PATIENT-REPORTED OUTCOME (PRO) CONSORTIUM

Symptoms of Major Depressive Disorder Scale (SMDDS)

User Manual

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VERSION CONTROL

Version	Changes from previous and rationale for changes	Date Issued
1.0	Initial released version based on final developmental Version 8 of the User Manual submitted to FDA for qualification. Contains all requested corrections and additions.	September 25, 2017
1.0	Revision to the intraclass correlation coefficient (ICC) results based on reanalysis using ICC (1,1)	October 31, 2017
1.0	Revision made to Appendix C: Item Definition Table (Items 13-16) to provide alternatives for translation of “how much of the time” that will allow for translations using “how often” or “how frequently” with some caveats.	November 1, 2017

LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
CDER	Center for Drug Evaluation and Research
C-Path	Critical Path Institute
ClinRO	clinician-reported outcome
DSM-IV	Diagnostic and Statistical Manual, Fourth Edition Text Revision
ePRO	electronic patient-reported outcome
FDA	Food and Drug Administration
HAM-D	Hamilton Depression Rating Scale
HRA	Health Research Associates, Inc.
ICC	intraclass correlation coefficient
ICD-10	International Statistical Classification of Diseases, 10th Revision
IDS	Inventory of Depressive Symptomatology
IVR	interactive voice response
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
PGIS	Patient Global Impression of Severity
PHQ-9	Patient Health Questionnaire
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
QIDS-SR_{16}	Quick Inventory of Depressive Symptomatology (Self-Report) (16-item)
SMDDS	*Symptoms of Major Depressive Disorder Scale*

1.0 BACKGROUND

1.1 Overview of the PRO Consortium

The PRO Consortium was formed in 2008 by the Critical Path Institute (C-Path) in cooperation with the U.S. Food and Drug Administration's (FDA) Center for Drug Evaluation and Research and the pharmaceutical industry (Coons et al. 2011, Hayes et al. 2015). Its mission is to establish and maintain a collaborative framework with appropriate stakeholders for the qualification (U.S. Food and Drug Administration 2014) of patient-reported outcome (PRO) measures and other clinical outcome assessment (COA) tools that will be publicly available for use in clinical trials where COA-based endpoints are used to support product labeling claims.

The PRO Consortium's structure consists of a Coordinating Committee, subcommittees that address consortium-wide topics, and therapeutic area working groups, which focus on diseases or conditions with an unmet measurement need. The goal of these working groups is to generate and/or compile the necessary evidence to enable new or existing COA measures to be qualified by FDA for use in assessing primary or secondary clinical trial endpoints.

1.2 Overview of disease

Major depressive disorder (MDD) is a highly prevalent and reportedly under-treated condition in the United States (US) and worldwide (Kessler et al. 2005). It is a severe mental health disorder affecting 16.9% of the US adult population and nearly 340 million people worldwide (Stewart et al. 2003) and a leading cause of disability, responsible for roughly 200 million lost workdays in the US each year costing employers $17-44 billion (Stewart et al. 2003). Although depression may occur only once during a person's life, usually people have multiple episodes of depression (Mayo Clinic 2016). During these episodes, symptoms occur most of the day, nearly every day and may include: feelings of sadness, tearfulness, emptiness or hopelessness, angry outbursts, irritability or frustration, loss of interest or pleasure in most or all normal activities, sleep disturbances, tiredness and lack of energy, changes in appetite, anxiety, agitation or restlessness, slowed thinking, speaking or body movements, feelings of worthlessness or guilt, trouble thinking, concentrating, making decisions, remembering things, frequent or recurrent thoughts of death, suicide attempts, and unexplained physical problems (Mayo Clinic 2016). For many people with depression, symptoms usually are severe enough to cause noticeable problems in day-to-day activities, such as work, school, social activities or relationships with others (Mayo Clinic 2016).

