

Development of a New Patient-Reported Outcome (PRO) Measure for Depression: *Progress and Results from the PRO Consortium*

Stephen Joel Coons, PhD
Elektra Papadopoulos, MD, MPH
Steven I. Blum, MBA, MA
Mona L. Martin, RN, MPA
Tuesday, June 25, 2013: 8:00 – 9:30am



Study Endpoint-related Sessions

DIA Annual Meeting

Session	Format	Session Title	Chair / Affiliation	Room	Day	Time
109	SESSION	<u>Evaluation and Selection of the Optimal Endpoints for Clinical Studies</u>	Freda W. Cooner, PhD / Food & Drug Admin	252AB	Monday	11:00
209	FORUM	<u>Development of a New Patient-reported Outcome (PRO) Measure for Depression: Progress and Results from the PRO Consortium</u>	Stephen Joel Coons, PhD / C-Path	251	Tuesday	8:00
210	SESSION	<u>Data from Everyone: Using Smartphones and the Internet to Connect with Subjects</u>	Anne M. Zielinski, MBA / Medidata	252AB	Tuesday	8:00
309	FORUM	<u>Challenges and Recommendations Related to the Use of ePRO Instruments in Clinical Trials</u>	J. Jason Lundy, PhD / C-Path	251	Wednesday	8:00
335	FORUM	<u>Advancing Endpoint Adjudication</u>	Jonathan Seltzer, / Applied Clinical Intelligence	252AB	Wednesday	10:15
424	SESSION	<u>What's the Point? Can Point of Care Devices Enhance Clinical Trials?</u>	Erin Iturriaga, RN / N.I.H.	253A	Thursday	10:45
425	SESSION	<u>Emerging Electronic Tools in Cardiovascular Outcomes Studies</u>	Jonathan Plehn, DrMed,FACC / Covance	253B	Thursday	10:45

Upcoming Study Endpoint Meeting

Beginning with the End in Mind – Study Endpoints: Targeting Patient-Centered Outcomes

Dates: October 21 – 23, 2013

Location: Bethesda, Maryland, USA

Chairs: Laurie B. Burke, FDA

Linda S. Deal, Shire

Overview: Attendees will have the opportunity to gain insight into the trade offs and various stakeholder perspectives for developing a study endpoint measurement strategy.

Day 3 of this workshop will provide detailed and practical tips for ensuring that measurement tools are adequate to support the targeted objectives with a focus on establishing instrument content validity for the specified clinical trial context of use.



Become Involved

DIA's Study Endpoints Community (formerly SIAC)

- Community focused on Study Endpoints with 200+ members
- Mission: To develop, share, evaluate, and disseminate information on the selection, development and qualification of study endpoints, including patient reported outcomes (PROs), clinician reported outcomes (ClinROs), observer reported outcomes (ObsROs), and other rating scales, and biomarkers, for use to demonstrate efficacy in medical product development.
- Monthly Educational Series: Next Presentation July 24th: ePRO Use by Industry
- To Join: Go to DIAHOME.org, My DIA, Manage My Communities



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Objectives

- **Discuss the FDA criteria for evaluating and qualifying PRO measures**
- **Discuss the results of qualitative research conducted to support development of a new clinical trial endpoint measure**
- **Describe how multiple stakeholders have collaborated to develop a PRO measure in a pre-competitive environment**



Panelists

- **Stephen Joel Coons, PhD**
 - Executive Director, Patient-Reported Outcome (PRO) Consortium, Critical Path Institute (C-Path)
 - *Introduction and Overview of the Critical Path Institute's PRO Consortium*
- **Elektra Papadopoulos, MD, MPH**
 - Endpoint Reviewer, SEALD, OND, CDER, FDA
 - *Overview of the FDA Patient-Reported Outcome and Drug Development Tool Guidance Documents*



Panelists

- **Steven I. Blum, MBA, MA**
 - Director, Health Economics, Forest Research Institute
 - Co-Chair, PRO Consortium Depression Working Group
 - *Key Findings from Systematic Reviews of Published Literature and Existing Instruments*
- **Mona L. Martin, RN, MPA**
 - Executive Director, Health Research Associates, Inc.
 - *Qualitative Development of the Symptoms of Major Depressive Disorder Scale (SMMDS)*



Introduction and Overview of the Critical Path Institute's PRO Consortium

Stephen Joel Coons, PhD
Executive Director

Patient-Reported Outcome (PRO) Consortium
Critical Path Institute (C-Path)



FDA's Critical Path Initiative

- As stated by the FDA, “To get medical advances to patients, product developers must successfully progress along a multidimensional *critical path* that leads from discovery or design concept to commercial marketing.”
- The FDA launched the *Critical Path Initiative* in 2004 to facilitate the steps along the critical path.
- The FDA recognized that better scientific tools were needed to increase the efficiency of clinical trial research, including new approaches to safety testing, trial design, endpoint development, and analyses.
- The intent is for these drug development tools to be developed collaboratively in a pre-competitive environment and made available to anyone that can use them.



Critical Path Institute (C-Path)

- Established in 2005 by the University of Arizona and the FDA
- Dedicated to implementing FDA's *Critical Path Initiative*
- An independent, non-profit organization
- Provides a neutral, pre-competitive venue for collaboration aimed at accelerated development of safe and effective medical products



C-Path (www.c-path.org)

- Primary sources of funding for C-Path operations:
 - Government agency grants
 - Foundation grants/contracts
 - Private philanthropy
 - Membership fees from member firms
- Consortia that receive funding from FDA Grant
 - Coalition Against Major Diseases (CAMD)
 - Predictive Safety Testing Consortium (PSTC)
 - Regulatory Science Consortium for Critical Path to TB Drug Regimens (CPTR)
 - **Patient-Reported Outcome (PRO) Consortium**



PRO Consortium

- Formed in late 2008 by C-Path, in cooperation with the FDA and the pharmaceutical industry
- Membership
 - Only available to medical product (pharmaceutical, device, and diagnostic) companies
 - 25 members in 2013 (all pharmaceutical firms)
- Non-Voting Participants
 - Representatives of governmental agencies
 - Clinical consultants, patients, academics, and CROs partnering in the development of the PRO instruments



PRO Consortium Members

abbvie



DIA 2013
49th Annual Meeting



PRO Consortium Mission Statement

To establish and maintain a collaborative framework with appropriate stakeholders for the development of qualified, publicly available PRO instruments for use in clinical trials where PRO endpoints are used to support product labeling claims.



