DDT COA QUALIFICATION REVIEW

CLINICAL OUTCOME ASSESSMENT (COA) TRACKING NUMBER	D2017-012
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REVIEW COMPLETION DATE	March 10, 2018
SUBMITTER	Depression Working Group (WG) PRO Consortium, Critical Path Institute
CLINICAL OUTCOME ASSESSMENT TYPE	Patient-reported Outcome (PRO)
ENDPOINT(S) CONCEPT(S)	Symptoms of Major Depressive Disorder (MDD)
MEASURE(S)	Symptoms of Major Depressive Disorder Scale (SMDDS)
INTENDED POPULATION(S)	Adults (age between 18 and 65 years old) with a clinical diagnosis of MDD who are being treated in an ambulatory setting

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A. EXECUTIVE SUMMARY

This drug development tool (DDT) clinical outcome assessment (COA) review concludes that Symptoms of Major Depressive Disorder Scale (SMDDS) has demonstrated adequate evidence of content validity and cross-sectional measurement properties (i.e., internal consistency reliability, test-retest reliability, convergent validity, and known-groups validity) to measure symptoms of major depressive disorder (MDD) in the context of use described below. Further evaluation is warranted on the instrument's longitudinal measurement properties (i.e., ability to detect change) and the interpretation of clinically meaningful within-patient change in score.

The Submitter's intended target patient population is adults (aged 18 years and older) with a clinical diagnosis of MDD who are being treated in an ambulatory setting. The target population includes those who experienced a major depressive episode within the previous 6 months, have a HAM-D score >18, and meet the DSM-IV or DSM-V criteria for MDD.

The SMDDS is intended for use as an efficacy outcome measure to support drug development. To support a drug development program for regulatory purposes, the specific study design, endpoint selection, positioning, and measurement approach would be determined by the study sponsor in concert with the appropriate regulatory review agencies.

Analyses are recommended to evaluate the SMDDS longitudinal measurement properties and the amount of change in an individual patient that can be considered meaningful for use in the interpretation of effectiveness. We expect that as further experience with the instrument is gained, the qualification statement will be expanded to include additional information to aid in interpretation of meaningful within-patient change as assessed by SMDDS.

B. CLINICAL OUTCOME ASSESSMENT REVIEW

Materials reviewed:

- **Cover letter:** "DDT008_20170328_CoverLtr_Qualification", March 28, 2017; Depression Working Group, PRO Consortium
- **Briefing document:** "DDT008_20170328_QualificationBriefingPkg", Version 4, March 20, 2017; Depression Working Group, PRO Consortium
- **Briefing document:** "PRO_Consortium-DepressionWG-DDTCOA008-20130913-FDA-QualitativeResearchSummary", September 13, 2013; Depression Working Group, PRO Consortium
- **Study report:** "Quantitative Pilot Study Report", Version 7, March 20, 2017; Depression Working Group, PRO Consortium
- **User manual:** "Symptoms of Major Depressive Disorder Scale (SMDDS) Provisional User Manual, Version 7, March 20, 2017; Depression Working Group, PRO Consortium

1 CONTEXT OF USE

1.1 Target Study Population and Clinical Setting

The SMDDS (Appendix A) assesses patient-reported symptoms associated with MDD. The Submitter's intended target patient population is adults (aged 18 years and older) with a clinical diagnosis of MDD who are being treated in an ambulatory setting. The target population includes those who experienced a major depressive episode within the previous 6 months, have a HAM-D score >18, and meet the DSM-IV or DSM-V criteria for MDD.

<Reviewer note: The inclusion criteria for qualitative study specified participants as age between 18 and 65 years old, who experienced a major depressive episode within the previous 6 months, had a HAM-D score > 18, met the DSM-IV criteria for MDD, and were expected to be treated for MDD in an outpatient setting. The inclusion criteria for quantitative study were patients between 18 and 65 years old, who experienced a major depressive episode within the previous 6 months, and met the DSM-IV criteria for MDD. There was a small difference in the inclusion criteria used between the qualitative study and the validation study but was deemed acceptable by the Division.>

The SMDDS has not been evaluated in patients with a history of a personality, bipolar, schizophrenic or other psychotic disorder, cognitive impairment (e.g., dementia). It also has not been evaluated in patients deemed to be at significant risk for suicide or with evidence of recent drug or alcohol abuse.