Although there are a number of safe and effective medications available for the treatment of depression, numerous studies have shown that a high proportion of patients with depression do not achieve remission of symptoms, even after switching treatments (Rush et al. 2006). As novel therapies continue to be developed, the ability to reliably and validly measure symptom improvement from the patient's perspective becomes imperative.

1.3 Purpose of the *Symptoms of Major Depressive Disorder Scale* (*SMDDS)*

In response to this need for high quality clinical outcome assessment tools, the Patient-Reported Outcome (PRO) Consortium's Depression Working Group at the Critical Path Institute (C-Path) embarked on the development of a new PRO measure designed to assess symptom concepts that are important and relevant to the patient's experience of MDD. This measure, named the *Symptoms of Major Depressive Disorder Scale* (*SMDDS*), was developed with consideration of the recommendations and scientific best practices set forth in the FDA PRO Guidance (U.S. Food and Drug Administration 2009) and recent scientific literature aimed at ensuring content validity of PRO measures (Patrick et al. 2007, Rothman et al. 2009, Patrick et al. 2011a, and Patrick et al. 2011b).

Existing PRO measures used in persons with clinical depression cover content similar to that assessed via physician appraisals, since both types of measures follow depression diagnostic criteria listed in the Diagnostic and Statistical Manual, Fourth Edition Text Revision (DSM-IV-TR) (Frances 2000) and the International Statistical Classification of Diseases and Related Health Problems 10th Revision, Chapter V (mental and behavioral disorders) (ICD-10) (WHO 1992). Existing PRO measures, including self-administered versions of measures originally developed for clinicians such as the Inventory of Depressive Symptomatology (IDS) (Rush 1986) and the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg1979) and clinician-reported outcome (ClinRO) concepts appearing in labeling claims broadly include sadness or dysphoria, suicidal tendencies, changes in appetite, loss of interest in customary activities, changes in sleep patterns, reduction in certain cognitive characteristics such as ability to concentrate or to make decisions, reduced energy level or sex drive, or some combination of the above. However, it is unclear to what degree the items included in these ClinRO and PRO measures reflect the concepts that are most salient to patients with depression. Since depression is primarily a subjectively-experienced condition, the patient is most likely to be the best source of valid information about the symptoms of depression. The *SMDDS* was developed with extensive patient input to ensure that symptoms most relevant to patients were included in the measure. The *SMDDS* is intended for inclusion in clinical research alongside clinician-reported endpoints to support the assessment of depression treatment benefit.

1.4 Context of use

The *SMDDS* assesses patient-reported symptoms associated with MDD. The *SMDDS* is intended to be used as a co-primary or secondary endpoint measure in clinical trials of MDD to assess self-reported symptom severity. The target population includes adults (aged 18 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* has been developed in a patient sample including both males and females, varying levels of age, race, education, marital status, and severity.

The intent is to use results from the *SMDDS* to evaluate treatment benefit in clinical trials for MDD therapies and potentially communicate this treatment effect in the product label. Other clinical measures, such as a ClinRO assessment, may serve as the source of primary or co-primary endpoints alongside the *SMDDS* as a measure of symptom severity. In instances where the *SMDDS* is employed to derive a secondary endpoint, the clinical trial would need to succeed

on the clinician-reported endpoint before success could be attained on the secondary endpoint relating to patient-reported symptom severity.

The specific endpoint selection, positioning, and measurement approach would be determined by the study sponsor in concert with the appropriate regulatory review agencies.