PRO Consortium

Establishing Working Groups

Criteria for selection of therapeutic areas:

- Disease/condition with unmet measurement need and a priority area for the member firms
- Disease/condition with regulatory 'demand' for pre-competitive PRO instrument based on FDA input
- Disease/condition currently reliant on more 'objective' measurement where subjective impact of disease via PRO assessment could provide unique information to support labeling claims



PRO Consortium Goals

- Develop qualified, publicly available PRO instruments
- Enable pre-competitive collaboration that includes FDA input/expertise
- Avoid development of multiple PRO instruments for the same purpose
- Share costs of developing new PRO instruments
- Facilitate FDA's review of medical products by standardizing PRO endpoints



FDA Qualification

- Qualification is based on an FDA review of evidence that supports the conclusion that a PRO instrument provides a **well-defined and reliable assessment of a targeted concept in a specified context of use.**
- FDA's *Guidance for Industry: Qualification Process for Drug Development Tools* (draft - October 2010)



PRO Consortium

Path to Instrument Qualification

- Letter of Intent
- Scoping Stage
- Vendor Selection and Contracting Stage
- Content Validity Stage
 - Qualitative component
 - Quantitative component
- Psychometric Analysis Stage
- Submission of Qualification (Evidence) Dossier



PRO Consortium

Current Working Groups

- Asthma – 11 firms
- Cognition – 9 firms
- Functional Dyspepsia – 3 firms
- Irritable Bowel Syndrome – 3 firms
- Lung Cancer (NSCLC) – 6 firms
- Rheumatoid Arthritis – 7 firms
- **Depression** – 9 firms



Depression Working Group: Sponsoring Firms

- AbbVie (Co-Chair – Nick Greco)
- Bristol-Myers Squibb
- Eli Lilly and Company
- Forest Research Institute (Co-Chair – Steve Blum)
- Janssen
- Pfizer
- Shire
- Sunovion
- Takeda



Depression Working Group: Other Participants

Expert Panel

- Madhukar Trivedi, MD - UT Southwestern Medical Center
- Linda Carpenter, MD - Brown University
- Michael Thase, MD - University of Pennsylvania

Non-member Participant

- Philip Ninan, MD – retired (Pfizer) WG member

CRO Partner

Health Research Associates, Inc.



Depression Working Group: Rationale

- PRO Consortium members and FDA advisors identified depression as a priority area
- The (then) director of FDA's Division of Psychiatry Products expressed an openness to a PRO-based primary endpoint for major depressive disorder (MDD) treatment trials
- It was unclear whether any existing PRO instruments were 'fit for purpose' as an efficacy endpoint in MDD



Depression Working Group: Goal

To assess the adequacy of existing PRO instruments for capturing important depressive symptom information from the patient's perspective and, if there is an unmet need, to either modify an existing instrument or develop a new MDD symptom measure



Depression Working Group Location on Qualification Path

- **Letter of Intent** - unnecessary
- **Scoping Stage** – completed, FDA feedback received
- **Vendor Selection and Contracting** - completed
- **Content Validity Stage**
 - **Qualitative component** – completed and FDA submission being prepared
 - **Quantitative component** – ready to launch
- **Psychometric Analysis Stage**
- **Submission of Qualification (Evidence) Dossier**



FDA Qualification

...has the potential to:

- More effectively incorporate the patient's voice into the evaluation of treatment effects
- Increase number of accepted PRO measures used to support claims in product labeling
- Enhance comparability/consistency of endpoints across clinical trials
- Improve efficiency for sponsors in endpoint selection
- Improve product labeling



Overview of the FDA Patient-Reported Outcome and Drug Development Tool Guidance Documents

Elektra Papadopoulos, MD, MPH
Endpoint Reviewer, SEALD, OND, CDER,
FDA





Drug Development Tool Qualification: Clinical Outcome Assessments (COAs)

DIA 2013

Elektra Papadopoulos, MD, MPH

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Treatment Benefit

- Treatment benefit is demonstrated by evidence that the treatment has a positive impact on:
 - How long a patient lives
 - How a patient feels or functions in daily life
- A claim of treatment benefit must be supported by substantial evidence
 - Adequate and well-controlled studies [21 CFR 314.126]
 - Well-defined and reliable assessments

Assessing Treatment Benefit

- Measures are well-defined and reliable when
 - Empiric evidence demonstrates that the score quantifies the concept of interest in the targeted context of use
- The concept of interest measured by the score and defined by the endpoint in the clinical trial context of use determines the appropriate labeling or advertising claim
- *The context of use* includes the targeted purpose and circumstances of measurement
 - FDA reviews whether the available data support the use of the measure in the context defined by the clinical studies that provide evidence of treatment benefit

Measurement Property Documentation

Guidance for Industry **Patient-Reported Outcome Measures:** **Use in Medical Product Development** **to Support Labeling Claims**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

- Defines how the Agency interprets “well-defined and reliable” (21 CFR 314.126) for PRO measures intended to provide evidence of treatment benefit
- Summarizes good measurement principles applicable to any PRO, ClinRO or ObsRO assessment

Measurement Properties

- Content validity
 - Evidence that the instrument measures the concept of interest including evidence that the items and domains of the instrument are **meaningful, comprehensive, appropriate** relative to its **intended measurement context, population and use**
- Established by:
 - Literature review,
 - Expert opinion,
 - Respondent input in the form of qualitative research in the targeted population
- An instrument's other measurement properties- reliability, construct validity, ability to detect change- cannot be interpreted without first establishing content validity

DDT Qualification Guidance (Draft)

Guidance for Industry

Qualification Process for Drug Development Tools

DRAFT GUIDANCE

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf>

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2010
Clinical/Medical

- Describe a process NOT evidentiary standards
- Qualification process described for Biomarkers, Animal Models, and Clinical Outcome Assessments (COA)
- Final Guidance expected in 2013

DDT Qualification

- A voluntary submission process for drug development tools (DDTs), intended for potential use in multiple drug development programs
 - Regulatory conclusion that within the stated context of use, the results of the DDT measurement can be relied upon to have a stated interpretation and utility – “fit for purpose”
 - Qualification allows an instrument to be reviewed once (for a particular context of use) and once qualified, further review will not be necessary when used in future clinical trials in the approved context of use
 - Stages of qualification:
 - Initiation, Consultation and Advice, Qualification Review

CDER Review of Letter of Intent

- Qualification review team (QRT) assembled to review the Letter of Intent (LOI)
 - Comprised of representatives from SEALD and the division, and other essential representatives (e.g., statisticians, other centers)
- Review of the LOI
 - Concept of interest and proposed conceptual framework
 - Context of use: disease definition; population; endpoint model; targeted claims
- Three potential CDER responses to LOI
 - Accept as is into qualification process
 - Request initial briefing package (content validity documentation)
 - Request a revised LOI
 - Provide recommendations on what to revise (where our disagreements are)
 - Do not accept this DDT project into the qualification program

Identifying the Concept of Interest

- Identifying and defining the concept (i.e., the thing to measure) is the foundation of instrument validity
- The concept represented by the score of an instrument will form the basis of:
 - Interpretation of clinical trial results
 - Communication of the measured treatment benefit in product labeling (the identified concept will be included in labeling)
- Clear identification of the concept(s) of interest is essential before selection or development of an assessment tool
- Making a final decision about the appropriateness of the concept of interest is impossible without an understanding of the context of use
 - Defining the concept of interest and the context of use is an iterative process
 - Targeted concepts of interest should be in alignment with the key study objectives and targeted labeling claims

Defining Context of Use: Consider the Following

- Disease definition including, if appropriate
 - Disease subtype
 - Disease severity
 - History of previous treatment
- Patient subpopulations
 - Patient demographics
 - Reporting ability
 - Culture and language
- Clinical trial design and objectives
 - Endpoint positioning
 - Endpoint definitions
 - Analysis plan
 - Methods for interpretation of study results
 - Targeted labeling claim
- Clinical practice and study setting
 - Inpatient vs. outpatient
 - Geographic location
 - Clinical practice variation

