Developing the Symptoms of Major Depressive Disorder Scale (SMDDS): From Patient Input to Final Instrument

Seventh Annual
Patient-Reported Outcome (PRO)
Consortium Workshop

April 27 - 28, 2016 ■ Silver Spring, MD

Disclaimer

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Session Participants

Moderator

- *Elizabeth (Nicki) Bush, MHS* – Research Scientist, Global Patient Outcomes and Real World Evidence, Eli Lilly and Company

Presenters

- *Elizabeth (Nicki) Bush, MHS* – Research Scientist, Global Patient Outcomes and Real World Evidence, Eli Lilly and Company
- *Kelly P. McCarrier, PhD, MPH* – Senior Research Scientist, Health Research Associates, Inc.
- *Donald Bushnell, MA* – Associate Director, Health Research Associates, Inc.
- *Valdo Arnera, MD* – Scientific Advisor and General Manager ERT Geneva, ERT

Panelists

- *Stephen Joel Coons, PhD* – Executive Director, Patient-Reported Outcome Consortium, Critical Path Institute
- *Tiffany R. Farchione, MD* – Deputy Director, Division of Psychiatry Products (DPP), CDER, FDA

Session Objectives

- To provide an overview of the development process of the SMDDS (from patient input to final measure)

- To highlight the usefulness and successes of the mixed methods approach in its development

Session Outline

- Introduction/Objectives
- Qualitative development of the draft SMDDS
- Quantitative study design (wave 1 and wave 2)
- Overview of the ePRO content and workflow
- Wave 1 quantitative analysis and results
- Overview of item reduction process and revised SMDDS
- Confirmatory interviews for the revised SMDDS
- Wave 2 quantitative analysis and results
- Summary of FDA interactions and mixed methods process
- Next steps for the SMDDS and the Depression WG
- Questions and open discussion

Working Group Goal

- Rationale for the Depression Working Group (WG)
  - PRO Consortium members and FDA advisors identified depression as a priority area
  - It was unclear whether any existing PRO instruments were 'fit for purpose' as an efficacy endpoint in major depressive disorder (MDD) treatment trials
  - There is an apparent lack of a PRO instrument developed in accordance with the FDA PRO Guidance for use in clinical trials
- Goal of the Depression WG
  - To assess the adequacy of existing PRO instruments for capturing important depressive symptoms information from the patient's perspective and, if there is an unmet need, to either modify an existing instrument or develop a new depression symptom inventory

SMDDS Development Team

- Depression Working Group
- Co-Chairs
  - Lucy Abraham
  - Nicki Bush
- Member Firms
  - AbbVie (former)
  - Bristol-Myers Squibb (former)
  - Eli Lilly & Co.
  - Forest / Actavis
  - Janssen
  - Pfizer
  - Shire
  - Sunovion
  - Steven Blum (former)
  - Nicholas Greco (former)
  - *Roche / Genentech**
  - *Takeda Pharmaceuticals**

**Joined WG Following Item Generation Meeting*

- *Phil Ninan (Pfizer-Retired; Non-member participant)*

SMDDS Development Team

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

- Health Research Associates
  - Mona L. Martin, RN, MPA, Executive Director
  - Donald M. Bushnell, MA, Associate Director
  - Kelly McCarrier, PhD, Senior Research Scientist
  - Cecilia Dedios, MS, Research Associate (former)
  - Talia Miller, MPH, Research Associate

- Critical Path Institute's PRO Consortium
  - Stephen Joel Coons, PhD, Executive Director
  - J. Jason Lundy, PhD, Assistant Director (Former)
  - Karla Lehman, Senior Project Manager (Former)
  - Theresa "T" Griffey, MBA, PMP, Senior Project Manager
  - Theresa Hall, Project Coordinator
  - Mabel Crescioni, DrPH, JD, LLM, Assistant Director
  - Sarah E. Mann, MBA, PMP, Senior Project Manager

Qualitative Development of the SMDDS

Kelly McCarrier, PhD, MPH
Senior Research Scientist,
HRA, Inc.

For Further Information…

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

McCarrier KP, Deal LS, Abraham L, Blum SI, Bush EN, Martin ML, Thase ME, Coons SJ. Patient-Centered Research to Support the Development of the Symptoms of Major Depressive Disorder Scale (SMDDS): Initial Qualitative Research. *The Patient - Patient-Centered Outcomes Research.* 2016; 9:117–134

DOI: 10.1007/s40271-015-0132-1

The Patient
DOI 10.1007/s40271-015-0132-1

ORIGINAL RESEARCH ARTICLE

Patient-Centered Research to Support the Development of the Symptoms of Major Depressive Disorder Scale (SMDDS): Initial Qualitative Research

Kelly P. McCarrier[1] · Linda S. Deal[2] · Lucy Abraham[3] · Steven I. Blum[4] · Elizabeth Nicole Bush[5] · Mona L. Martin[3] · Michael E. Thase[6,7] · Stephen Joel Coons[8] · On behalf of the PRO Consortium's Depression Working Group

Abstract

Background Content valid, patient-reported outcome (PRO) measures of major depressive disorder (MDD) symptoms are needed to assess MDD treatment benefit. While a range of questionnaires are currently available to evaluate aspects of depression from the patient's perspective, their comprehensiveness and qualitative development histories are unclear.

Objective The objective of this study was to describe the process and results of the preliminary qualitative development of a new symptom-based PRO measure intended to assess treatment benefit in MDD clinical trials.

Methods Qualitative interviews were conducted with adult MDD patients in the USA who recently experienced a major depressive episode. Experienced interviewers conducted concept elicitation (CE) and cognitive interviews using semi-structured interview guides. The CE interview guide was used to elicit spontaneous reports of symptom experiences along with probing to further explore and confirm concepts. The cognitive interview guide was developed to evaluate concept relevance, understandability, and structure of the draft items, and to facilitate further instrument refinement.

Results Forty patients participated in the CE interviews. A total of 3022 symptom codes, representing 84 different concepts were derived from the transcripts. Data from the CE interviews were considered alongside existing literature and clinical expert opinion during an item-generation process, leading to development of a preliminary version of the Symptoms of Major Depressive Disorder Scale (SMDDS). Fifteen patients participated in three waves of cognitive interviews, during which the SMDDS was further refined.

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 uses a 7-day recall period and verbal rating scales. It was developed in accordance with the US Food and Drug Administration (FDA)'s PRO Guidance and best practices. Qualitative interviews have provided evidence for content validity. Future quantitative studies will confirm the SMDDS's measurement properties and support FDA qualification.

Published online: 26 June 2015

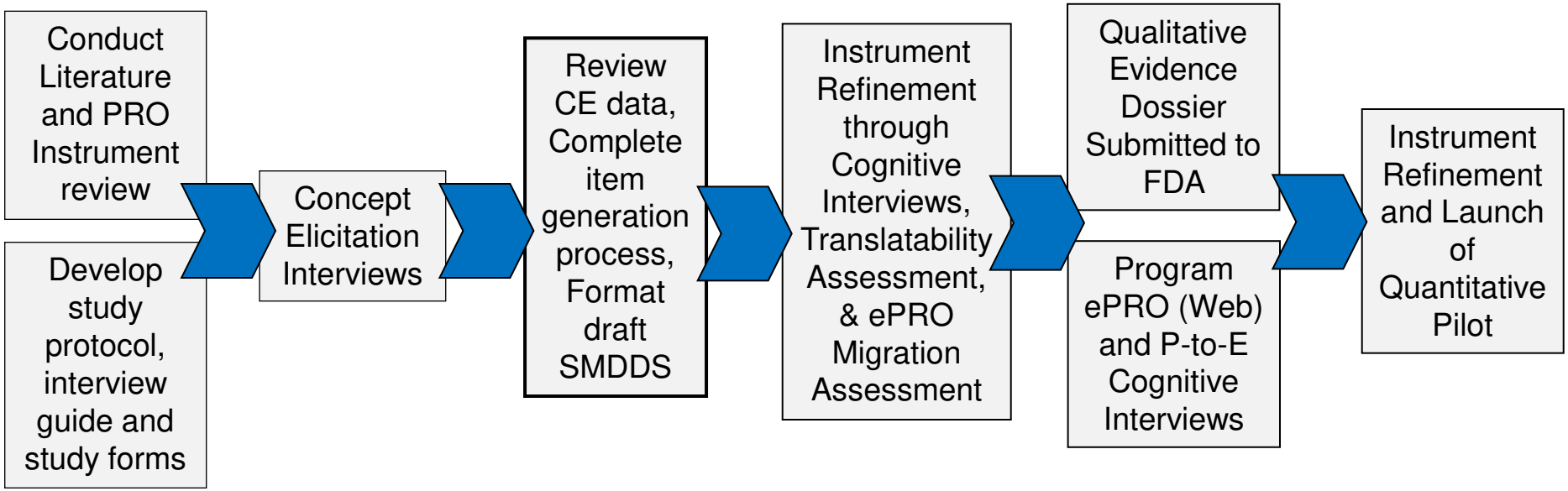
Steven I. Blum was affiliated with Forest Research Institute, Jersey City, NJ, USA (now part of Actavis) at the time of his involvement in the study.

Kelly P. McCarrier
mccarrier@hmisc.net

1 Health Research Associates, Inc., 6505 216th St. SW - Suite 105, Mountlake Terrace, WA 98043, USA
2 Clinical Outcomes Assessment, Shire, Wayne, PA, USA
3 Outcomes and Evidence, Pfizer Ltd, Tadworth, Surrey, UK
4 Patient Reported Outcomes, GlaxoSmithKline, King of Prussia, PA, USA
5 PRO Center of Expertise, Eli Lilly and Company, Indianapolis, IN, USA
6 Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA
7 Philadelphia Veterans Affairs Medical Center, Philadelphia, PA, USA
8 Patient-Reported Outcome Consortium, Critical Path Institute, Tucson, AZ, USA

Electronic supplementary material The online version of this article (doi:10.1007/s40271-015-0132-1) contains supplementary material, which is available to authorized users.

Flow of Qualitative Development Steps



Literature Review

- Objective/Approach:
  - To identify published qualitative or mixed methods research on the patient experience with symptoms and impacts of MDD
  - Searches conducted in Medline and PsycINFO (limited to English articles published between 1991 and 2011)
- Findings:
  - Between primary and secondary searches, 205 abstracts reviewed; 28 articles retained for initial full review; and final review included 19 articles
  - 30 sign/symptom concepts were identified across included articles.
  - 5 major impact areas were reported in which distal effects of MDD are experienced by patients.

Literature Review

- Identified symptom concepts include:
  - Physical signs and symptoms (11 concepts)
  - Emotion and cognition symptoms (16 concepts)
  - Co-Occurring experiences and behavioral aspects (3 concepts)

- The concepts found in the review influenced the development of the CE interview guide.

Concept Elicitation (CE) Interviews

- Objective:
  - To support measurement development decisions by identifying and documenting concepts relevant and important to the patient experience with symptoms of MDD and related impacts.
- Methods:
  - N=40 individual, face-to-face qualitative CE interviews
  - Patients recruited from 6 psychiatric clinics in US
  - 60-90 minutes; following a semi-structured CE interview guide (including open-ended items, day-reconstruction, probing, and rating exercises)

Eligibility Criteria

- Key Inclusion Criteria:
  - English-speaking patients ages 18 to 65 years, inclusive.
  - Documented current primary diagnosis of MDD (DSM-IV-TR and DSM-5 criteria) with a documented major depressive episode in last 6 months.
  - HAM-D score of > 18 at time of enrollment and expect to be treated on an outpatient basis for the duration of the study.
- Exclusions:
  - Current / past history of personality disorder, bipolar disorder, schizophrenia or other psychotic disorder, OCD, PTSD, mental retardation, organic mental disorders, or mental disorders due to a general medical condition. [Co-morbid GAD allowed].
  - Significant risk of suicide (investigator opinion or via C-SSRS)
  - Recent (12-month) history of clinically significant drug or alcohol abuse or dependence, excluding nicotine.

Eligibility Criteria

- Exclusion Criteria (cont):
  - Positive urine drug screen (UDS) for Cocaine, Methamphetamine, Opiates, Phencyclidine, Methadone, or Ecstasy at enrollment. Positive UDS for amphetamines, barbiturates, or benzodiazepines allowed with evidence of current prescription.
  - History of MDD treatment by electroconvulsive therapy, vagal nerve stimulation, or deep brain stimulation.
  - Enrollment in investigational study in past 30 days.
  - Clinically significant history of renal, neurologic, gastrointestinal, pulmonary, cardiovascular, hepatic, hematopoietic, or endocrine disease or disorder.
    - Or any other medical condition or disorder that could (in site investigator's opinion) interfere with successful participation in an interview about patient's depression experience.

CE Interviews - Sample

		Total N=40 (100%)
Age (Years):	- Mean (SD)	46.2 (11.8)
	- Median	47.0
	- Range	21-63
Gender:	- Male	13 (32.5%)
	- Female	27 (67.5%)
Marital status:	- 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:	- White (Non-Hispanic)	19 (47.5%)
	- White (Hispanic)	9 (22.5%)
	- Black/African American	9 (22.5%)
	- Asian	1 (2.5%)
	- Other: Mixed Race	2 (5.0%)

- Participants were between 21 and 63 years with an average age of 46 years.
- Roughly 2/3 Female
- Approx. 40% either married or living as married
- 30% non-White

CE Interviews - Sample

		Total N=40 (100%)
Highest Level of Education Completed:	- 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:	- 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%)
Household income:	- Under $9,999	9 (22.5%)
	- $10,000 - $24,999	5 (12.5%)
	- $25,000 - $34,999	5 (12.5%)
	- $35,000 - $49,999	6 (15.0%)
	- $50,000- $59,999	4 (10.0%)
	- $60,000-$69,999	4 (10.0%)
	- $70,000 and Over	7 (17.5%)

- 22% had only high school diplomas, most participants had at least some college.
- Most were employed full time
- Income ranges are well distributed

CE Findings: Saturation

Concept Description	Group 1 (N=8 transcripts)	Group 2 (N=8 transcripts)	Group 3 (N=8 transcripts)	Group 4 (N=8 transcripts)	Group 5 (N=8 transcripts)
Physical Symptoms					
Breathing Problems	X				
Chest Pressure		X			
Dizziness	X				
GI Problems	X				
Headaches	X				
Heart Palpitations	X				
Pain	X				
Muscle Stiffness	X				
Restlessness	X				
Stomach Discomfort	X				
Sweat		X			
Tingling in Extremeties	X				
Energy					
Drained	X				
Fatigue/Exhaustion	X				
Lethargic	X				
No/Low Energy	X				
Sleepiness	X				
Tiredness	X				
Weakness			X		
Motivation					
Desire to Be Alone	X				
Lack of Drive	X				
(Table Truncated)					
Insight/Relaxation/Other Personal Strategies	X				
Number of concepts coded in each group	**96**	**5**	**2**	**2**	**0**
Percent of relevant concepts coded (N=105)	**91.4%**	**4.8%**	**1.9%**	**1.9%**	**0.0%**

CE Findings: Saturation

- Within 40 CE transcripts, over 5000 expressions from subjects were coded.
- Expressions grouped into 84 distinct symptom concepts and 21 areas of life impact (impact concepts).
- Evidence of concept saturation was observed:
  - 96% of concepts were identified within the first 16 interviews (40% of transcripts)
  - No new concepts appeared within the final 20% of transcripts.

