A Multi-Stakeholder Collaborative Approach to Developing a Patient-Reported Outcome (PRO) Measure for FDA Drug Development Tool Qualification: The PRO Consortium’s Depression Working Group Experience

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Learning Objectives

- Describe the goal of FDA’s Drug Development Tool Qualification Program
- Discuss the benefits and challenges of a pre-competitive, collaborative approach to PRO measure development and qualification
- Summarize why the PRO Consortium’s Depression Working Group decided to develop a new PRO measure rather than modify an existing measure for qualification
- Outline the steps taken to develop the Symptoms of Major Depressive Disorder Scale (SMDDS) for qualification
- List the aspects of FDA’s Clinical Outcome Assessment (COA) Qualification Program that have improved since its inception

Discussion Leaders

**Moderator:**
- Elizabeth (Nicki) Bush, MHS – Director, Patient Focused Outcomes Center of Expertise, Eli Lilly and Company and Industry Co-Director, Patient-Reported Outcome Consortium

**Presenters:**
- Stephen Joel Coons, PhD – Executive Director, Patient-Reported Outcome (PRO) Consortium, Critical Path Institute
- Elizabeth (Nicki) Bush, MHS
- Kelly McCarrier, PhD – Senior Research Scientist, Health Research Associates, Inc.
- Wen-Hung Chen, PhD – Reviewer, COA Staff, Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA)
A Consortium Approach to the Qualification of Clinical Trial Endpoint Measures

Stephen Joel Coons, PhD – Executive Director, Patient-Reported Outcome (PRO) Consortium, Critical Path Institute

Critical Path Institute (C-Path)

- Established in 2005 by the University of Arizona and FDA’s Center for Drug Evaluation and Research (CDER) as a public-private partnership
- An independent, non-profit organization
- Funded, in part, by grant number 1U18FD005320 from the FDA
- Dedicated to implementing FDA's Critical Path Initiative by providing a neutral, pre-competitive venue for collaboration aimed at accelerating development of safe and effective medical products
Twelve global consortia collaborating with 1,300+ scientists and 61 companies

C-Path Consortia

- Coalition Against Major Diseases: Focusing on diseases of the brain
- Coalition For Accelerating Standards and Therapies: Data standards
- Critical Path for Parkinson’s Consortium: Focusing on diseases of the brain
- Critical Path to TB Drug Regimens: Accelerating the development of TB drug regimens and diagnostics
- The Duchenne Regulatory Science Consortium: Duchenne Muscular Dystrophy
- International Neonatal Consortium: Neonatal clinical trials
- Multiple Sclerosis Outcome Assessments Consortium: Measuring drug effectiveness in MS
- Polycystic Kidney Disease Outcomes Consortium: New imaging biomarkers
- Patient-Reported Outcome Consortium: Assessing treatment benefit
- Electronic Patient-Reported Outcome Consortium: Electronic capture of treatment benefit
- Predictive Safety Testing Consortium: Drug safety
- Pediatric Trials Consortium: Developing effective therapies for children

Patient-Reported Outcome (PRO) Consortium

Formed in late 2008 by C-Path in cooperation with FDA’s CDER and the pharmaceutical industry

- **Membership**
  - 26 members (pharmaceutical firms)

- **Non-Voting Participants**
  - Representatives of governmental agencies (FDA, NIH)
  - Clinical consultants, patients, academic researchers, and contract research organizations partnering in the development of PRO measures and other clinical outcome assessment (COA) tools
PRO Consortium Members

PRO Consortium Mission

To establish and maintain a collaborative framework with appropriate stakeholders for the qualification of patient-reported outcome (PRO) instruments and other clinical outcome assessment (COA) tools that will be publicly available for use in clinical trials where COA-based endpoints are used to support product labeling claims.
PRO Consortium Goals

- Enable pre-competitive collaboration that includes FDA input and expertise
- Develop and obtain FDA qualification of PRO measures and other COA tools for use in assessing primary or secondary clinical trial endpoints
- Avoid development of multiple endpoint measures for the same purpose
- Share costs of developing new endpoint measures
- Facilitate FDA’s review of medical products by standardizing COA-based endpoint measures that will be publicly available

Current Working Groups (WG)

- Asthma WG – 10 firms
- Cognition WG – 9 firms
- **Depression WG – 9 firms**
- Functional Dyspepsia WG – 2 firms
- Irritable Bowel Syndrome (IBS) WG – 3 firms
- Multiple Sclerosis (MS) WG – 5 firms
- Myelofibrosis WG – 2 firms
- Non-Small Cell Lung Cancer (NSCLC) WG – 10 firms
- Pediatric Asthma WG – 3 firms
- Rheumatoid Arthritis (RA) WG – 5 firms
Goal of Working Groups

To produce and/or compile the necessary evidence to enable new or existing clinical outcome assessment (COA) tools to be qualified by the FDA for use in clinical trials where COA endpoints can be used to support product labeling claims.