1.2 Clinical Trial Design

The SMDDS is intended for use as a clinical trial study endpoint to support drug development program. However, at this time, it has not been used in randomized controlled clinical trials where an approved or experimental treatment for MDD is being tested. To support a drug development program for regulatory purpose, the specific study design, endpoint selection, positioning, and measurement approach would be determined by the study sponsor in concert with the appropriate regulatory review agencies.

The study design for quantitative pilot study used to collect data for psychometric analysis is described in "Section 5: Other Measurement Properties".

1.3 Intended Endpoint Positioning

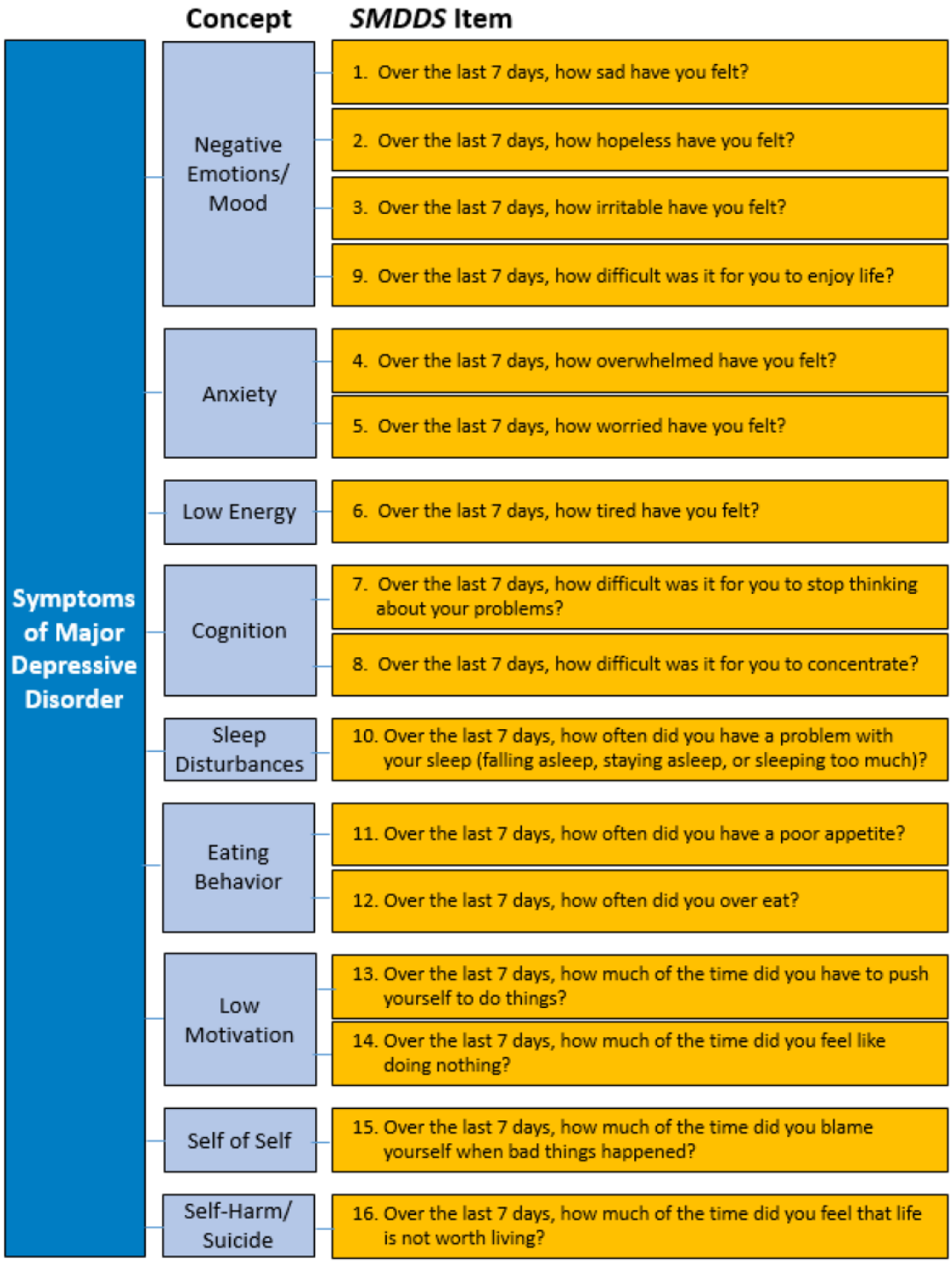
As further experience is gained with the use of the SMDDS, the qualified context of use may be expanded in the future to include the SMDDS as a primary, co-primary or secondary endpoint measure in clinical trials of MDD to assess self-reported symptom severity.