CE Findings: Concept Predominance

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

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

CE Findings: Concept Predominance

Depression Symptom Sub-Domains and Concepts	Number Patient Language Expressions within Concept	% of Total Symptom Expressions (=3022)	Number of Transcripts Contributing to Concept Expression	% of Transcripts Contributing (N=40)
Physical Symptoms	**271**	**9%**		
Low Energy	**237**	**8%**		
Drained	10	0.3%	7	17.5%
Fatigue/Exhaustion	64	2.1%	17	42.5%
Lethargic	8	0.3%	4	10.0%
No/Low Energy	36	1.2%	19	47.5%
Daytime Sleepiness	14	0.5%	11	27.5%
Tiredness	95	3.1%	30	75.0%
Weak	6	0.2%	5	12.5%
Other Energy Symptoms	4	0.1%	4	10.0%
Low Motivation	**247**	**8%**		
Lack of Drive	48	1.6%	25	62.5%
No Interest in Activities	18	0.6%	8	20.0%
No Interest in Chores	9	0.3%	7	17.5%
No Interest in Leaving Home	12	0.4%	7	17.5%
No Interest in Self-Care	16	0.5%	6	15.0%
Not Wanting to Get Out of Bed	60	2.0%	23	57.5%

CE Findings: Concept Relevance

- Key features examined for expressed concepts
  - Frequency of mention (by subject, across all coded expressions)
  - Spontaneous mentions (vs. Probed)
  - Subject ratings of bother and severity
    - 0-10 NRS Exercise for each expressed symptom
  - Subject ratings of meaningful attributes
    - Frequency, Severity, Duration

Item Generation Process

- Attended by WG, Expert Panel, C-Path, and HRA
- Reviewed key evidence from:
  - Literature and Instrument Review
  - CE Interview Findings
  - Expert Input
- Consensus reduced 84 symptom concepts to 36 targeted for PRO measurement
- Decision to create SMDDS as a new PRO instrument

Item Generation Process

- Draft SMDDS formatted for cognitive interviews
  - Stem wording drafted for each concept/item using patient language from CE data
  - 7-day recall period
  - 5-point (0-4) verbal rating scales of symptom intensity (17 items) and frequency (19 items)

Sample Symptom Intensity Item	***Sample Symptom Frequency Item***
6. Over the past 7 days, how sad have you felt? ☐ Not at All ☐ A Little Bit ☐ Moderately ☐ Quite a Bit ☐ Extremely	30. Over the past 7 days, how much of the time did you feel critical about yourself? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

Refinement of the draft SMDDS

- Draft SMDDS evaluated and refined through:
  - Cognitive Interviews (3 waves)
  - Translatability Assessment (TA)
  - Electronic Implementation Assessment
  - Interviews to assess comparability of paper and ePRO formats

Cognitive Interviews

- Objective:
  - To evaluate clarity, comprehension, and relevance of the draft SMDDS items, instructions, and response options.
- Methods:
  - N=15 individual, face-to-face cognitive interviews, conducted in three waves
  - Identical recruitment process as CE phase
  - 90-minute interviews using paper format of draft SMDDS

Translatability Assessment

- Objective:
  - To identify potential difficulty in maintaining conceptual equivalence in translations.
- Methods:
  - Conducted between Wave 2 and 3 of Cognitive Interviews
  - Examined SMDDS in German, Spanish, French, Russian, and Chinese.
  - Linguistics consultants rated each element (items and instructions) from 1 (no difficulty) to 5 (extremely difficult)

Electronic Implementation Assessment

- Objective:
  - To identify potential difficulty in implementing across full range of ePRO formats.
- Methods:
  - Conducted following Wave 3 of Cognitive Interviews, prior to ePRO Migration Interviews
  - Provided suggested revisions to maximize equivalence between paper and ePRO (generally) as well as across different ePRO formats

ePRO Migration Cognitive Interviews

- Objective:
  - To evaluate conceptual and cognitive equivalence of paper and ePRO (web-based) format of the developmental SMDDS
- Methods:
  - N=15 individual, face-to-face cognitive interviews, conducted in three waves
  - 90 minute interviews using paper and ePRO format of draft SMDDS to identify differences in understanding, interpretation, and selection of response

Key SMDDS Modifications

- Wave 1 Cognitive Interviews
  - Reverse-scoring removed (2 items)
  - Items re-ordered (somatic symptoms moved) and transitions between item types minimized

- Wave 2 and Translatability Assessment
  - One item removed
  - Focus of 2 items moved from intensity to frequency to aid in translatability
  - Rewording of 2 items

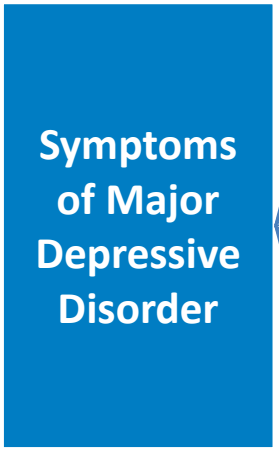
Key SMDDS Modifications

- Wave 3 and ePRO Implementation Assessment
  - Format changes (removal of tabular format for select items) to support single-item-per-screen
  - Minor wording revisions to recall period reference for consistency across items

- Qualitative Research Summary Report Submitted to FDA

- ePRO Migration Cognitive Interviews and FDA response
  - Minor format/presentation changes (font sizing, spacing, etc.)
  - Inclusion of self-blame item based on FDA recommendation and review of CE data

Conceptual framework for draft SMDDS (36 items for quantitative testing)



- **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

Quantitative Study Design

Don Bushnell, Associate Director,
HRA, Inc.

Quantitative Study Design

- Cross-sectional pilot study using a Web-based data entry platform
- Respondents with a diagnosis of MDD recruited through clinics within the US
- Data collection was conducted as:
  - **Wave 1:** data collected from 300 subjects to evaluate the individual item performance
  - **Cognitive interviews** to evaluate changes based on Wave 1 findings
  - **Wave 2:** data collected from 200 subjects (subset) to assess measurement properties of revised SMDDS

Eligibility Criteria

- Inclusion Criteria:
  - Subject is able to read, write, and speak English well enough to understand and complete Informed Consent Form (ICF) and take part in the study.
  - Subject is male or female between the ages of 18 and 65 years, inclusive.
  - Subject has a documented primary diagnosis of major depressive disorder (meeting the DSM-IV-TR criteria for MDD) and has a documented major depressive episode within the last 6 months.

Eligibility Criteria

- Exclusion Criteria:
  - Current or past history of a personality disorder, bipolar disorder, schizophrenia or other psychotic disorder (including MD with psychotic features), OCD, PTSD, mental retardation, organic mental disorders, or mental disorders due to a general medical condition. [Comorbid GAD not exclusion criterion].
  - Recent (12-month) history of clinically significant drug or alcohol abuse or dependence, excluding nicotine.
  - History of MDD treatment by electroconvulsive therapy, vagal nerve stimulation, or deep brain stimulation.
  - Clinically significant history of renal, neurologic, gastrointestinal, pulmonary, cardiovascular, hepatic, hematopoietic, or endocrine disease or disorder.
  - In the opinion of the site investigator or study director, subject has any medical condition or disorder that could prevent or interfere with the patient's ability to successfully participate in a Web-based study and provide meaningful information about his or her depression experience.

Quantitative Data Collection Schema

WAVE 1 (N=300 subjects)

		Day						
	1	2	3	4	5	6	7	8
Clinician Screening Form ***<completed prior to Day 1>***								
Study information letter ***<sent prior to Day 1>***								
Electronic Consent†	X							
Demographic information†	X							
SMDDS †	X							
QIDS-SR_{16}†	X							
PROMIS Emotional Distress-Anxiety Short Form 8 †	X							
PHQ-9†	X							
Patient Global Impression of Severity†	X							

† Completed via Web, subjects had a unique password.

Quantitative Data Collection Schema

WAVE 2 (N=200 subjects that participated in Wave 1)
Completed after analyses of Wave 1 data were completed

		Day						
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Demographic information	X							
SMDDS (Final)†	X							X
QIDS-SR_{16}†	X							
PROMIS Emotional Distress-Anxiety Short Form 8 †	X							
PHQ-9†	X							X
Patient Global Impression of Severity†	X							X
Patient Global Impression of Change†								X

† Completed via Web, subjects were required to enter their unique password defined in Wave 1.

Description of the ePRO Assessment used in the Quantitative Study and Lessons Learned

Valdo Arnera, MD – Scientific Advisor and General Manager ERT Geneva, ERT

ePRO Consortium

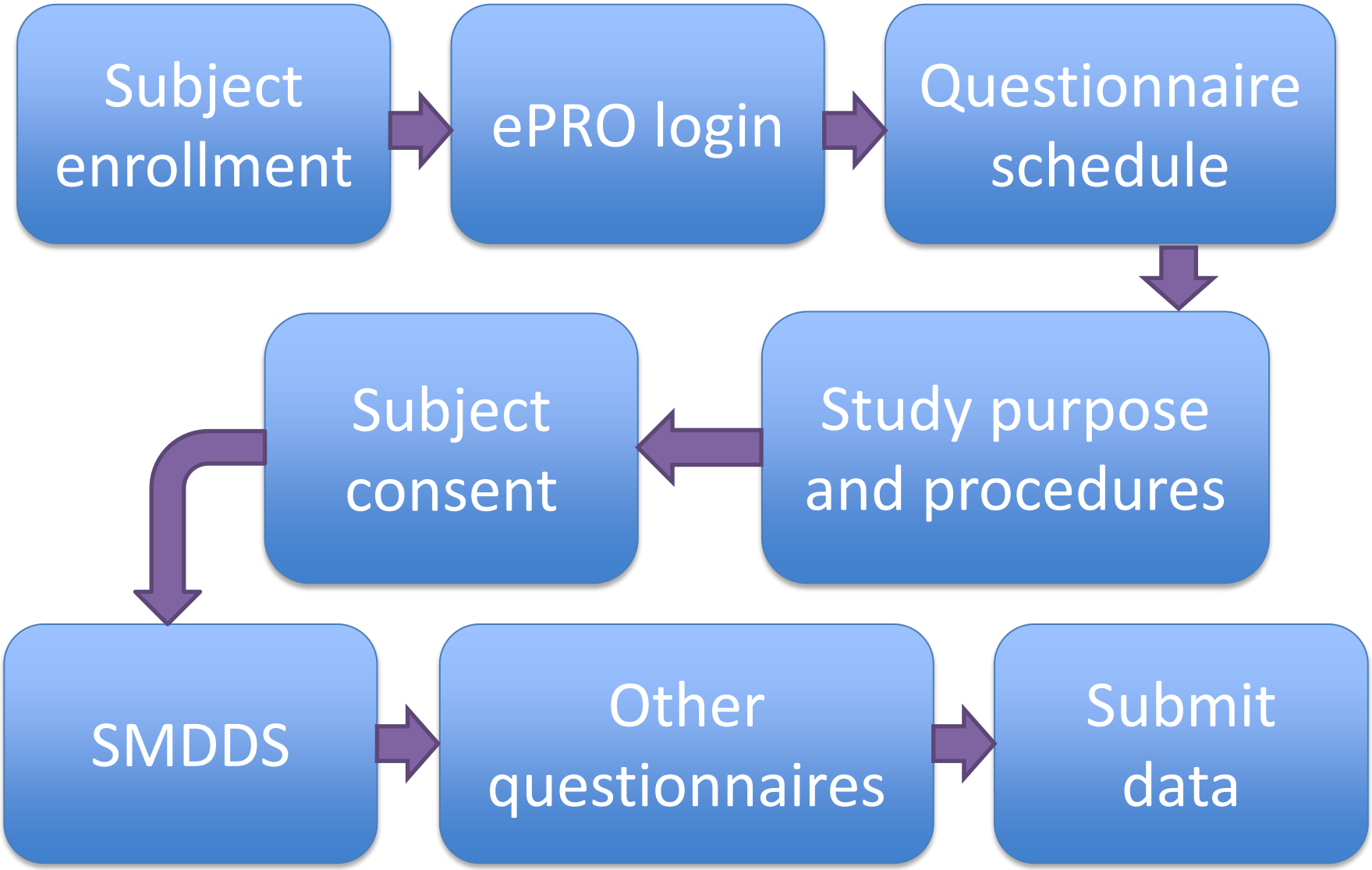
- The Electronic Patient-Reported Outcome (ePRO) Consortium was established by C-Path in 2011 with the mission to:
  - advance the science of clinical trial endpoint assessment by collaboratively supporting and conducting research, designing and delivering educational opportunities, and developing and disseminating best practice recommendations for electronic collection of clinical outcome data.
- Members are firms that provide electronic data-collection technologies/services to the medical products industry for capturing PRO endpoints in clinical trials.