CDER’s “DDT Guidance”

- Describes CDER’s drug development tool (DDT) qualification process. Includes biomarkers, animal models, and clinical outcome assessment (COA) tools
- Draft: October 2010
- Final: January 2014

**Drug Development Tool (DDT) Qualification Process**

**Intent:** To expedite development of publicly available DDTs that can be widely used in drug development

**Definition:** Qualification is based on an FDA review of evidence that supports the conclusion that within the stated context of use, the DDT can be relied upon to have a specific interpretation and application in drug development and regulatory review.


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**Why the Consortium Approach?**

As stated by FDA,

“Because substantial effort is involved in achieving qualification, CDER encourages the formation of collaborative groups to work jointly to increase the efficiency of DDT development.”

Consortium Approach to Drug Development Tool Qualification

Advantages
Brings together multiple stakeholders to work collaboratively toward a common goal

Disadvantages
Brings together multiple stakeholders to work collaboratively toward a common goal

Benefits of a Consortium Approach

- Leverages financial resources from multiple stakeholders
- Leverages human resources and expertise from multiple stakeholders
- Collectively addresses scientific, technical, and practical issues with FDA to gain consensus or agreement
- Collectively advances the science of endpoint measurement
- Facilitates a partnership with the FDA to optimize the qualification process
Challenges of a Consortium Approach

- Gaining consensus within working groups regarding concept of interest, context of use, ...
- Executing project agreements with member firms in a timely manner for multi-company projects
- Measure development and qualification within a consortium may take longer than it would take for an individual company to do it
- Maintaining sponsor interest and support during the qualification process

Depression Working Group

Co-Chairs: Nicki Bush (Eli Lilly and Company) and Lucy Abraham (Pfizer, Inc.)
Target population: Adults with a clinical diagnosis of major depressive disorder
Measurement concepts: Symptoms of major depressive disorder
Role in endpoint hierarchy: Primary or secondary endpoint to establish or support treatment benefit
Name of PRO instrument: Symptoms of Major Depressive Disorder Scale (SMDDS)
An Industry Perspective

Elizabeth (Nicki) Bush, MHS – Director, Patient Focused Outcomes Center of Expertise, Eli Lilly and Company and Industry Co-Director, Patient-Reported Outcome Consortium

Why develop ANOTHER measure?

- May 14, 2010: An existing measure (QIDS-SR16) was proposed as part of the Scoping Stage Summary Document (SSSD)
- September 21 and October 14, 2010: FDA response included comments regarding adoption and/or modification of an existing instrument:
  - WG has not provided a specific methodology for selecting and modifying an existing instrument
  - Selection of the instrument is premature without patient input in the form of well-documented qualitative research conducted in the target patient population
• April 6, 2012: Literature and Instrument Review completed; decision to put off decision about de novo development until after primary collection of qualitative data

• May 14, 2012: Face-to-face meeting with WG, C-Path, Expert Panel, and Measurement Experts
  • Decision was made to develop a new measure, using existing measures as guides due to:
    • Lack of documentation of patient input on existing measures;
    • Expert opinion that existing measures were limited in ability to follow people across time and to assess “typical” patients with MDD.