<Reviewer note: The Division's ultimate goal is to qualify fit-for-purpose PRO assessments for use as the primary endpoint to support labeling of MDD drug products. The SMDDS may be a candidate for this purpose.>

2 CONCEPT OF INTEREST (COI) AND CONCEPTUAL FRAMEWORK

The SMDDS total score is proposed for use as the study endpoint that encompasses the 16 items addressing nine different domains of MDD symptoms: negative emotions/mood (four items), anxiety (two items), low energy (one item), cognition (two items), sleep disturbances (one item), self-harm/suicide (one item), sense-of-self (one item) and eating behavior (two items - scored as a single item). Figure 1 shows the conceptual framework of the SMDDS.

Figure 1. Conceptual Framework for SMDDS (Version 1)



3 CLINICAL OUTCOME ASSESSMENT (COA) MEASURE(S)

The 16-item SMDDS addresses nine different domains of MDD: negative emotions/mood (four items), anxiety (two items), low energy (one item), cognition (two items), sleep disturbances (one item), self-harm/suicide (one item), sense-of-self (one item) and eating behavior (two items, scored as a single item) (see Figure 1).

The SMDDS uses a recall of "Over the past 7 days." Each item requires a response on a 5-point verbal rating scale using either "Not at all/A little bit/Moderately/Quite a bit/Extremely" (for intensity items) or "Never/Rarely/ Sometimes/Often/Always" (for frequency items). In the early development stages, it was first drafted using pencil and paper format. It was then programmed for web-based administration and cognitively evaluated for equivalence between the two formats.

The mode of administration for SMDDS is patient self-report, with data collection by web-based entry for the development. The SMDDS has also been tested for its ability to be programmed onto other electronic platforms.

The sum score of 15 of the 16 items, the SMDDS Total score, is the provisional scoring algorithm proposed for SMDDS. First, two of the items ["11. Over the past 7 days, how often did you have a poor appetite?" and "12. Over the past 7 days, how often did you over eat?"] are combined into a single "Eating Behavior" value by selecting the response with the highest level of severity from either of the items. The "Eating Behavior" score is then summed with the other 14 items. Table 1 shows the provisional scoring algorithm of SMDDS.

A greater than 50% rule will be employed for missing data at the item level. First, for the Eating Behavior score, there must be a response to at least one of the two items (poor appetite and over eat) to calculate a score, otherwise the Eating Behavior item score is set to missing. Second, for the SMDDS Total Score, a respondent must complete eight of the fifteen scorable items or an SMDDS score should not be computed. If a respondent completes at least eight of the items, the SMDDS Total score is calculated as the mean of the completed items multiplied by 15 (essentially substituting the missing responses with the mean of the completed items).

The SMDDS User Manual is reviewed and discussed in Section 9.

Table 1. Provisional Scoring of SMDDS

Original item		Response
1. …how sad have you felt?		0, 1, 2, 3, 4
2. …how hopeless have you felt?		0, 1, 2, 3, 4
3. …how irritable have you felt?		0, 1, 2, 3, 4
4. …how overwhelmed have you felt?		0, 1, 2, 3, 4
5. …how worried have you felt?		0, 1, 2, 3, 4
6. …how tired have you felt?		0, 1, 2, 3, 4
7. …how difficult was it for you to stop thinking about your problems?		0, 1, 2, 3, 4
8. …how difficult was it for you to concentrate?		0, 1, 2, 3, 4
9. …how difficult was it for you to enjoy life?		0, 1, 2, 3, 4
10. …how often did you have a problem with your sleep…?		0, 1, 2, 3, 4
11. …how often did you have a poor appetite?	*Create a single score by selecting the highest severity (i.e., value) on either item*	0, 1, 2, 3, 4
12. …how often did you over eat?		
13. …how much of the time did you have to push yourself to do things?		0, 1, 2, 3, 4
14. …how much of the time did you feel like doing nothing?		0, 1, 2, 3, 4
15. …how much of the time did you blame yourself when bad things happened?		0, 1, 2, 3, 4
16. …how much of the time did you feel that life is not worth living?		0, 1, 2, 3, 4
***SMDDS* Total Score (Sum the 15 item responses)**		**Range 0 to 60**

