Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000148: Diary for Irritable Bowel Syndrome Symptoms-Diarrhea (DIBSS-D)
507 Update: Transition Summary

Administrative Structure:

Description of the submitter including, but not limited to, principal investigator(s), working group member(s), institutions, and contact information not contained within the cover letter.

This proposal is being submitted by the Patient-Reported Outcome (PRO) Consortium at the Critical Path Institute (C-Path).

The PRO Consortium enables pre-competitive collaboration that leverages human and financial resources from multiple stakeholders. The PRO Consortium's Irritable Bowel Syndrome (IBS) Working Group currently has members representing the following pharmaceutical firms: AbbVie and Ironwood. The development work for the *Diary for Irritable Bowel Syndrome Symptoms – Diarrhea* (*DIBBS-D*) was conducted in partnership with RTI Health Solutions in collaboration with Bracket as the eCOA provider. C-Path's principal investigator is Stephen Joel Coons, PhD.

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Concept(s) of Interest (COI) for Meaningful Treatment Benefit:

A description of the meaningful aspect of patient experience that will represent the intended benefit of treatment (e.g., presence/severity of symptoms, limitations in performance of daily activities).

Diarrhea-predominant irritable bowel syndrome (IBS-D) is a chronic, functional bowel disorder characterized by recurrent episodes of abdominal pain associated with diarrhea. Although not required for diagnosis, patients with IBS-D are commonly bothered by additional bowel movement (BM-related) symptoms such as stool consistency, stool frequency, recurrent BMs, and urgency, as well as additional abdominal symptoms, such as abdominal pain, abdominal discomfort, abdominal bloating, and abdominal cramping[1]. Each of these symptoms is addressed in the *DIBSS-D*.

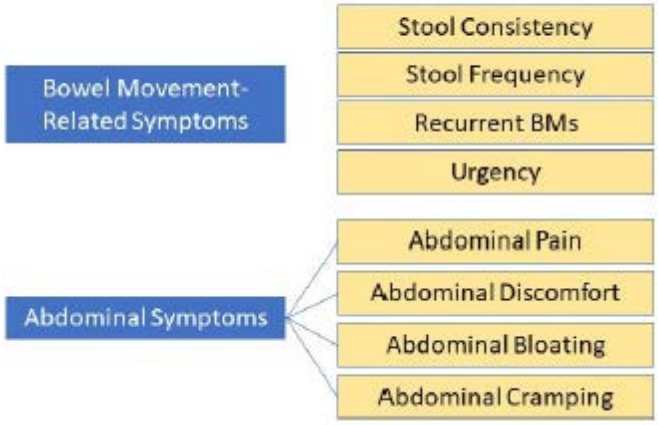
The concept of interest is IBS-D symptom severity. The meaningful treatment benefit is a reduction in or relief of the core symptoms associated with IBS-D. The *DIBSS-D* is intended to support the evaluation of both primary and key secondary endpoints related to improvements in IBS-D symptom severity within the context of clinical trials. The content of the *DIBSS-D* has been carefully crafted to provide a comprehensive assessment of IBS-D

symptom severity. As such, it addresses the severity of both bowel and abdominal symptoms experienced by adults with IBS-D.

Provide a conceptual framework for the COA(s)

The conceptual framework of the *DIBSS-D* is provided in Figure 1.

Figure 1. *DIBSS-D* Conceptual Framework



Context of Use for COA Qualification:

Targeted study population including a definition of the disease and selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, comorbidities, language/culture groups).

