# Clinical Outcome Assessments (COA) Qualification Program
# DDT COA #000005: Diary for Irritable Bowel Syndrome Symptoms – Constipation (DIBSS-C)
# Full Qualification Package

## Section 1: Proposed COA Qualification
### 1.1 Introduction and overview

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder characterized by recurrent episodes of abdominal pain associated with alterations in bowel movements (BMs). The alterations in BMs can principally manifest as diarrhea, constipation, or an alternation between diarrhea and constipation; these subtypes of IBS are denoted as IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), and mixed IBS (IBS-M), respectively. Diagnosis of functional bowel disorders, like IBS, is based on symptom criteria because there are no consistent and reliable diagnostic biomarkers. Thus, outcomes of treatment for IBS are best assessed through direct patient report.

Although a number of patient-reported outcome (PRO) measures have been used to measure individual symptoms of IBS and support the approval of treatments for this condition, the United States (US) Food and Drug Administration (FDA) has expressed a preference for the development of a comprehensive symptom measure that meets the requirements described in FDA's PRO guidance, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (US Food and Drug Administration, 2009). To provide a path forward for IBS drugs currently in development, FDA released a guidance document, Irritable Bowel Syndrome – Clinical Evaluation of Products for Treatment (US Food and Drug Administration, 2012), describing interim endpoints for use in trials of new medications for IBS-C and IBS-D. The IBS guidance also refers to the development and anticipated utilization of new endpoints in both of these IBS subtypes:

> We are actively participating with the PRO Consortium and others in the consultation and advice stage of qualification for the development of PRO measures of the signs and symptoms of IBS-C and IBS-D. 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.

The PRO Consortium's IBS Working Group at the Critical Path Institute (C-Path) has completed development of the following three PRO measures addressing the severity of IBS-C, IBS-D, and IBS-M symptoms in accordance with FDA's PRO guidance and FDA's guidance for industry, titled Qualification Process for Drug Development Tools (US Food and Drug Administration, 2014):

- Diary for Irritable Bowel Syndrome Symptoms–Constipation (DIBSS-C)
- Diary for Irritable Bowel Syndrome Symptoms–Diarrhea (DIBSS-D)

- Diary for Irritable Bowel Syndrome Symptoms–Mixed (DIBSS-M)

Each of these measures includes a common set of items supplemented with subtype specific items. These measures were developed to assess primary and key secondary efficacy endpoints in future clinical trials of new treatments for IBS-D, IBS-C, and IBS-M to support product approval and labeling.

This full qualification package (FQP) describes the overall development process and both the qualitative and quantitative evidence supporting the qualification of the DIBSS-C. It should be noted that although this full qualification package has been submitted to support the qualification of the DIBSS-C for IBS-C, the DIBSS-C was developed in parallel with the DIBSS-D/M. Regulatory and expert consensus at the study onset (2010) agreed with this aggregated approach, understanding that the hallmark symptoms of IBS across IBS subtypes are largely similar (with some important symptom variations; as exemplified by the Rome diagnostic criteria). As such it is important to review the IBS-C data in light of the full body of IBS evidence. Therefore, where relevant, all IBS subtype information is presented.

### 1.2 Concept of Interest for meaningful treatment benefit

As described in Section 1.1, IBS-C is a chronic, functional bowel disorder characterized by recurrent episodes of abdominal pain associated with constipation. Although not required for diagnosis, patients with IBS-C are commonly bothered by additional bowel (BM-related) symptoms such as straining, hard stools that are difficult to pass, and incomplete evacuation, as well as additional abdominal symptoms, such as bloating and abdominal discomfort (Fehnel et al., 2017). Each of these symptoms is addressed in the DIBSS-C.

