Irritable Bowel Syndrome Working Group

Prepared for the 11th Annual PRO Consortium Workshop (April 22-23, 2020), which was cancelled due to COVID-19

PRO CONSORTIUM CRITICAL PATH INSTITUTE

Background

Rationale for Irritable Bowel Syndrome (IBS) Working Group (WG)

- IBS is one of the most common gastrointestinal (GI) disorders
- IBS lacks a standard "fit-for-purpose" PRO instrument for assessing important patient-experienced signs and symptoms of IBS
- PRO Consortium member firm representatives and FDA advisors identified IBS as a priority area for the development of a PRO instrument

Goal of the IBS WG

- To develop three PRO measures for patient-reported symptoms in IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), and IBS with mixed symptoms (IBS-M) for use in clinical trials as a primary endpoint measure to establish treatment benefit

Concept of Interest

- IBS sign and symptom severity

Targeted Labeling Language

- [*Drug X*] is indicated in adults for the treatment of symptoms associated with irritable bowel syndrome [with constipation (IBS-C), with diarrhea (IBS-D), or mixed (IBS-M)]
- [*Drug X*] improved abdominal symptoms and bowel movement (BM)-related signs and symptoms

Note: This indication would be supported by an improvement in both abdominal symptoms and bowel movement-related signs and symptoms

Milestones

Milestone	Expected Date	Completed Date
Briefing package submission to FDA (final Cognitive Interview Report and updated Briefing Document)		AUG 2014
Received FDA response and approval to conduct quantitative pilot study		DEC 2014
Quantitative pilot study protocol and quantitative analysis plan (QAP) submission to FDA		DEC 2015
Full Qualification Package submission for *DIBSS-C* to FDA		DEC 2018
Responded to Information Request 1 received from FDA on February 14, 2019		MAR 2019
Responded to Information Request 2 received from FDA on June 6, 2019		DEC 2019
Responded to Information Request 3 received from FDA on March 14, 2020		MAR 2020
Full Qualification Package submission for *DIBSS-D* to FDA	TBD	
Full Qualification Package submission for *DIBSS-M* to FDA	TBD	

Highlights

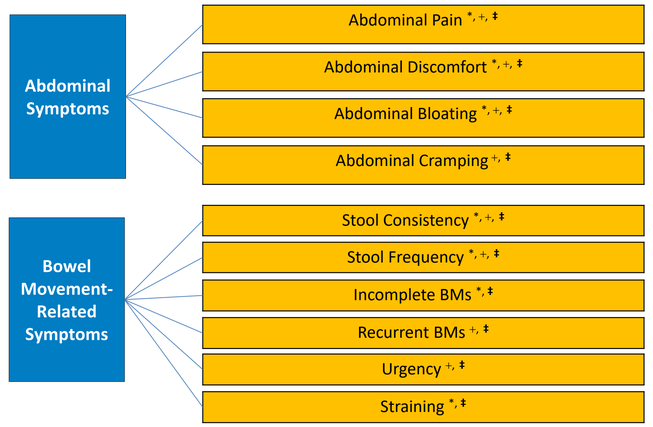
Example Endpoint Model for Treatment of IBS-C

Endpoint Hierarchy	Endpoint Concept(s)	Endpoint Type
Primary	Overall response (TBD) indicating improvement in IBS-C symptom severity • Improvement in abdominal symptoms (abdominal pain, discomfort, and bloating) • Improvement in selected BM-related symptoms (BM frequency, incomplete BMs, straining during BM, and stool consistency)	PRO (*DIBSS-C)*

Target Population

- Adult patients (18 years and older; males and non-pregnant females)
- Diagnosis of one of the three main IBS subtypes: IBS-C, IBS-D, or IBS-M
- Patients without known or suspected organic disorder (e.g., Crohn's disease) that would better explain symptoms
- Patients not concomitantly using medications known to affect GI motility, constipation, or other IBS symptoms

