekly average,*" whereas a stool frequency responder "*is defined as a patient who experiences an increase of at least one CSBM per week from baseline.*" A whole study responder is a responder for both parameters simultaneously for at least 6 weeks in a 12-week clinical trial.

For D-IBS, both entry and responder abdominal pain criteria outlined in the FDA IBS Guidance are identical to those for C-IBS described above. The bowel-function entry criterion centers on stool consistency: "*at least one stool with a consistency of Type 6 or Type 7 Bristol stool scale on at least 2 days per week.*" A stool consistency weekly responder is defined as "*a patient who experiences a 50% or greater reduction in the number of days per week with at least one stool that has a consistency of Type 6 or 7 compared with baseline.*" A whole study responder is a dual weekly responder for pain and consistency for at least 6 out of 12 weeks.

The FDA Guidance also defines daily responders. This is relevant only for medications that will work within the first few days or first week. Considering the large initial placebo effect in IBS, this author does not believe a daily responder definition is required.

■ European Medicine Agency

The 2003 European Medicine Agency Guidance references patients fulfilling the Rome II criteria for inclusion [102], although the more recently published Committee for Medicinal Products for Human Use (CHMP) 'points to consider' document recommends accepting Rome III [103]. The European Medicine Agency recommends a co-primary end point, with a patient's global assessment of symptoms and abdominal discomfort/pain scores as the two component parts [102]. The European Medicine Agency Guidance states that there are no widely accepted, validated outcome measures and asks sponsors to justify the choice of the measures they would like to use. Measures should include: items understandable to the patients and sensitive to change; deterioration as well as improvement of state; and validated scales. However, the CHMP 'points to consider' document from 2012 recommends an evaluation to consider harmonizing end points with the FDA IBS Guidance document [103].

It is of key importance that the Critical Path Institute, a public–private consortium, is evaluating, among other disease states, the best end points to use in IBS. With time, it will be determined whether the recommendations in the FDA Guidance are optimal.

Evaluation of regulatory guidance documents

In the evaluation of therapeutic agents targeted to treat IBS, multiple different primary end points have been considered acceptable over the past 15 years. With the publishing of the FDA's patient-reported outcomes guidance (as stated in the agency's IBS guidance [101]) [104], increased scrutiny of the psychometric properties and validation of end points has emerged. However, in IBS, it appears that the FDA has selected instruments and parameters for end points without the same degree of scrutiny that is required for sponsor pharmaceutical companies. For example, for almost 20 years, four- or five-point pain scales have been used for the assessment of baseline pain, as well as for the evaluation of changes in pain during the course of a study [23–30]. These scales were responsive to efficacious versus nonefficacious treatments, and showed reproducibility. However, with issuance of the FDA Draft Guidance for IBS, the pain scale considered acceptable by the FDA was changed to an 11-point scale, presumably only for harmonization with other non-IBS pain states. At the time the 11-point scale was recommended by the FDA, to the best of the author's knowledge, no evaluation or validation of this scale was done in IBS patients. As baseline pain level is a key entry criterion for inclusion in IBS studies, as well as a key component of evaluation of the therapeutic response, the measurement instrument for abdominal pain is of critical significance.

Both the FDA [101] and European Medicine Agency [102] have made the decision that binary end points are no longer acceptable choices for primary end points in IBS studies. The foundation for this decision is centered on the inability of a binary end point to show worsening, since, for instance, a patient may only report relief or no relief but not indicate that their present state is worse than that occurring at baseline. Overall, this is a difficult position to understand, as multiple other

meaningful end points (e.g., pain, frequency, consistency, urgency, bloating or straining) are collected in IBS clinical trials. Each of these end points is collected using ordinal scales, and worsening from baseline can be easily detected. Must the primary end point of a study be able to detect worsening? Worsening is not usually an evaluation parameter for distinguishing the efficacy of a therapeutic agent from placebo – rather, just an increased proportion of responders on active treatment versus placebo.

The adequate relief end point was the most widely used binary end point in IBS clinical trials. Adequate relief was found to be responsive and reproducible, and to move in the same direction as other meaningful measures [31–35]. Thus, adequate relief displays validation parameters. Notably, in drug studies in which adequate relief was the primary end point and statistical and clinical significance was achieved as compared with placebo, then benefit was also observed on several other study end points. In contrast, when other agents failed to show benefit on the adequate relief end point, then benefit was not seen on multiple other parameters in each of the studies. Thus, adequate relief is able to distinguish an active from an inactive agent.

In determining what should be the primary end point in IBS studies, an understanding of the disease and symptoms of relevance to patients needs to be fully appreciated. Without a doubt, abdominal pain is a hallmark feature of IBS. This is true whether the patient has D-IBS, C-IBS, or M-IBS. In a questionnaire provided to D-IBS patients in a large Phase III program, pain was reported as the most bothersome symptom by patients, followed by urgency [24]. Urgency is the sensation that a patient needs to rush to the bathroom or they may soil their underpants. Over the years, urgency was always a readily understandable concept by D-IBS patients. Indeed, the fear of soiling their pants was a key determinant in negatively impacting patients' quality of life, as they were fearful of venturing too far from a bathroom. Many D-IBS patients do not venture out of their routine without mapping pathways of where toilets are, as this fear is so great. The FDA does not allow urgency to represent part of a primary end point, and in its guidance document states that "*there are insufficient data to adequately quantify and qualify the concept of urgency based on patient's perspective and thus to support its use as a component of the primary end point definition of treatment response. Until an adequate urgency assessment tool is developed, stool urgency should be assessed as an exploratory end point…*" [101]. Considering the use of the 11-point scale for pain in IBS, a similar urgency scale could also be devised. Alternatively,

