Clinical Outcome Assessments (COA) Qualification Program
DDTCOA #000013: Functional Dyspepsia Symptom Diary (FDSD)
October 27, 2017 Update

EXECUTIVE SUMMARY

Patient self-assessment is critical in functional dyspepsia (FD) because it is a symptom-defined disorder. For example, diagnostic criteria for FD were defined in 2016 by the Rome IV task force[1] and, consistent with those previously defined in 2006 by the Rome III task force,[2] include symptoms of postprandial fullness, early satiety, and epigastric pain and burning without any evidence of a structural disorder thought to explain the symptoms. Symptoms of FD can be known only to patients themselves and are therefore best reported via patient-reported outcome (PRO) measures. Although PRO measures have been developed for GI disorders including FD, to date, none can be considered "fit for purpose" as measures to evaluate treatment efficacy in regulated clinical trials because they do not meet the measurement principles (e.g., patient involvement in item generation and pilot testing) set forth in the United States (US) Food and Drug Administration's (FDA) guidance for industry titled *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (hereafter called FDA PRO Guidance).[3,4]

To fill this measurement gap, the PRO Consortium's Functional Dyspepsia Working Group at the Critical Path Institute (C-Path) embarked upon the development and qualification of the *Functional Dyspepsia Symptom Diary* (*FDSD*), a daily FD symptom diary developed according to recommendations in the FDA PRO Guidance to assess severity of FD symptoms among adults (age 18 and over) with FD. The intention is that the *FDSD* will be used as a primary endpoint measure in FD clinical trials to inform treatment approval decisions and product labeling goals. The *FDSD* is an eight-item daily measure assessing seven FD symptoms and includes an item that assesses the self-reported bother associated with one of those symptoms (burping/belching). Respondents are required to rate the severity (at its worst) of their FD symptoms over the past 24 hours on an 11-point numeric rating scale (NRS) ranging from 0 (no [symptom]) to 10 (worst imaginable [symptom]) and the bother associated with one symptom on an NRS ranging from 0 (no bother) to 10 (worst imaginable bother).

Evidence supporting the content validity of the *FDSD* was generated via a number of qualitative and quantitative research activities including: a review of the peer-reviewed literature regarding FD symptomatology, a review of the peer-reviewed literature to identify existing PRO measures designed to evaluate FD symptoms in adults, concept elicitation interviews, concept selection and item generation, cognitive interviews, and a preliminary psychometric evaluation. At each stage of the *FDSD* development process, input was obtained from the Functional Dyspepsia Working Group, C-Path scientists, scientific/clinical advisors in the field of gastroenterology, and representatives of FDA's Center for Drug Evaluation and Research via the formal drug development tool qualification process.[5] Input was also obtained from a linguistic validation specialist to provide insight into the linguistic/cultural adaptability of the *FDSD* and an electronic PRO system provider who contributed expertise and assistance regarding the development of the *FDSD* for completion using an electronic handheld device.

Content of the *FDSD* was informed via a review of the peer-reviewed literature, review of existing measures, and findings from open-ended concept elicitation interviews conducted with a diverse

sample of adults with FD (N=45). Informed by these data, as well as input from scientific advisors, and findings of both an electronic implementation assessment and translatability assessment, it was decided to focus the assessment on the following five core symptoms of FD: stomach pain, burning in the stomach, bloating, postprandial fullness, and early satiety. Given their potential relevance to the target patient population, two additional symptoms were selected for assessment: nausea and burping/belching. For the specific purpose of assessing the primary FD symptoms to evaluate treatment benefit in regulated clinical trials for primary labeling considerations, the responses to only five *FDSD* items, Items 1 (burning in the stomach), 2 (stomach pain), 4 (bloating), 5 (postprandial fullness), and 6 (early satiety), are considered to be "core" symptoms of FD and are aggregated to generate a Total Symptom Score (TSS). It is the *FDSD* TSS for which qualification is currently sought. While the items reflecting nausea (one item) and burping/belching (two items) are considered relevant to FD and supportive criteria in diagnosis, they are not considered cardinal symptoms of the condition, and are therefore not included in the TSS. A daily diary format was chosen to minimize the impact of recall bias, to account for day-to-day variation in FD symptoms, and also to facilitate the calculation of symptom-free days and the assessment of changes in symptom severity over time.

Semi-structured cognitive interviews were conducted with a second (independent) sample of 57 participants to collect qualitative evidence regarding the readability, comprehensibility, relevance, comprehensiveness, and usability of the preliminary *FDSD* items, instructions, response options, as well as ease of *FDSD* completion using the handheld electronic device.

Interviews were conducted in two waves to allow for modifications to the *FDSD* and subsequent testing among different participants. During the first wave of interviews, participants (n=8) were asked to complete the *FDSD* in a paper-based format depicting screenshots of the handheld electronic device. The remainder of the participants (n=49) completed the *FDSD* on the handheld electronic device itself (LG Nexus 5 smartphone). Findings indicated that the *FDSD* offered sufficient conceptual coverage of participants' FD symptom experience and was well understood and consistently interpreted across sociodemographic and clinical subgroups of participants. Minor changes to language were implemented following analysis of the cognitive interview data to improve patient interpretation.

