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		Q1 2018
Endpoint Finalization Meeting and final quantitative pilot study report	Q3 2018	
Submit Full Qualification Package to FDA for *DIBSS-C*	Q4 2018	
Submit Full Qualification Package to FDA for exploratory use of *DIBSS-D*	Q1 2019	
Submit Full Qualification Package to FDA for exploratory use of *DIBSS-M*	Q3 2019	

Highlights

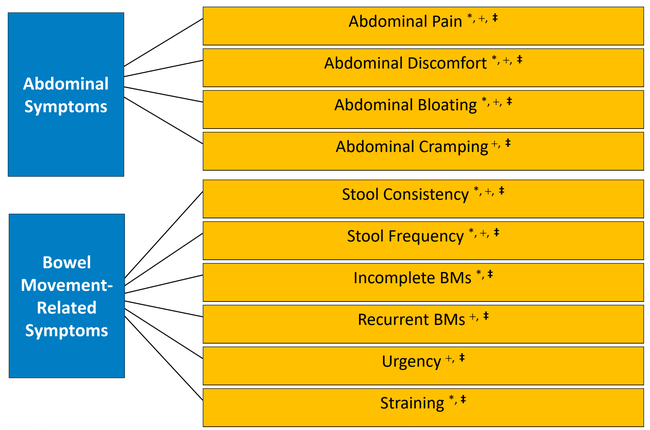
Example Endpoint Model for Treatment of IBS-M

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

Target Population

- Adult patients (18 years and older; males and non-pregnant females)
- Diagnosis of IBS of three main subtypes (i.e., IBS-C, IBS-M, and IBS-D)
- 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 Updates

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
- Develop three subtype-specific manuscripts based on quantitative pilot study results after qualification

Lessons Learned

- Close collaboration is required between the eCOA provider and instrument development team to ensure successful implementation
- Include team members with expertise in both instrument development and eCOA system development (requirements, design, build, implementation)
- Evening diary should be programmed as a continuous flow with appropriate order of items to prevent missing data due to requiring re-entry into the diary to complete each component
- Collaboration with sponsors to identify experienced study sites in therapeutic area can greatly expedite the data collection process
- Across IBS subtypes, participants were willing to complete an event-driven diary to record BM-related symptoms

Next Steps

- Complete data analyses and review results from quantitative pilot study with Expert Panel and FDA to determine final item set and recommended endpoints for each measure
- Prepare and submit separate Full Qualification Package (FQP) for each measure
- *DIBSS-C* FQP will include longitudinal clinical trial data that was analyzed by sponsors to support measurement properties in an IBS-C patient sample to support qualification for use as a primary endpoint measure

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	Maria Claudia Perez, MD
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Nancy Norton, BS	International Foundation for Functional Gastrointestinal Disorders (IFFGD)
Expert Panel Members	**Affiliation**
Lin Chang, MD	University of California, Los Angeles
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RTI Health Solutions	Sheri Fehnel, PhD; Claire Ervin, MPH; Lori McLeod, PhD; Diana Goss
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