Irritable Bowel Syndrome Working Group
Presented at the Fifth Annual PRO Consortium Workshop – Silver Spring, MD – April 29-30, 2014

Background
Rationale for Irritable Bowel Syndrome (IBS) Working Group (WG)
• IBS is one of the most commonly diagnosed GI disorders
• IBS lacks a standard and fit for purpose PRO instrument for measuring important patient-experienced aspects of IBS
• PRO Consortium member 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

Targeted Labeling Language
Product X improved abdominal symptoms (as measured by the abdominal symptom severity subscale) and bowel movement-related symptoms (as measured by an appropriate BM-related symptom subscale).

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

Milestones

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Expected Date</th>
<th>Completed Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scoping Stage</td>
<td>04/29/2010</td>
<td></td>
</tr>
<tr>
<td>Content Validity Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vendor selection and contracting</td>
<td>10/29/2010</td>
<td></td>
</tr>
<tr>
<td>Complete background research (literature review and Expert Panel Meeting)</td>
<td>02/22/2011</td>
<td></td>
</tr>
<tr>
<td>Draft Instrument: Complete initial qualitative research and generate items (concept elicitation interviews, item generation, expert panel input, and two rounds of cognitive interviews)</td>
<td>09/09/2011</td>
<td></td>
</tr>
<tr>
<td>Submit Qualitative Research Summary interim Briefing Document to FDA for review and feedback</td>
<td>09/26/2011</td>
<td></td>
</tr>
<tr>
<td>QRT written responses</td>
<td>12/6/2013</td>
<td></td>
</tr>
<tr>
<td>Teleconference with QRT</td>
<td>12/11/2013</td>
<td></td>
</tr>
<tr>
<td>Refine initial instrument (final cognitive interviews on demo ePRO device)</td>
<td>1Q 2014 2/11/2014</td>
<td></td>
</tr>
<tr>
<td>Complete qualitative research phase; submit briefing package to FDA (final Cognitive Interview Report and updated Briefing Document)</td>
<td>3 Q 2014</td>
<td></td>
</tr>
<tr>
<td>Complete documentation of content validity via quantitative evaluation of item functioning</td>
<td>TBD</td>
<td></td>
</tr>
<tr>
<td>Submit exploratory endpoint qualification briefing document to FDA</td>
<td>TBD</td>
<td></td>
</tr>
</tbody>
</table>

Content of Interest

Endpoint Model for Treatment of IBS (Example provided for IBS-M)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Endpoint Concept(s)</th>
<th>Endpoint Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Overall response (TBD) indicating improvement in IBS-M symptom severity</td>
<td>PRO</td>
</tr>
<tr>
<td></td>
<td>Improvement in abdominal symptoms (abdominal pain, discomfort, bloating, cramping)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Improvement in selected BM-related symptoms (stool consistency, stool frequency, incomplete BMs, straining, recurrent BMs, urgency)</td>
<td></td>
</tr>
</tbody>
</table>

Target Population
• US-based adult patients (18 years and older; males and non-pregnant females)
• Diagnosis of IBS of three main subtypes based on Rome III criteria (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 mobility, constipation, or other IBS symptoms

Hypothesized Conceptual Framework

Abdominal Symptoms

- Abdominal Pain *
- Abdominal Discomfort *
- Bloating *
- Abdominal Cramping *

Bowel Movement-Related Symptoms

- Stool Consistency *
- Stool Frequency *
- Incomplete BMs *
- Recurrent BMs *
- Urgency *
- Straining *

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

Updates

• Successful teleconference held with QRT and IBS WG on December 11, 2013
• Agreement reached with QRT on current conceptual framework, item sets for IBS-C, IBS-D, IBS-M, endpoint models, and proposed indication statements
• Completed 3rd round of cognitive interviews using demo ePRO device February 21, 2014
• Data analysis complete and draft report under review by WG

Working Group Plans

Next Steps
• Revisions to instrument to be discussed (if any)
• Develop preliminary scoring algorithm and scope for quantitative evaluation for content validity
• Developing data dissemination plan for additional abstracts/manuscripts

Dissemination Plan
• Poster summarizing concept elicitation results presented at Digestive Disease Week, May 17 – 21, 2013
• Dissemination plan under review by WG

Topics for Discussion

Unique Issues for the Working Group and Their Resolution
• Optimal response scales varied across abdominal symptom measures; however, for consistency, a decision was made to use the 0-10 NRS for all abdominal symptom items
• Combination of BM-related symptom measures (e.g., BSFS, CSBM/SBM frequency, straining, urgency) challenging due to differences in response scales and directionality; therefore, key indicators of BM-related symptom improvement will be identified
• Ideal frequency of data capture varied across IBS sub-types; however, for consistency, real-time data capture is being pursued for all sub-types

Lessons learned
• Important to consider and develop hypothesized preliminary scoring algorithm prior to quantitative phase

Working Group Participants

Company/Organization | Name | Affiliation
--- | --- | ---
Forest Research Institute | Robin T. Carson, MPH (Co-Chair); Steven J. Shift, MD | University of California, Los Angeles
Ironwood Pharmaceuticals, Inc. | Brooke Witherspoon; Joe Lavins, MD; David Reasner, PhD | University at Buffalo, SUNY
Takeda Pharmaceuticals International | Gianna Riggs, PharmD (Co-Chair); Karen Lasch, MD; Charles Baum, MD | University of California, Los Angeles
Takeda Pharmaceuticals International | Lin Chang, MD; Brennan M.R. Spiegel, MD, MSHS | University of California, Los Angeles

Nonmember Participants | Affiliation
--- | ---
Jim Chang, MD | University of California, Los Angeles
Jeffrey M. Lackner, PsyD | University at Buffalo, SUNY
Nancy Norton, BS | International Foundation for Functional Gastrointestinal Disorders (IFFGD)
Brennan M.R. Spiegel, MD, MSHS | University of California, Los Angeles

Expert Panel Members | Affiliation
--- | ---
William D. Chey, MD | University of Michigan
Douglas A. Drossman, MD | University of North Carolina, Chapel Hill
Mark P. Jensen, PhD | University of Washington
Brian E. Lacy, MD, PhD | Dartmouth-Hitchcock Medical Center

Contract Research Organization | Research Team
--- | ---
RTI Health Solutions | Sheri Fehnel, PhD; Claire Ervin, MPH; Diana Goss