The performance, reliability, and validity of *FDSD* items and the *FDSD* TSS were explored using data collected during the cognitive interviews (N=57). The *FDSD* items demonstrated strong item performance, internal consistency reliability, and construct validity (in terms of the ability of the items to distinguish between known groups). Future development work will seek to explore additional measurement properties of the *FDSD* in longitudinal studies, including test- retest reliability and sensitivity to change over time, as well as in interventional studies to generate further evidence regarding construct validity and the interpretation of the TSS in terms of meaningful change.

This document details the development and evaluation of the *FDSD* and provides evidence to support the qualification of the *FDSD* for use as an exploratory endpoint measure in clinical studies.

1.0 OVERVIEW OF *FUNCTIONAL DYSPEPSIA SYMPTOM DIARY* FOR QUALIFICATION FOR EXPLORATORY USE

1.1 Introduction and Overview

Patient self-assessment is critical in functional dyspepsia (FD) because it is a symptom-defined disorder. For example, diagnostic criteria for FD were defined in 2016 by the Rome IV task force[1] and, consistent with those previously defined in 2006 by the Rome III task force,[2] include symptoms of postprandial fullness, early satiety, and epigastric pain and burning without any evidence of a structural disorder thought to explain the symptoms. Further, it is important to note that FD is subdivided into two diagnostic categories of dyspeptic symptoms:
(1) postprandial distress syndrome (PDS, characterized by postprandial fullness and early satiation) and (2) epigastric pain syndrome (EPS, characterized by epigastric pain and burning). The PDS and EPS subtypes can co-exist in the same individual.
(2)
Symptoms of FD are known only to patients themselves and are therefore best reported via patient-reported outcome (PRO) measures. Although PRO measures have been developed for GI disorders including FD (e.g., Dyspepsia Symptom Severity Index [DSSI],[6] Nepean Dyspepsia Index [NDI][7]), a review of the literature[8] concluded that none of these questionnaires could be used as measures to evaluate treatment efficacy in regulated clinical trials because they do not meet the measurement principles (e.g., patient involvement in item generation and pilot testing) set forth in the United States (US) Food and Drug Administration's (FDA) guidance for industry titled *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (hereafter called FDA PRO Guidance).[3]

To fill this measurement gap, the PRO Consortium's Functional Dyspepsia Working Group at the Critical Path Institute (C-Path) embarked upon the development and qualification of the *Functional Dyspepsia Symptom Diary* (*FDSD;* Appendix A), a daily FD symptom diary developed according to recommendations in the FDA PRO Guidance to assess severity of FD symptoms among adults (age 18 and over) with FD.

1.2 Concept of Interest (COI) for Meaningful Treatment Benefit

The concept of interest (COI) is FD symptom severity. The *FDSD* is intended to be used as a primary endpoint measure in FD clinical trials to assess self-reported FD symptom severity in adults. The *FDSD* assesses the following seven FD symptoms: (1) burning in the stomach, (3) stomach pain, (3) nausea, (4) bloating, (5) postprandial fullness, (6) early satiety, and (7) burping/belching. However, for the specific purpose of assessing the primary FD symptoms to evaluate treatment benefit in regulated clinical trials for primary labeling considerations, the responses to only five *FDSD* items, Items 1 (burning in the stomach), 2 (stomach pain), 4 (bloating), 5 (postprandial fullness), and 6 (early satiety) are considered as "core" symptoms of FD and are aggregated to generate a Total Symptom Score (TSS). It is the *FDSD* TSS for which qualification is currently sought. The additional symptoms of nausea and burping/belching, which are listed as supportive in the diagnosis of FD based on Rome criteria,[1,2] are considered supplementary items and are not included in the TSS.

Product-specific claims and labeling language would be the responsibility of the sponsor and should be based on product attributes, study design and hypotheses, and discussions with the

appropriate regulatory agencies. Nevertheless, using the *FDSD*, product-specific claims and labeling language pertaining to the severity of the FD symptom experience and/or occurrence of symptom-free days (SFDs) could be targeted with example label language presented in Table 2.