The concept of interest is IBS-C symptom severity. The meaningful treatment benefit is a reduction in or relief of the core symptoms associated with IBS-C. The DIBSS-C is intended to support the evaluation of both primary and key secondary endpoints related to improvements in IBS-C symptom severity within the context of clinical trials. The content of the DIBSS-C has been carefully crafted to provide a comprehensive assessment of IBS-C symptom severity. As such, it addresses the severity of both bowel and abdominal symptoms experienced by adults with IBS-C. Because these symptoms are subject to natural variability, the DIBSS-C has been developed as a daily diary to facilitate the collection of reliable data. Specifically, this measure is comprised of two domains encompassing items that assess both the BM-related and abdominal symptoms associated with IBS-C (a total of seven items across the two domains) on a daily basis. The BM-related symptoms (BM frequency, stool consistency, incomplete BMs, and straining) are designed to be assessed in real time via event-based completion. The abdominal symptom items (assessing abdominal pain, abdominal discomfort, and bloating) are completed on a once-daily basis (24-hour recall). Taken together, the design of the diary and the evidence provided in this FQP support our

assertion that the DIBSS-C is capable of demonstrating improvements in the symptoms important to patients with IBS-C.

### 1.3 Context of Use

The DIBSS-C was developed to assess change (as compared to placebo) in IBS-C symptom severity within randomized, placebo-controlled clinical trials of new treatments for IBS-C. The targeted study populations and design of these trials are fully consistent with the recommendations in FDA's IBS guidance document (US Food and Drug Administration, 2012) and IBS-C clinical trials previously conducted by study sponsors.

Specifically, the intended study population for the DIBSS-C is expected to include adult males and females who meet Rome diagnostic criteria (either Rome III or IV) for IBS-C and have active symptoms, including a clinically significant level of abdominal pain (as defined by the Rome criteria and the current FDA IBS Guidance [2012]). The core screening criteria used during the development of the DIBSS-C is provided below:

- Patient meets the Rome III criteria for IBS: reports recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with two or more of the following:
    - Improvement with defecation
    - Onset associated with a change in frequency of stool
    - Onset associated with a change in form (appearance) of stool
- Patient is 18 years of age or older.
- Patient is an English-speaking, ambulatory (i.e., has the ability to walk without assistance), community-dwelling male or female.
- Female patients must not be pregnant.
- Patient's IBS was diagnosed at least 6 months before screening.
- Patient reports an average abdominal pain level of at least 3 on a scale of 0-10 across the past 7 days.
- Patient has not had any previous surgeries, been diagnosed with another gastrointestinal disorder (e.g., Crohn's disease), or taking medications known to affect gastrointestinal motility (e.g., opioids).

Additional inclusion criteria for IBS-C included the following:

IBS-C: Patient reports hard or lumpy stools for at least 25% of BMs and loose (mushy) or watery stools in the absence of any laxative, suppository, or enema for less than 25% of BMs during the 12 weeks before screening.

The DIBSS-C scoring includes item-level scores across the two domains as well as an abdominal symptom subscale score. Based upon the quantitative

evidence, historical precedence, and guidance from clinical experts and FDA, it is anticipated that the primary endpoints for the treatment of IBS-C derived from the DIBSS-C will be based on overall responder analyses requiring a product to show benefit in the following signs and symptoms:

- An increase in the frequency of complete, spontaneous BMs (CSBMs)
- A decrease in the severity of abdominal symptoms, as measured by the abdominal symptom subscale score (a reduction in symptom severity based on the items assessing abdominal pain, discomfort, and bloating)

While the specific responder definitions for each of these endpoint components have not yet been discussed with FDA, consistent with the current IBS guidance, an increase of one CSBM per week (from baseline) and a reduction of 30% in the abdominal symptom subscale score are proposed to define a weekly responder. A responder definition based on absolute change (rather than percent change) could also be considered by FDA for the abdominal symptom subscale. Results from the longitudinal psychometric evaluation using data from the phase 2b clinical trial provide evidence to support a change of 2 points (on the 0 to 10 scale metric) to indicate a meaningful change in the abdominal symptoms subscale.