Conceptual Framework



Abdominal and Bowel movement-related symptoms pertain to the following subtypes:
* IBS-C; + IBS-D; ‡ IBS-M

Measures– *Diary for Irritable Bowel Syndrome Symptoms (C, D, M)*

Measures developed for each subtype:
***Diary for Irritable Bowel Syndrome Symptoms–C (DIBSS-C)* for constipation predominant**
***Diary for Irritable Bowel Syndrome Symptoms–D (DIBSS-D)* for diarrhea predominant**
***Diary for Irritable Bowel Syndrome Symptoms–M (DIBSS-M)* for mixed symptoms**

Core Items: Abdominal symptoms and bowel movement-related signs/symptoms
Recall Period: Event-driven and 24-hour (end of day)
Response Options: Verbal rating scales, bivariate response, 11-point numeric rating scales
Data Collection Mode: Handheld smartphone device used for quantitative pilot study

Working Group Activities

Information Dissemination

- Fehnel, S. et al. Development of the Diary for Irritable Bowel Syndrome Symptoms (DIBSS) to assess treatment benefit in clinical trials: Foundational qualitative research. *Value in Health* 2017;20(4):618-626
- Poster titled "Psychometric Evaluation of the *Diary for Irritable Bowel Syndrome Symptoms-Constipation* (*DIBSS-C*)" presented at the 21st Annual European Congress, November 10-14, 2018, Barcelona, Spain
- Coon, C. et al. Psychometric Analysis of the Abdominal Score From the Diary for Irritable Bowel Syndrome Symptoms-Constipation Using Phase IIb Clinical Trial Data. *Value in Health* 2020;23(3):362-369

Lessons Learned

- Following completion of the quantitative pilot study, RTI-HS and C-Path held a full-day, face-to-face meeting on July 12, 2018, with members of the IBS Working Group, FDA Qualification Review Team (QRT), a patient representative from the International Foundation for Gastrointestinal Disorders, and the project's expert panel members. This meeting was key to obtain patient, expert, and regulatory input regarding finalization of the *DIBSS-C/D/M* content, to identify the most appropriate endpoints for IBS-C in clinical trials and discuss plans for further evaluation of the *DIBSS-D* and *DIBSS-M* in the context of clinical trials.
- Ensure there is clarity about what is being qualified (i.e., measure versus endpoint)
- The submission to FDA of patient-level interventional trial data and the related statistical programs is required to support qualification as a primary or secondary endpoint measure.
- Close collaboration is vital between the eCOA provider and measure development team to ensure successful implementation

Next Steps

- Prepare and submit separate Full Qualification Package for *DIBSS-D* and *DIBSS-M* to FDA

Working Group Participants

Company/Organization	Representatives
Allergan	Robyn T. Carson, MPH (Co-Chair); Steven J. Shiff, MD
Ironwood Pharmaceuticals, Inc.	Andrew I. Damokosh, PhD (Co-Chair)
Takeda Pharmaceuticals International	Note: Takeda provided funding for the IBS WG but is no longer an active participant in it.
Other Participant	**Affiliation**
Ceciel T. Rooker	International Foundation for Gastrointestinal Disorders (IFFGD)
Expert Panel Members	**Affiliation**
Lin Chang, MD	University of California, Los Angeles
William D. Chey, MD	University of Michigan
Douglas A. Drossman, MD	Drossman Gastroenterology, PLLC
Jeffrey M. Lackner, PsyD	University at Buffalo, SUNY
Brian E. Lacy, MD, PhD	Mayo Clinic, Jacksonville, Florida
Contract Research Organization	**Research Team**
RTI Health Solutions	Sheri Fehnel, PhD; Claire Ervin, MPH; Lori McLeod, PhD; Nicole Williams, BS; Diana Goss
ePRO System Provider	**Representative**
Signant Health	Bill Byrom, PhD