Communication with FDA

• Between 2010 and 2016, communication with FDA changed drastically
• Initial communication was very formal and infrequent
• Over time, communication grew more frequent, interactive, and collaborative
  • FDA representation at Item Refinement/Reduction Meeting in 2016
• It was important to determine how to make more frequent and “informal” interaction a documented part of the qualification process
Industry Perspective

- Collaboration is great, atypical contracting is difficult
- TIME – this was a slow process
- Company priorities change quickly
- WG member participation waxes and wanes over time
- Having an organized coordinator (in this case, C-Path) is KEY

SMDDS Developmental Research

Kelly McCarrier, PhD, MPH – Senior Research Scientist, Health Research Associates, Inc.
**SMDDS Development Steps**

1. **Scoping Stage**
   - Submit Document to FDA (5/14/2010)

2. **Concept Elicitation**
   - Conduct Literature and PRO Instrument review
   - Develop study protocol, interview guide and study forms

3. **Review**
   - Review CE data, Complete item generation process, Format draft SMDDS

4. **Instrument Refinement**
   - Cognitive Interviews
   - Translatability Assessment
   - Electronic Implementation Assessment

5. **Qualitative Research**
   - Complete item generation process, Format draft SMDDS

6. **Program ePRO (Web) and P-to-E Cognitive Interviews**

7. **Qualitative Research**
   - Submit to FDA (9/13/2013)

8. **Final Instrument Refinement and Launch of Wave 1 Quantitative Pilot**

9. **Wave 1 Analyses**
   - Item Reduction (7/22/2015)

10. **Cognitive Interviews to Evaluate Revised SMDDS**

11. **Wave 2 Quantitative Data Collection / Analyses**

**Concept Elicitation**

- **N=40 individual, face-to-face qualitative CE interviews**
- **MDD-diagnosed patients (HAM-D > 18 at enrollment, major depressive episode within last 6 months), recruited from 6 psychiatric clinics in US**
- **Over 3,000 symptom expressions were coded in content analysis**
- **Evidence of concept saturation was observed, with no novel concepts observed in the final 20% of interviews**
- **Expressions grouped into 84 distinct symptom concepts and 21 areas of life impact (impact concepts)**
Concept Elicitation

- 84 symptom concepts were grouped into 11 symptom sub-domains

<table>
<thead>
<tr>
<th>Depression Symptom Sub-Domains and Concepts</th>
<th>Number Patient Language Expressions within Concept</th>
<th>% of Total Symptom Expressions (~3022)</th>
<th>Number of Transcripts Contributing to Concept Expression</th>
<th>% of Transcripts Contributing (N=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Symptoms</td>
<td>271</td>
<td>9.0%</td>
<td>34</td>
<td>85.0%</td>
</tr>
<tr>
<td>Low Energy</td>
<td>237</td>
<td>7.8%</td>
<td>38</td>
<td>95.0%</td>
</tr>
<tr>
<td>Motivation</td>
<td>247</td>
<td>8.2%</td>
<td>39</td>
<td>97.5%</td>
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<tr>
<td>Emotions/Mood</td>
<td>624</td>
<td>20.6%</td>
<td>39</td>
<td>97.5%</td>
</tr>
<tr>
<td>Negative Affect</td>
<td>272</td>
<td>9.0%</td>
<td>38</td>
<td>95.0%</td>
</tr>
<tr>
<td>Cognition</td>
<td>358</td>
<td>11.8%</td>
<td>40</td>
<td>100.0%</td>
</tr>
<tr>
<td>Sleep Disturbances</td>
<td>251</td>
<td>8.3%</td>
<td>40</td>
<td>100.0%</td>
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<tr>
<td>Sense of Self</td>
<td>147</td>
<td>4.9%</td>
<td>33</td>
<td>82.5%</td>
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<tr>
<td>Self-Harm/Suicide</td>
<td>66</td>
<td>2.2%</td>
<td>27</td>
<td>67.5%</td>
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<tr>
<td>Eating Behaviors</td>
<td>151</td>
<td>5.0%</td>
<td>34</td>
<td>85.0%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>398</td>
<td>13.2%</td>
<td>39</td>
<td>97.5%</td>
</tr>
</tbody>
</table>

Initial Development of Draft SMDDS

- Face-to-face meeting conducted with WG, Expert Panel, C-Path and HRA
- Reviewed CE findings, literature and instrument review, and expert input
- Consensus reduced 84 symptom concepts to 36 targeted for PRO measurement
- Draft 36-item SMDDS formatted for cognitive interviews
  - Stem wording drafted for each concept/item using patient language from CE data
  - 7-day recall period
  - 5-point (0 to 4) verbal rating scales of symptom intensity (17 items) and frequency (19 items)
Qualitative SMDDS Evaluation/Changes

- Initial cognitive interviews (3 waves; total n=15)
  - Resulted in removal of 1 item, refinement of stem wording
- Translatability assessment
- Electronic implementation assessment
- ePRO migration interviews to assess comparability of paper and ePRO formats
  - Inclusion of 1 additional item (self-blame) based on FDA review of CE data
- Resulted in the preparation of a 36-item revised instrument for use in pilot quantitative testing