- The ePRO consortium works closely with the PRO Consortium working groups to make newly developed PRO instruments available in multiple data-collection formats

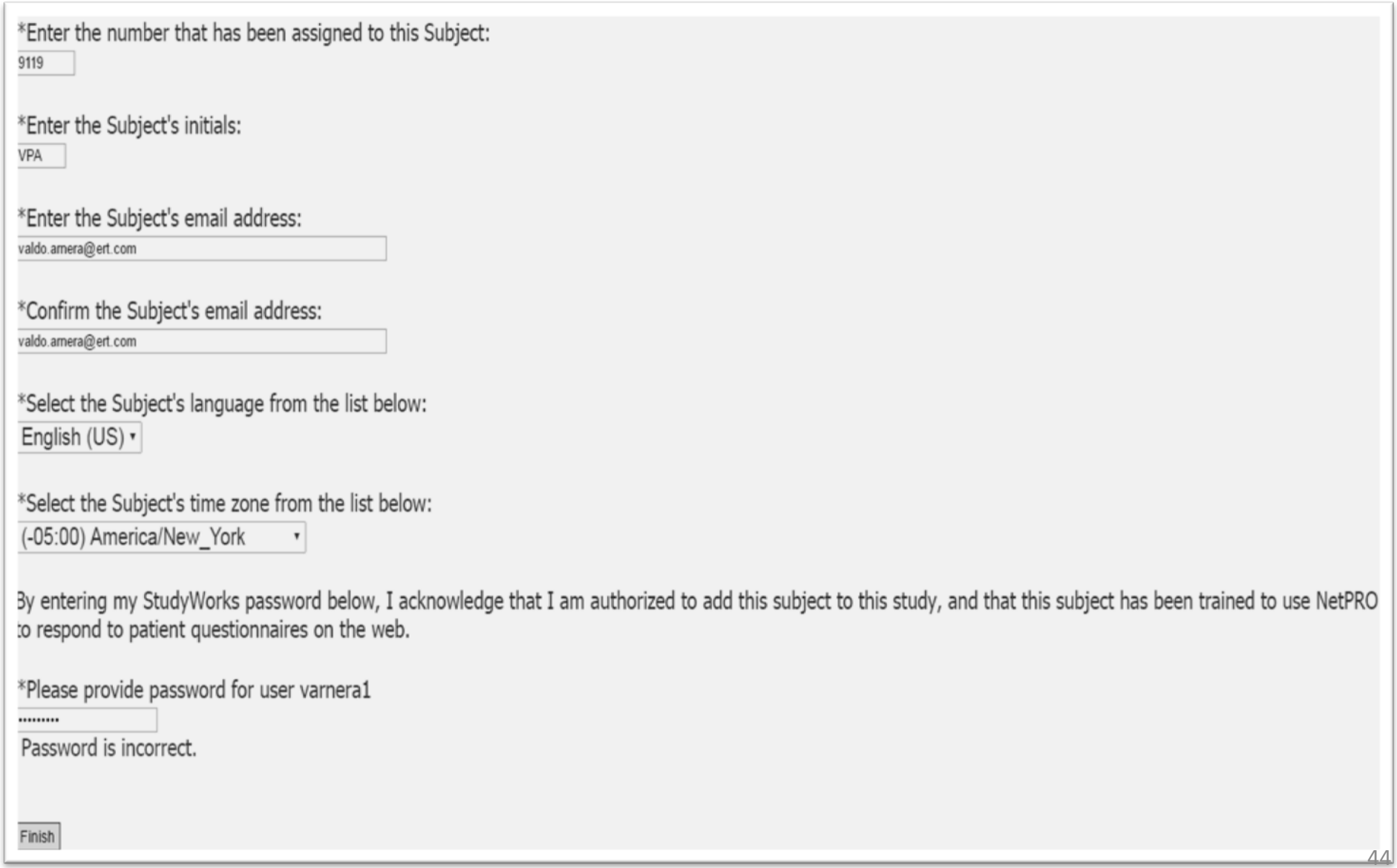
ePRO Consortium

- In this case, the Depression Working Group made the decision to collect quantitative pilot study data through a Web-based data entry portal.
- An RFP was sent to all ePRO Consortium members willing to bid.
- PHT was selected from among the bidders to build the on-line data collection system.
  - PHT was acquired by ERT in 2015

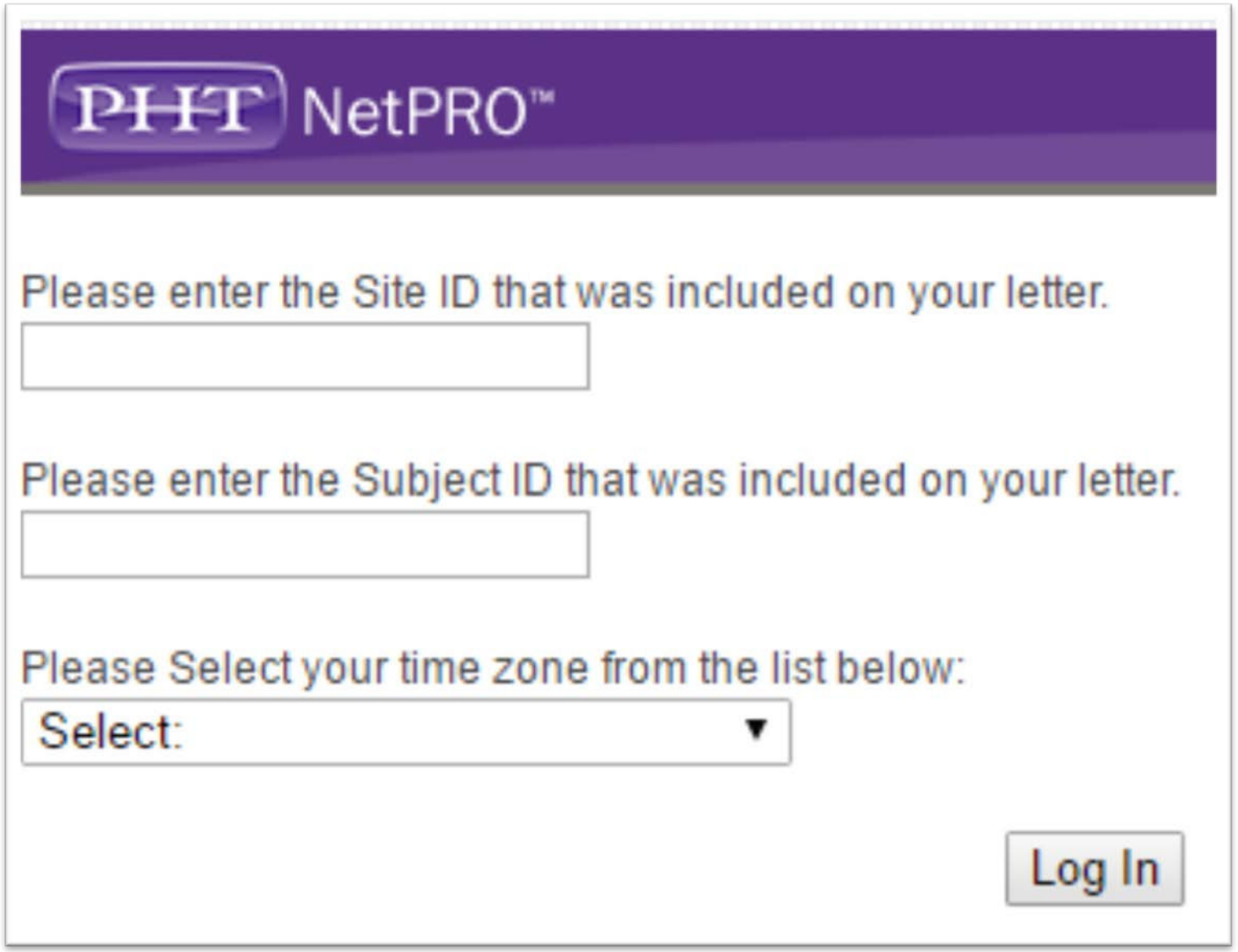
Workflow of ePRO Content



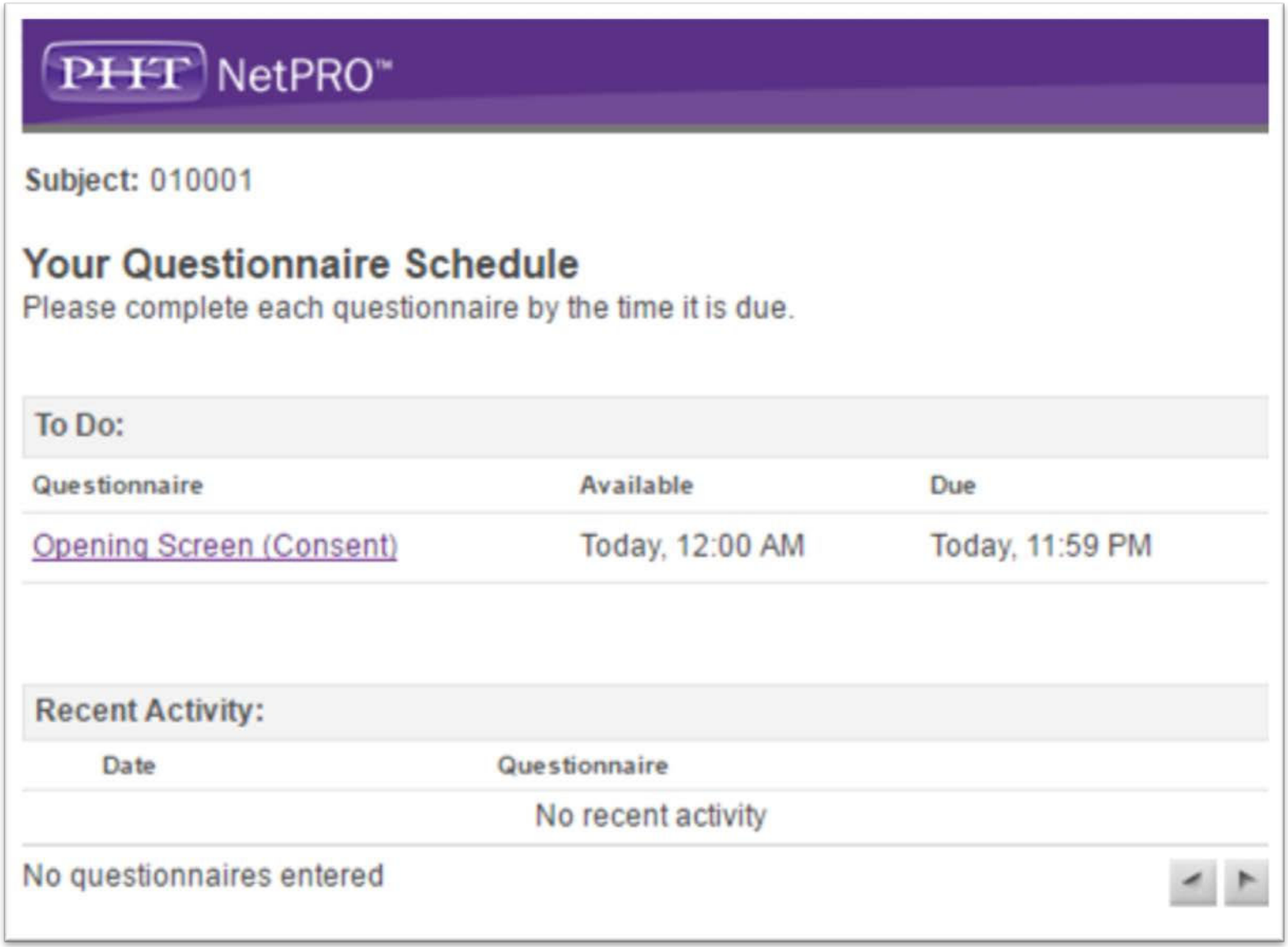
Example screenshots: Subject Enrollment



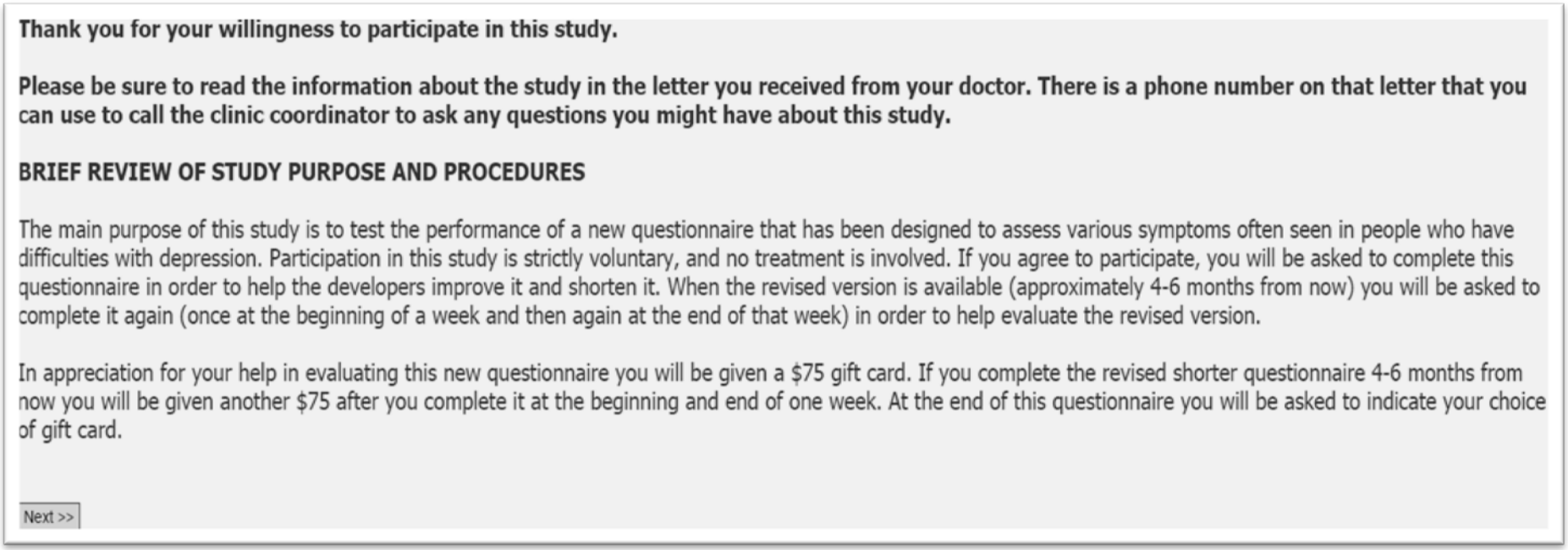
Example screenshots: Subject Login



Example screenshots: Subject Start



Example screenshots: Review of Study Purpose and Procedures



Thank you for your willingness to participate in this study.

Please be sure to read the information about the study in the letter you received from your doctor. There is a phone number on that letter that you can use to call the clinic coordinator to ask any questions you might have about this study.