patients clearly know whether they have urgency or not. The percentage of days with urgency at baseline, with an entry criterion of at least 70% of days for D-IBS patients, would represent a satisfactory baseline criterion. Evaluation of the percentage of days with urgency during treatment would be a satisfactory evaluation metric. The author's experience with patients has been that urgency and the fear of having to rush to the toilet are much more meaningful to patients as compared with patients having frequent, too-soft or liquid stools in which patients can go to the bathroom without stress. It is the author's opinion that neither frequency nor consistency is more significant than the other as a bowel function in D-IBS patients. However, the FDA, based on a vote at a scientific meeting, has decided to endorse only consistency [36].

In D-IBS, patients report significantly more frequent and looser stools on the days that they report urgency as compared with the days that they do not report urgency [37]. In an interview study with D-IBS patients, the patients were asked three questions:

■ Question 1: "did you experience bowel urgency today?"

■ Question 2: "did you experience bowel urgency today? (Bowel urgency means that when you feel the need for a bowel movement you have to rush to the toilet to avoid an accident.)"

■ Question 3: "did you experience urgency for bowel movement today? (Urgency for bowel movement means that when you feel the strong need to have a bowel movement, you have to rush to the toilet to avoid an accident.)"

Patients consistently reported that Question 1 was easy for them to understand and answer, although they commonly indicated a preference for Question 2 and that the definition of urgency was appropriate. In a second set of interviews, patients rank ordered their most bothersome IBS symptoms, and pain and urgency were the most bothersome symptoms [37].

However, as with pain, not all D-IBS patients consider urgency the most bothersome symptom [24]. Urgency should also be considered as an end point only for D-IBS patients or M-IBS patients in their diarrheal phase. Urgency is generally not an important symptom to C-IBS patients. As with urgency, many IBS patients also experience bloating and consider it an important symptom. Historically, bloating has not been considered a key end point. Whether this is a reflection of the lack of importance of bloating versus the inability of therapeutic agents to treat bloating requires further evaluation.

C-IBS is also principally characterized by abdominal pain. The primary bowel defect is stools that are too

Box 1. Dual or co-primary end point construct for diarrhea-predominant irritable bowel syndrome.

Pain

- Assessment of pain by proportion of pain-free days. Pain is measured on a four-point scale:
  - 0 = none
  - 1 = mild
  - 2 = moderate
  - 3 = severe
- At baseline, an eligible patient has <15% of days pain free (i.e., score = 0)
- A responder has >40% of days pain free on a weekly basis

Bowel function

- Assessment of bowel function by proportion of days with urgency
- At baseline, patients have >70% of days with urgency
- A weekly responder has <50% of days with urgency

Whole study responders

- A whole study responder is a weekly responder for both pain and urgency for at least 6 out of 12 weeks

infrequent and too hard. For C-IBS end points, the FDA requires measures of abdominal pain and increased frequency of a complete spontaneous bowel movement. This author agrees agree with the FDA's measures for bowel functions in C-IBS, as these seem better grounded than those for patients with D-IBS.

Recommendations: what should be the primary end point in IBS clinical trials

Considering that the principal features of IBS are abdominal pain and altered bowel function, the primary end point in IBS clinical trials should revolve around those two functionalities. For D-IBS, the author recommends a dual or co-primary end point of the construct shown in Box 1.

For C-IBS, this author recommends the same scale and metric for pain assessment as for D-IBS. For the assessment of bowel function, this author agrees with the FDA recommendation of an increase of one or more CSBMs per week compared with baseline and baseline entry criteria of fewer than three CSBMs per week.

For M-IBS or A-IBS, this author's recommendation is to study the patients in their predominant bowel phase of diarrhea or constipation. This author believes it is very unlikely that a treatment for M-IBS will ever be developed successfully that treats patients irrespective of their bowel pattern; more likely, M-IBS patients will receive D-IBS or C-IBS treatments depending on their current bowel state.

Future perspective

Over the years IBS has been considered a 'tough nut to crack'. Selection of suitable end points in clinical tirals is of the utmost importance. This author anticipates that over the next 5 years, the output of the rigorously conducted Critical Path Institute, instrument development and validation process for IBS end points will be published and critically evaluated. Ideally, regulatory agencies globally will adopt the recommendations and harmonize.

Executive summary

Background
- Irritable bowel syndrome (IBS) is a common gastrointestinal disorder.
- IBS has significant impacts on patients' quality of life as well as resource use.

US FDA & European Medicines Agency recommendations
- The FDA and European Medicines Agency have published guidance documents for primary end points in IBS.
- These regulatory guidance documents are evaluated.
- The FDA Guidance uses a pain scale not validated in IBS patients and a bowel-function measure for diarrhea-predominant IBS patients without a sound validated basis.

Recommendations for what should be the primary end point in IBS
- Recommendations for alternative co-primary end points are provided.
- The recommendations focus upon pain, using a measure of pain free days and urgency in diarrhea-predominant IBS patients. Stool frequency in constipation-predominant IBS patients is recommended as per the FDA Guidance.

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