Consultation and Advice Stage

- Summary of content validity documentation
 - Includes draft instrument
 - Iterative approach of qualitative and quantitative methods
- Summary of other measurement properties documentation
 - Longitudinal psychometric validation study
- Periodic submissions of status updates (every 6 months)
- Submissions of specific materials for comment (e.g., protocols)

Review of Full Qualification Package

- Full dossier of evidence submitted and reviewed
- When a decision to qualify is made by CDER, notice published as guidance in Federal Register
- Requirement of qualification: instrument made publically available

Benefit of Qualification of COA Instruments

- More effectively incorporate the patient's voice into the evaluation of treatment benefit and improved product labeling
- Improve comparability/consistency of endpoints across clinical trials
- Improve efficiency for sponsors in endpoint selection
- Instruments would not have to be reviewed by CDER with every IND/NDA/BLA application
- FDA participation during development of these instruments ensures agreement on:
 - Concepts of interest and context of use (including endpoint positioning)
 - Methods of instrument development
- Confidence that the instrument will be accepted by CDER in the qualified context of use

Key Findings from Systematic Reviews of Published Literature and Existing Instruments

Steven I. Blum, MBA, MA

Director, Health Economics, Forest Research Institute
Co-Chair, PRO Consortium Depression Working Group

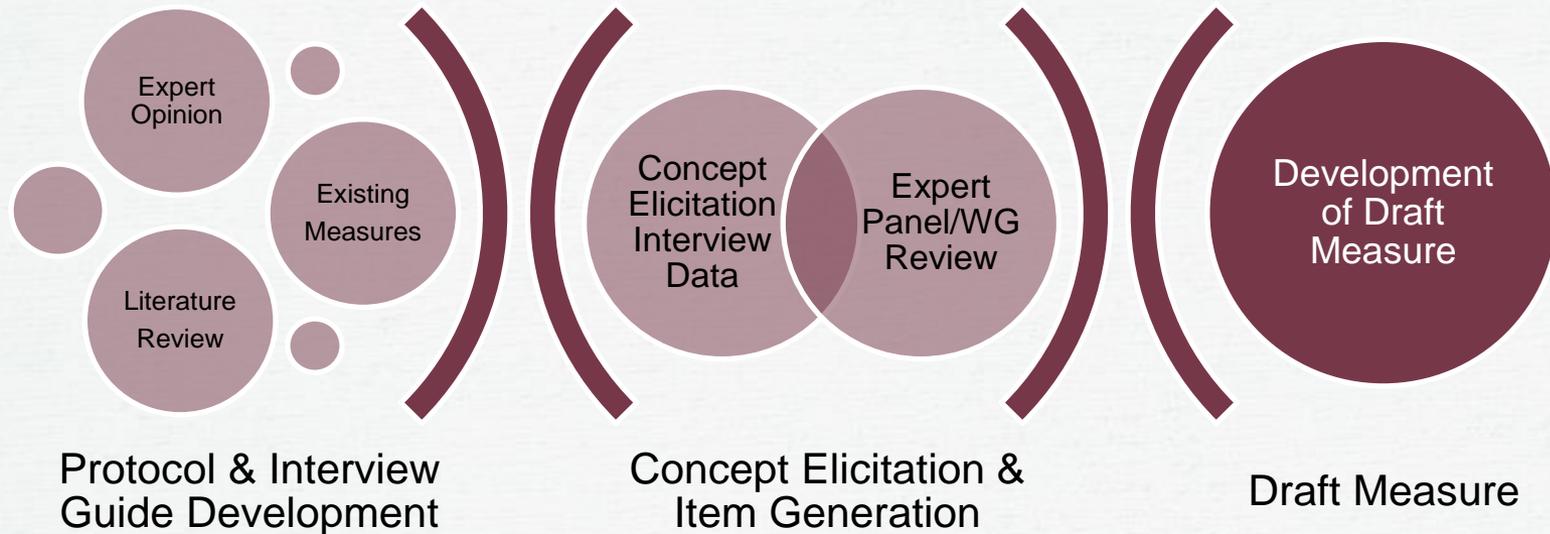


Financial Disclosure

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- Critical Path Institute's PRO Consortium is supported by grant No. U01FD003865 from the United States Food and Drug Administration and by Science Foundation Arizona under Grant No. SRG 0335-08.



Inputs to Qualitative Development Process



Literature Review

- Conducted to understand patient's perspective based on published qualitative studies, including the language that patient's use to describe their condition, and the symptoms and disease impacts of greatest importance to them
- Inform on the development of the Concept Elicitation Interview Guide