1.5 Development and evaluation of the *SMDDS*

To date, the development of the *SMDDS* has included:

- Completion of systematic reviews of the depression literature and existing PRO and ClinRO measures
- The formation of an expert panel of clinical and methodological experts to provide advice during the development process
- Completion of qualitative concept elicitation interviews conducted to identify the depressive symptom-related concepts that are most important and relevant to the patients' experience
- A formal item-generation process in which evidence from the concept elicitation interviews, systematic literature reviews, and expert input was used to develop the content of the *SMDDS*
- Qualitative cognitive interviews with patients with depression to evaluate and refine the draft measure
- A translatability assessment, conducted concurrently with the early cognitive interview process
- An electronic implementation assessment (by the Electronic Patient-Reported Outcome [ePRO] Consortium's Instrument Migration Subcommittee) to assess the viability for implementation of the PRO measure on all available and appropriate electronic platforms
- Programming for web-based data collection and cognitive interviews to assess conceptual equivalence between the paper and electronic formats
- Quantitative testing to further evaluate the measurement properties of the *SMDDS* that involved development of a provisional scoring approach and an assessment of item and scale performance prior to submission to the FDA for qualification of the *SMDDS* for use as an exploratory endpoint measure in clinical trials.

At each stage of this process, input was obtained from the Depression Working Group, C-Path scientists, scientific advisors (independent clinical experts), and representatives of FDA's Center for Drug Evaluation and Research (CDER) via the formal Drug Development Tool Qualification Program (U.S. Food and Drug Administration 2014).

1.5.1 Evidence of content validity

Content validity is important for any PRO measure and necessary for those intended to support claims in approved medical product labeling (U.S. Food and Drug Administration 2009, Coons et al. 2011). The content validity of PRO measures is generally established through evidence confirming the measure provides a sufficiently comprehensive assessment of concepts that are

relevant and important to the target population and does so in a manner that is easily understood and consistently interpreted by respondents.

SMDDS content was informed via a review of existing published research studies conducted in MDD and findings from open-ended concept elicitation interviews with a diverse sample of 40 adults. The 40 participants in the concept elicitation interviews were 46.2 years old (range 21-63) on average, 67.5% female, 45.0% white (non-Hispanic), and had an average HAM-D total score of 24.4 at enrollment.

Saturation of concepts (the point at which no new concepts were elicited) was achieved after the fourth of five transcript groups (eight transcripts per group). Determined by number of participant expressions, the predominant symptom-related concepts were “Sadness,” “Irritability,” “Anger,” “Anxiety,” “Tiredness,” and “Feeling overwhelmed.” “Tiredness" and “Anger” were the symptoms most often offered spontaneously by study participants. The most bothersome symptoms (rated on a 0 to 10 scale with 0 being “not bothersome at all” and 10 being “extremely bothersome”) were “Self-harm,” “Thoughts of death,” “Hating self,” “Indecisiveness,” “Restlessness,” “No/low energy,” and “Desire to be alone.” The symptoms that participants rated as most severe (rated on 0 to 10 scale with 0 being “none” and 10 being “extremely severe”) were “Having no interest in activities,” “Self-harm,” “No/low energy,” “Low self-efficacy,” “Weight gain,” and “Mood swings.” Participants also described the most difficult symptoms to be “Sharp Pain,” “Throbbing Pain,” and “Spasms.” Frequency and intensity were identified by respondents as the most relevant attributes to assess their MDD symptoms.

During an item-generation meeting, the development team (composed of the Depression Working Group, outcomes research scientists from Health Research Associates [HRA] and C-Path, and external expert panelists) reviewed the 59 symptom and 16 impact concepts identified from published literature, existing measures, and the qualitative data from the concept elicitation interviews as the basis for selection of concepts for inclusion in the PRO measure. 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 redundant or problematic concepts, and a 36-item draft questionnaire was prepared for evaluation in cognitive interviews as well as an electronic implementation assessment and a translatability assessment.

A total of 15 adults participated in three waves of cognitive interviews, during which the draft measure items were completed and evaluated by participants with MDD. 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. Following feedback on the draft instrument by FDA’s Qualification Review Team (QRT), an item to assess self-blame was added, which left the total item count at 36. Other minor measure formatting and wording modifications were made based on the results of the electronic implementation assessment for electronic data collection platforms. Findings prompted the following changes to the measure: 1) to maintain consistency between modes, the paper format was modified from a grid-format to a single item format with the item followed by the response options; and 2) the recall stem for all 36 items was changed to “Over the past 7 days” (13 items had “Overall, during the past 7 days” and 4 items had “Overall, in the past 7 days”).

