Functional Dyspepsia Working Group

Presented at the Eighth Annual PRO Consortium Workshop – Bethesda, MD – April 26-27, 2017

PRO CONSORTIUM CRITICAL PATH INSTITUTE

Background

Rationale for Functional Dyspepsia (FD) Working Group (WG)

- PRO Consortium member representatives and FDA advisors identified FD as an area lacking a "well-defined and reliable" measure of treatment benefit

Goal of the FD WG

- To develop a PRO measure to assess the symptoms of FD for use in clinical trials as a primary endpoint measure to establish treatment benefit

Targeted Labeling Language

- The PRO measure would support an indication for the treatment of the FD subtype as defined by the Rome III diagnostic criteria:
  1) Postprandial distress syndrome (PDS), which includes symptoms such as postprandial fullness and early satiation;
  2) Epigastric pain syndrome (EPS), which involves symptoms such as epigastric pain and burning; or
  3) Co-existing PDS and EPS subtypes

Milestones

Milestone	Expected Date	Completed Date
Vendor selection and contracting		SEP 2012
Complete background research (Literature Review Report and Expert Panel input)		AUG 2013
Submit Literature Review and Concept Elicitation Protocol to FDA for consultation and advice		OCT 2013
Received written comments from the FDA		DEC 2013
Submitted working group's responses to FDA comments		FEB 2014
Complete initial concept elicitation interviews and generate items (concept elicitation interviews, item generation, expert panel input)		MAR 2015
Complete translatability and electronic implementation assessments		APR 2015
Complete cognitive interviews and revise instrument		FEB 2017
Submit Qualitative Briefing Package to FDA for exploratory use of *FDSD*	2Q 2017	

Highlights

Example Endpoint Model for Treatment of FD – Postprandial Distress Syndrome (PDS) Subtype

Endpoint Hierarchy	Concept(s)	Endpoint Type
Primary	Total Symptom Score (epigastric pain, epigastric burning, bloating, postprandial fullness, early satiety)	PRO

Example Endpoint Model for Treatment of FD – Epigastric Pain Syndrome (EPS) Subtype

Endpoint Hierarchy	Concept(s)	Endpoint Type
Primary	Total Symptom Score (epigastric pain, epigastric burning, bloating, postprandial fullness, early satiety)	PRO

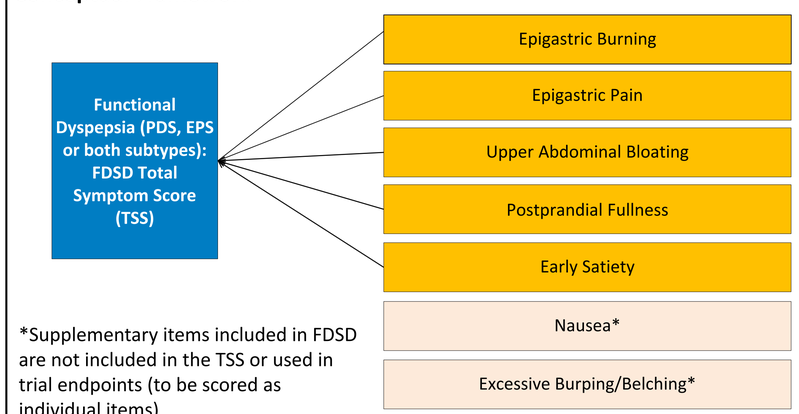
Example Endpoint Model for Treatment of FD – Co-existing PDS and EPS Symptoms

Endpoint Hierarchy	Concept(s)	Endpoint Type
Primary	Total Symptom Score (epigastric pain, epigastric burning, bloating, postprandial fullness, early satiety)	PRO

Target Population

- U.S. adult patients aged 18 years and older, with a diagnosis of FD (including PDS, EPS, or both) according to the Rome III diagnostic criteria, inclusive of a recent negative endoscopy
- Exclusion criteria include the following conditions: patients with gastroparesis, active irritable bowel syndrome, active chronic constipation, and active GERD (list not exhaustive)

Conceptual Framework



*Supplementary items included in FDSD are not included in the TSS or used in trial endpoints (to be scored as individual items)

Measure – *Functional Dyspepsia Symptom Diary* (*FDSD*)

Core items: Eight items addressing five core symptom domains plus two supplementary domains
Recall Period: 24-hour
Response Options: 11-point numeric rating scale
Symptom Attribute: Severity was chosen based on patient descriptions of FD symptom experience

Working Group Updates

Completed Activities

- Preliminary psychometric evaluation
- Expert consultation on the qualitative and quantitative analysis results

Information Dissemination

- Taylor F, et al. Development of a Symptom-Based Patient-Reported Outcome Instrument for Functional Dyspepsia: A Preliminary Conceptual Model and an Evaluation of the Adequacy of Existing Instruments. *The Patient--Patient-Centered Outcomes Research* 2016;*9*:409-418
- Taylor F, et al. Development of a Symptom-Focused Patient-Reported Outcome Measure for Functional Dyspepsia: The Functional Dyspepsia Symptom Diary (FDSD). *American Journal of Gastroenterology* (Submitted)
- Mazar I, et al. Placement of recall period in patient-reported outcome questionnaire items: Does it matter? ISPOR 22nd Annual Meeting on May 24, 2017 in Boston, MA, USA.

Unique Issues for the Working Group

- Recruitment challenges encountered in identifying patients with FD diagnosis that do not have other co-existing GI disorders
  - Very extensive list of exclusion criteria from FDA, further complicated by potential discrepancy between clinician-reported and patient-reported symptoms
  - Compromise reached with the FDA's Qualification Review Team to allow enrollment of patients with comorbid conditions with future evaluation planned regarding the impact of these comorbid conditions on the patients' FD-symptom experience
- Challenge articulating concepts when developing several key items (i.e., early satiety and burping/belching)
  - Item wording was successfully tested in cognitive interviews

Lessons Learned

- Do not assume an accepted definition of condition exists and that certain terminology is universally understood (e.g., conceptual framework and conceptual model)
- When possible, consult recruiting agencies and clinical sites to assess feasibility of inclusion/exclusion criteria before finalizing
- Despite FDA's interest in having the instrument development sample free of confounding conditions (i.e., a "pure-FD" sample), it is critical that the sample represents the real-world FD population to ensure that future research is feasible and relevant

Working Group Participants

Company/Organization	Representatives
Allergan	Robyn T. Carson, MPH (Co-Chair); Steven J. Shiff, MD
Ironwood Pharmaceuticals, Inc.	David Reasner, PhD (Co-Chair)
Expert Panel Members	**Affiliation**
Brian E. Lacy, MD, PhD	Dartmouth-Hitchcock Medical Center
Henry P. Parkman, MD	Temple University
Jan Tack, MD	University of Leuven
Nicholas Talley, MD, PhD	University of Newcastle
Contract Research Organization	**Research Team**
Adelphi Values	Alan Shields, PhD; Fiona Taylor, MBiochem; Catherine Foley, MPH, MA; Megan Daggett, BA; Sophie Higgins, MPH; Emily Brennan, MPH
ePRO System Provider	**Representative**
Biomedical Systems	Serge Bodart, MS