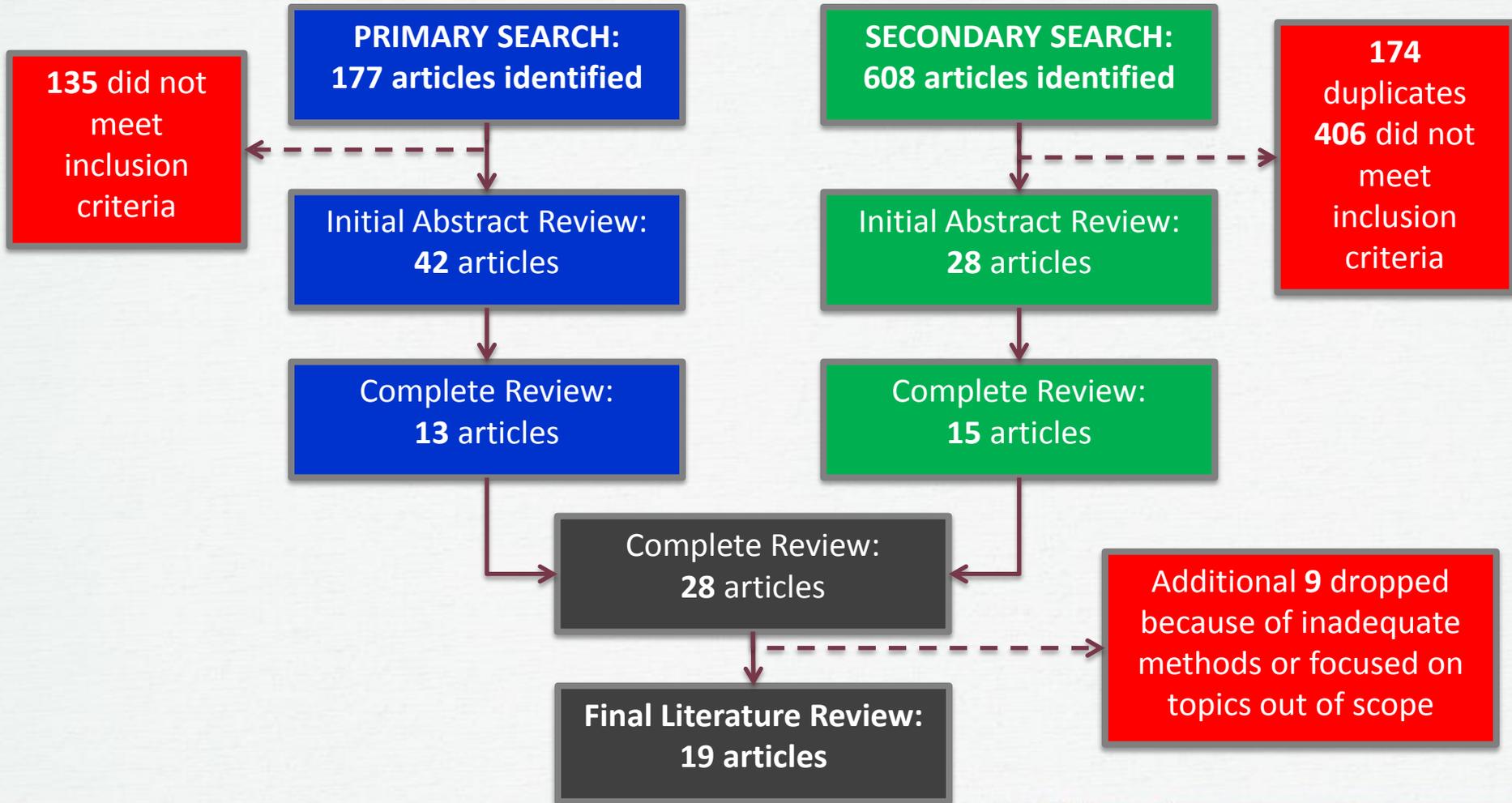


Instrument Review

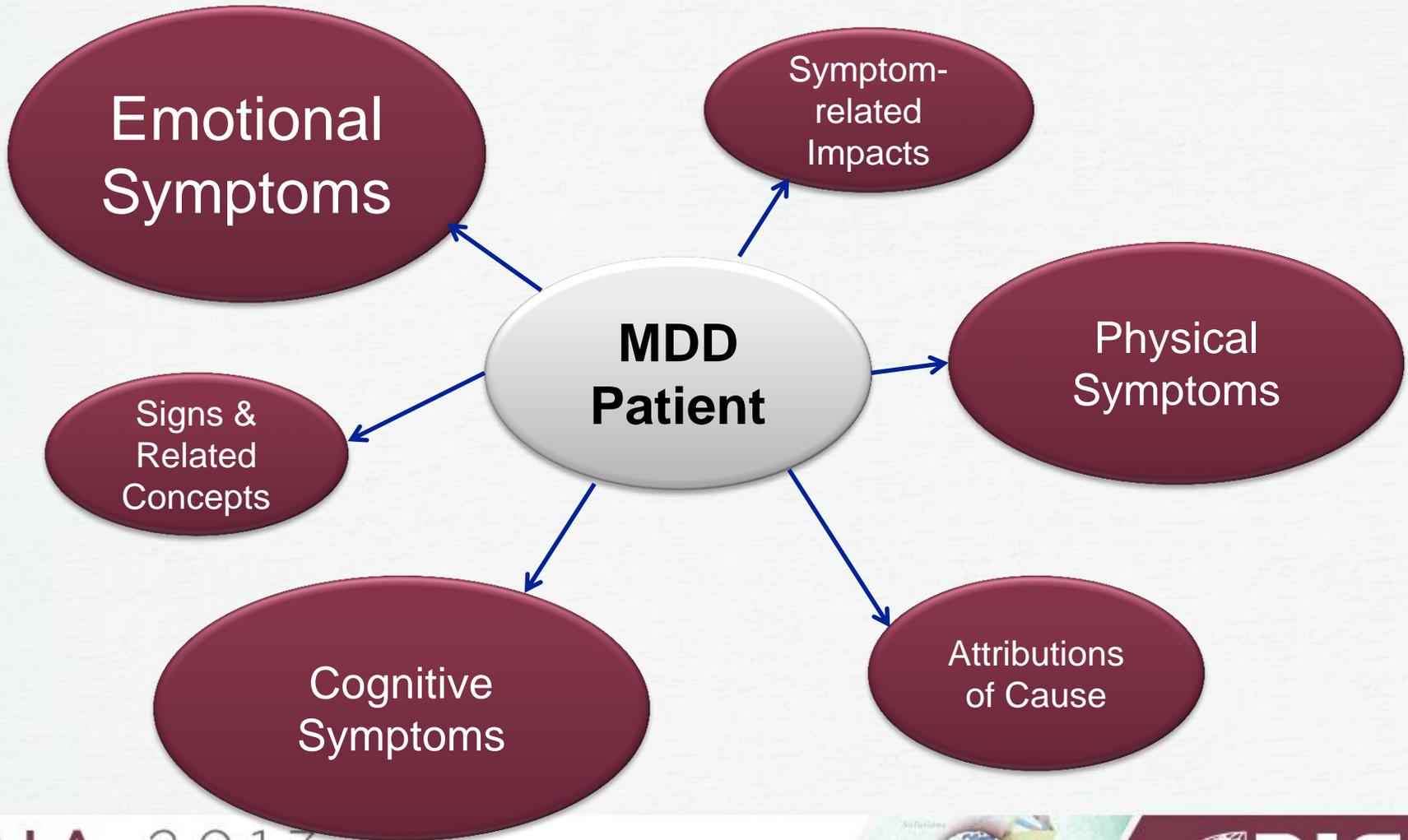
- Assess key characteristics of a selection of existing instruments, including extent of direct patient input
- Inform on the revision of conceptual (disease) model, identification of preliminary key concepts to measure, and development of our qualitative interview guide
- Guide working group on whether to:
 - Seek qualification of an existing instrument,
 - Recommend modifications to an existing instrument; or
 - Develop a new instrument (items from existing instruments could contribute to item bank).



Search Results



Results: Concepts



Symptoms of Depression: Emotional

Symptoms

Sadness/wanting to cry

Guilt

Low self-esteem/self-efficacy

Irritability/Anger

Helplessness/Hopelessness

Loneliness

Thoughts of death

“...when I got to work and got into the office, I would just sit there and cry.”

“It’s embarrassing, you feel guilty, you feel weak”

“Avoiding things, denying things, being more agitated and aggressive for no apparent reason”

“It’s like a doorway that I know I can’t go through. I can’t do that to my parents....but I so much would just like to go to sleep and not wake up”



Symptoms of Depression: Physical

Symptoms

Fatigue

Sleep Disturbance

Bodily Aches & Pains

Heart Palpitations

Chest Pressure

Tingling in extremities

Dizziness

Gastrointestinal problems

Weight Changes

“You feel as though you are walking through a bog in the fog, like you’re dragging your limbs around”

“For me, it’s the sleeping and the withdrawing [that] are a key that something’s wrong”

“I get real, what I think is physical pain in my arms, my shoulders, my chest, I have headaches at the back of my head”

“Everybody notices the weight loss. Everybody would be like, ‘Oh my God, what’s going on, what happened to you?’