The targeted study population is fully consistent with the recommendations in FDA's IBS guidance for industry titled Irritable Bowel Syndrome – Clinical Evaluation for Drugs for Treatment[2] and IBS-D clinical trials previously conducted by study sponsors. Specifically, the intended study population for the *DIBSS-D* is expected to include adult males and females who meet Rome diagnostic criteria (either Rome III or IV) for IBS-D and have active symptoms, including a clinically significant level of abdominal pain (as defined by the Rome criteria and the current FDA IBS guidance[2]). The core inclusion criteria used during the development of the *DIBSS-D* are provided below:

- Patient meets the Rome III or IV criteria for IBS: reports recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with 2 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 18 years of age or older.
- Patient is an 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 to 10 across the past 7 days.
- Patient reports loose (mushy) or watery stools in the absence of any laxative, suppository, or enema for at least 25% of BMs and hard or lumpy stools in less than 25% of BMs during the 12 weeks before screening.

The exclusion criteria were as follows:

- Patient has a history of any condition that could confound attribution of symptoms to IBS including the following:
    - Gastroparesis
    - Gastrointestinal (GI) obstruction
    - Carcinoid syndrome
    - Chronic pancreatitis
    - Amyloidosis
    - Functional dyspepsia
    - Colitis (e.g., microscopic, lymphocytic, collagenous)
    - Ulcerative colitis (including ulcerative proctitis)
    - Ischemic colitis
    - Celiac sprue
    - Crohn's disease
    - HIV infection
    - Pelvic floor dysfunction (e.g., rectal prolapse, defecation disorder, anismus)
    - Symptomatic cholelithiasis
    - Recurrent diverticulitis
    - Active duodenal or gastric ulcer
    - History of lactose intolerance in which IBS-like symptoms are completely relieved by a lactose-free diet
    - Unexplained alarm symptoms (e.g., anemia, weight loss, rectal bleeding)
    - Chronically taking antibiotics (i.e., > 5 courses in the past 12 months)
    - Endometriosis
    - Diabetes with significant neuropathy
- Patient has had an appendectomy within the past 3 months or any other type of abdominal or pelvic surgery in the past 6 months
- Patient has had a cholecystectomy in the past year
- Patient has ever had a GI resection
- Patient has ever had any type of bariatric surgery (includes banding)
- Patient has taken opioids in the past 6 months
- Patient is unable to fully comprehend the consent form.

***Targeted study design and statistical analysis plan (includes the role of the planned COA in future drug development clinical trials, including the planned set of primary and secondary endpoints with hierarchy, if appropriate*).**

The *DIBSS-D* was developed to assess change (as compared to placebo) in IBS-D symptom severity within randomized, placebo-controlled clinical trials of new treatments for IBS-D. The design of these trials is fully consistent with the recommendations in FDA's IBS

guidance for industry titled Irritable Bowel Syndrome – Clinical Evaluation for Drugs for Treatment[2] and IBS-D clinical trials previously conducted by study sponsors.

The scores resulting from the *DIBSS-D* will be positioned to derive key endpoints in IBS-D treatment trials. The specific endpoint selection, positioning, and measurement approach will be determined by the study sponsor in concert with the appropriate regulatory review agencies. A statistical analysis plan for an IBS-D treatment trial cannot be developed in the absence of a specific study protocol, which does not exist at this time.

Applicable study settings for future clinical trials

- ***Geographic location with language/culture groups***
  The *DIBSS-D* will be translated as needed and is intended for use in multinational trials or trials within a single country where multiple language and cultural groups may be enrolled.

- ***Other study setting specifics (e.g., inpatient versus outpatient)***
  The *DIBSS-D* is intended for clinical trials enrolling outpatients.

COA Type: Patient- Reported Outcome (PRO)

References:

1. Fehnel SE, Ervin CM, Carson RT, Rigoni G, Lackner JM, Coons SJ. Development of the Diary for Irritable Bowel Syndrome Symptoms to Assess Treatment Benefit in Clinical Trials: Foundational Qualitative Research. Value in Health 2017;20(4):618-626.

2. US Food and Drug Administration (FDA). Guidance for industry Irritable Bowel Syndrome – Clinical Evaluation for Drugs for Treatment. May 2012. Available at: https://www.fda.gov/downloads/Drugs/Guidances/UCM205269.pdf. Accessed March 18, 2021.