Conceptual framework for draft SMDDS

Symptoms of Major Depressive Disorder

- **Negative Emotions/Mood** - 7 Items: Anger, Frustration, Crying, Hopeless/Helpless, Irritability, Sadness, Pleasure in Doing Things
- **Negative Affect** - 2 Items: Feeling Lonely, Worthlessness
- **Anxiety** - 3 Items: Feeling Overwhelmed, Anxiety/Nervousness, Worry
- **Low Energy** - 1 Item: Tiredness
- **Cognition** - 4 Items: Cognitive Lethargy, Intrusive Thoughts, Poor Concentration, Difficulty Remembering
- **Physical Symptoms** - 4 Items: Breathing Problems, Headaches, Bodily Pain, GI Problems/Stomach Discomfort
- **Sleep Disturbances** - 2 Items: General Sleep Adequacy, Oversleeping
- **Eating Behavior** - 2 Items: Under Eating, Overeating
- **Low Motivation** - 4 Items: Not wanting to Get Out of Bed, Less/Lack of Interest, Lack of Drive, No Interest in Activities
- **Sense of Self** - 4 Items: Dislike Self, Self-Criticism, Usefulness, Self-Blame
- **Self-Harm/Suicide** - 3 Items: Feeling Better Off Dead, Thoughts of Death, Suicidal Ideation

Symptoms of Major Depressive Disorder
Quantitative Pilot Study

- Cross-sectional pilot study using a Web-based data entry platform
- Clinic-based recruitment of patients with MDD (U.S. sites)
- Data collection was conducted as:
  - **Wave 1**: Targeted ~300 subjects to evaluate the individual item performance
  - **Cognitive interviews** to evaluate changes based on Wave 1 findings
  - **Wave 2**: Targeted ~200 subjects (subset of Wave 1) to assess measurement properties of revised *SMDDS*

Item Reduction

- Based on Wave 1 data analyses (n=315), the *SMDDS* was reduced to a 17-item scale:
  - Deleted 12 redundant items
  - Deleted all 4 physical (somatic) symptom items
  - Deleted 3 items due to evidence of potential bias (gender, co-morbid conditions, living situation)
  - Reordered items and revised wording of 3 items
Confirmatory Cognitive Interviews

• Conducted in 3 waves (total n=20) using same eligibility criteria as pilot study
• Resulted in additional refinements
  • Finalized wording of appetite and enjoyment items
  • Revised and finalized wording of sleep interference item
  • Removed “sleep too much” item
• Prepared *SMDDS* (16-item) for confirmatory (Wave 2) quantitative testing

Conceptual Framework for Revised *SMDDS* (16-item)

**Symptoms of Major Depressive Disorder**

- **Negative Emotions/Mood** - 4 Items: Sadness, Hopeless/Helpless, Irritability, Difficulty enjoying daily life (anhedonia)
- **Anxiety** - 2 Items: Feeling Overwhelmed, Worry
- **Low Energy** - 1 Item: Tiredness
- **Cognition** - 2 Items: Intrusive Thoughts, Poor Concentration
- **Sleep Disturbances** - 1 Item: General Sleep Adequacy
- **Self-Harm/Suicide** - 1 Item: Life Not Worth Living
- **Low Motivation** - 2 Items: Lack of Drive, No Interest in Activities
- **Sense of Self** - 1 Item: Self-Blame
- **Eating Behavior** - 2 Items: Poor Appetite, Over Eating
Wave 2 Quantitative Pilot

- N=207 participants (returning from Wave 1 cohort)
  - 147 completed additional 7-day retest
- SMDDS demonstrated appropriate measurement properties and psychometric performance
  - Evaluated with Rasch (RMT), factor analysis, internal consistency, 7-day reproducibility, and construct validity analyses (via PHQ-9 and PGIS-based known groups, and convergence testing against QIDS-SR16, PROMIS Anxiety, and PHQ-9)
- Item content finalized and provisional scoring algorithm established
  - Score uses responses to 15 of the 16-item scale