Symptoms of Depression: Cognitive

Symptoms

Intrusive thoughts

Desynchrony with environment

Cognitive Lethargy

“I will be released from all of this, all of these thoughts”

“I just started waking up early...two in the morning, wide awake ...and you start worrying about the next day, and then... you worry about not sleeping. It's a vicious cycle”

“And my mental acuity also went.. it just scared the hee-gee-bees out of me, the lack of concentration I had at work”



Disease-related Impacts

Impacts

Social isolation, decreased social support, stigma

“you want to isolate yourself and you don’t actually want to be a part of all the normal things”

Relationship difficulties

“You don’t like to admit you’re a depressed person... there’s a negative view of someone with depression so you didn’t really let a lot of people know about it.”

Difficulties at work

Difficulties doing chores at home

“I get depressed and I don’t wanna do anything. If I didn’t have those symptoms I believe that I would be more active or more motivated to do more”

Decreased self-care



Signs and related concepts

- Concepts not easily defined by patients as symptoms, impacts or a cause of MDD

Concept
Significant life changes
Stress
General anxiety
Drug & alcohol abuse

“I had to actually leave the province, how’s that for embarrassment?”

“Extremely stressed at work and feeling physiological effects of the stress”

“Because of being depressed I have made really stupid choices... I started having sex with heaps of different people, and drugs and alcohol were even worse. And then the depression came...”



Attributions of Cause

Concept
Life events, significant losses
Discrimination
Poverty

“One of the things that affected me is the two children that died so close together...”

“I know a lot of black people that's depressed. Every black person I know is depressed”

“Poverty is the reason. If you can meet your needs, the problems will lessen”

- However, many patients reported limited or no understanding of the condition or its causes
 - Increased feelings of despair and impotence, anxiety, shame and guilt
 - Made it more likely that patients would blame external factors for their symptoms



Summary

- Depression is understood by patients in the terms of the symptoms, signs and disease-related impacts they are experiencing.
- Patients with depression focus their discourse more on their emotions as compared with other known clinical symptoms, such as cognitive and executive functioning symptoms



Summary

- A range of concepts not easily defined as symptoms of depression or as disease-related impacts were also a substantial focus of patient discourse, suggesting that from the patient's perspective comorbid symptoms are not distinctively derived from other conditions
- Patients' attributions of cause of depression should be investigated in detail during the qualitative interviews to provide important information on how they see the causes and impacts of their disease, but it may not be relevant for assessing illness severity



Articles Contributing to the Review

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Articles Contributing to the Review

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Literature Review

- 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
 - Principal search terms (used alone and in combination): Major depression; qualitative; focus groups, symptoms, impacts, patient attitude
- Secondary Search Strategy
 - Searched for 'depression' AND 'qualitative' since January 2009



Methods

- 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)”*



Methods

- 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)



Methods

Search limited to those articles and instruments in English for which information on both their development process and psychometric properties were available.

Category	Inclusion Criteria	Exclusion Criteria
Languages	English only	Other languages
Population	Humans only	Animal studies
Type of Studies	Cross-sectional or longitudinal; Used original data; included patients with depression	Letter, editorial, commentary, discussion paper, non-systematic reviews that have no original data, practice guidelines
Type of Instruments	Patient reported outcomes; Clinician Reported outcomes; Measure depressive symptoms; Had to describe development process; Had to include psychometric properties	Instruments which do not measure depressive symptoms or primarily measure health related quality of life, functional status and satisfaction

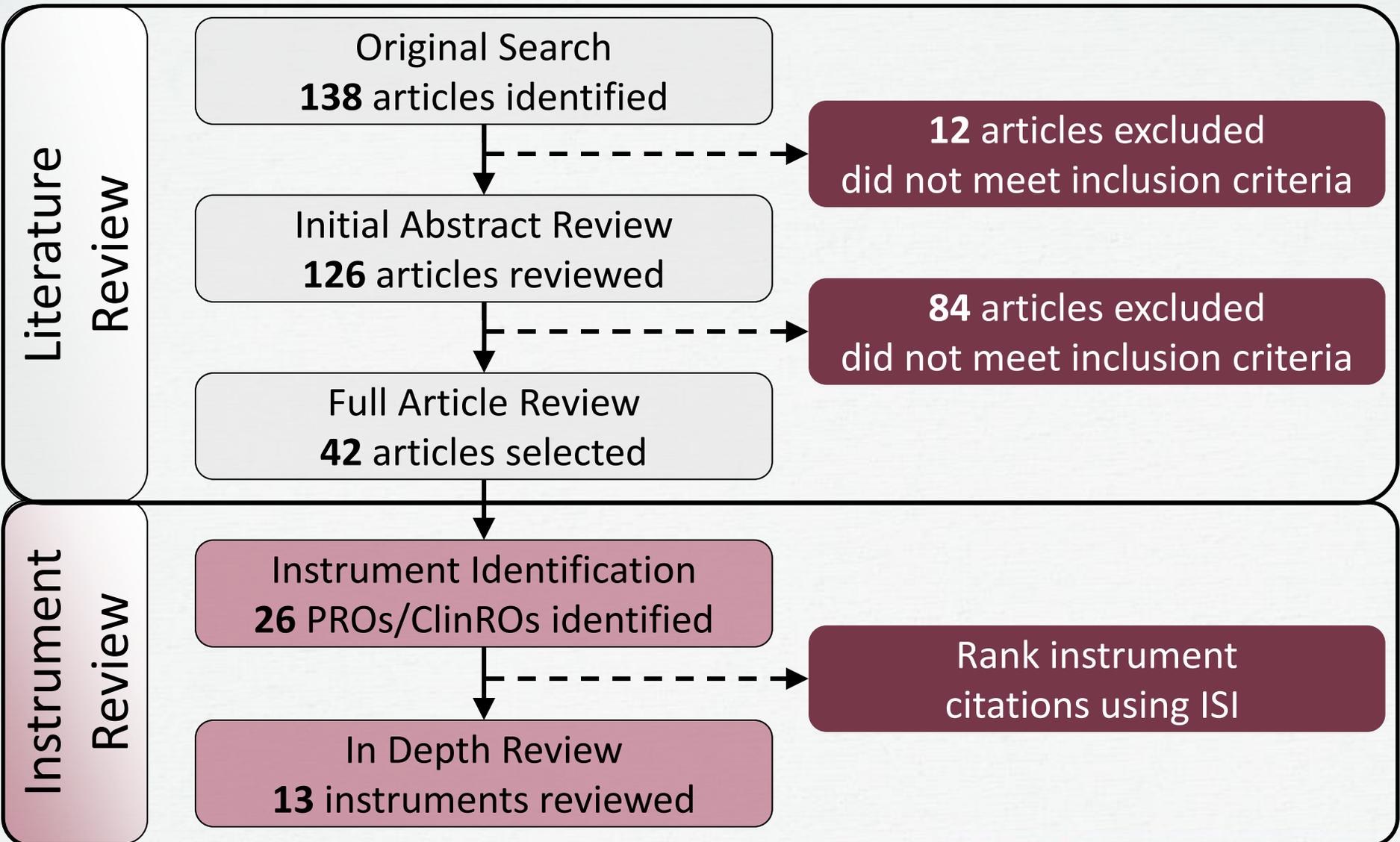


Methods

- Instruments were ranked based on number of citations from the Institute of Scientific Information Web of Science database with detailed reviews conducted for top-cited instruments.
- Areas of inquiry for candidate instrument review:
 - Name of Measure, Acronym, and Purpose
 - Concepts measured, number of items in each (sub)scale
 - Overall content coverage of targeted concepts
 - Developmental History
 - Published use in mental health studies & in clinical trials
 - Reliability results (internal consistency, test-retest reproducibility)
 - Results related to convergent and discriminant validity
 - Ability to detect change over time
 - Other useful information



