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Development of the Diary for Irritable Bowel Syndrome Symptoms to Assess Treatment Benefit in Clinical Trials: Foundational Qualitative Research

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ABSTRACT

Background: Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder characterized by abdominal pain and alterations in bowel habits. Three subtypes are defined on the basis of stool patterns: diarrhea-predominant IBS, constipation-predominant IBS, and alternating or mixed IBS. **Objectives:** To develop patient-reported outcome measures for qualification by the Food and Drug Administration to support product approvals and labeling in IBS; the article focuses on the qualitative research that provided the foundation for the new measures. **Methods:** Forty-nine concept elicitation and 42 cognitive debriefing interviews were conducted with subjects meeting Rome III criteria; additional criteria were imposed to yield a sample representative of the target patient population. **Results:** Although incomplete bowel movements, abnormal stool frequency and consistency, and abdominal pain, discomfort, and bloating were reported most frequently across concept elicitation interviews, the relative importance of specific symptoms varied by subtype. Among their five symptoms most important to treat, diarrhea-predominant and alternating or mixed IBS subjects frequently identified urgency, loose/watery stools, abdominal pain, and cramping, whereas constipation-predominant IBS subjects commonly included infrequent and incomplete bowel movements, bloating, and abdominal pain. The cognitive debriefing interviews facilitated refinement of each item set, supported minor modifications following translatability assessment, and suggested improvements to the electronic interface. Furthermore, subjects reported that every item was relevant and no concepts of importance were missing. **Conclusions:** Results support the content validity of the IBS patient-reported outcome measures. A pilot study was recently initiated to inform item reduction, develop scoring algorithms, and provide preliminary psychometric information. Comprehensive psychometric evaluation and responder definition development will follow.

Keywords: content validity, irritable bowel syndrome, patient-reported outcome measures, symptoms.

Introduction

In 2008, the Critical Path Institute, a private, nonprofit organization, established the Patient-Reported Outcome (PRO) Consortium in conjunction with the US Food and Drug Administration (FDA) and the pharmaceutical industry [1]. Concurrently, FDA's Center for Drug Evaluation and Research was advancing a program to provide a pathway for qualifying drug development tools for use in multiple programs to support product approval and labeling claims [2]. To achieve qualification, the center encouraged the creation of collaborative groups (e.g., consortia) to increase efficiency and share resources because of the substantial effort involved. The PRO Consortium is a public-private partnership involving the FDA, the pharmaceutical industry, consulting organizations, academia, and patient advocacy groups that facilitates collaborative, precompetitive development of PRO measures intended for qualification by the FDA.

One of the PRO Consortium's first areas of focus was the assessment of treatment benefit in irritable bowel syndrome (IBS). IBS is a chronic, oftentimes disabling gastrointestinal (GI) disorder characterized by abdominal pain associated with alterations in bowel habits (diarrhea and/or constipation). Although not required for diagnosis, additional bothersome symptoms such as urgency, straining, bloating, incomplete evacuation, and abdominal discomfort are commonly experienced. With a prevalence of 10% to 15%, IBS is one of the most common GI disorders seen by primary care physicians and gastroenterologists [3]. Three subtypes of IBS have been defined on the basis of stool

Conflicts of interest: S. E. Fehnel and C. M. Ervin are employees of RTI Health Solutions. R. T. Carson is an employee of Allergan plc and owns stock and stock options in Allergan plc. G. Rigoni was an employee of Takeda at the time of this study.

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patterns: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), and alternating or mixed IBS (IBS-M). Because a reliable biomarker has not been identified, symptom severity and treatment response in clinical trials must be assessed through PRO measures.

Although global and symptom-specific PRO measures have been used to support approval of treatments for IBS [4], the FDA has encouraged the development of comprehensive subtype-specific symptom severity measures that meet the expectations described in its PRO guidance [5]. The FDA provided a path forward for IBS drugs presently in development by describing endpoints for IBS-C and IBS-D trials in its IBS guidance [6]; this document, however, also refers to the current effort: "Once qualified, these IBS subtype-specific PRO measures will replace the provisional endpoints described in this guidance as the FDA's recommended measures of treatment benefit for use in IBS-C and IBS-D clinical trials" [6, p. 11].