Further, it is anticipated that the results of responder analyses based on the final responder definitions will be described in the Clinical Studies section (Section 14) of future labels, in addition to the proposed claim language provided in the preliminary endpoint model for clinical trials in IBS-C. While the abdominal symptom component of the primary endpoint is expected to address three abdominal symptoms rather than being limited to abdominal pain, this approach is generally consistent with the FDA IBS guidance document. Also consistent with this guidance document, it is anticipated that a primary endpoint based on improvement in a single symptom, such as abdominal pain, could support a more specific (limited) indication: “Product [X] is indicated in adults for the treatment of abdominal pain associated with irritable bowel syndrome with constipation (IBS-C).”

Table 1 presents an IBS-C endpoint model describing the use of the DIBSS-C as a primary endpoint measure of overall improvement in IBS-C symptom severity and as a key secondary endpoint measure of improvement in severity of individual symptoms.

**Table 1. IBS-C Endpoint Model**

| Hierarchy | Endpoint Concept | Claim Language |
|---|---|---|
| Primary endpoint | Overall response (TBD) indicating improvement in IBS-C symptom severity *(DIBSS-C)*<br>• Improvement (increase) in CSBM frequency<br>• Improvement (reduction) in the abdominal symptoms severity subscale (abdominal pain, discomfort, bloating) | **Section 1, Indications and Usage:**<br>***Product [X]*** *is indicated in adults for the treatment of irritable bowel syndrome with constipation (IBS-C)*<br><br>**Section 14, Clinical Studies:**<br>***Product X*** *increased the frequency of complete, spontaneous bowel movements and improved the abdominal symptoms severity subscale (measuring abdominal pain, discomfort, and bloating).* |
| Key secondary endpoint(s) | Improvement in the severity of symptoms *A, B, and C (e.g., stool consistency, stool frequency [SBMs], incomplete BMs, straining).* | **Section 14, Clinical Studies:**<br>***Product X*** *improved symptoms A, B, and C (e.g., stool consistency, stool frequency [SBMs], incomplete BMs, straining).* |

BM = bowel movement; CSBM = complete, spontaneous bowel movement; *DIBSS-C = Diary for Irritable Bowel Syndrome Symptoms–Constipation*; IBS-C = irritable bowel syndrome with constipation; SBM = spontaneous bowel movement; TBD = to be determined.

## 1.4 Critical details of the measure to the degree known

The DIBSS-C is designed to be patient-reported and completed via electronic diary (eDiary). Respondents are instructed to complete the items addressing the severity of their BM-related symptoms on a real-time or event-driven basis (i.e., every time they have a BM) and to complete the items addressing abdominal symptom severity at a consistent time every evening (recalling the past 24 hours). In addition, after completing the abdominal symptom items each evening, respondents are asked to report any BM-specific information (if any) that they were unable to report since the previous night's entry to minimize missing data. Patients should be unable to enter any data (regarding bowel or abdominal symptoms) past their previous night's entry and all entries should be time-stamped.

Table 2 provides an overview of the DIBSS-C content.

**Table 2.** ***DIBSS-C*** **Content Overview**

| Concept | Response Description | Recall Period |
|---|---|---|
| **BM-Related Symptoms** | | |
| Stool frequency | Frequency (count) | Event-based; up to 24 hours |
| Stool consistency | VRS | Event-based; up to 24 hours |
| Incomplete BMs | Dichotomous | Event-based; up to 24 hours |
| Straining | VRS | Event-based; up to 24 hours |
| **Abdominal Symptoms** | | |
| Abdominal pain | NRS | 24 hours |
| Abdominal discomfort | NRS | 24 hours |
| Abdominal bloating | NRS | 24 hours |

BM = bowel movement; *DIBSS-C = Diary for Irritable Bowel Syndrome Symptoms–Constipation*; NRS = numeric rating scale; VRS = verbal rating scale.