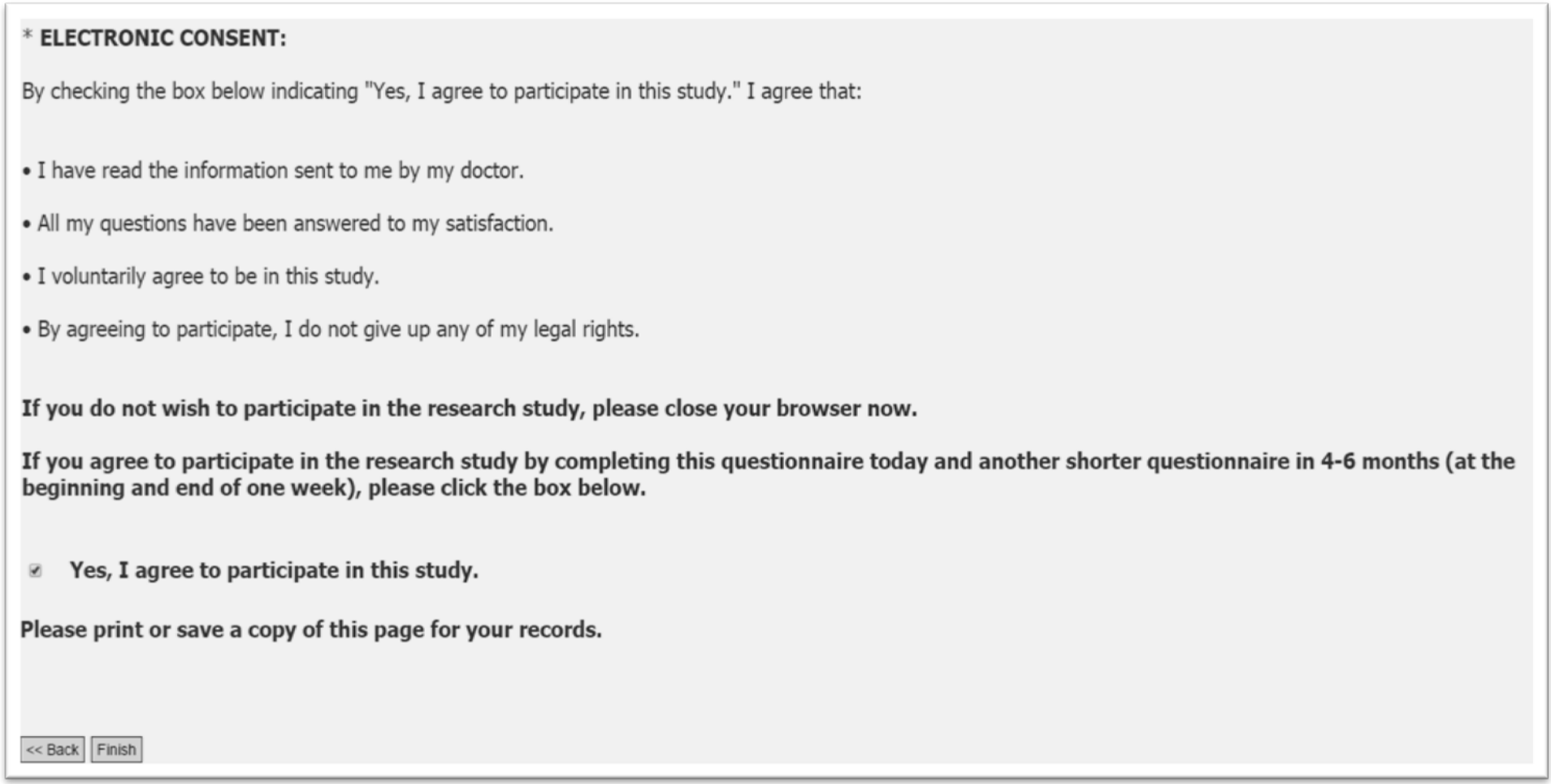
BRIEF REVIEW OF STUDY PURPOSE AND PROCEDURES

The main purpose of this study is to test the performance of a new questionnaire that has been designed to assess various symptoms often seen in people who have difficulties with depression. Participation in this study is strictly voluntary, and no treatment is involved. If you agree to participate, you will be asked to complete this questionnaire in order to help the developers improve it and shorten it. When the revised version is available (approximately 4-6 months from now) you will be asked to complete it again (once at the beginning of a week and then again at the end of that week) in order to help evaluate the revised version.

In appreciation for your help in evaluating this new questionnaire you will be given a $75 gift card. If you complete the revised shorter questionnaire 4-6 months from now you will be given another $75 after you complete it at the beginning and end of one week. At the end of this questionnaire you will be asked to indicate your choice of gift card.

Next >>

Workflow: Patient Consent



* **ELECTRONIC CONSENT:**

By checking the box below indicating "Yes, I agree to participate in this study." I agree that:

- I have read the information sent to me by my doctor.
- All my questions have been answered to my satisfaction.
- I voluntarily agree to be in this study.
- By agreeing to participate, I do not give up any of my legal rights.

If you do not wish to participate in the research study, please close your browser now.

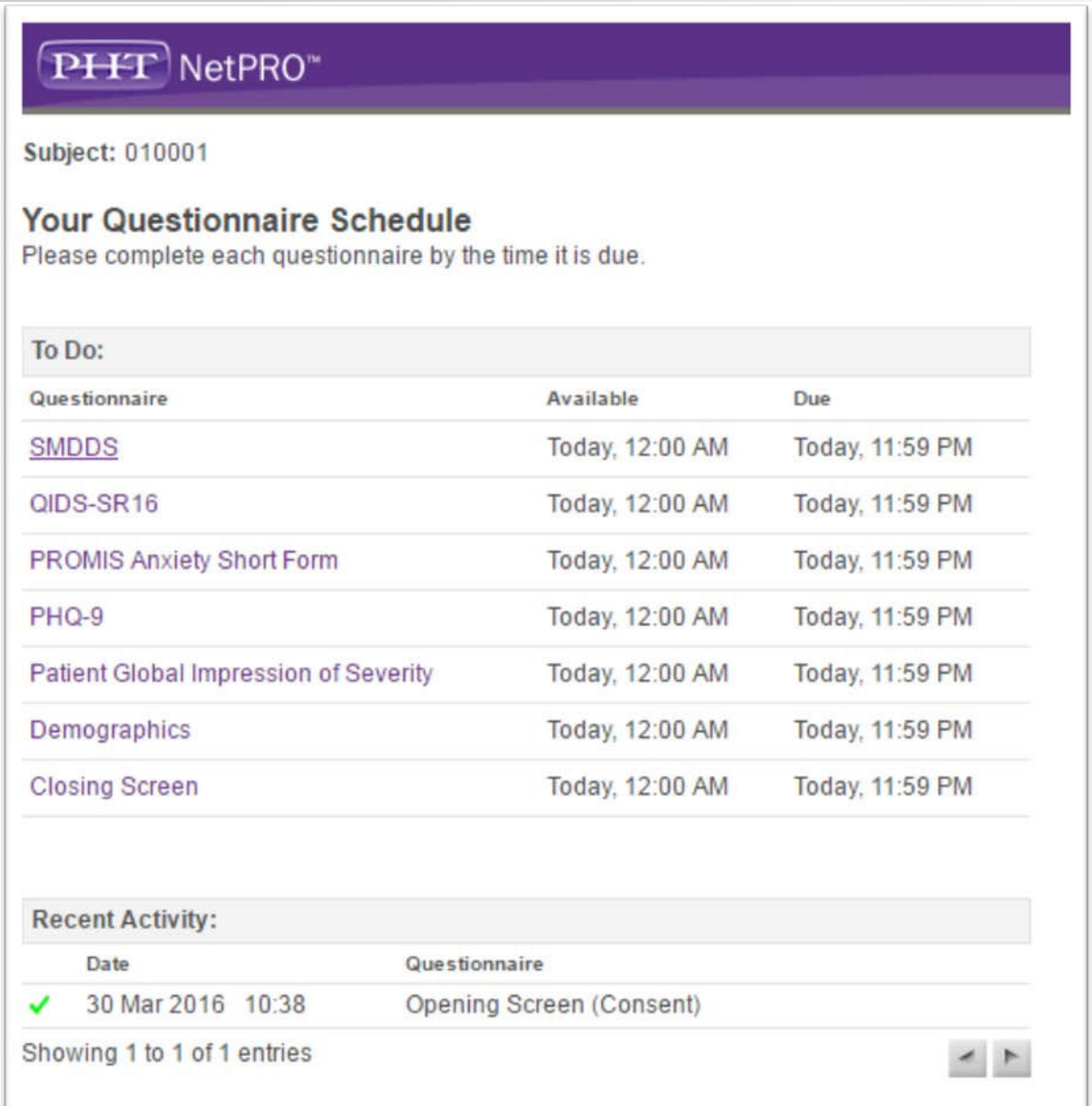
If you agree to participate in the research study by completing this questionnaire today and another shorter questionnaire in 4-6 months (at the beginning and end of one week), please click the box below.

☑ **Yes, I agree to participate in this study.**

Please print or save a copy of this page for your records.

<< Back | Finish

Workflow: Questionnaire Schedule


PHT NetPRO™

Subject: 010001

Your Questionnaire Schedule

Please complete each questionnaire by the time it is due.

To Do:

Questionnaire	Available	Due
SMDDS	Today, 12:00 AM	Today, 11:59 PM
QIDS-SR16	Today, 12:00 AM	Today, 11:59 PM
PROMIS Anxiety Short Form	Today, 12:00 AM	Today, 11:59 PM
PHQ-9	Today, 12:00 AM	Today, 11:59 PM
Patient Global Impression of Severity	Today, 12:00 AM	Today, 11:59 PM
Demographics	Today, 12:00 AM	Today, 11:59 PM
Closing Screen	Today, 12:00 AM	Today, 11:59 PM

Recent Activity:

	Date	Questionnaire
✓	30 Mar 2016 10:38	Opening Screen (Consent)

Showing 1 to 1 of 1 entries

Workflow: Initial SMDDS Question

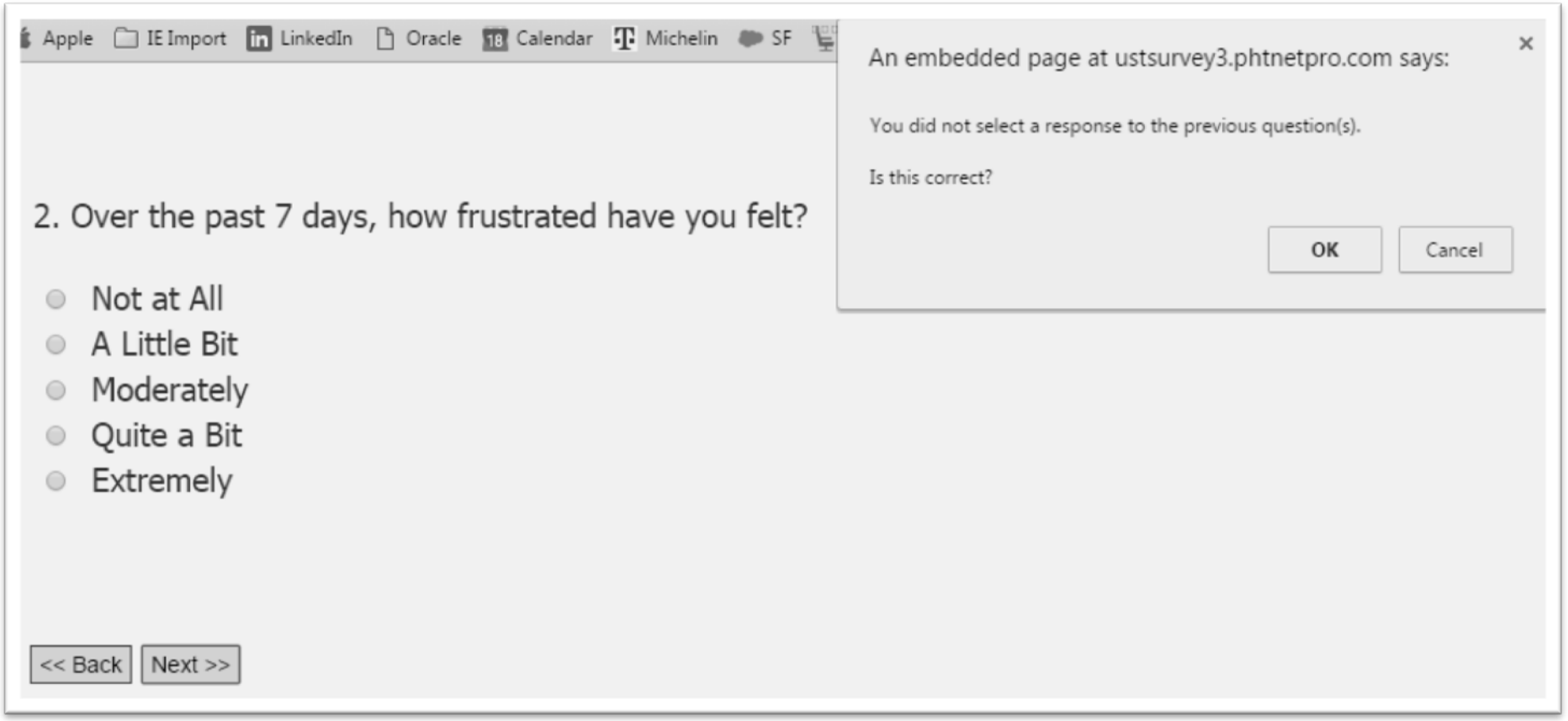
For each of the following questions, please choose the one response that best describes your experience over the past 7 days.

1. Over the past 7 days, how angry have you felt?

- Not at All
- A Little Bit
- Moderately
- Quite a Bit
- Extremely

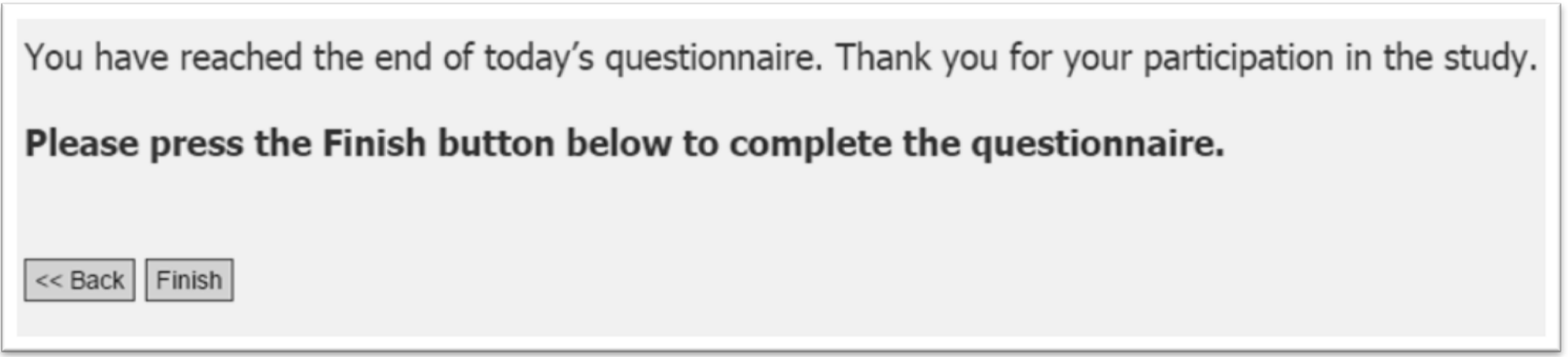
Next >>

Example screenshots: Item Skipping



- **Of note, there was no skipping possibilities for other questionnaires**

Example screenshots: End of Participation



Timelines for data collection

- Wave 1 took place from May to July 2015
  - Data from 315 subjects were included
  - Based on Wave 1 analysis, the content of the SMDDS was revised
- Wave 2 was estimated to start in Oct 2015; however, UST took longer than anticipated.
  - An e-mail was created to inform subjects about the timing of Wave 2.
  - However technical problems resulted in a failure to send the email to all subjects which led to the following experience:
    - Part 1 was launched in mid-November following the original email
    - Once subjects completed part 1, a second email was launched 8 days later requesting that they complete part 2 (the retest).
    - Part 2 required subjects to complete the ePRO within 3 days of the email or the retest data entry window timed out.
    - Due to the timing of the launch of part 2, the 3-day window may have coincided with the Thanksgiving holiday potentially resulting in them missing the window before the data entry window timed out.