Table 2. Example of Targeted Labeling Language

"Drug X is indicated for the treatment of FD in patients 18 years of age and older"
"Among patients treated with Drug X compared to Drug Z over y weeks of treatment, patients treated with Drug X reported significant reductions in FD symptom severity"
"Significantly more patients treated with Drug X reported improvements in FD symptom severity"
"Patients treated with Drug X reported significantly fewer days with FD symptoms"
"Patients treated with Drug X reported a significantly higher number of symptom-free days"

1.3 Context of Use

The *FDSD* was developed to assess the symptoms associated with adult FD and is intended for use in regulated clinical trials as a primary endpoint measure to assess treatment benefit and inform product labeling. In this way, the target patient population includes adults who meet the newly developed Rome IV diagnostic criteria for FD (Appendix B), without evidence of any other confounding GI disorder (including gastroparesis, vomiting [more than once a week on a chronic basis over the past six months], or active GERD). To support its use in clinical trial samples with varied demographic and clinical characteristics, the *FDSD* was developed with input from a diverse group of people diagnosed with FD who also varied with respect to gender, ethnicity, race, level of educational attainment, subtypes of FD (i.e., EPS, PDS, and co-existing EPS and PDS), FD symptom severity levels, and other clinical characteristics (e.g., medication use; co-morbid, but not confounding, conditions).

In regulated clinical trials, the intention is that the *FDSD* will be used as a primary endpoint measure to facilitate the comparison of FD symptom severity change between or among study groups/arms or within study subjects. The clinical trial would need to succeed on this primary endpoint to support an FD indication or symptom severity claim(s). The specific endpoint selection, positioning, and measurement approach would be determined by the study sponsor for its specific context of use and in concert with the appropriate regulatory review agencies.

1.4 *Functional Dyspepsia Symptom Diary* Conceptual Framework

The conceptual framework for the *FDSD* is presented in Table 3. The *FDSD* assesses seven FD symptoms and includes an item that assesses the self-reported bother associated with one of those symptoms (burping/belching). Thus, the *FDSD* is constructed as an eight-item daily assessment. As mentioned previously, for the specific purpose of assessing the primary FD symptoms to evaluate treatment benefit in regulated clinical trials for primary labeling considerations, the responses to only five *FDSD* items, Items 1 (burning in the stomach), 2 (stomach pain), 4 (bloating), 5 (postprandial fullness), and 6 (early satiety) are included in the TSS. While the items reflecting nausea (one item) and burping/belching (two items) are considered relevant to FD, they are not considered cardinal symptoms of the condition.

Table 3. Conceptual Framework of the *Functional Dyspepsia Symptom Diary* Total Symptom Score*

Domain		Concept		*FDSD* Item
Functional dyspepsia-related symptom severity (Total Symptom Score)	→	Burning in the stomach	→	1. Over the past 24 hours, rate the worst burning in your stomach
		Stomach pain	→	2. Over the past 24 hours, rate your worst stomach pain
		Bloating	→	4. Over the past 24 hours, rate your worst bloating (feeling like your stomach is full of air or gas)
		Postprandial fullness	→	5. Over the past 24 hours, rate your worst stomach fullness after you finished eating (feeling uncomfortably full of food)
		Early satiety	→	6. Over the past 24 hours, rate the difficulty you had finishing your meals because you felt full too quickly

*Item 3 ("Over the past 24 hours, rate your worst nausea [feeling like you might throw up]"), Item 7 ("Over the past 24 hours, rate your burping/belching"), and Item 8 ("Over the past 24 hours, rate how bothered you were by burping/belching") are included in the *FDSD*; however, because they are considered supplementary assessments, they are not included in the TSS or to be used in trial endpoints (they will instead be scored as individual items).

1.5 Critical Details of the *Functional Dyspepsia Symptom Diary*

1.5.1 Patient Population

The *FDSD* is a self-administered PRO measure for use among adults (age 18 years and older) with FD.

1.5.2 Item Content

As indicated, the TSS of the *FDSD* assesses the daily severity of five FD symptoms, including (1) burning in the stomach, (2) stomach pain, (4) bloating, (5) postprandial fullness, and (6) early satiety. In addition to these five TSS items, three supplementary items are included in the *FDSD*, assessing (3) nausea, (7) burping/belching, and (8) bother associated with burping/belching. Items 1 to 7 ask respondents to rate the severity (at its worst) of their FD symptoms over the past 24 hours on an 11-point numeric rating scale (NRS) ranging from 0 (no symptom) to 10 (worst imaginable symptom) and Item 8 is rated on an NRS ranging from 0 (no bother) to 10 (worst imaginable bother).

1.5.3 Mode of Administration and Method of Data Collection

The *FDSD* is a self-administered PRO measure to be completed once daily at the end of the day. As an end-of-day diary, the *FDSD* was developed for use in an electronic format and was initially tested using paper printouts of the screenshots from the electronic PRO (ePRO) device (round 1 of the cognitive interviews). The *FDSD* was implemented on a handheld electronic device (LG Nexus 5 smartphone) in accordance with industry best practices.[9,10] Subsequent testing in round 2 of the cognitive interviews confirmed respondent understanding and usability of the *FDSD* in the electronic data collection format. The preliminary quantitative analysis utilized the data collected via both ePRO screenshots (round 1) and the handheld electronic device (round 2). It should be noted that future use of the *FDSD* using a different method of data collection (e.g., paper and pen, tablet, computer, interactive voice response system [IVRS]) may require additional usability and equivalence testing.

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