Irritable Bowel Syndrome Working Group

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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

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 (as measured by the abdominal symptom severity subscale) and bowel movement (BM)-related symptoms (as measured by the BM-related symptom subscale).

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

Milestones

Milestone	Expected Date	Completed Date
Vendor selection and contracting		OCT 2010
Complete background research (Literature Review Report and Expert Panel Meeting)		FEB 2011
Draft Instrument: Complete initial qualitative research and generate items (concept elicitation interviews, item generation, expert panel input, and two rounds of cognitive interviews)		SEP 2011
Complete qualitative research phase; submit briefing package to FDA (final Cognitive Interview Report and updated Briefing Document)		AUG 2014
Received FDA response and approval to conduct quantitative pilot study		DEC 2014
Submit quantitative pilot study protocol and quantitative analysis plan (QAP) to FDA for review		DEC 2015
Met with QRT to discuss comments provided regarding QAP submission; Response to QRT's comments regarding QAP submission		MAY 2016
Complete quantitative pilot study		SEP 2017
Complete data analysis and draft quantitative pilot study report		FEB 2018
Endpoint Finalization Meeting and final quantitative pilot study report		SEP 2018
Submit Full Qualification Package for *DIBSS-C* to FDA		DEC 2018
Submit Full Qualification Package for *DIBSS-D* to FDA	TBD	
Submit Full Qualification Package for *DIBSS-M* to FDA	TBD	

Highlights

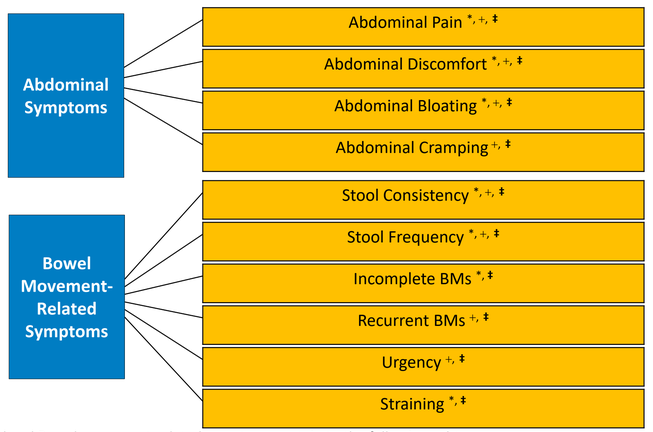
Example Endpoint Model for Treatment of IBS-C

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

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., instrument versus endpoint)
- The submission to FDA of longitudinal, interventional trial data and the related statistical programs is required to support qualification of an instrument as a primary or secondary endpoint measure.
- Be open-minded for use of the measures within other patient populations (e.g., Fabry disease)
- Close collaboration is vital between the eCOA provider and instrument development team to ensure successful implementation

Next Steps

- Prepare and submit separate Full Qualification Package for *DIBSS-D* and *DIBSS-M* to FDA
- Develop three subtype-specific manuscripts based on quantitative pilot study results after qualification

Working Group Participants

Company/Organization	Representatives
Allergan	Robyn T. Carson, MPH (Co-Chair); Steven J. Shiff, MD
Ironwood Pharmaceuticals, Inc.	Jennifer Hanlon, MPH (Co-Chair); David Reasner, PhD
Takeda Pharmaceuticals International	Note: Takeda funded but is no longer an active participant in the IBS WG.
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**
CRF Bracket	Jennifer Olt, PhD