### 1.5 Description of the involvement of external expertise, including scientific communities or other international regulatory agencies, if applicable (i.e., working group, consortia)

The development of the DIBSS-C has been a collaborative process, involving not only RTI-HS and the IBS Working Group (a group comprised of representatives from the sponsoring pharmaceutical companies and C-Path staff, and a patient) but also representatives from FDA and clinical and measurement experts from academia and the Rome Foundation (Expert Panel).

#### 1.5.1 Expert Panel Expertise

The names and affiliations of the clinical experts currently participating in DIBSS-C development activities (external to the IBS Working Group) are provided in Table 3, followed by brief biographical summaries for each of these individuals. Additional information regarding the DIBSS-C development activities in which the experts were directly involved are provided in Table 4.

**Table 3. Experts Contributing to DIBSS-C Development**

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| Attendee | Affiliation | Role |
|---|---|---|
| Lin Chang, MD | University of California, Los Angeles | Expert Panel |
| William Chey, MD | University of Michigan, Ann Arbor | Expert Panel |
| Douglas Drossman, MD | University of North Carolina, Chapel Hill | Expert Panel |
| Jeffrey Lackner, PsyD | University of Buffalo (SUNY), Buffalo | Expert Panel |
| Brian Lacy, MD, PhD | Mayo Clinic, Jacksonville | Expert Panel |

Note: Although not currently involved with the project, Brennan M.R. Spiegel, MD, MSHS (University of California, Los Angeles); Mark P. Jensen, PhD (University of Washington); and Nancy Norton, BS (IFFGD) provided expert input and consultation during the development of the *DIBSS-C*.

Members of the Expert Panel were selected to provide expert consultation during the DIBSS-C development due to their extensive experience in IBS, including the measurement of symptom severity and treatment benefit. Brief biographies for each of the external clinical experts is provided below:

**Lin Chang, MD:** is a Professor of Medicine and Vice-Chief of the Vatche and Tamar Manoukian Division of Digestive Diseases at the David Geffen School of Medicine at UCLA. She serves as the Co-Director of the G. Oppenheimer Center for Neurobiology of Stress and Resilience at UCLA. Her clinical expertise is in functional gastrointestinal disorders. Her research focuses on brain-gut interactions underlying irritable bowel syndrome (IBS). Dr. Chang is the Clinical Research Councilor of the AGA Governing Board. She is also a member of the Rome Foundation Board of Directors, NIH/NIDDK study section and FDA GI Drug Advisory Committee.

**William Chey, MD:** is the Timothy T. Nostrant Collegiate Professor of Gastroenterology & Nutrition Sciences at Michigan Medicine in Ann Arbor, MI. He serves as Director of the GI Physiology Lab, Digestive Disorders Nutrition & Lifestyle Program, and Medical Director of the Michigan Bowel Control Program. He is a member of the Board of Trustees of the American College of Gastroenterology and Board of Directors of the Rome Foundation.

**Douglas Drossman, MD:** serves as the President of the Drossman Center for the Education and Practice of Biopsychosocial Care LLC, President of Drossman Consulting LLC and Drossman Gastroenterology PLLC, President of the Rome Foundation, Professor Emeritus of Medicine and Psychiatry, University of North

Carolina School of Medicine, and Founder and Co-Director Emeritus, UNC Center for Functional GI and Motility Disorders. Dr. Drossman has developed and validated several clinical and psychosocial assessment measures widely used in research and clinical practice: the IBS-QOL, Rating Form for IBD Concerns, Functional Bowel Disorder Severity Index, UC-CD Health Status Scale, Abuse Severity Measure, the Patient Provider Relationship and the Patient Satisfaction Scales for IBS; all instruments are used internationally and distributed through the Rome Foundation and MAPI. He is considered a world expert in the use antidepressants and other centrally acting medication for treating painful GI disorders.