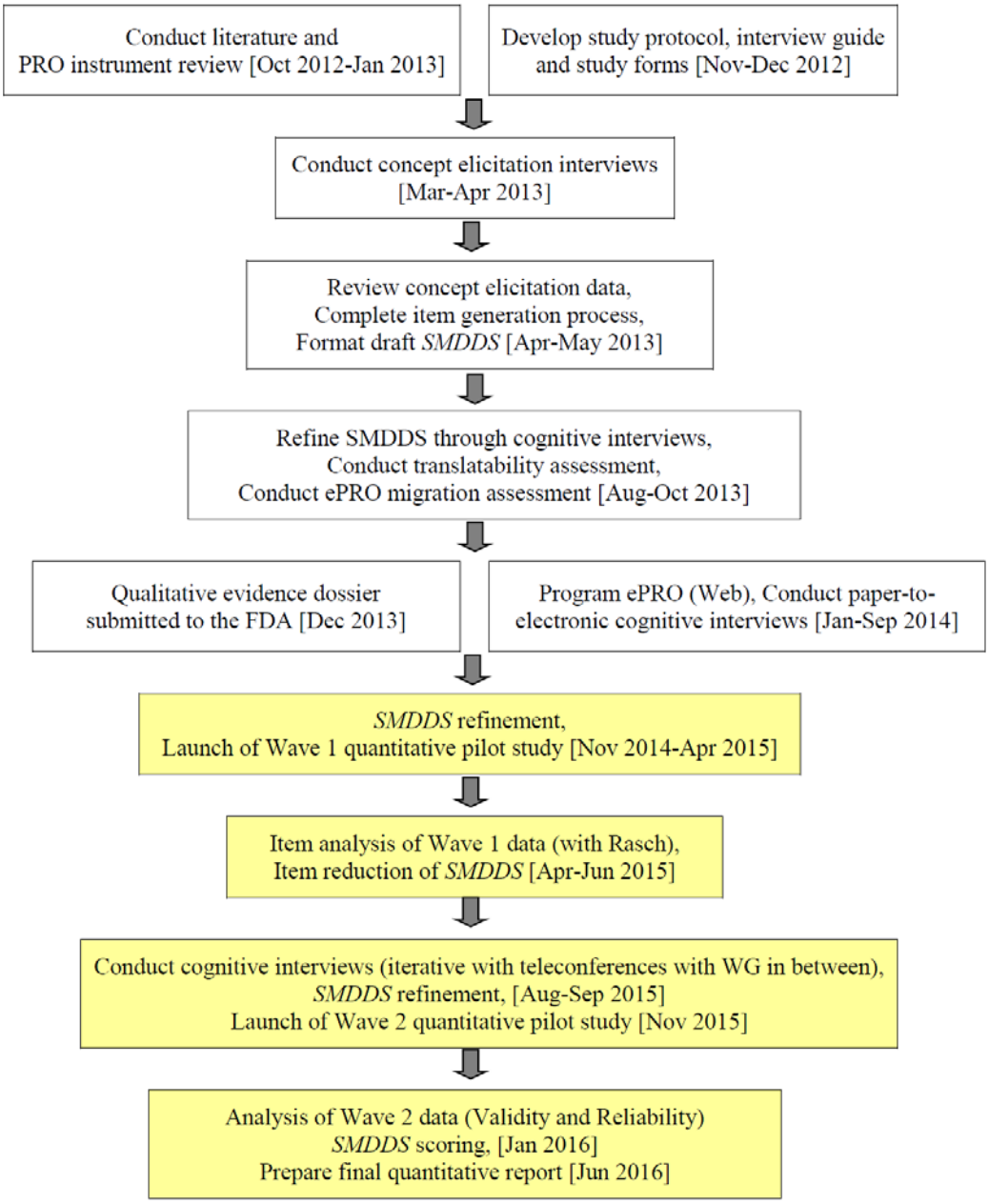
4 CONTENT VALIDITY

To date, the following information has been submitted (check all that apply):

☒Literature review and/or publications
☒Documentation of expert input
☒Qualitative study protocols and interview guides for focus group or patient interviews
☒Chronology of events for item generation, modification, and finalization (item tracking matrix)
☒Qualitative study summary with evidence to support item relevance, item stems and response options, and recall period
☐Qualitative support for meaningful change
☒Quantitative study summary with evidence to support item retention and scoring
☐Transcripts (if available)

The qualitative studies conducted to develop the content of SMDDS literature review, expert input, concept elicitation interviews, item generation, cognitive interviews, translatability assessment, and electronic implementation assessment. Figure 2, provides an overview of the sequence of activities during the qualitative and quantitative development of the *SMDDS*.