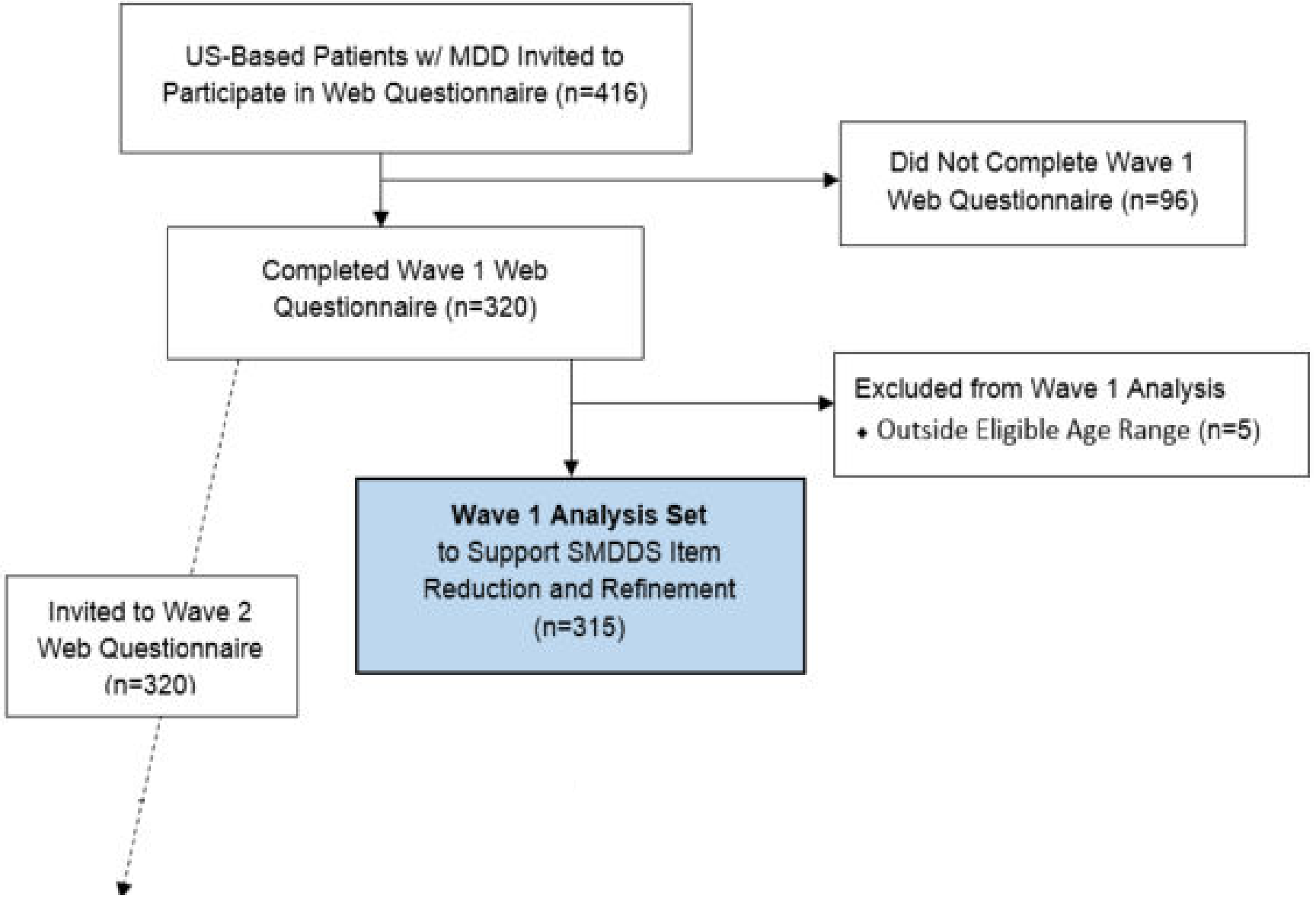
Helpdesk Specifications

- This study is solely NetPro. Subjects were asked to enter data on their own desktop or laptop and not on tablets or handheld devices, though this was not restricted.
- Subjects were highly unlikely to know the protocol number.
- For Wave 2, subjects would not remember the ID given to them in the initial Wave 1 invitation letter.
- For all assessments, once a subject started the questionnaire battery, they had until midnight of the same day to complete the questionnaires or the data entry window timed out and they would not be able to complete the remaining questionnaires.

Quantitative Results from Wave 1

Don Bushnell, Associate Director,
HRA, Inc.

Wave 1 Analysis Schema

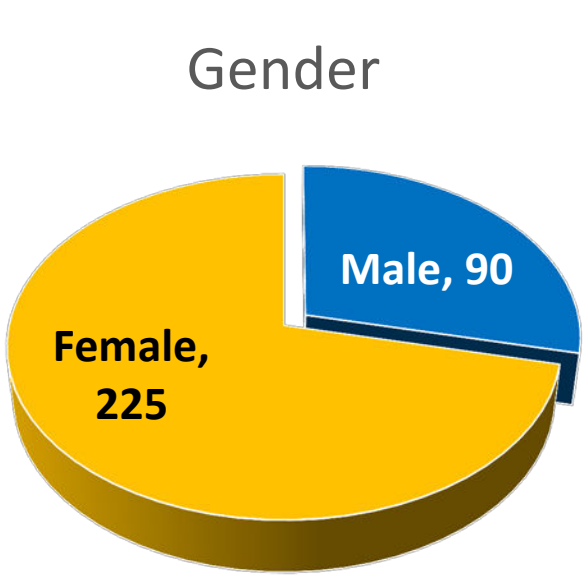


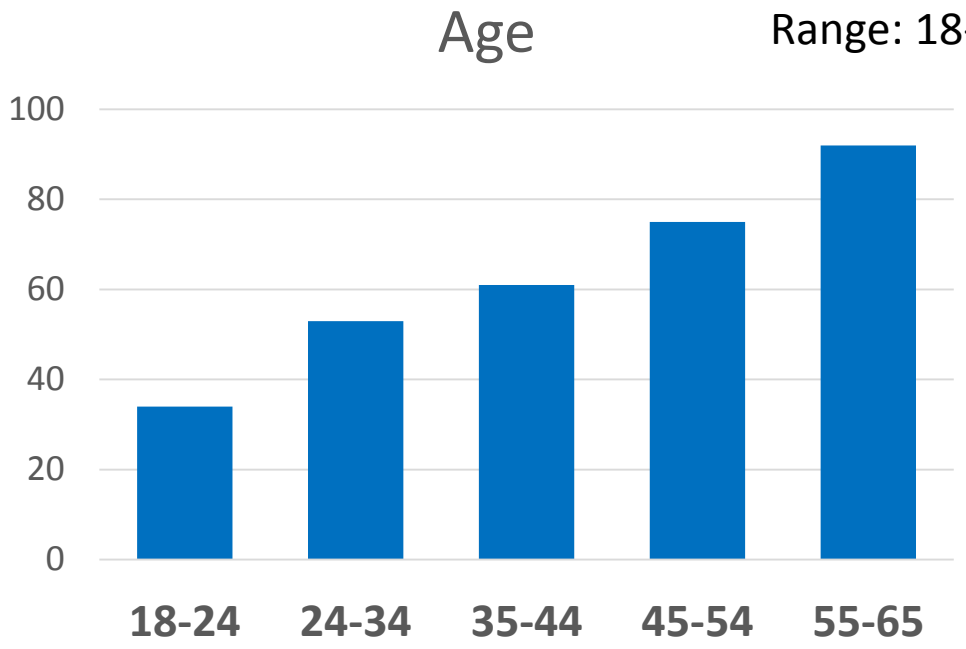
Wave 1 Analytical Approach

- Item descriptives
- Item reduction statistics
- Rasch Measurement Theory
- Exploratory factor analysis
- Reliability (alphas if items removed)
- Validity

Wave 1 Results - Sample

Mean: 44.4
StDev: 13.8
Range: 18-65

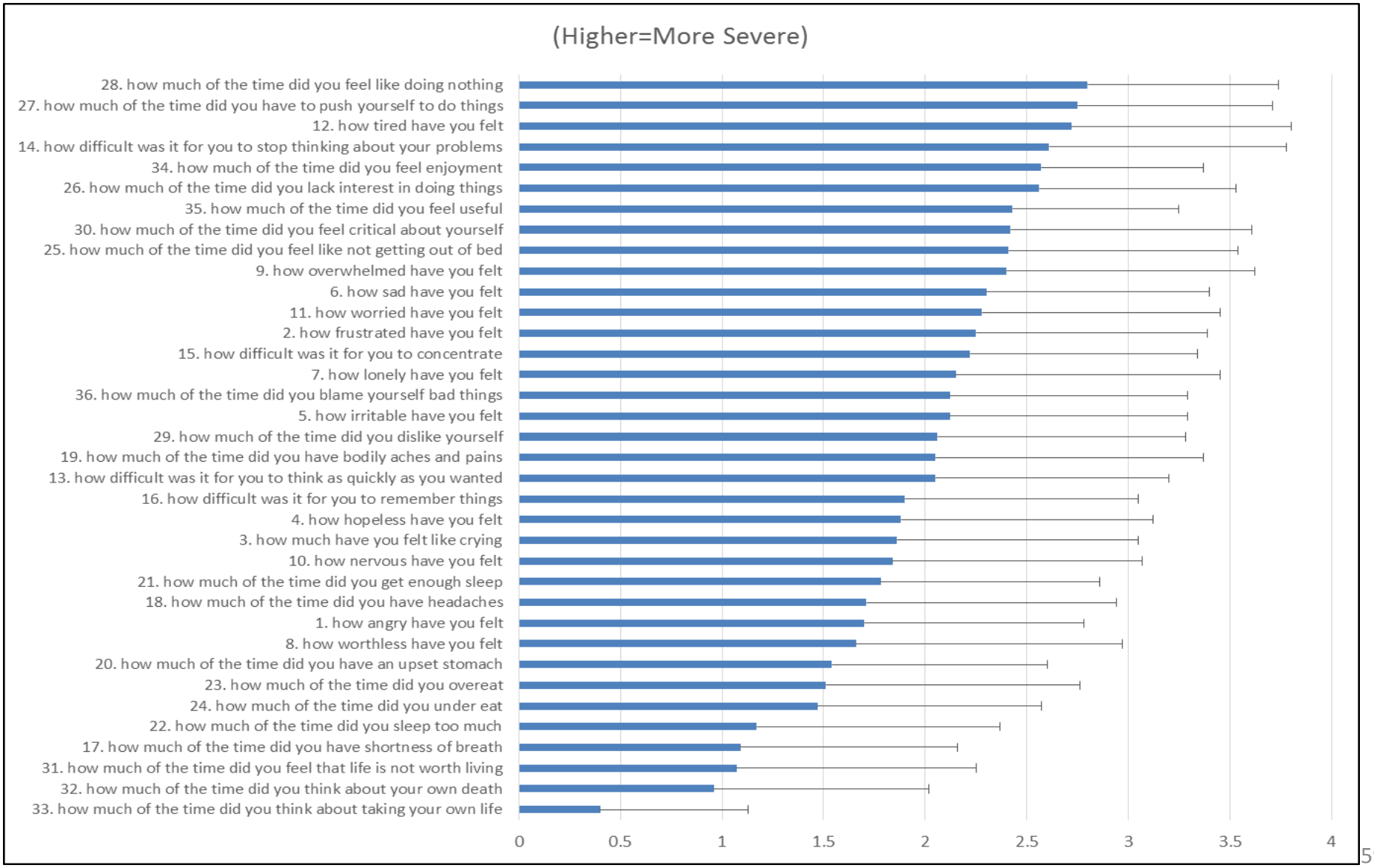




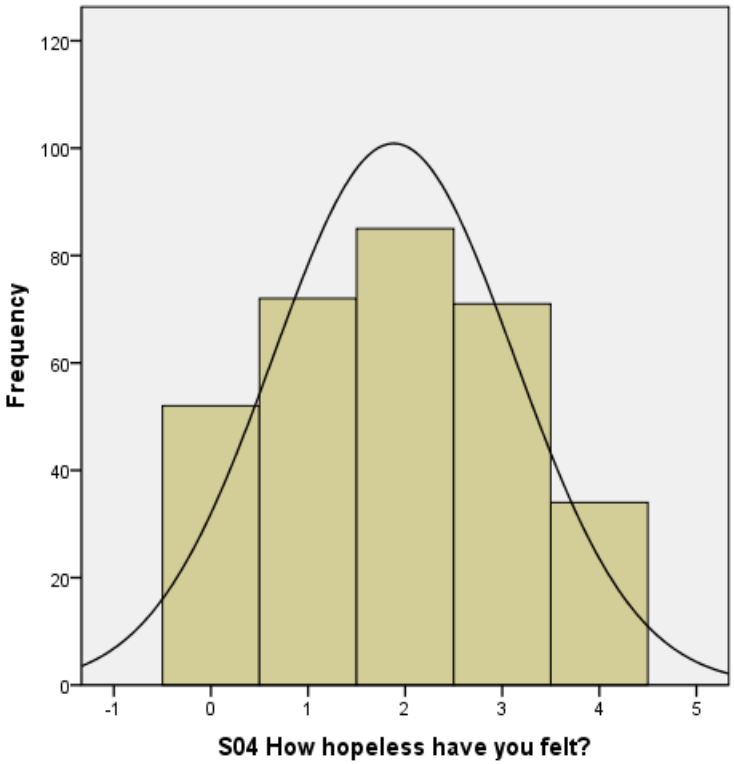
Race	n (%)
White	255 (81.0)
Black/African American	41 (13.0)

Marital Status	n (%)
Married/living as married	129 (41.0)
Divorced	58 (18.4)
Never married	103 (32.7)

SMDDS Items by Mean Score (Wave 1)



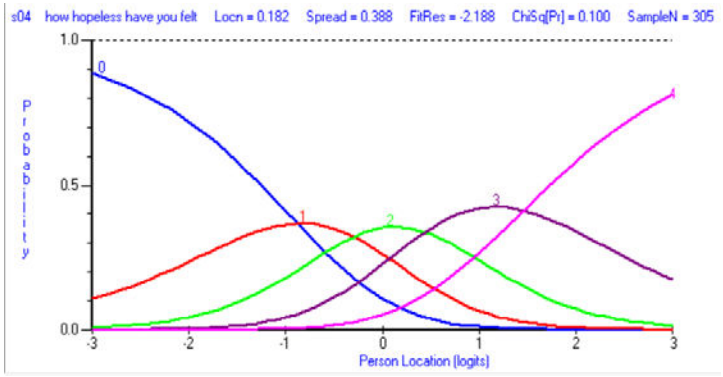
Over the past 7 days,
4. how hopeless have you felt?