**Jeffrey Lackner, PsyD:** is of Professor of Medicine at the Jacobs School of Medicine at the University at Buffalo and Chief of its Division of Behavioral Medicine. Dr. Lackner's primary research interests include biobehavioral aspects of irritable bowel syndrome. His research program focuses on identifying biobehavioral mechanisms underlying IBS; utilizing this information to develop novel treatment using innovative delivery systems; testing the efficacy of these treatments in randomized controlled trials using psychometrically sound PROs; and specifying how these treatments work, the conditions under which they are most efficacious, and their economic value.

**Brian Lacy, Ph.D., M.D., FACG:** is currently Senior Associate Consultant at Mayo Clinic Jacksonville. He previously worked at the Dartmouth-Hitchcock Medical Center where he was Section Chief of Gastroenterology and Hepatology and Professor of Medicine at the Geisel School of Medicine at Dartmouth. Dr. Lacy's clinical and basic science research interests focus on disorders of gastrointestinal motility, with an emphasis on irritable bowel syndrome, achalasia, dyspepsia, gastroparesis, acid reflux disease, constipation, intestinal pseudo-obstruction and visceral pain. Dr. Lacy is the current co-Editor in Chief of the American Journal of Gastroenterology. He is the former Editor in Chief of Clinical and Translational Gastroenterology. Dr. Lacy was the co-Chairman for the Rome IV Committee on Functional Bowel Disorders. He is board certified in Gastroenterology and Hepatology.

The Expert Panel provided instrumental insight at pivotal DIBSS-C development milestones. Specifically, each of the external experts participated in the activities described in Table 4.

**Table 4. Involvement of External Experts Throughout *DIBSS-C* Development**

| *DIBSS-C* Development Phase | Involvement of External Experts |
|---|---|
| **Concept elicitation** | The expert panel members were responsible for reviewing the draft study protocol and providing input into the study design, specifically the development of the recruitment criteria and content of the concept elicitation interview guides. The expert panel also reviewed the concept elicitation study report. |
| **Item generation** | The expert panel members were instrumental in identifying the most important IBS concepts to include in the *DIBSS-C*. Prior to their review of the qualitative research results, each member was asked to identify the most important IBS symptoms to treat within each subtype based on his or her own clinical and research experience. The expert panel members then participated in a face-to-face Item Generation meeting in June 2011. The expert panel members contributed to the following, providing input from a clinical perspective:<br>• Review and interpretation of findings from the concept elicitation interviews;<br>• Draft wording of the *DIBSS-C* items, instructions, and response options;<br>• Hypothesized structure and measurement principles of the draft symptom measure. |
| **Cognitive interviews** | The expert panel was responsible for reviewing the draft cognitive interview study protocol and provided input to the design of the study, specifically the selection and definition of recruitment quotas and content of the cognitive interview guide.<br>The expert panel also reviewed the qualitative briefing document submitted to the FDA and confirmed the appropriateness of the *DIBSS-C* version for implementation in the quantitative pilot study. |
| **Quantitative pilot study** | The expert panel members participated in a face-to-face Measure Finalization Meeting with the IBS Working Group and FDA in July 2018. During this meeting, the psychometric results from the quantitative pilot study as well as a longitudinal clinical trial were presented. The experts provided strategic advice based on the psychometric results (in light of the qualitative data and their clinical expertise) regarding potential item reduction, scoring, and endpoint generation. |

*DIBSS-C = Diary for Irritable Bowel Syndrome Symptoms–Constipation*; FDA = Food and Drug Administration; IBS = irritable bowel syndrome.

### 1.5.2 Translation Experts

To facilitate future translation and use outside the US, a translatability assessment was conducted in collaboration with PharmaQuest following the second set of cognitive interviews. Specifically, a survey research expert, working with a team of native speakers, reviewed the draft DIBSS-C items to identify potential translation difficulties and, where appropriate, suggested revisions to facilitate translation into the following five languages: French (Canada), German
(Germany), Portuguese (Brazil), Spanish (US), and Ukrainian (Ukraine). These five languages were chosen to represent the various cultural regions in which clinical trials are commonly conducted by the project sponsors.