Since 2010, the PRO Consortium's IBS Working Group (IBS WG)—including representatives from Allergan plc (formerly, Forest Research Institute), Ironwood Pharmaceuticals, and Takeda Pharmaceuticals; three academic experts in IBS; and a patient advocate—has been collaborating with RTI Health Solutions to develop PRO measures for each of the three IBS subtypes. Consistent with FDA's IBS guidance, the target patient population for future clinical trials in IBS includes adult males and females meeting Rome III diagnostic criteria and experiencing active symptoms, including a clinically significant level of abdominal pain, and excludes individuals with previous surgeries, other disorders, or taking medications known to affect GI motility. It is anticipated that patients' responses to the PRO measures will be used to generate primary and key secondary efficacy endpoints in clinical trials of new treatments to support product approval and labeling.

The development of the IBS PRO measures has proceeded in accordance with both the PRO guidance and a scoping-stage summary document previously reviewed by FDA's qualification review team. Specifically, a comprehensive literature and instrument review was first conducted to identify symptoms associated with each subtype and how these symptoms had been measured in previous clinical studies. The review of 81 studies involved the identification, description, and/or rating of IBS symptoms by patients, including qualitative, survey, and observational studies. Results revealed that symptoms assessed most commonly included those relevant to all three IBS subtypes: abdominal pain and/or discomfort, abdominal bloating, abnormal stool frequency, and abnormal stool form/consistency. The description and/or assessment of symptoms beyond this core set was dependent on the IBS subtype under study. For example, urgency and straining were featured prominently among studies involving patients with IBS-D and IBS-C, respectively.

An expert panel, including four clinical and/or measurement experts, was also assembled to provide input and supplement the expertise of IBS WG members. Before seeing the results of the literature and instrument review, each clinician on the expert panel provided a list of symptoms he or she deemed important for measurement within each IBS subtype; the results of this exercise closely mirrored those of the literature review.

Although these preliminary efforts identified concepts likely to be important for assessment in future trials, patient input is paramount in PRO measure development. As such, this article focuses on two phases of qualitative research conducted with patients with IBS—concept elicitation (CE) and cognitive debriefing (CD) interviews—to inform both the development of the initial item pools and the subsequent refinement of the three PRO measures: the Diary of Irritable Bowel Syndrome Symptoms—Constipation (DIBSS-C), the DIBSS-Diarrhea (DIBSS-D), and the DIBSS-Mixed (DIBSS-M). Additional inputs, including further guidance from the expert panel, as well as translatability and electronic device usability assessments, are also summarized briefly.

Methods

Subjects

Subjects were recruited through gastroenterology clinics in six US regions and needed to meet the following criteria for participation in the CE and CD interviews:

1. male or nonpregnant female (≥18 years);
2. meets Rome III criteria for IBS-C, IBS-D, or IBS-M [7] and was diagnosed 6 months or more before screening;
3. English-speaking, ambulatory, and community-dwelling; and
4. reports an average abdominal pain intensity level of 3 or more on a 0 to 10 scale over the 7 days before screening.

Potential subjects were excluded if they had previous GI surgeries or recent pelvic surgeries, had other GI disorders with overlapping symptoms (e.g., Crohn disease), were taking medications known to affect GI motility, or had a psychological disorder that, in the referring gastroenterologist's opinion, could potentially hinder their ability to comply with study requirements.

Recruitment targets were also imposed to yield a sample representative of participants in IBS clinical trials recently conducted by IBS WG sponsors in terms of age, sex, race, ethnicity, and varied educational levels. This study was approved by RTI International's institutional review board before the recruitment of any subject.

CE Interviews

Each CE interview was conducted using a subtype-specific, semi-structured interview guide with three components (conducted in the following order):

1. *Spontaneous CE*: Open-ended questions were designed to identify all relevant IBS symptoms, the ways in which subjects experience and speak about these symptoms, the relationships among these symptoms, and the most bothersome symptoms among all those identified spontaneously.
2. *Probed CE*: If not mentioned spontaneously, subjects were asked about other symptoms considered clinically relevant on the basis of expert input and the literature to fully assess the potential relevance and importance of these symptoms.
3. *Most important concepts*: Subjects were asked to describe how bothered they were by their IBS symptoms, the extent to which these symptoms interfered with their lives, and the five symptoms they would most want an IBS medication to improve.

The results of the CE interviews were reviewed and summarized on the basis of field notes and analysis of interview transcripts, facilitated by the use of ATLAS.ti, version 6.2 Scientific Software Development GmbH; Berlin, Germany. To assess concept saturation (i.e., the point at which no new symptoms of importance are reported), the IBS-D, IBS-C, and IBS-M interviews were each divided into three sequential groups (approximately one-third of the interviews per group), and the number and nature of new concepts reported by subjects in each subsequent group were reviewed to determine whether additional symptoms were being identified.