Functional Dyspepsia Working Group

Presented at the Fifth Annual PRO Consortium Workshop – Silver Spring, MD – April 29-30, 2014

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 instrument, in accordance with the FDA PRO Guidance, to measure the symptoms of FD for use in clinical trials as a primary endpoint to establish treatment benefit

Targeted Labeling Language*

- The PRO measure would support an indication of 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
Scoping Stage		February 29, 2012
Content Validity Stage		
Vendor selection and contracting		September 18, 2012
Complete background research (Literature Review Report and Expert Panel input)		August 30, 2013
Submit Literature Review & Concept Elicitation Protocol to FDA for consultation and advice		October 31, 2013
Received FDA Written Responses		December 20, 2013
Submitted Responses to FDA		February 7, 2014
Complete initial concept elicitation interviews and generate items (concept elicitation interviews, item generation, expert panel input)	July 2014	
Complete translatability assessment	August 2014	
Complete cognitive debriefing interviews and revise instrument	April 2015	
Submit Qualitative Research Summary Briefing Document to FDA for review and feedback	2 Q 2015	
Complete documentation of content validity and cross-sectional evaluation of other measurement properties	TBD	
Submit exploratory endpoint qualification dossier to FDA	TBD	

Content of Interest

Endpoint model for treatment of FD – Postprandial Distress Syndrome(PDS) Subtype

Endpoint Hierarchy	Concept(s)	Endpoint Type
Primary	FD-PDS Subtype • PDS Symptoms Score	PRO instrument under development

Endpoint model for treatment of FD – Epigastric Pain Syndrome (EPS) Subtype

Endpoint Hierarchy	Concept(s)	Endpoint Type
Primary	FD-EPS Subtype • EPS Symptom Score	PRO instrument under development

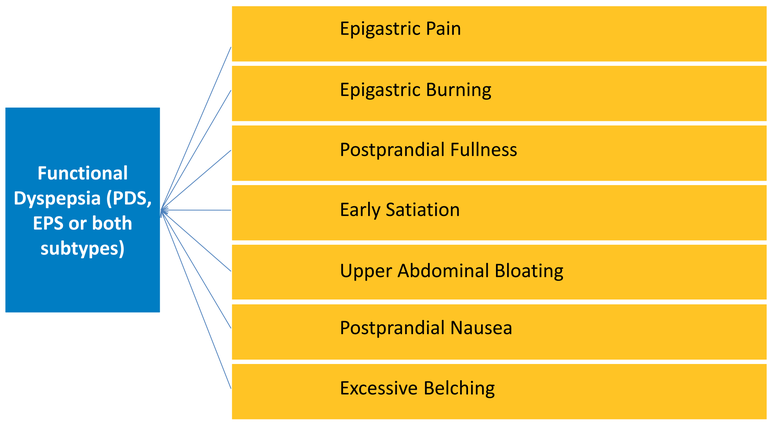
Endpoint model for treatment of FD – Co-existing PDS and EPS symptoms

Endpoint Hierarchy	Concept(s)	Endpoint Type
Primary	FD • PDS and EPS Symptoms Score	PRO instrument under development

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)

Hypothesized Conceptual Framework*



- The conceptual framework was developed for the Summary Stage Scoping Document based on a preliminary review of the literature

Updates

- Finalized and updated concept elicitation study documents based on recent FDA feedback
- Developed and finalized qualitative analysis plan
- Site and patient recruitment underway (Target Sample = 45; 15 EPS, 15 PDS, 15 EPS+PDS)

Working Group Plans

Next Steps

- Complete concept elicitation interviews by end of April
- Finalize CE report outline in April
- Draft manuscript summarizing literature and instrument review
- Conduct item generation meeting in July

Dissemination Plan

- First manuscript will focus on literature/instrument review

Topics for Discussion

Unique Issues for the Working Group and the Resolution

- Challenges encountered in identifying patients with FD diagnosis that also do not have other overlapping GI disorders
  - Very extensive list of exclusion criteria from FDA
  - Requirement for negative upper endoscopy in past
  - Exclusion criteria complicated by potential discrepancy between clinician-reported and patient-reported symptoms
- Recruitment challenges mitigated by reaching out to 30+ clinical sites, including involvement of the Expert Panel members
  - When possible, consult recruiting agencies and clinical sites before finalizing inclusion/exclusion criteria.

Lessons Learned

- Don't assume an accepted definition of condition exists
- Don't assume that certain terminology is universally understood (e.g., conceptual framework and conceptual model)
- FDA would like the qualitative development sample to be free of confounding conditions from the disease under study.
  - However, It is important that the sample represents the clinical trial population in which it will be utilized.
  - To mitigate this, teams can prospectively collect concept elicitation information for participants with and without co-occurring symptomatology to determine whether any differences are present and meaningful

Working Group Participants

Organization	Name
Forest Research Institute, Inc.	Robyn Carson, MPH (Co-Chair), Steven J. Shiff, MD
Ironwood Pharmaceuticals, Inc.	Brooke Witherspoon, Vineeta Belanger, PhD
Shire Development Inc.	Linda Deal, MS (Co-Chair), Debra G. Silberg, MD, PhD
Contract Research Organization	**Research Team**
Adelphi Values	Alan Shields, PhD; Fiona Taylor, MBiochem; Farrah Pompilus, MA; Catherine Foley, MPH, MA; Ramon Iovin, PhD; Megan Daggett, BA

* Note: Prior to conducting qualitative research with patients, it is not known whether a separate symptom complex exists between the two individual subtypes of FD (EPS and PDS), nor is it known at this point whether these subtypes would be evaluated in a particular clinical trial. Target labeling language and the conceptual framework will evolve based upon patient feedback and qualitative findings.