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

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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 instruments intended for use in medical product development to support labeling claims. The first guidance document discusses the criteria by which FDA evaluates PRO instruments and their use. The second document (draft guidance) describes the FDA’s process for qualification of drug development tools (IDTs), including PRO instruments.

We describe the process and progress to date of the Depression Working Group within the Critical Path Institute’s (CPI) 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 endpoint in clinical trials for the target disease/condition. It is anticipated that in a formal validation 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.

Figure 1: PRO Consortium Qualification Pathway

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

Scoping Stage Summary Document: Evidence that supports the content validity of draft PRO measure, including confirmatory or revision of conceptual framework

Table 1: Qualitative Research Study Summary Document: Evidence supporting other measurement properties (e.g., reliability, construct validity), not captured through PRO instrument, along with user manual, and other documentation

Table 2: Submission of Qualifier Dossier to Regulatory Authority

METHODS: The scoping 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 reference databases were used for the searches: "patient-reported Outcome()", "Clinician-reported Outcome()", "ADP-Depression Outcome()", "Disability Measure", "Depression Index", "Depression Scale()", "Depression Instrument()", "Depression Measure()"

• Conducted searches of the following internet sources
• PRO Measure Library of the National Institute of Health (NIH)
• DIMES (Data Inventory for Measuring Emotional State) library
• 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 evidence obtained from the Institute of Scientific Information’s (ISI) Web of Science database with detailed review 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 in the development of the instrument.

Systematic Literature Review of Patient-Focused Research: Systematic search of MEDLINE and PsychINFO

• Scoping Search: Published in English language between 1991 and 2011
• Peer-reviewed journal
• Published research
• Case control or cohort studies, cross sectional studies, and qualitative studies
• Studies had to include adult patients diagnosed with MDD

• The following combinations of keywords were searched for the search: ["major depressive episode" OR "major depression"] AND ["Focus Group" OR "Qualitative" OR "patient attitude" OR "sani- structured"] AND [symptoms OR "patient perception"]

• Secondary Search Strategy: Search for ‘depression’ AND ‘qualitative’ since January 2009

Input from Expert Panel

• The expert panel is to help guide and provide clinical perspective during the project.

• Expert Panel provided input on key documents and deliverables, assisted in the consensus building process

• Review and provide input on literature review

• Review and provide input on instrument Interface for Concept Elucidation Interviews

• Scoping Stage Summary Document (April 2011)

• Review results of Literature Review and Instrument Interface

• Review results of Concept Elucidation interviews

• Help identify concepts for measurement and recommendations to shape preliminary instruments

• Third Expert Panel Meeting (October 2012)

• Review results of qualitative debriefing interviews and modifications to conceptual framework.

Consort Elucidation Interviews

• Qualitative interviews were conducted for cross-sectional assessment in a sample of adult (≥ 18 years) meeting DSM-IV TR criteria for MDD

• Subjects were recruited from G.L.’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 interview protocols were conducted by trained research staff

• Interviews were a pre-agreed interview guide and used open-ended and day-long re-creation exercises to elicit spontaneous reports of symptoms/image concepts

• Subsequent probing was used to assess concepts not captured in initial interview

• 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

• Interviews were audio-recorded and transcribed

• Transcripts were coded using ATLAS.8 and summarized by like-content using an iterative coding framework.

• A draft PRO measure was developed from the interviews and assessment of 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 new concepts emerged.

RESULTS

Table 2: Demographic Characteristics

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<tr>
<th>Category</th>
<th>Mean (SD)</th>
<th>Median</th>
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<tbody>
<tr>
<td>Age in years</td>
<td>42.6 (11.3)</td>
<td>42.5</td>
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<tr>
<td>Gender</td>
<td>Female: 77.5%</td>
<td>76.5%</td>
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<tr>
<td>Marital status</td>
<td>Single: 17.5%</td>
<td>16.7%</td>
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<tr>
<td>Living with Partner</td>
<td>Widowed: 12.5%</td>
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<tr>
<td>Separated</td>
<td>Divorced: 21.0%</td>
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<tr>
<td>Never Married</td>
<td>Married: 30.5%</td>
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<tr>
<td>Ethnicity</td>
<td>White (Non-Hispanic): 18.5%</td>
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<tr>
<td>Hispanic: 81.5%</td>
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<tr>
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<td>Black/African American: 9.0%</td>
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<td>Asian: 0.0%</td>
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The final PRO measure, based on this qualitative research, was designed to assess the impact of depressive symptoms on a patient’s life, and includes measures of physical symptoms, mood, cognition, and daily activity. The measure is intended to be used in clinical trials for depression, as well as in other settings where depression is a significant concern. The PRO measure is designed to be administered in patient interviews, and the data collected can be used to inform clinical decisions and improve patient outcomes. The measure is also intended to be used in combination with other PRO measures to provide a comprehensive assessment of depression.

CONCLUSIONS:
The consortium-based approach has been successful in developing a new MDD PRO measure, which incorporates evidence from published literature and qualitative interviews to reflect patients’ voice and perspective. Evidence was developed through synthesis of existing literature, input from an expert panel and 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 for future development.

FINANCIAL DISCLOSURES:
One or more authors report potential conflicts which can be reviewed at the following website: www.clinicaltrials.gov.

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REFERENCE:

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