Following the quantitative pilot study, the *SMDDS* was revised from 36 items down to the final 16 items. After revisions were made, the *SMDDS* was included in 20 confirmatory cognitive interviews where participants found it to be relevant and comprehensive.

1.5.2 Measurement properties and psychometric evaluation

Initial measurement properties of the *SMDDS* were assessed in a quantitative pilot study consisting of two waves:

Wave 1 (n=320): the data were used to assess item performance of the 36-item version using classical analyses and Rasch Measurement Theory to guide refinement of the *SMDDS*. Upon review and discussion of analytic results, final decisions regarding revisions to the *SMDDS* included: dropping redundant items (13 items), dropping all physical (somatic) symptom items (4 items), dropping items due to conceptual vulnerability and potential bias (3 items), rewording of items (5 items), and reordering of items.

Wave 2 (n=207): these data were used to examine the 16-item *SMDDS* (emerging from Wave 1) and its one-week test-retest reliability, construct validity, and the measurement model and scoring. Participants were 45 years of age (range 19-66) on average ,73.5% female, and 82% white. Less than half were married/living as married (42%), 17% were divorced, 95% had at least a high school education, and 59% were employed with 43% having a household yearly income of $35,000 or higher. Time since diagnosis of MDD was “more than 1 year ago” for 72% of participants. A little over one-quarter of participants (28%) had a clinical diagnosis of generalized anxiety disorder.

Mean scores for the 16 items of the *SMDDS* ranged from 0.8 to 2.7 using a rating scale between 0 (“Not at all” or “Never”) to 4 (“Extremely” or “Always”). Respondents used the full range (0, 1, 2, 3, and 4) of responses for all items. One item (“how much of the time did you feel that life is not worth living?”) had a ceiling effect of 55%. Missing data were minimal for all items.

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. The suicidal ideation item (“how much of the time did you feel that life is not worth living?”) was disordered due to the frequency and high ceiling effect observed. The person-item distribution showed that the items covered the range of severities of the study sample.

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 Patient Global Impression of Severity (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 0.841 with a 95% confidence interval of 0.770 to 0.892 and the Pearson’s *r* was 0.850. These

reproducibility values indicated that the *SMDDS* demonstrated good test-retest reliability in this sample.

Convergent construct validity was assessed by examining the magnitude of correlations between the *SMDDS* items and total score and the scores on the QIDS-SR_{16}, PHQ-9, and PROMIS Emotional Distress-Anxiety–Short Form 8a. *SMDDS* total score correlations were 0.76 with the PROMIS Anxiety Short Form, 0.79 with the QIDS-$SR_{16,}$ and 0.83 with the PHQ-9. These associations were hypothesized and provide evidence of convergent construct validity with these measures of similar but not identical constructs of depressive symptoms. Known-groups evidence of construct validity of the *SMDDS* total score was examined using the PGIS and PHQ-9. The *SMDDS* was able to significantly differentiate between varying levels of severity ($p<0.001$) as measured by both the PGIS and PHQ-9.