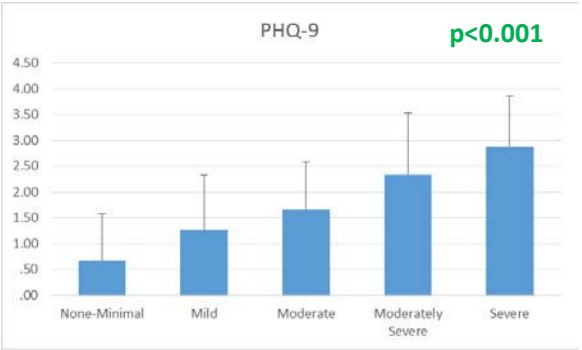


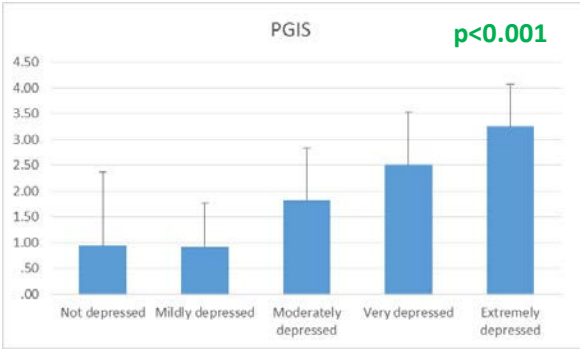
N	314
Mean (SD)	1.88 (1.24)
Median	2.00
Range	0-4
N(%) Ceiling	52 (16.6)
N(%) Floor	34 (10.8)
N(%) Missing	1 (0.3)
Correlation with:	
QIDS-SR$_{16}$	0.48**
PROMIS	0.55**

Item-to-item correlation
0.732 (6. sad) 0.684 (8. worthless)

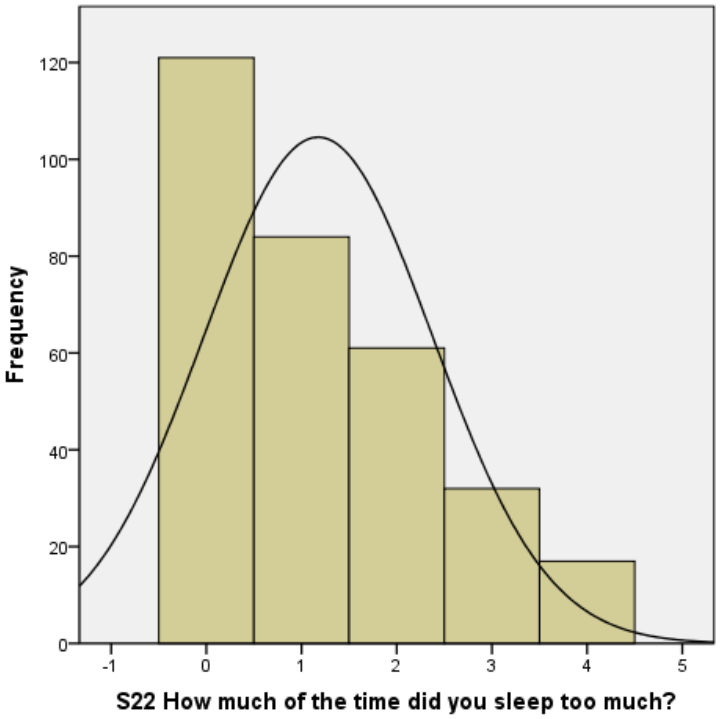
Item-to-total correlation
.687







Over the past 7 days,
22. how much of the time did you sleep too much?

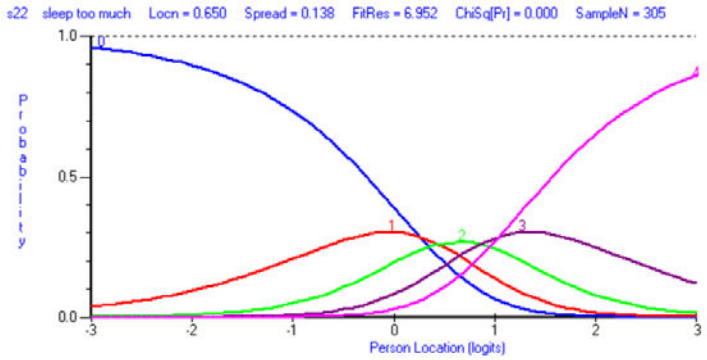


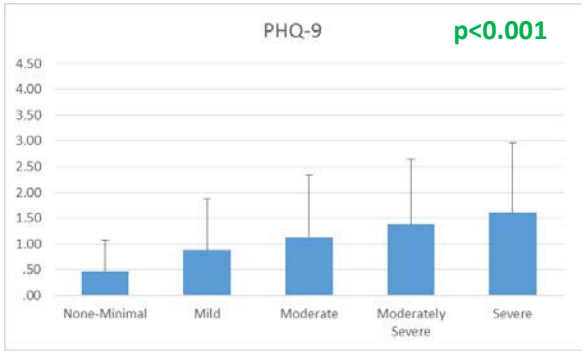
N	315
Mean (SD)	1.17 (1.20)
Median	1.00
Range	0-4
N(%) Ceiling	**121 (38.4)**
N(%) Floor	17 (5.4)
N(%) Missing	0 (0.0)
Correlation with:	
QIDS-SR$_{16}$	0.10
PROMIS	0.22**

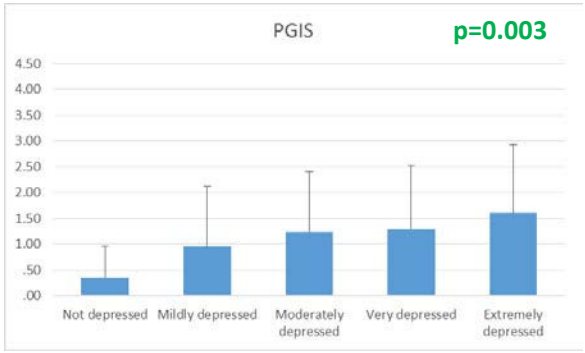
Item-to-item correlation
None

Item-to-total correlation
-.203

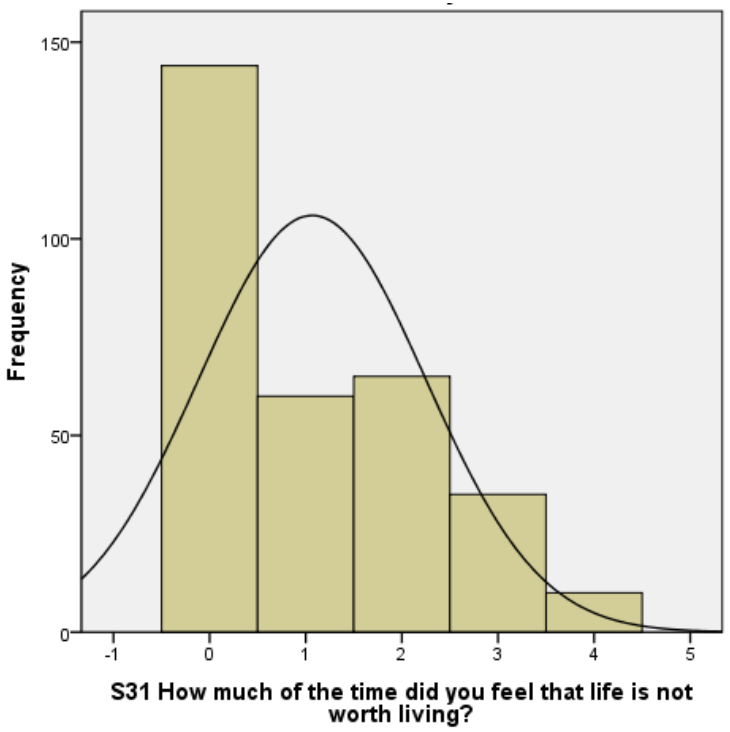
GAD: p=0.010







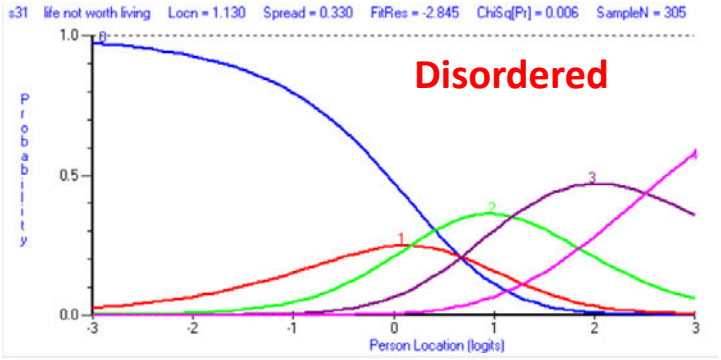
Over the past 7 days,
31. how much of the time did you feel that life is not worth living?

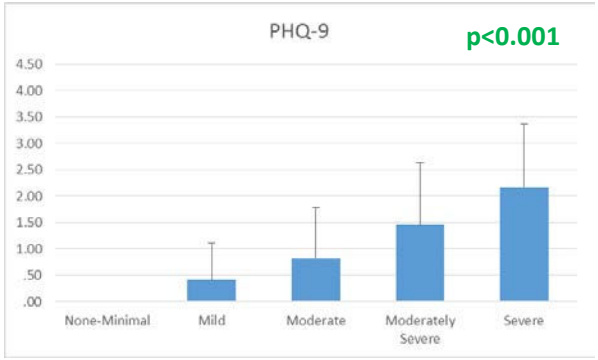


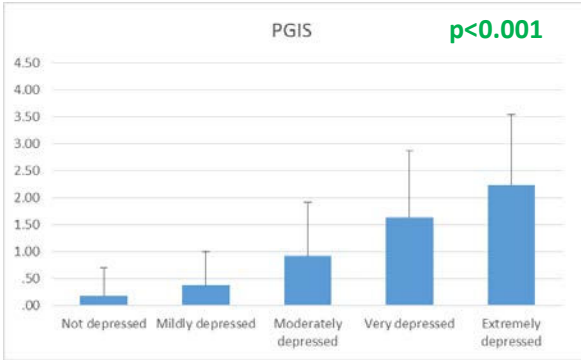
N	314
Mean (SD)	1.07 (1.18)
Median	1.00
Range	0-4
N(%) Ceiling	**144 (45.9)**
N(%) Floor	10 (3.2)
N(%) Missing	1 (0.3)
Correlation with:	
QIDS-SR$_{16}$	0.50**
PROMIS	0.58**

Item-to-item correlation
0.606 (29. dislike self)
0.616 (32. think about own death)
0.691 (33. think about taking life)

Item-to-total correlation
.668







Suicidal Ideation

Total subjects in analysis	**315**
Total subjects triggered	142 (45%)
1 item triggered	39 (27%)
2 items triggered	42 (30%)
3 items triggered	61 (43%)
No suicide ideation	*173 (55%)*
Number of Suicide Ideation (SI) forms sent to clinic	142
Number of SI forms returned to HRA detailing follow-up action by clinic	142

(S) 33. Over the past 7 days, how much of the time did you think about taking your own life? Options 2-5: Rarely(52)/Sometimes(30)/Often(3)/Always(1)

(Q) 12. Thoughts of Death or Suicide: Options 2-4: I feel that life is empty or wonder if it's worth living(98)/I think of suicide or death several times a week for several minutes(19)/I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life(5)

(P) 9. Over the **last 2 weeks**, how often have you been bothered by thoughts that you would be better off dead or of hurting yourself in some way? Options 2-4: Several days(70)/More than half the days(21)/Nearly every day(7)

Item Reduction Meeting

- The aim of the meeting was to:
  - Present the SMDDS analytic results
  - Present the item level analyses for the 36 SMDDS items
  - Gain consensus on which items to retain and delete
  - Have opportunity to pose questions to FDA representatives from the COA Staff, Office of Biostatistics, and Division of Psychiatry Products

Item Reduction Meeting Decisions

- Based on Wave 1 data analyses, the SMDDS was revised to a 17-item scale:
  - Deleted 12 redundant items
  - Deleted all physical (somatic) symptom items
    - Despite understanding that this domain could be relevant for a pediatric measure (4 items)
  - Deleted 3 items due to conceptual vulnerability and potential bias
  - Reordered items
  - Revised wording of 3 items

Confirmatory Cognitive Interviews

Kelly McCarrier, PhD, MPH

Senior Research Scientist, HRA, Inc.