Search Strategy and Outcome



Results – Instruments Selected

Instrument	Full Name	Citations
BDI/BDI-II	Beck Depression Inventory	5,893
GHQ	General Health Questionnaire	2,759
HADS	Hospital Anxiety and Depression Scale	2,519
HAM-D	Hamilton Rating Scale for Depression	1,777
GDS	Geriatric Depression Scale	1,522
POMS/POMS-SF	Profile of Mood States	1,183
MADRS/MADRS-S	Montgomery-Åsberg Depression Rating Scale	1,089
CES-D	Center for Epidemiological Studies – Depression Scale	976
BSI	Brief Symptom Inventory	938
PHQ-9	Patient Health Questionnaire	667
ZUNG SDS	Zung Self-Rating Depression Scale	498
IDS-C/IDS-SR	Inventory of Depressive Symptomatology	133
QIDS-C/QIDS-SR	Quick Inventory of Depressive Symptomatology	
PROMIS	Patient-Reported Outcomes Measurement Information System	48



Results – Other Instruments Identified

Not Selected for In-Depth Review

Instrument	Full Name	Citations
PRIME-MD	Primary Care Evaluation of Mental Disorders	158
CGIS	Clinical Global Impression of Severity	88
MDI	Major Depression Inventory	59
HDI	Hamilton Depression Inventory	26
EURO-D	EURO-D Scale	18
CRS	Carroll Rating Scale for Depression	15
QLDS	Quality of Life Depression Scale	8
DUKE-AD	Duke Anxiety Depression	5
SDI	Short Depression Inventory	4
DS	Depression Scale	0
RDS	RAND Depression Screener	0
SDSS	Signs of Depression Screening Scale	0



Results – Instrument Versions

- There are often a number of Different Versions of instruments, including versions with differing lengths
 - For the 13 instruments evaluated, over 40 different iterations or versions were identified
 - Clinician- (ClinRO) versus Patient-reported (PRO) versions
 - Versions ranged in length from 1 item (GDS-1) to 65 items (Original POMS)
- *Implication: need to ensure that instrument has adequate coverage of key concepts while at the same time not creating unnecessary patient burden*



Results – Concepts Measured

- Instruments vary in terms of Concept Coverage: which concepts are measured and how they are measured.
 - Coverage varies across different instruments as well as between different versions of the same instrument (due to length or additional concepts being added/deleted in newer versions).
 - Some instruments have items which include descriptions of multiple concepts in a single item.



Results – Concepts Measured

Emotions/Mood

Domain/ Concept	BDI	HADS	HAM-D	GHQ	GDS	POMS	PHQ	ZUNG	MADRS	CES-D	BSI	IDS	PROMIS
Emotions/Mood													
Anger						X							
Crying	X		X		X					X			
Decreased Pleasure	X	X						X		X		X	
Despair				X	X	X							
Empty					X				X				
Frustration						X							
Irritability/Hostility	X		X	X	X	X		X	X	X		X	
Less Compassion						X							
Mood Swings												X	
Rage						X							
Sadness	X		X	X	X	X	X	X		X	X	X	X

Results – Concepts Measured

Cognition

Domain/ Concept	BDI	HADS	HAM-D	GHQ	GDS	POMS	PHQ	ZUNG	MADRS	CES-D	BSI	IDS	PROMIS
Cognition													
Cognitive Lethargy			X		X	X							
Distraction					X					X			
Feel Overwhelmed				X		X							
Fixation on Problem				X									
Indecisiveness	X		X	X	X	X		X				X	
Intrusive Thoughts		X	X		X								
Memory Issues					X								
Concentration	X			X	X	X	X		X				
Other Cognitive			X					X					



Results – Concepts Measured

Energy/Fatigue/Motivation

Domain/ Concept	BDI	HADS	HAM-D	GHQ	GDS	POMS	PHQ	ZUNG	MADRS	CES-D	BSI	IDS	PROMIS
Energy/Fatigue													
Fatigue/Exhaustion	X		X	X		X	X					X	
Lethargic						X				X		X	
No/Low Energy	X			X	X	X	X			X		X	
Daytime Sleepiness												X	
Tiredness				X		X		X					
Weak											X		
Motivation													
Level of Drive		X		X									
Level of Interest	X					X					X	X	
Interest in Self-Care		X											



Results – Concepts Measured

Social Function/Activity Impairment

Domain/ Concept	BDI	HADS	HAM-D	GHQ	GDS	POMS	PHQ	ZUNG	MADRS	CES-D	BSI	IDS	PROMIS
Social Function													
Few Social Engage	X				X								
Isolation				X		X				X			
Impact Relationship				X			X						
Sexual Activity	X		X					X				X	
Activity Impairment													
General Difficulty w/ Daily Activities			X	X				X	X				
Household Activity							X						
Personal Care				X									
Work Impacts	X		X	X			X						

Results – Concepts Measured

Sleep Impacts/Self-Harm

Domain/ Concept	BDI	HADS	HAM-D	GHQ	GDS	POMS	PHQ	ZUNG	MADRS	CES-D	BSI	IDS	PROMIS
Sleep Impacts													
Early Awakening			X	X								X	
Difficulty Fall Asleep			X	X			X					X	
General Sleep Diff	X							X				X	
Oversleeping	X						X					X	
Diff Remain Asleep			X	X			X		X	X			
Self-Harm													
Better Off Dead			X	X	X			X	X				
Self-Harm	X								X				
Suicidal Ideation	X		X	X			X				X	X	
Thoughts of Death				X								X	



Results – Response Scale/Recall Period

- A variety of Response Scales are used including numerical, categorical/Likert-type and dichotomous
- *Implication: response scale may vary depending on whether measuring severity, frequency, duration of signs, symptoms and impacts. Response scale needs to be interpretable for patients*
- Recall Periods vary from “present time” (BDI-I, HAM-D, Zung) to “last few weeks” (GHQ)
 - 7-day recall period was the most utilized recall period (50% of instruments reviewed).
 - Recall period may vary between mode of administration: MADRS-C (no specific period), MADRS-S: 3 days
- *Implication: need to ensure that recall period is sensitive enough to detect changes in status and variability of symptom or impact being measured*



Results – Patient Input

- Many existing instruments have limited documentation of patient involvement during the initial development process.
 - HADS: patients completed self-assessment scale and were interviewed
 - PROMIS Depression Item Bank included patient focus groups and cognitive interviews.
- Many instruments were developed based on expert clinical opinion or were derived from other instruments
- *Implication: need to avoid use of medical terminology and ensure language used is accessible and understandable by patients*
- Most instruments used patients during “validation period”
 - Most instruments demonstrate acceptable scores for reliability and validity
- *Implication: documentation of “content validity” required for qualification of a PRO instrument under the FDA PRO Guidance.*