Figure 2. Chronology of *SMDDS* Development Activities



The review process revealed a final total of 19 articles which offered evidence for the patient perspective of depression. A wide range of physical and psychological complaints were identified in this review. However, patients with depression focus primarily on their emotions.

A single protocol was developed for the concept elicitation and cognitive interview process of this cross-sectional qualitative interview study. Patients from six different sites in the US with a current diagnosis of MDD and a *Hamilton Depression Rating Scale (HAM-D)* score >18 were recruited as interview participants. A total of 40 participants participated in the concept elicitation interviews. These participants were an average of 46.2 years old, (ranging 21 to 63 years), were 67.5% female, 45.0% white (non-Hispanic), and had an average HAM-D total score of 24.4 at enrollment.

Determined by number of participant expressions, the most predominant symptom-related concepts were “Sadness,” “Irritability,” “Anger,” “Anxiety,” “Tiredness,” and “Feeling overwhelmed.” Frequency and intensity were identified by participants as the most relevant attributes to assess their MDD symptoms.

The 59 symptom and 16 impact concepts identified from published literature, existing instruments, and the qualitative data from the concept elicitation interviews were used to select concepts for inclusion in the drafting of the new PRO measure. During subsequent teleconference discussions, the development team further reduced the initial list of concepts by removing those that were redundant or problematic. This effort resulted in reduction of the original 59 candidate concepts to a 36-item draft questionnaire.

A total of 15 participants were recruited to participate in three waves of cognitive interviews, during which the 36 draft items were completed and evaluated by participants with MDD. These participants were an average of 44.6 years old (ranging 18 to 59), were 60.0% female, 33.4% white (non-Hispanic), and had an average HAM-D total score of 24.4 at enrollment.

During the interview process, participants were asked to help identify the attribute that made the most sense to them for reporting their depression-related symptoms. Frequency was identified as the attribute most often selected as first choice. Intensity was selected second most often, and duration received the least support. In addition, due to clinical assessment norms, the chronic long-term nature of MDD, and the patients’ symptom experience, a seven-day retrospective recall period was selected at the onset of the item generation process.

As a result of the three waves of cognitive interviews, one item was removed from the draft measure and four others were substantially modified based on cognitive interview findings and recommendations from a formal translatability assessment. Other minor formatting and wording modifications were made based on the results of a formal electronic implementation assessment for electronic PRO data collection platform.

Following the modifications made during the three waves of cognitive interviews, translatability assessment, and expert input (as detailed in sections above), the pre-final draft of the *SMDDS* measure was further evaluated through a formal electronic implementation assessment.

Following the programming of the *SMDDS* onto a web-based format, an additional 16 cognitive interviews were conducted to evaluate the success of the migration of the draft *SMDDS* from paper to electronic format. In these cognitive interviews, the draft *SMDDS* measure was completed by participants on both paper and web formats and evaluated through interviewer probing. Feedback from participants' responses during the interviews showed no indication that the understanding of the instructions, items, or response options was affected by the mode of data collection.

The 35-item *SMDDS* measure that resulted from the above process was intended to be used to assess changes in the patient's MDD symptoms using a single summative score that represented the severity of MDD symptoms. The content validity of the *SMDDS* has been preliminarily supported by the qualitative studies conducted. Further quantitative support for the content validity of the *SMDDS* appears in the following section on quantitative development.

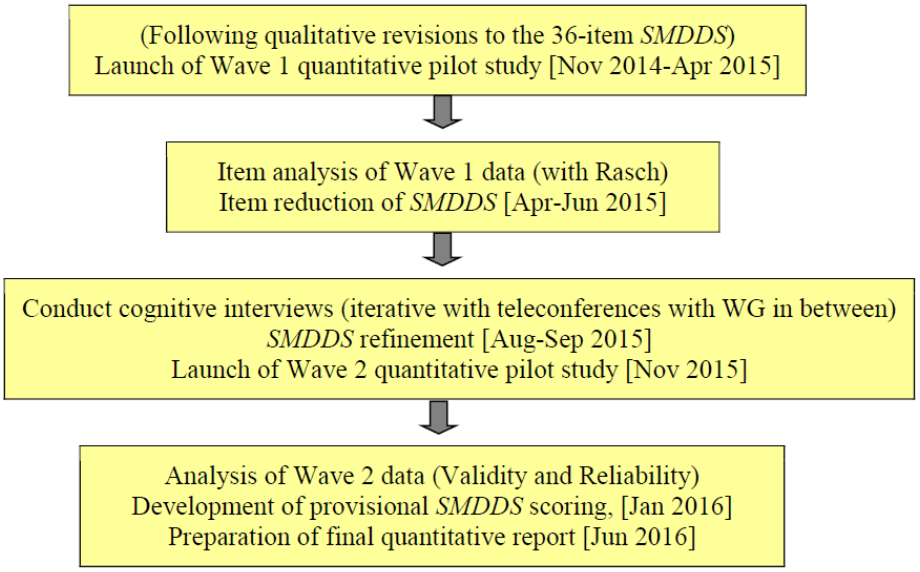
The QRT members representing the Review Division concurred with the conclusion of content validity of SMDDS at the filing meeting on June 9, 2017.