- SMDDS submitted for qualification for exploratory use on March 28, 2017

Conceptual Framework for SMDDS (16 items) as Submitted for Qualification

- **Symptoms of Major Depressive Disorder**
  - **Negative Emotions/Mood** - 4 Items: Sadness, Hopeless/Helpless, Irritability, Difficulty enjoying daily life (anhedonia)
  - **Anxiety** - 2 Items: Feeling Overwhelmed, Worry
  - **Low Energy** - 1 Item: Tiredness
  - **Cognition** - 2 Items: Intrusive Thoughts, Poor Concentration
  - **Sleep Disturbances** - 1 Item: General Sleep Adequacy
  - **Self-Harm/Suicide** - 1 Item: Life Not Worth Living
  - **Low Motivation** - 2 Items: Lack of Drive, No Interest in Activities
  - **Sense of Self** - 1 Item: Self-Blame
  - **Eating Behavior** - 2 Items: Poor Appetite, Over Eating

Recoded into single variable for scoring
For Further Information...

• The initial qualitative development research has recently been published in *The Patient*:

DOI: 10.1007/s40271-015-0132-1

A Peek Inside the FDA COA Qualification Review Process

*Wen-Hung Chen, PhD* – Reviewer, COA Staff, Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA)
Who are in the Qualification Review Team (QRT)?

- Clinical Outcome Assessment Staff (COA Staff), Office of New Drug (OND), CDER
  - Lead and coordinate the review process and submitter communication within FDA
  - Review measurement properties of the COAs (qualitative and quantitative)
  - Point of contact for submitters
- Review Divisions, OND, CDER
  - Clinical lead on the relevance and importance of the submission related to the indication
- Office of Biostatistics, Office of Translational Science (OTS), CDER
  - Biostatistics lead on the psychometric, scoring, handling of missing data, and any issues related to data analysis
- Representatives from other Centers, Offices, or Review Divisions (when necessary)
  - Provide consults
  - Coordinate with other related submissions

How frequently does the QRT meet?

- QRT meets
  - When a submission (e.g., letter of intent, initial briefing package, full package) is received
  - When a submitter requests
  - When necessary
What does the QRT discuss?

- **QRT discusses issues depending on the stages of the COA development and qualification**:  
  - Does the submission meet the criteria to be accepted into the qualification program (letter of intent stage)
  - Advice to move the submission forward
  - Responses to submitters’ questions
  - The qualitative and quantitative data provided for review
  - Whether there is sufficient evidence to support qualifying the submission

**Tracking FDA on qualification submission of the SMDDS**

<table>
<thead>
<tr>
<th>Event</th>
<th>Description</th>
<th>Duration</th>
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<tbody>
<tr>
<td>DWG: Scoping stage summary</td>
<td>(5/13/10)</td>
<td></td>
</tr>
<tr>
<td>FDA: Comments</td>
<td>(9/21/10) 132 days</td>
<td></td>
</tr>
<tr>
<td>DWG: Qualitative research</td>
<td>(9/13/13) 66 days</td>
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</tr>
<tr>
<td>FDA: Comments</td>
<td>(11/18/13) 56 days</td>
<td></td>
</tr>
<tr>
<td>DWG: Responses to FDA feedback</td>
<td>(4/8/14) 1 day</td>
<td></td>
</tr>
<tr>
<td>FDA: Comments</td>
<td>(6/2/14) 56 days</td>
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</tbody>
</table>
Tracking FDA on qualification submission of the SMDDS (continued)

Things that have been improved

- Increase resources
- Increase communication with submitters
- Engage stakeholders within FDA
- Conduct internal training on COA development and qualification
- Establish coordinated process
- Reduce response time
- Transparent and open discussion
- Exercise flexibility
Room for improvement

• More resources
• Engage stakeholders outside FDA
• Outreach (external training) on COA development and qualification
• Streamline review process
• Establish milestones
• Promote collaboration
• Showcase qualification successes

FDA’s recommendations

• Frequent communication and update (can be just an email or a phone call)
• Ask questions
• Engage stakeholders (e.g., patients, caregivers, clinicians, sponsors)
• Consult with experts (e.g., clinical experts, instrument development experts, clinical study experts)
• Consider QRT’s recommendations
• Push back (if you have good reasons)
• Invite QRT participation in critical meetings
Open Discussion

Discussion Leaders

- **Elizabeth (Nicki) Bush, MHS** – Director, Patient Focused Outcomes Center of Expertise, Eli Lilly and Company and Industry Co-Director, Patient-Reported Outcome Consortium

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