Limitations

- Information on patient involvement in the development process for existing measures is limited.
 - Importance of “content validity” and “patient-centered” outcomes research have increased in recent years.
 - Many older published articles focus primarily on the psychometric measures for validity and do not describe the instrument development process in detail.
 - This review included reports of patient-involvement to the extent that such reports were published.
- This systematic review focused on instruments predominantly measuring MDD symptoms, and not those that measure more distal concepts like quality-of-life, functional status and satisfaction.
 - FDA is less likely to accept measures which measure more distal impacts (such as social function) or more general HRQOL concepts



Limitations

- The detailed review did not include less frequently cited instruments.
 - Potentially excludes new instrument or ones that have been less frequently used
- Use in clinical trials is limited to uses identified in publications included in our review, which focused on the articles related to the instrument development process and psychometric properties.
 - It did not include articles pertaining use of the instrument in clinical trials for assessing efficacy, as this was beyond the scope of our research objectives



Conclusions

- There are a large number of existing patient-reported outcome measures for major depressive disorder
 - These instruments vary greatly in terms of concepts measured, instrument length, response options, anchoring, scoring algorithms, and recall period
 - Limited information is available in the literature on the developmental history of existing depression symptom inventories, making it unclear whether the inventory items were developed with direct patient input.



Conclusions

- In the absence of additional information about the patient's involvement during development of these instruments it is unlikely these scales will satisfy the requirements set forth in the FDA PRO Guidance
 - Qualitative research could support qualification of an existing scale - if an existing measure could be shown to have content validity.
 - An existing scale could also provide the basis for modification or development of a new scale.
- Further research is required to understand whether the concepts measured by these instruments are adequately supported by direct patient input and can provide a basis for qualification according to the PRO/DDT Guidance.
 - Alternatively, development of a new patient-reported outcome measure could be considered



Qualitative Development of the Symptoms of Major Depressive Disorder Scale (SMMDS)

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Objectives

- Complete qualitative concept elicitation (CE) and cognitive interviews with subjects diagnosed with MDD to support preliminary development of a patient-reported outcome (PRO) measure to assess treatment benefit in major depressive disorder clinical trials.



Methods - Study Population

- Recruitment was designed to enroll a diverse sample of patients similar to those who would be using the PRO instrument in future clinical trials of MDD treatments.
 - No formal recruitment quotas were employed, each site targeted recruitment of a mix of patients with varying severity of MDD and MDD-treatment histories, as well as broad representation across demographic characteristics such as age, sex, race/ethnicity, marital status, and educational attainment and employment status.
 - Subjects were recruited from 6 U.S. clinical sites (CT, FL, IL, NY, OK, WA)



Methods - Study Population

- The eligibility criteria for the targeted interview population were designed to reflect common entry criteria for clinical trials in major depression:
 - Inclusion Criteria: Male and Female subjects between the ages of 18 to 65, inclusive, who met DSM-IV-TR criteria for MDD; and were being treated on an outpatient basis; and had experienced a major depressive episode within the previous 6 months; and had a Hamilton Rating Scale for Depression (HAM-D) score of > 18 at the time of screening
 - Exclusion Criteria: Current or past history of a personality disorder, schizophrenia or other psychotic disorder, obsessive compulsive disorder, or post-traumatic stress disorder; significant risk of suicide; positive urine drug screen or recent clinically significant alcohol abuse or drug use.



Methods – Concept Elicitation Interviews

- Semi-structured qualitative interviews were conducted by trained research staff with a representative sample of adult MDD patients in the US who recently experienced a major depressive event.
 - 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 level of bother or difficulty for reported symptoms and impacts
 - To guide item development, subjects were asked about appropriateness of measuring the severity, frequency, or duration of each concept



Methods - Content Analysis

- All interview sessions were audio recorded and transcribed.
- The CE Interview transcripts were coded and analyzed by trained qualitative coders using Atlas.ti, and were summarized by like-content using an iterative coding framework.
 - Coded concepts were grouped by similarity of content and analyzed to identify the most relevant expressions and most common language used by patients.
- 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 any new additional unique concepts emerged.



Methods - Item Generation

- An item-generation meeting was held by the development team, where concepts identified from published literature, existing instruments, and the qualitative data from the CE interviews were reviewed as the basis for selection of concepts for inclusion in PRO measurement.
 - This initial evaluation process resulted in the selection of candidate symptom concepts to be targeted for PRO measurement.
 - During subsequent review by the development team, these targeted concepts were further reduced by removing synonymous or problematic concepts, and a draft version of the questionnaire was prepared for evaluation in cognitive interviews and a translatability assessment.



Methods – Cognitive Interviews

- Cognitive interviews were conducted to evaluate concept relevance, understandability, and structure of the draft items, and to facilitate further instrument refinement.
- Three separate waves of interviews with patients with MDD were conducted
 - Following each wave, the development team considered the findings and used the information to modify the draft instrument
- A semi-structured cognitive interview guide was designed to capture the subject's comprehension of items and ability to complete the draft PRO instrument.
 - Updated versions of the interview guide were created for each of the three interview waves
 - Questions in the interview process asked about: the comprehension and relevance of the individual items; the fit of the response scales; the appropriateness of the recall period and item wording; and any lack of clarity of items, terminology, instructions, or sentence structure.



Methods – Cognitive Interviews

- During the cognitive interviews, the draft instrument items were completed and evaluated by patients with MDD, recruited through the same process and eligibility criteria as used previously for the CE interviews.
- Cognitive interview transcripts were summarized in cognitive report tables for analysis.
- In parallel with the cognitive interview process, a translatability assessment (TA) was conducted on the draft instrument to assess the potential for difficulty in translating the items to maintain content equivalency
 - The findings from the TA process were used to make revisions to select PRO items prior to the closure of the cognitive interview process.



Results – Subject Characteristics

Characteristic	Concept Elicitation N=40	Cognitive Interviews N=15
Age in years: mean (SD); [range]	46.2 (11.8); [21-63]	44.6 (13.4); [18-59]
Gender: Female: n (%)	27 (67.5%)	9 (60.0%)
Racial and Ethnic Group: n (%)		
White (Non-Hispanic):	18 (45.0%)	11 (73.3%)
White (Hispanic):	9 (22.5%)	1 (6.7%)
White (Ethnicity not reported):	1 (2.5%)	---
Black/African American:	9 (22.5%)	2 (13.3%)
Other:	3 (7.5%)	1 (6.7%)



Results – Subject Characteristics

Characteristic	Concept Elicitation N=40	Cognitive Interviews N=15
Highest Level of Education Completed: n (%)		
High School	9 (22.5%)	7 (46.7%)
Some College	17 (42.5%)	5 (33.3%)
Bachelor's Degree	7 (17.5%)	---
Graduate or Professional School	7 (17.5%)	2 (13.3%)
Clinical Characteristics		
Years since diagnosis with MDD: mean (SD); [range]	7.8 (8.7); [0-40]	12.3 (12.0); [0.9-42.8]
Years since onset of most recent MDE: mean (SD); [range]	1.0 (1.8); [0-8]	1.9 (1.5); [0.5-4.8]
HAM-D Total Score at Screening: mean (SD); [range]	24.4 (4.3); [19-39]	24.4 (5.3); [19-36]



