DEVELOPMENT OF A NEW PATIENT-REPORTED OUTCOME (PRO) MEASURE FOR MAJOR DEPRESSIVE DISORDER: RESULTS OF A CONSORTIUM-BASED APPROACH

Blum, SI[1]; Greco, N[2]; Martin, ML[3]; Hayes, RP[4]; Coons, SJ[5] on behalf of the PRO Consortium Depression Working Group

[1]Forest Research Institute, Jersey City, NJ; [2]Abbott Laboratories, Abbott Park, IL; [3]Health Research Associates, Mountlake Terrace, WA; [4]Eli Lilly and Company, Indianapolis, IN; [5]Critical Path Institute, Tucson, AZ

METHODOLOGICAL QUESTION ADDRESSED:

- Development and qualification of a new patient-reported outcome (PRO) measure for use in assessing treatment benefit in major depressive disorder (MDD) clinical trials.

INTRODUCTION:

- The U.S. Food and Drug Administration (FDA) has issued two guidance documents pertaining to development and qualification of PRO measures intended for use in medical product development to support labeling claims.
  - The first guidance discusses the criteria by which FDA evaluates PRO instruments and their use.[1]
  - The second (draft) guidance describes the FDA's process for qualification of drug development tools (DDTs), including PRO measures.[2]
- We describe the process and progress to date of the Depression Working Group within the Critical Path Institute's (C-Path) PRO Consortium; a multi-stakeholder approach to develop and qualify a new MDD symptom-based PRO instrument.
  - The objective of the working group is to develop a PRO instrument that can be "qualified" by the FDA for use as a primary or key secondary efficacy endpoint in clinical trials for the target disease/condition
  - Qualification is a formal conclusion by the FDA that the results obtained from the PRO instrument within a stated context of use can be relied upon to measure important aspects of clinical benefit and can be used as the basis of medical product approval and labeling claims.[2]

Figure 1: ***PRO Consortium Qualification Pathway***

Scoping Stage Summary Document:
Proposed target population, concepts, conceptual framework, labeling language, and endpoint model (showing endpoint hierarchy)

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Qualitative Research Summary Document:
Evidence that supports the content validity of draft PRO measure, including confirmation or revision of the proposed conceptual framework

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Quantitative Research Summary Document:
Evidence supporting other measurement properties (e.g., reliability, construct validity, responsiveness) of final PRO instrument, along with user manual, and other documentation

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Submission of Qualification Dossier to Regulatory Authority

METHODS:

- The initial stage of the instrument development process incorporates several work streams:
  - a systematic review of existing MDD instruments;
  - a literature review of published studies describing patient experience with MDD; and
  - input from an advisory panel of clinical and methodological experts.
- These preliminary work streams resulted in the development of a protocol and interview guide for in-depth interviews designed to elicit those concepts most important to MDD patients and the language used by patients to describe their symptoms.

Systematic Review of Existing Instruments

- Systematic review of existing MDD symptom measures and related published literature was conducted using PubMed, University of Oxford PRO Measurement Group and the Cochrane Library
  - The following combinations of keywords were used for the search: "Patient Reported Outcome(s)", "Clinician Reported Outcome(s) AND "Depression", "Depressive Symptoms", "Depressed Mood", "Depression Index", "Depression Scale(s)", "Depression Instrument(s)", "Depression Measure(s)"
- Conducted searches of the following internet sources
  - PROQOLID (Patient Reported Outcome and Quality of Life Instruments Database)
  - OLGA (Online Guide to Quality of Life Assessment)
  - ISPOR Databases (International Society for Pharmacoeconomics and Outcomes Research)
- Search limited to those articles and instruments in English for which information on both their development process and psychometric properties were available
- Instruments were ranked based on number of citations from the Institute of Scientific Information (ISI) Web of Science database with detailed reviews conducted for top-cited instruments.
- Instruments were compared to assess the concepts measured by the instrument, the measurement properties of the instrument and the role of patients during the instrument development.

Systematic Literature Review of Patient-Focused Research

- Systematic search of MEDLINE and PsychINFO
- Primary Search Strategy
  - Published in English language between 1991 and 2011
  - Peer-reviewed journal
  - Included community trials, case control studies, cohort studies, cross sectional studies, and qualitative studies
  - Studies had to include adults with diagnosed MDD
  - The following combinations of keywords were used for the search: ("major depressive episode" OR "major depression") AND ("focus group" OR "qualitative" OR "patient attitude" OR "semi-structured") AND (symptoms OR impacts OR limitations)
- Secondary Search Strategy
  - Searched for 'depression' AND 'qualitative' since January 2009