Confirmatory Cognitive Interviews

- Objective:
  - To evaluate comprehension, relevance, and comprehensiveness of revised (17-item) SMDDS
    - Particular focus on revised items / alternative phrasing
- Methods:
  - N=20 individual, face-to-face cognitive interviews, conducted in three waves
  - Same eligibility and recruitment as quant. pilot study
  - ~60-minute interviews using revised SMDDS

Key Revisions from Confirmatory Cognitive Interviews

W1 Quant Version	Revised for Cognitive Interviews	W2 Quant Version
23. Over the past 7 days, how much of the time did you overeat? Never Rarely Sometimes Often Always	12. Over the past 7 days, how often did you overeat? Never Rarely Sometimes Often Always	12. Over the past 7 days, how often did you over eat? Never Rarely Sometimes Often Always
24. Over the past 7 days, how much of the time did you under eat? Never Rarely Sometimes Often Always	13. Over the past 7 days, how often did you have a poor appetite? Never Rarely Sometimes Often Always	11. Over the past 7 days, how often did you have a poor appetite? Never Rarely Sometimes Often Always

Key Revisions from Confirmatory Cognitive Interviews

W1 Quant Version	Revised for Cognitive Interviews	W2 Quant Version
34. Over the past 7 days, how much of the time did you feel enjoyment? Never Rarely Sometimes Often Always	9. Over the past 7 days, how difficult was it for you to enjoy life? Not at All A Little Bit Moderately Quite a Bit Extremely **ALT stem:** Over the past 7 days, how difficult was it for you to find pleasure in your daily life?	9. Over the past 7 days, how difficult was it for you to enjoy your daily life? Not at all A Little Bit Moderately Quite a Bit Extremely

Key Revisions from Confirmatory Cognitive Interviews

W1 Quant Version	Revised for Cognitive Interviews	W2 Quant Version
21. Over the past 7 days, how much of the time did you get enough sleep? Never Rarely Sometimes Often Always	10. Over the past 7 days, how difficult was it for you to sleep? Not at all A Little Bit Moderately Quite a Bit Extremely Test alternative stems: ALT 1: Over the past 7 days, how difficult was it for you to sleep (trouble falling asleep, staying asleep, or waking too early)? ALT 2: Over the past 7 days, how often did you have difficulty sleeping? ALT 3: Over the past 7 days, how often did you have a problem with your sleep (falling asleep, staying asleep, or sleeping too much)?	10. Over the past 7 days, how often did you have a problem with your sleep (falling asleep, staying asleep, or sleeping too much)? Never Rarely Sometimes Often Always

Confirmatory Cognitive Interviews

- Interview Findings and Changes
  - Finalized wording of appetite and enjoyment items
  - Revised and finalized wording of sleep interference item
  - Removed “sleep too much” item

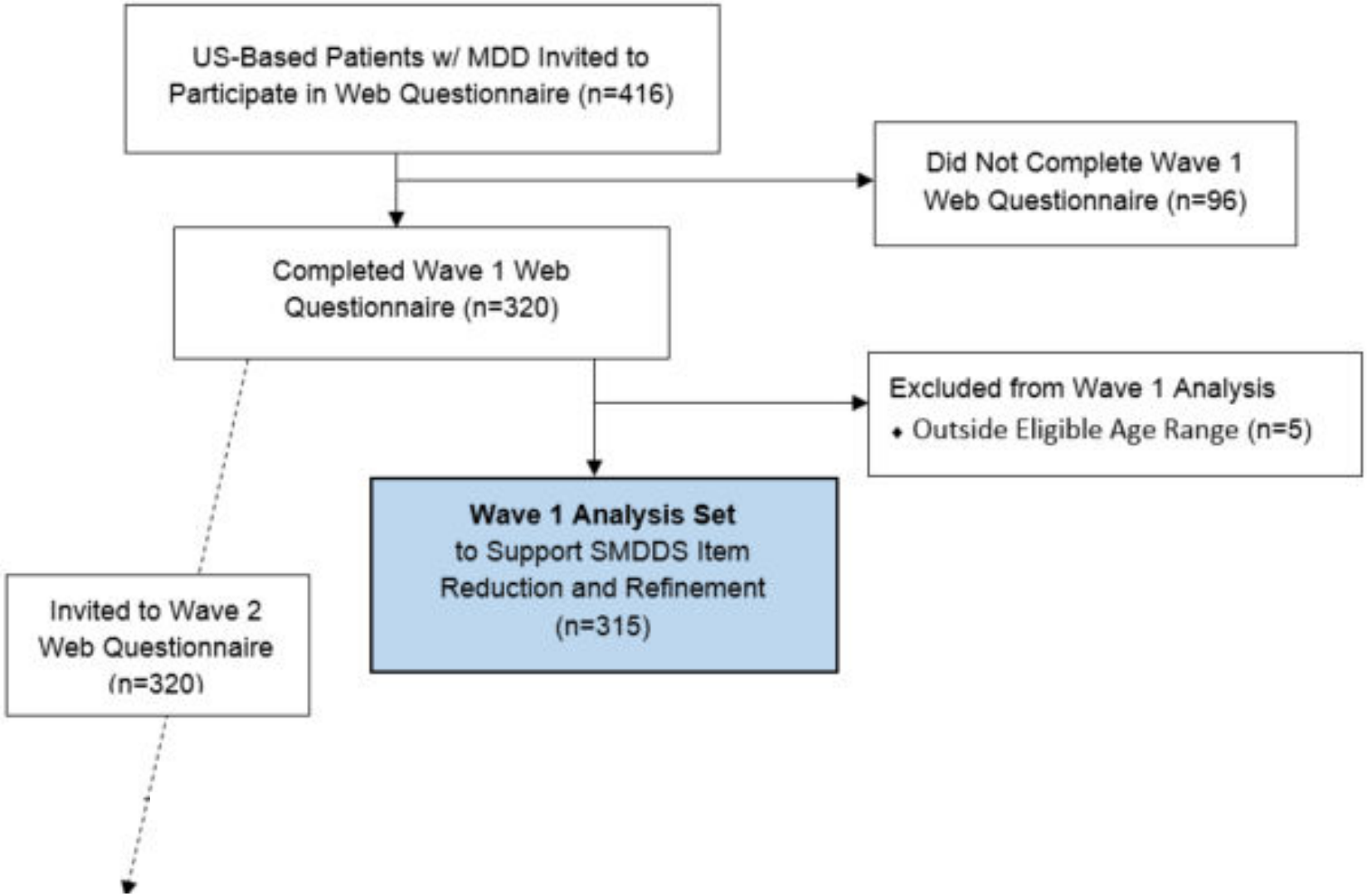
- Prepared SMDDS (16-item) for Confirmatory (Wave 2) Quantitative Testing

Conceptual Framework for Revised 16-item SMDDS following Confirmatory Cognitive Interviews

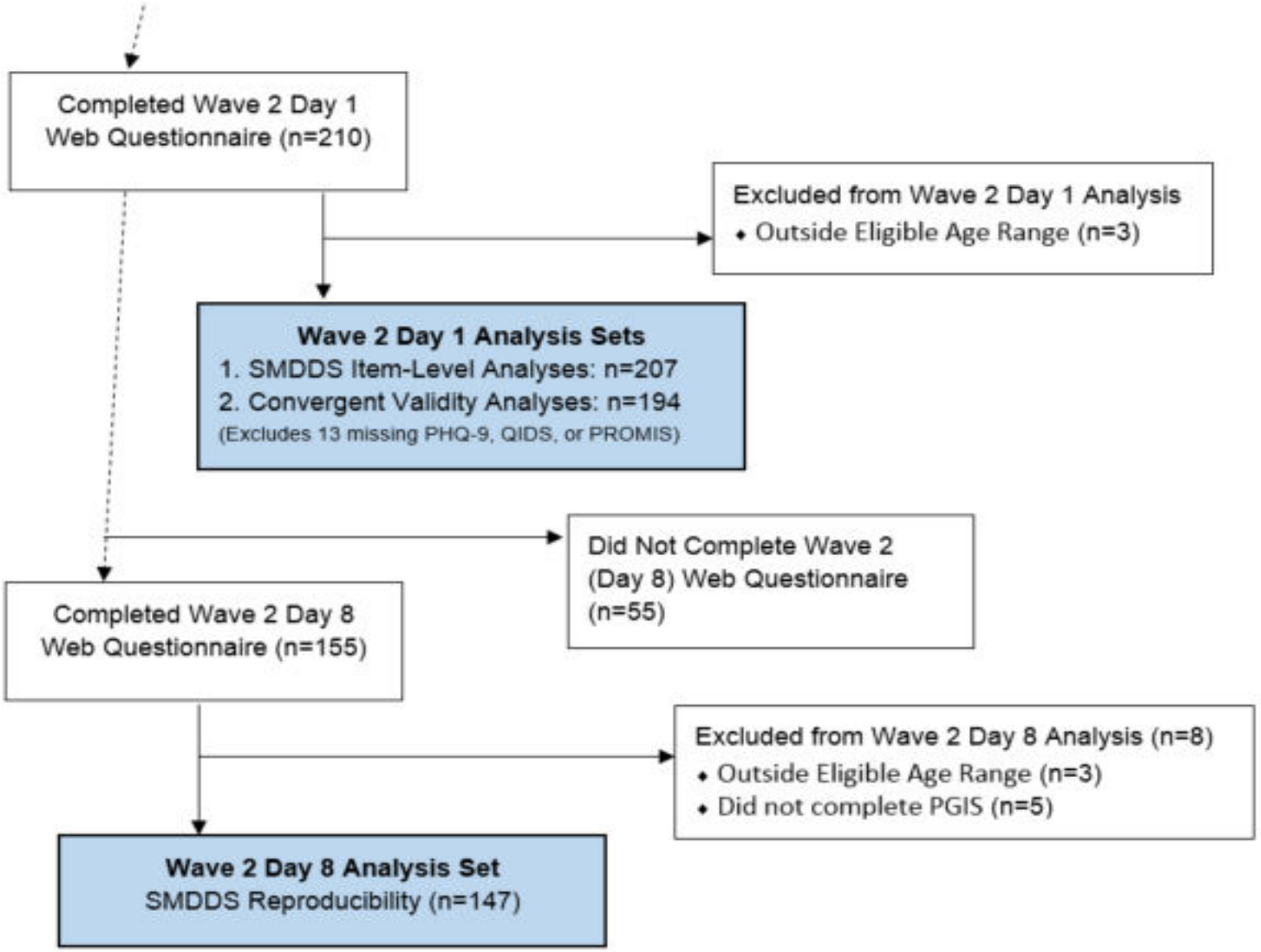
Quantitative Results from Wave 2

Don Bushnell, Associate Director,
HRA, Inc.

Wave 1 Analysis Schema



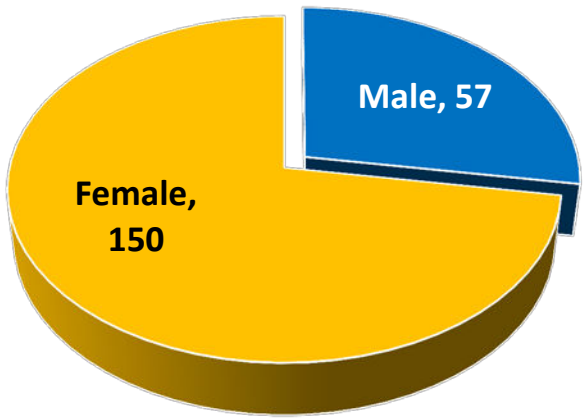
Wave 2 Analysis Schema



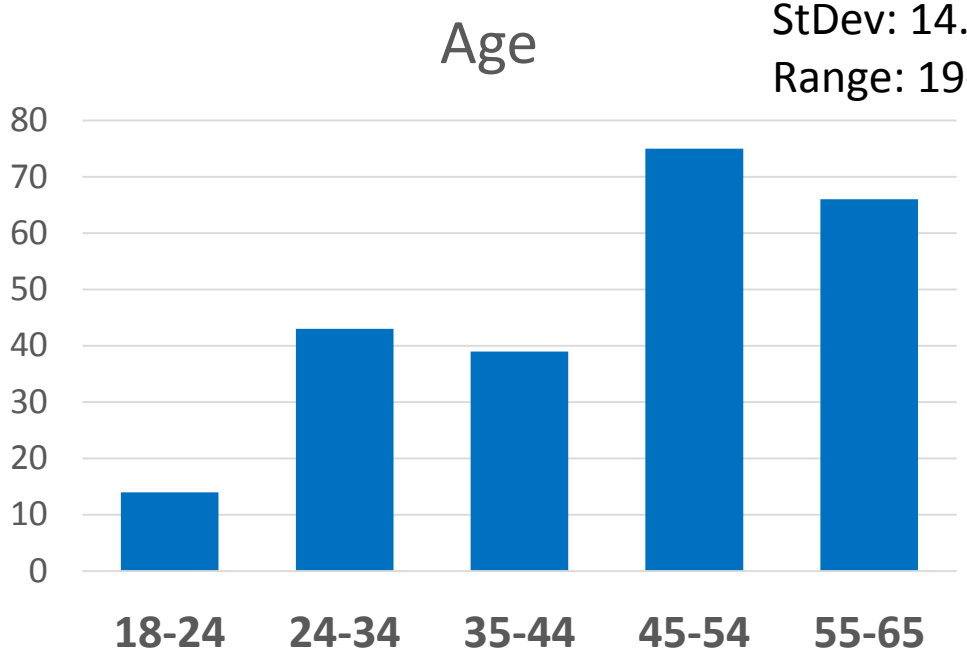
Wave 2 Analytical Approach

- Rasch Measurement Theory
- Factor analysis
- Reliability
- Validity
- PGIS vs. PGIC (Exploratory)