The cultural appropriateness and clarity of instructions, questions, and response choices were also reviewed, and only extremely minor modifications were recommended. All modifications were subsequently tested (and their appropriateness confirmed) with patients in the third round of cognitive interviews.

### 1.5.3 ePRO Experts

Dedicated electronic patient-reported outcome (ePRO) specialists provided expertise and assistance with regard to the development of the DIBSS-C ePRO platform. The C-Path ePRO Consortium's Instrument Migration Subcommittee (comprised of personnel from seven ePRO technology providers at the time) was provided with an initial draft of the DIBSS-C which was subject to an Electronic Implementation Assessment. The goal of the Electronic Implementation Assessment was to assess the viability of implementing the DIBSS-C on all available electronic platforms. This subcommittee of the ePRO Consortium member firms was asked for general comments on the measure's ability to be migrated across platforms, as well as item-level comments for each currently available data capture platform (i.e., tablet, handheld, interactive voice response [IVR], web, and digital pen). The subcommittee reviewed and discussed the comments; the subcommittee subsequently summarized this feedback and provided recommendations to the IBS Working Group. As a result of the Electronic Implementation Assessment, minor formatting changes to a few of the items were recommended and subsequently implemented to facilitate electronic implementation on the various electronic platforms. The electronic implementation was assessed in the third and final round of cognitive interviews and, ultimately the appropriateness of electronic administration was confirmed.

## Section 2: Executive Summary

### 2.0 High-level summary of what is included in the full qualification package and results to be described in the sections below

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder characterized by recurrent episodes of abdominal pain associated with alterations in bowel movements (BMs). The alterations in BMs can principally manifest as diarrhea, constipation, or an alternation between diarrhea and constipation; these subtypes of IBS are denoted as

IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), and mixed IBS (IBS-M), respectively
The PRO Consortium's IBS Working Group at C-Path has completed development of three PRO measures addressing the severity of IBS-C, IBS-D, and IBS-M symptoms in accordance with FDA's PRO guidance and FDA's guidance for industry, titled Qualification Process for Drug Development Tools (US Food and Drug Administration, 2014):