Input from Expert Panel

- Role of Expert Panel is to help guide and provide clinical perspective during project.
- Expert Panel provided input on key documents and deliverables, assisted in the consensus building process
- First Expert Panel Meeting (02/15/2012)
  - Review and Provide input on Literature Review
  - Review and Provide input on Protocol and Interview Guide for Concept Elicitation Interviews
- Second Expert Panel Meeting (05/15/2012)
  - Review results of Literature Review and Instrument Review
  - Review results of Concept Elicitation interviews
  - Help identify concepts for measurement and recommendations to shape preliminary instrument
- Third Expert Panel Meeting (planned October 2012)
  - Review results of cognitive debriefing interviews and modifications to instrument

Concept Elicitation Interviews

- Qualitative interviews were conducted for cross-sectional assessment in a sample of adults (18-65 years) meeting DSM-IV-TR criteria for MDD
  - Subjects were recruited from 6 U.S. clinical sites
  - Subjects had to have had a major depressive episode (MDE) within the last 6 months and Hamilton Rating Scale for Depression (HAM-D) score >18 at screening.
- Semi-structured individual interviews were conducted by trained research staff
- Interviews followed a pre-approved interview guide and used open-ended questions and day-reconstruction exercises to elicit spontaneous reports of symptom/impact concepts.
  - Subsequent probing was used to assess concepts not spontaneously reported by subjects.
  - Subjects were asked to rate the severity and how bothersome or difficult reported symptoms and impacts are for them.
  - Subjects were asked whether they had preferences for identifying concepts with questions that measure severity, frequency or duration to guide item development
- Interviews were audio-recorded and transcribed.
  - Transcripts were coded and analyzed using Atlas.ti and summarized by like-content using an iterative coding framework.
- A Saturation Grid was used to track symptoms and impacts expressed during the interviews and assess saturation of concept.
  - Transcripts were ordered chronologically in groups of 8 transcripts. Codes from each group were compared with previous groups to determine whether or not any new concepts emerged.

RESULTS:

Table 1: ***Depression Working Group Key Milestones***

Stage/Milestone	Date
Scoping Stage:	
• Scoping Stage Summary Document submitted to FDA	05/14/2010
• Comments Received by FDA	10/14/2010
Vendor Selection Stage	
• RFP released	02/18/2011
• Vendor selected	05/04/2011
Development Stage I (qualitative research stage)	
• Contracts executed by member firms/vendor kickoff	10/12/2011
• Protocol approved by IRB	03/09/2012
• Concept Elicitation Interviews completed	04/23/2012
• Draft instrument approved for Cognitive Debriefing	07/25/2012
• Cognitive Debriefing Interviews completed	*Ongoing**
• Qualitative Research Summary Document Completed	*Target 2013*
Development Stage II (quantitative research stage)	
• Conduct Quantitative Research	*Start 2013*
• Quantitative Research Summary Document Completed	*TBD*
Submission of Qualification Dossier	*TBD*

Milestones in *Red italic text* are planned future milestones – timelines are to be determined
*Cognitive debriefing interviews underway, 3 waves completed from 08/16/2012-09/20/2012

Instrument Review

- The instrument review identified 138 articles, from which 42 articles describing the development and/or testing of MDD symptom measures were retained.
- These articles addressed 26 existing instruments, from which 13 were evaluated in-depth.
  - Instruments included in the detailed review included the: Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS), Hamilton Rating Scale for Depression (HAM-D), General Health Questionnaire (GHQ), Geriatric Depression Scale (GDS), Profile of Mood States (POMS), Patient Health Questionnaire (PHQ), Zung Self-Rating Depression Scale (Zung SDS), Montgomery-Åsberg Depression Rating Scale (MADRS), Center for Epidemiologic Studies – Depression Scale (CES-D), Brief Symptom Inventory (BSI), [Quick] Inventory of Depressive Symptomatology (QIDS/IDS) and the PROMIS Depression Item Bank
- Instruments appeared in multiple versions and varied with regard to the number and specific concepts being measured
- Documentation of patient involvement during development was often limited. Most evidence of patient involvement was during the quantitative or psychometric testing phase.

Literature Review

- The primary search identified 177 articles, from which 135 did not meet inclusion criteria. Following initial abstract review 13 of the 42 remaining abstracts were retained.
- The secondary search identified 608 articles, of which 174 were duplicates and 406 did not meet selection criteria. Fifteen of the 28 remaining articles were retained in the search.
- Of the 28 articles resulting from the primary and secondary searches, 9 were dropped due to inadequate methods or topics that were out of scope. This resulted in 19 articles that were reviewed in full
- Concepts relevant to depression patients include: 1) Emotional Symptoms, 2) Physical Symptoms, 3) Cognitive Symptoms, 4) Disease-Related Impacts, 5) Signs & Related Concepts, 6) Attribution of Cause

Concept Elicitation Interviews

- A total of 40 in-depth individual interviews were conducted with subjects with MDD from a broad representation of educational, socio-economic and ethnic/racial backgrounds *(Table 2)*.
  - Interviews were conducted between 03/26/2012 – 04/23/2012.
- Analysis of the transcripts resulted in 3022 symptom expressions and 830 impact expressions
- Expressions were coded and grouped into 105 concepts in 15 domains *(Table 3)*
  - Saturation was achieved with the first 32 coded transcripts
  - Inter-rater agreement between assignment of coders between raters was > 97%.