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

A quantitative pilot study was conducted to assess item performance and to provide an assessment of the initial measurement properties of the 36-item *SMDDS*. The quantitative pilot study was a cross-sectional study using a web-based data entry platform to collect data from respondents with a diagnosis of MDD recruited through clinics within the United States. The study included two waves of data collection and analysis. The appropriateness of the measurement properties is further support of the content validity of *SMDDS*. A mixed methods approach was utilized in order to provide maximum information to support the finalization of the measure.

The quantitative study was administered in two waves ("Wave 1" and "Wave 2") of data collection and analysis. Figure 3 shows the activities of the quantitative study.

Figure 3. Chronology of Study Activities for Quantitative Pilot Study



The main objectives for the Wave 1 (n=300) cross-sectional analyses were to:

1) Assess item performance using standard classical test theory item reduction methods (including evaluation of missing data, ceiling/floor effects, item-to-item correlations, item-to-total correlations, factor analysis and reliability [internal consistency] estimation),
2) Assess item performance using Rasch measurement model (including unidimensionality and item order), and
3) Guide the Depression Working Group (Depression WG) in refining the SMDDS and developing the next version of it for further testing in Wave 2.

The main objectives for the Wave 2 (n=200) analyses were to:

1) Assess item performance using standard classical test theory item reduction methods (including evaluation of missing data, ceiling/floor effects, item-to-item correlations, item-to-total correlations, factor analysis and reliability [internal consistency] estimation),
2) Assess item performance using Rasch measurement model (including unidimensionality and item order),
3) Examine the measurement model and scoring of the SMDDS,
4) Examine one-week test-retest reliability, and
5) Examine construct validity.

During Wave 1 data collection, a targeted group of 300 patients (recruited to complete two waves of data collection) with clinician-diagnosed MDD from 12 clinical sites participated in online data collection in which participants completed a Web-based questionnaire battery using a personal

computer. An additional 20 participants were recruited to participate in confirmatory cognitive interviews conducted between the two quantitative waves (Waves 1 and 2) in order to assess subject understanding of changes made to the SMDDS as a result of the Wave 1 analyses.

During Wave 1, each participant's data was collected on a single day (Figure 4). Each subject completed demographic items and the SMDDS, which asked about his or her symptom experience over the past 7 days. Along with the SMDDS, each subject completed the Quick Inventory of Depressive Symptomatology Self-Report (16-item) QIDS-SR16, the Emotional Distress-Anxiety Short Form 8a (PROMIS), the Patient Health Questionnaire (PHQ-9), and a single Patient Global Impression of Severity (PGIS) item.

Figure 4. Quantitative Data Collection Schema, Wave 1 (Target N=300)

Day	**1**
Clinician Screening Form <*completed prior to Day 1*>	
Study information letter <*sent prior to Day 1*>	
Electronic Consent†	**X**
Demographic information†	**X**
***SMDDS* (Wave 1)** †	**X**
QIDS-SR16†	**X**
PROMIS Emotional Distress-Anxiety Short Form 8a †	**X**
PHQ-9†	**X**
Patient Global Impression of Severity†	**X**

† Completed via web, participants will be required to supply a unique password.
Gray cells indicate no activity on the given day. Days 2-8 are included as a comparison to Wave 2.