Wave 2 Results - Sample



Mean: 45.3
StDev: 14.0
Range: 19-65



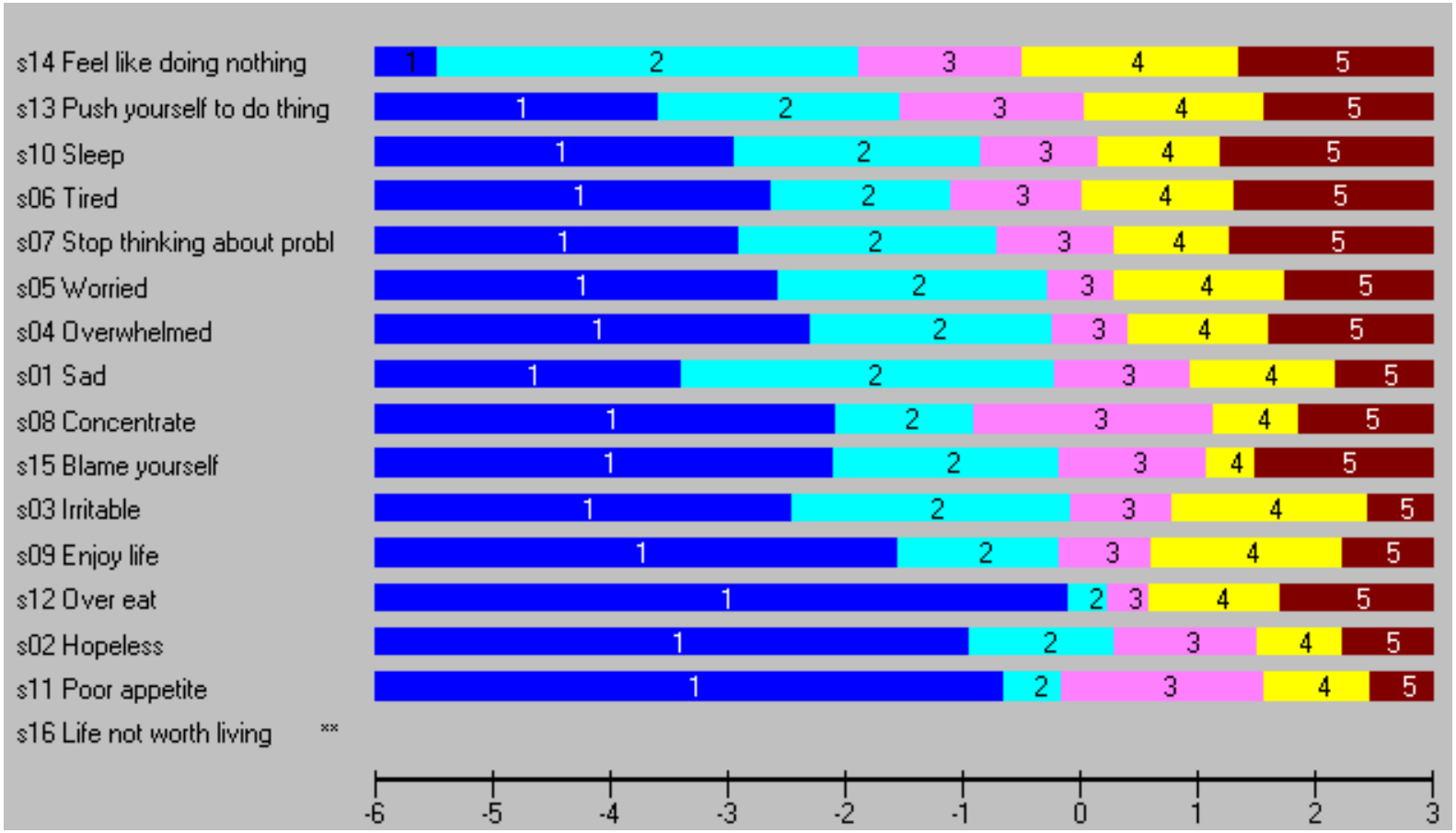
Race	n (%)
White	169 (81.6)
Black/African American	25 (12.1)

Marital Status	n (%)
Married/living as married	87 (42.0)
Divorced	36 (17.4)
Never married	67 (32.4)

Wave 2 Results - Sample

Depression diagnosis, n (%)	
Less than 6 months ago	17 (8.2)
Between 6 months and 1 year ago	42 (20.3)
More than 1 year ago	148 (71.5)
Clinical diagnosis of GAD, n (%)	
No	146 (70.5)
Yes	57 (27.5)
Missing	4 (2.0)
QIDS-SR$_{16}$ (n=193)	
Mean (SD) [Range] possible range 0-27	12.4 (5.0) [1-24]
PROMIS Anxiety Short Form (raw score) (n=193)	
Mean (SD) [Range] possible range 8-40	22.2 (7.1) [8-39]
PROMIS Anxiety Short Form (t-score) (n=193)	
Mean (SD) [Range] possible range 37.1-83.1	60.5 (7.9) [37.1-80.0]
PHQ-9 categories, n (%) (n=191); Mean 11.5 (6.1)	
0-4 (none-minimal)	25 (13.1)
5-9 (mild)	53 (27.7)
10-14 (moderate)	56 (29.3)
15-19 (moderately severe)	32 (16.8)
20-27 (severe)	25 (13.1)

Wave 2 Results – RMT Threshold Map



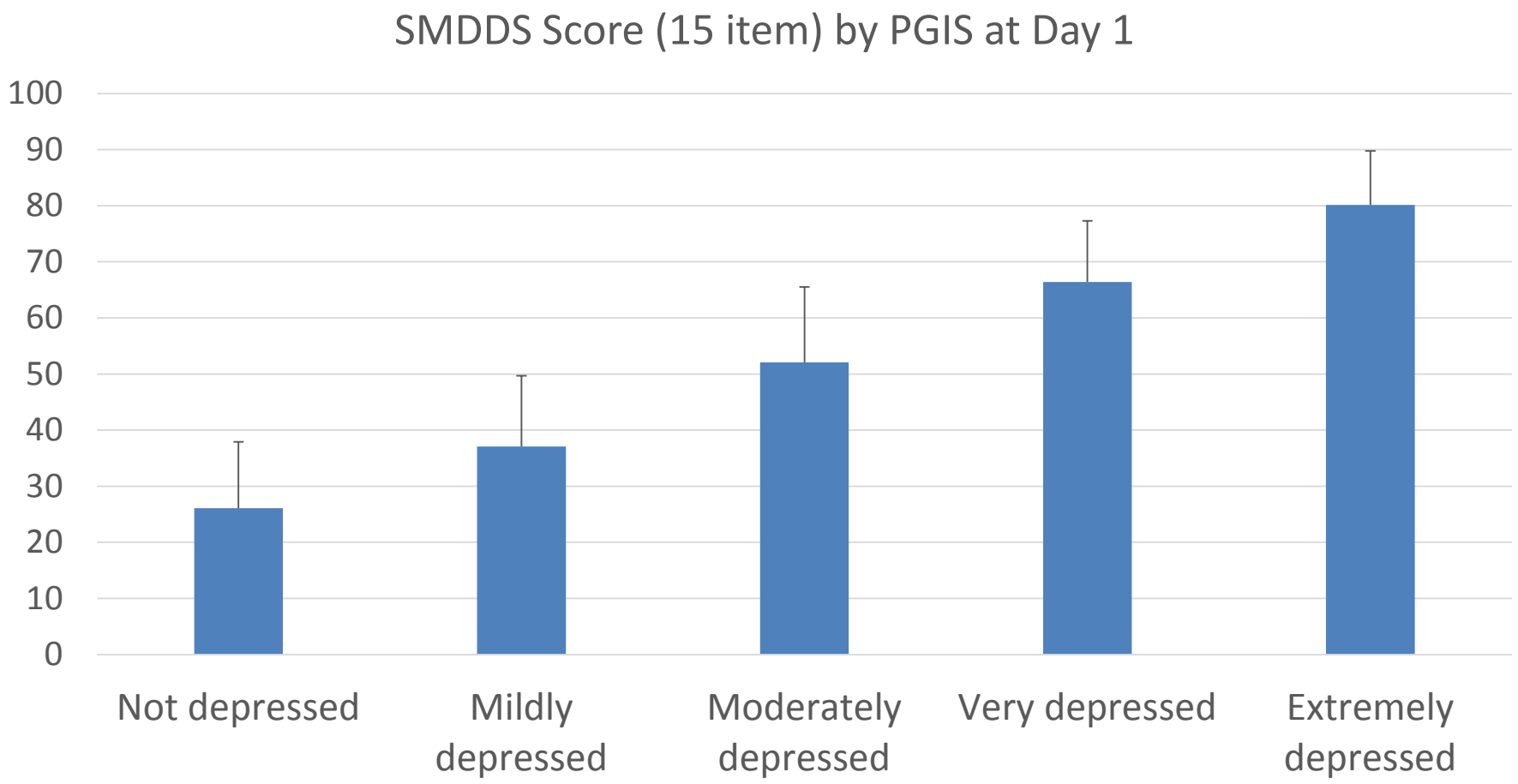
** Disordered threshold

Note: items are in location order.

Wave 2 Results – Construct Validity

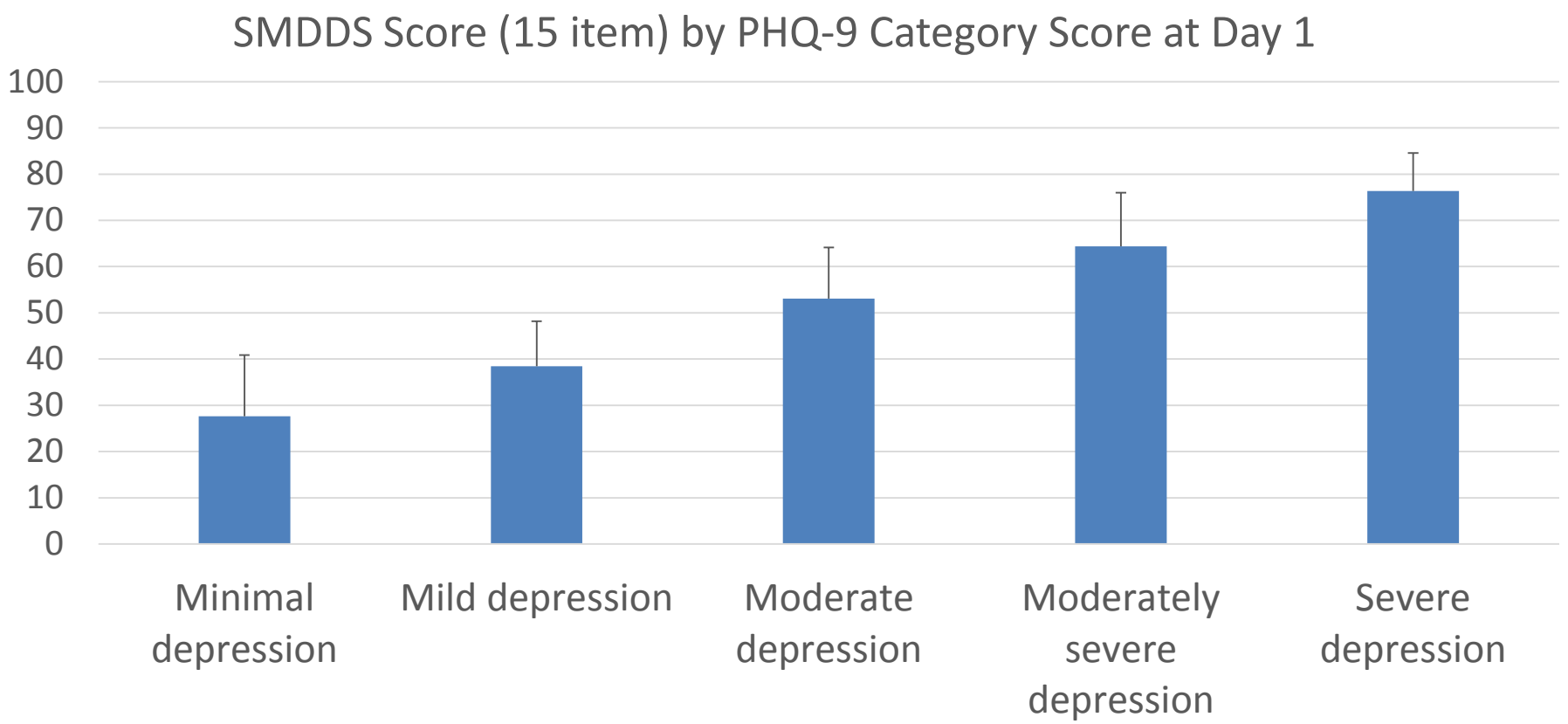
	Pearson Correlation															
	1 sad	2 hopeless	3 irritable	4 overwhelmed	5 worried	6 tired	7 stop thinking	8 concentrate	9 enjoy life	10 sleep	eating behavior (computed)	13 push yourself	14 doing nothing	15 blame self	16 life not worth living	SMDDS15
QIDS-SR16	.581	.613	.348	.539	.556	.447	.546	.612	.666	.553	.426	.671	.623	.645	.541	**.789**
PROMIS Anxiety	.564	.510	.453	.634	.706	.340	.713	.574	.549	.497	.357	.517	.441	.589	.571	**.758**
PHQ-9	.639	.617	.389	.551	.606	.463	.625	.643	.659	.579	.532	.656	.629	.674	.582	**.831**

Wave 2 Results – Known-Groups Validity



F=61.438, p<0.001

Wave 2 Results – Known-Groups Validity



F=94.577, p<0.001

PGIS vs. PGIC

PGIC	PGIS Change						Total
	-2	-1	0	1	2	3	
Much worse	0	0	1	0	0	0	1
Worse	1	1	4	1	0	0	7
A little worse	0	3	7	0	0	0	10
No change	0	13	48	12	1	0	74
A little better	0	2	21	12	1	0	36
Better	0	0	8	5	0	1	14
Much better	0	0	4	1	0	0	5
	1	19	93	31	2	1	146

	No change	
	PGIS (n=93)	PGIC (n=74)
SMDDS Score	0.848 (0.799-0.897)	0.748 (0.627-0.833)

Conceptual Framework for 16-item SMDDS

Summary and Overview of Regulatory Interactions and Mixed Methods Process

Elizabeth (Nicki) Bush, MHS –
Research Scientist, Global Patient Outcomes and Real World Evidence,
Eli Lilly and Company

Regulatory Interactions

- Scoping Stage (May-October 2010)
  - Written feedback
  - Topics included draft conceptual framework
- Qualitative Research Summary (September 2013-July 2014)
  - Written feedback
  - Topics included clarification of patient population and item/domain wording
- Final Item Selection and Refinement Meeting (Face-to-face, July 2015)
  - Email follow-up prior to Wave 2 of quantitative pilot study (September 2015)

Mixed Methods

- Non-linear instrument development
  - Qualitative concept elicitation data "revisited" with each revision
- Rasch analyses used in context of qualitative data
  - "Poorly-performing" and redundant items identified using Rasch
  - Concepts and wording revised based on CE
  - All changes to SMDDS confirmed using CI
  - Expert opinion consistently integrated

Looking Back

- What worked well?
  - Item reduction meeting with FDA, KOLs, C-Path and Working Group
- Lessons learned
  - First draft of instrument was too long
  - Over time, interaction with FDA became more efficient
  - Over time, contracting with multiple stakeholders became more efficient

Looking Ahead

- Dissemination
  - Summary of qualitative research has been published
  - Once qualified
    - Manuscript describing development
    - Presentation of instrument and development methods at ISPOR
- Next Steps
  - Inclusion in an appropriate treatment trial to allow for full evaluation of psychometric properties

Panel Discussion

Moderator

- *Elizabeth (Nicki) Bush, MHS* – Research Scientist, Global Patient Outcomes and Real World Evidence, Eli Lilly and Company

Presenters

- *Elizabeth (Nicki) Bush, MHS* – Research Scientist, Global Patient Outcomes and Real World Evidence, Eli Lilly and Company
- *Kelly P. McCarrier, PhD, MPH* – Senior Research Scientist, Health Research Associates, Inc.
- *Donald Bushnell, MA* – Associate Director, Health Research Associates, Inc.
- *Valdo Arnera, MD* – Scientific Advisor and General Manager ERT Geneva, ERT

Panelists

- *Stephen Joel Coons, PhD* – Executive Director, Patient-Reported Outcome Consortium, Critical Path Institute
- *Tiffany R. Farchione, MD* – Deputy Director, Division of Psychiatry Products (DPP), CDER, FDA