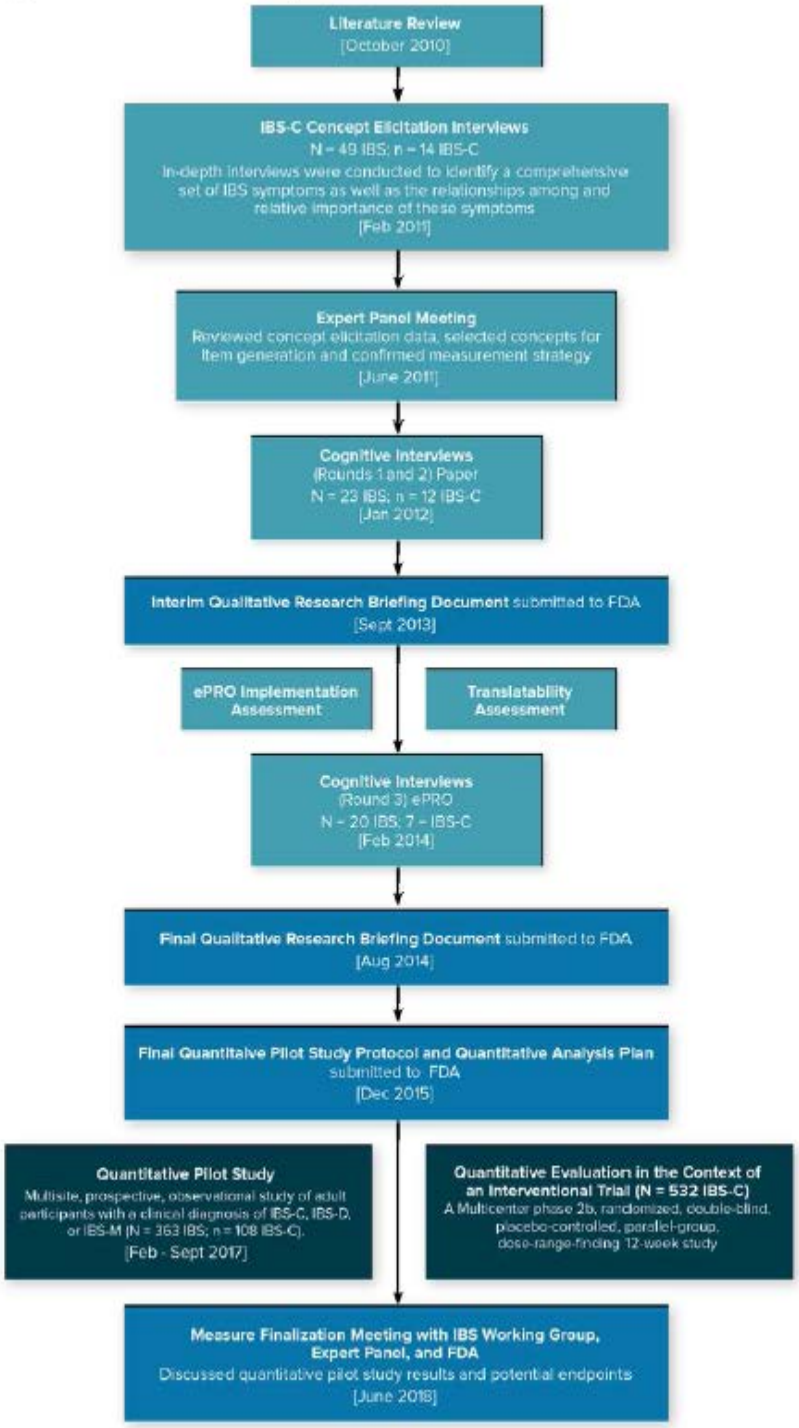
- Diary for Irritable Bowel Syndrome Symptoms–Constipation (DIBSS-C)
- Diary for Irritable Bowel Syndrome Symptoms–Diarrhea (DIBSS-D)
- Diary for Irritable Bowel Syndrome Symptoms–Mixed (DIBSS-M)

Although the focus of this Full Qualification Package is on the measure developed for IBS-C, each of these measures includes a common set of items supplemented with subtype-specific items. These measures were developed in parallel to assess primary and key secondary efficacy endpoints in future clinical trials of new treatments for IBS-C, IBS-D, and IBS-M to support product approval and labeling. Regulatory and expert consensus at the study onset (2010) agreed with this aggregated approach, recognizing that the hallmark symptoms of IBS are largely similar across IBS subtypes, with some important symptom variations (as exemplified by the Rome diagnostic criteria).

It should be noted that from the inception of the IBS Working Group, the development of the DIBSS-C/D/M has been a collaborative process, involving the members of the IBS Working Group (sponsoring pharmaceutical companies, C-Path, patient advocates, and clinical experts), RTI Health Solutions (RTI-HS), and an expert panel composed of clinical and measurement experts. Clinical and COA experts at FDA have also provided strategic advice throughout the development of these measures.

This Full Qualification Package describes, in detail, the overall development process and both the qualitative and quantitative evidence supporting the qualification of the DIBSS-C, a patient-reported diary designed to assess IBS-C symptom severity (concept of interest) within randomized, placebo-controlled clinical trials of new treatments for IBS-C (context of use). Specifically, this qualification package details the results and implications of the activities outlined in Figure 1, the DIBSS-C Development Flow Chart.

**Figure 1.** ***DIBSS-C*** **Development Flow Chart**




ePRO = electronic patient-reported outcome; FDA = Food and Drug Administration; IBS = irritable bowel syndrome; IBS-C = irritable bowel syndrome with constipation; IBS-D = irritable bowel syndrome with diarrhea; IBS-M = mixed irritable bowel syndrome.