<Reviewer note: The quantitative study was conducted in two waves where participants in Wave 2 were those who also completed the Wave 1 data collection. The recycling of the participants from Wave 1 was uncommon in instrument validation as a different sample was generally used for confirmation study. Recycling of participants has been mentioned as having the advantages that the same participants will be able to provide more detailed insight and follow-ups when they are completing the revised instrument. Recycling of participants also has the advantage of being more efficient and economical as collecting data especially when studying rare diseases. However, the submitter has not stated its rationale or discussed the strength and weakness of this approach. We recommend that for future submission if this approach will be used, the rationale(s) should be provided.>

Once these participants completed the questionnaire battery, SMDDS item analyses were completed and any necessary revisions were made to the SMDDS in preparation for the Wave 2 data collection. All changes to the measure as a result of the Wave 1 analyses were cognitively tested in a separate group of 20 participants prior to launching Wave 2 data collection,

Wave 2 had a target of 200 participants (from among the 300 participants from Wave 1) who agreed to again complete the questionnaire battery with the modified SMDDS (refined after Wave 1 data analysis and cognitive interviews). During Wave 2, the participants completed the study measures on Days 1 and 8. (Figure 5). On Day 1, the participated completed the same measures as in Wave 1. The participants also complete in a 1-week retest (on Day 8) which included only the SMDDS, PHQ-9, single PGIS item, and a single Patient Global Impression of Change (PGIC) item.

Figure 5. Quantitative Data Collection Schema, Wave 2 (Target N=200 from Wave 1)

		Day						
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8***
***SMDDS* (Final Wave 2)†**	**X**							**X**
QIDS-SR16†	**X**							
PROMIS Emotional Distress-Anxiety Short Form 8a †	**X**							
PHQ-9†	**X**							**X**
Patient Global Impression of Severity†	**X**							**X**
Patient Global Impression of Change†								**X**

* Retest capped at n=200.
† Completed via Web, participants were required to enter their unique password defined in Wave 1.
Gray cells indicate no activity on the given day.
Note: Demographic information for Wave 2 was collected during Wave 1.

Quantitative Study Results:

A total of 416 participants were invited to participate in the study. Of these, 320 completed Wave 1 and 315 were included in the analysis. Participants were on average 44 years of age (range 18 to 65), 71% were female, and 81% were white. Less than half (41%) were married or living as married, 33% were divorced, 93% had at least a high school education, and 57% were employed with 43% having a yearly household income of $35,000 or higher. Time since diagnosis of MDD was “more than 1 year ago” for 74% of participants. About a quarter of participants (26%) had a clinical diagnosis of GAD. See Table 8 for all demographic and clinical characteristics.

Following the Wave 1 analyses, an item reduction meeting was held including the expert panel and representatives of the FDA QRT in discussions regarding changes to the measure. The agreed item reduction to 17 items and varied item revisions were then put in front of participants in one last group of 20 cognitive interviews (three rounds consisting of 7,7, and 6 interviews) to assess participant

comprehension, relevance, and the overall comprehensiveness of the revised 17-item *SMDDS*. As a result of the first round of interviews, the *SMDDS* was reduced further from 17 to 16 items. At the close of the second round of 14 cognitive interviews, the 16 items were retained.

An exploratory factor analysis using all 36 items resulted in the following eight components: negative emotions/affect, self-harm, low energy, sense of self, physical symptoms, cognition, eating behavior, and sleep disturbance. Rasch analyses showed that 29 of the 36 items were appropriately ordered. Convergent evidence for construct validity was assessed by examining the magnitude of correlations between the *SMDDS* items and the QIDS-SR16 and PROMIS Emotional Distress–Anxiety–Short Form 8a. Known-groups evidence for construct validity was examined using the PGIS and PHQ-9 with most *SMDDS* items demonstrating that they were able to differentiate between levels of severity.

Analytic results from Wave 1 were presented at an item reduction meeting (held July 22, 2015 in Beltsville, Maryland) attended by the full development team (Depression Working Group, C-Path team, and HRA team), the three clinical experts, and representatives from the FDA QRT. Final decisions for refinement of the *SMDDS* included: deleting redundant items (13 items), deleting all physical (somatic) symptom items (4 items), deleting items due to conceptual vulnerability and potential bias (3 items), rewording of selected items, and reordering of selected items. The *SMDDS* was revised to a 17-item scale to be assessed during the confirmatory cognitive interviews prior to testing in Wave 2.

A total of 320 participants from Wave 1 were invited to participate in Wave 2 of the study. Of these, 207 participants were included in the *SMDDS* item-level analyses, 194 participants were included in the convergent construct validity analyses, and 147 participants were included in the test-retest analysis.

The two items of the eating behavior domain were combined into a single score by using the most severe response from either of the items as the domain score. An exploratory factor analysis was performed with all items of the *SMDDS* using the computed eating behavior score. A single component was derived with all standardized factor loadings exceeding 0.46. The Rasch item threshold map showed that all but one item was appropriately ordered.