Table 2: ***Demographic Characteristics***

Characteristic	Total N=40
Age in years: mean (SD); [range]	46.2 (11.8); [21-63]
Gender: Female: n (%)	27 (67.5%)
Marital status: n (%)	
Married	13 (32.5%)
Living with Partner	3 (7.5%)
Widowed	1 (2.5%)
Separated	4 (10.0%)
Divorced	9 (22.5%)
Never Married	10 (25.0%)
Racial and Ethnic Group: n (%)	
White (Non-Hispanic):	18 (45.0%)
White (Hispanic):	9 (22.5%)
White:	1 (2.5%)
Black/African American:	9 (22.5%)
Asian:	1 (2.5%)
Other: Mixed Race:	2 (5.0%)
Highest Level of Education Completed: n (%)	
High School	9 (22.5%)
Some College	17 (42.5%)
Bachelor's Degree	7 (17.5%)
Graduate or Professional School	7 (17.5%)
Employment outside home: n (%)	
Not Employed Outside Home	3 (7.5%)
Full-Time	14 (35.0%)
Part-Time	7 (17.5%)
Retired	1 (2.5%)
Not Employed	15 (37.5)
Clinical Characteristics	
Years since diagnosis with MDD: mean (SD); [range]	7.8 (8.7); [0-40]
Years since most recent MDE: mean (SD); [range]	1.0 (1.8); [0-8]
HAM-D Total Score at Screening: mean (SD); [range]	24.4 (4.3); [19-39]

Table 3: Saturation of Disease-Relevant Concepts

Domain	# of New Concepts Identified Per Domain				
	Group* 1	Group* 2	Group* 3	Group* 4	Group* 5
Physical Symptoms	10	2	0	0	0
Energy	6	0	1	0	0
Motivation	8	0	0	0	0
Emotions/Mood	10	2	0	0	0
Negative Affect	6	0	0	0	0
Cognition	11	0	0	1	0
Sleep Disturbances	5	1	0	0	0
Sense of Self	5	0	0	0	0
Self-Harm/Suicide	3	0	0	1	0
Eating Behaviors	6	0	0	0	0
Anxiety	6	0	0	0	0
Social/Relationship	5	0	0	0	0
Aspects of Burden	3	0	1	0	0
Difficulty with Activities	7	0	0	0	0
Coping Strategies	5	0	0	0	0
Total new concepts per transcript group (n/105)	96 (91.4%)	5 (4.8%)	2 (1.9%)	2 (1.9%)	0 (0.0%)

*Transcript data were analyzed in groups of 8 transcripts
Numbers in the table represent the number of concepts identified within each domain. Numbers represent the first time a concept was identified, regardless of whether or not that concept was identified in subsequent transcripts. No new concepts emerged in the final group of transcripts.

Preliminary Instrument Development

- Following qualitative analysis of the interview transcripts, a consensus-building meeting (Second Expert Panel Meeting) was held to identify the relevant concepts to be measured, evaluate existing PRO measures and subsequently to guide the development of a draft item-pool suitable for further evaluation using both qualitative (cognitive interviews) and quantitative techniques.
- Existing measures were evaluated as potential candidates for qualification or modification. However the working group decided to move forward with the development of a new measure
  - None of the existing measures provided coverage for all concepts identified
  - Existing instruments lacked adequate documentation of patient-input necessary to satisfy FDA evidentiary standards
    - Data from concept elicitation interviews could have been considered to support content validity of existing instruments.
- Following the decision to develop a new measure, a preliminary draft measure containing 36 items was created by the research team.
  - Additional qualitative and quantitative research will further test and refine this draft instrument prior to submission for qualification by FDA.

CONCLUSIONS:

- A consortium-based approach has been able to successfully develop a new draft PRO measure for MDD, which incorporates evidence from published literature and insights from qualitative interviews to reflect the patient's voice and perspective.
- Evidence was developed through synthesis of existing literature, input from an expert panel and direct patient input from concept elicitation interviews.
- This approach was designed to adhere to best research practices and follow current FDA guidance for PRO instrument development and qualification.
- Further testing and refinement of this instrument is planned and ongoing.

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