Results – Concept Elicitation

- A total of 40 subjects participated in the CE interviews. They were an average of 46.2 years old, were 67.5% female, 45.0% white (non-Hispanic), and had an average HAM-D total score of 24.4 at enrollment
- Analysis of the transcripts resulted in 3022 symptom expressions and 830 impact expressions
 - Expressions were coded and grouped into 105 concepts (91 symptom and 14 impact) in 15 hypothesized domains (11 symptom and 4 impact)



Results – Concept Elicitation

- Saturation of concept (the point at which no new concepts were elicited) was achieved after the fourth of five transcript groups (eight transcripts per group)
- Inter-rater reliability was assessed in five transcript pairs, and was observed to be high with 85.4 to 92.1% agreement between raters for the identification of symptom concepts being expressed in the transcripts, and 97.5 to 99.1% agreement between raters on code assignment for identified concepts.



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



Results – Item Generation

- The item generation evaluation process resulted in the selection of candidate symptom concepts to be targeted for PRO measurement.
 - Predominance of symptom mentions as well as whether such mentions were spontaneous or probed and the relative severity and bother of the symptoms/impacts provided a context for evaluating individual concepts
 - The development team agreed to focus on symptoms and not disease impacts for the measure



Results – Item Generation

- Because no existing PRO measure comprehensively assessed the selected concepts, the development team decided to develop a new measure, rather than attempting to either qualify or modify an existing measure
- During subsequent review by the development team, the targeted concepts were further reduced by removing synonymous or problematic concepts, and a 36-item draft questionnaire was prepared for evaluation in cognitive interviews and the translatability assessment



Results – Cognitive Interviews

- A total of 15 subjects participated in three waves of CIs. The subjects were an average of 44.6 years old, were 60.0% female, 73.3% white (non-Hispanic), and had an average HAM-D total score of 24.4 at enrollment (Table 1).
- Over the three waves, one item was removed and four others were substantially modified based on cognitive interview findings and recommendations from a formal translatability assessment.⁵
- Other minor instrument formatting and wording modifications were made based on the results of a formal migratability assessment for electronic PRO data collection platforms (ePRO).

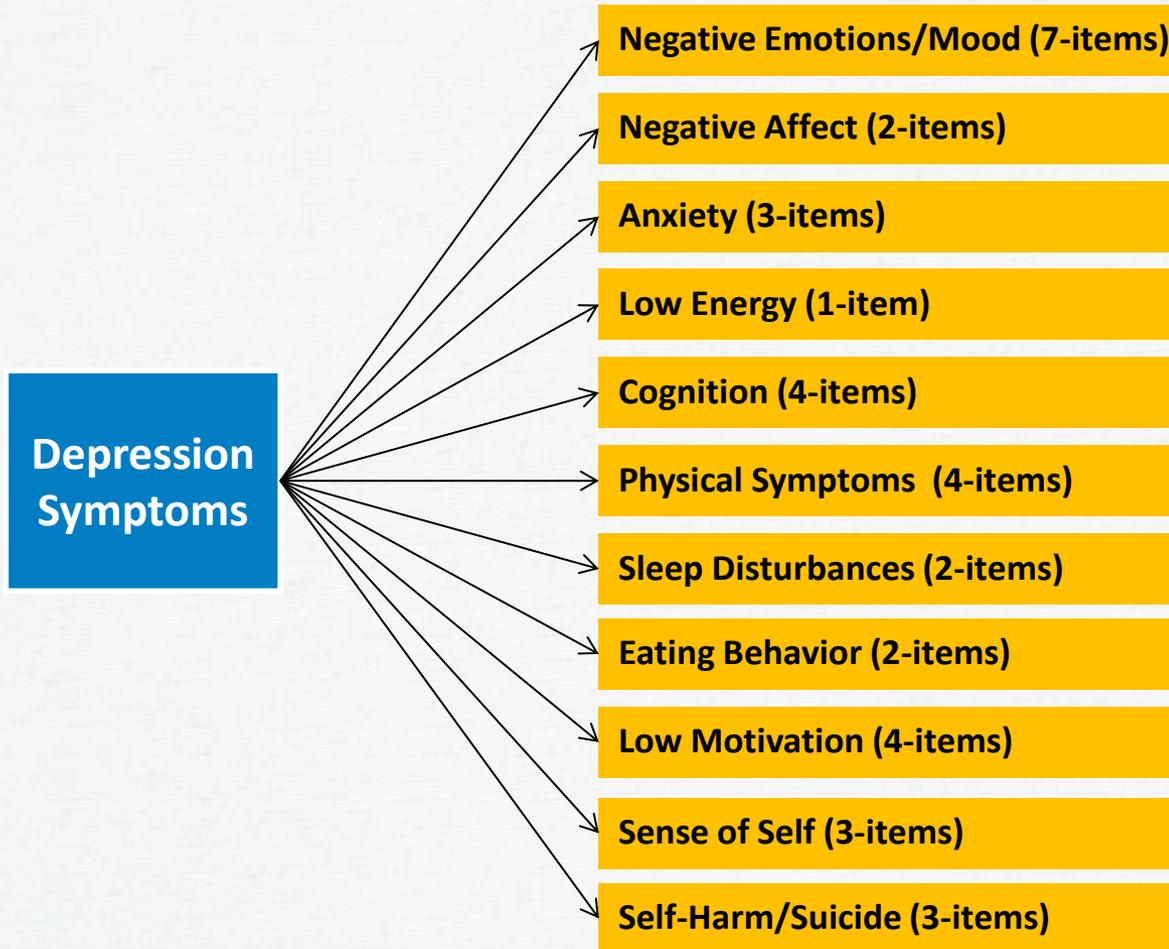


Symptoms of Major Depressive Disorder Scale (SMDDDS)

- The newly-created scale, the Symptoms of Major Depressive Disorder Scale (SMDDDS), is a 35- item instrument that measures each concept using a 5-point verbal rating scale and a 7-day retrospective recall period for each of the items.
 - Items in the SMDDDS are hypothesized to be organized into 11 sub-domains
 - Sixteen of the items focus on the intensity of symptoms with a rating scale from “not at all” to “extremely.”
 - The remaining nineteen items focus on the frequency or the amount of time a symptom was experienced and employ a rating scale from “never” to “always.”



Proposed Conceptual Framework



Conclusions

- The SMDDS is a 35-item PRO measure intended for use as an endpoint in MDD clinical trials to support medical product labeling.
 - The SMDDS was developed in accordance with the FDA's PRO Guidance and best practices.
 - Qualitative interviews have provided evidence for content validity.
 - Cognitive interviews provided evidence that the instructions, items and response options are comprehensible, easy to complete and address key symptoms of MDD that are relevant to patients with the condition.
- Future quantitative studies will confirm the measurement properties of the SMDDS and support FDA qualification.