Internal consistency reliability was examined with Cronbach's alpha. An alpha of 0.929 was calculated indicating a highly reliable scale. Test-retest reproducibility was examined using the intraclass correlation coefficient (ICC) and Pearson's product-moment correlation. These analyses were restricted to the subset of participants whose disease remained stable during the study period as defined by having no change in responses to the PGIS from Day 1 to Day 8. Of the 147 participants that completed the Day 8 (retest) data collection, 93 (63.3%) provided the same PGIS response on Day 1 and Day 8. The ICC was 0.848 with a 95% confidence interval of 0.779 to 0.897 and the Pearson's *r* was 0.850. These reproducibility values indicated that the *SMDDS* demonstrated good test-retest reliability in this sample.

Convergent evidence of construct validity was assessed by examining magnitude of correlations between the *SMDDS* items and total score and the scores on the *QIDS-SR16*, *PHQ-9*, and *PROMIS Emotional Distress-Anxiety–Short Form 8a*. *SMDDS* total score correlations were 0.76 with the *PROMIS Anxiety*, 0.79 with the *QIDS-SR16* and 0.83 with the *PHQ-9*. These associations provided evidence of concurrent construct validity.

Known-groups evidence of construct validity of the *SMDDS* total score was examined using the *PGIS* and *PHQ-9*. The *SMDDS* was able to differentiate significantly between varying levels of severity ($p<0.001$) as measured by both the PGIS and PHQ-9.
The results of the Wave 1 and Wave 2 quantitative study support the test-retest reliability and concurrent construct validity of the 16-item *SMDDS*. The ability of the SMDDS score to detect within-patient change and guidelines for interpretation of clinically meaningful change should be assessed and provided to the FDA as a DDT submission as longitudinal data become available.

6 INTERPRETATION OF SCORES

This submission does not include information regarding the interpretation of scores. The SMDDS has not been used in randomized controlled clinical trials where an approved or experimental treatment for MDD is being tested. An outline of psychometric analysis plan has been drafted and provided for any sponsor who is interested in including SMDDS as an exploratory endpoint in clinical trials. The outline includes recommendations on deriving interpretation of scores.

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

Currently, only an English version of SMDDS is available. However, a translatability assessment was conducted on the wave 2 draft items. Five languages were selected to represent larger families of similar language groups (German, Spanish, French, Russian and Chinese). The overall results of the translatability assessment showed that most of the items in the SMDDS can be rendered in a way that maintains conceptual equivalence. However, translation issues were found to be substantial for three items. Changes made to those items were made as a combined result of the translatability review and the final cognitive interview process.

8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Not applicable.

9 REVIEW USER MANUAL

A user manual for the *SMDDS* has been developed which outlines information relating to the qualitative and quantitative development and testing of the *SMDDS* Information on the administration procedures, methods and modes are outlined as well as patient and investigator training processes. Scoring and interpretation procedures are also included to provide guidance to users of the *SMDDS* and to ensure consistent implementation in clinical studies.

Appendix A. Symptoms of Major Depressive Disorder Scale (SMDDS)

Items in the *Symptoms of Major Depressive Disorder Scale (SMDDS)*

1. Over the past 7 days, how sad have you felt?
2. Over the past 7 days, how hopeless have you felt?
3. Over the past 7 days, how irritable have you felt?
4. Over the past 7 days, how overwhelmed have you felt?
5. Over the past 7 days, how worried have you felt?
6. Over the past 7 days, how tired have you felt?
7. Over the past 7 days, how difficult was it for you to stop thinking about your problems?
8. Over the past 7 days, how difficult was it for you to concentrate?
9. Over the past 7 days, how difficult was it for you to enjoy your daily life?
Response scale for items 1-9: Verbal rating scale with the following descriptors: Not at all/A little bit/Moderately/Quite a bit/Extremely
10. Over the past 7 days, how often did you have a problem with your sleep (falling asleep, staying asleep, or sleeping too much)?
11. Over the past 7 days, how often did you have a poor appetite?
12. Over the past 7 days, how often did you over eat?
13. Over the past 7 days, how much of the time did you have to push yourself to do things?
14. Over the past 7 days, how much of the time did you feel like doing nothing?
15. Over the past 7 days, how much of the time did you blame yourself when bad things happened?
16. Over the past 7 days, how much of the time did you feel that life is not worth living?
Response scale for items 10-16: Verbal rating scale with the following descriptors: Never/Rarely/Sometimes/Often/Always

Symptoms of Major Depressive Disorder Scale (SMDDS) Version 1.0