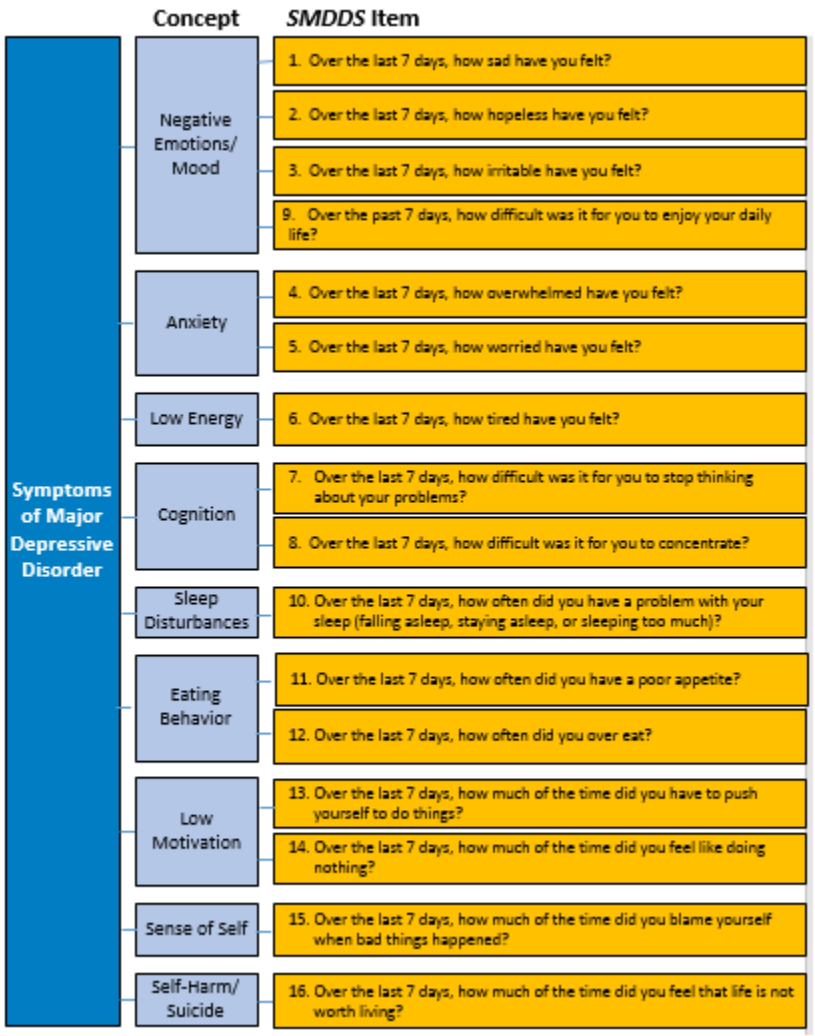
2.0 OVERVIEW OF THE *SMDDS*

2.1 Content

The *SMDDS* is a 16-item PRO measure (see Appendix A) designed for use in adults diagnosed with MDD to assess the self-reported severity of the defining symptoms of MDD. The *SMDDS* has a seven-day recall period. It contains nine domains and accompanying items that were identified as symptoms of MDD: negative emotions/mood (4 items), anxiety (2 items), low energy (1 item), cognition (2 items), sleep disturbances (1 item), self-harm/suicide (1 item), low motivation (2 items), sense of self (1 item), and eating behavior (2 items). The *SMDDS* takes approximately five minutes to complete.

2.1.1 Conceptual framework

Figure 1. Conceptual Framework for the *SMDDS*



2.1.2 Instructions and recall period

The *SMDDS* has been developed to present a low burden to respondents. For each of the 16 items, the respondent is asked to "please choose the one response that best describes your experience over the past 7 days." Each item begins with "Over the past 7 days" to remind the respondent to answer the question thinking about the seven days prior to providing the response.

2.1.3 Items and response options

During the item generation process, it was decided that each item's response set would be a five-level verbal rating scale. To better facilitate administration of one-item per screen on ePRO devices, each item carries a reference to the recall period within the item stem and displays the response options vertically under the item stem. See Appendix A for screenshots depicting the preferred layout of the items and responses. Based on findings during the concept elicitation interviews, the *SMDDS* includes items measuring the attributes of symptom intensity and frequency. Items 1 through 9 are framed to assess intensity and have response options of: "Not at all," "A little bit," "Moderately," "Quite a bit," and "Extremely." Items 10 through 16 are framed to assess frequency and have response options of: "Never," "Rarely," "Sometimes," "Often," and "Always." Subsequent qualitative and quantitative testing has confirmed the adequacy of *SMDDS* response options in terms of respondent understanding, reliability, and validity.

2.2 Translations

2.2.1 Translation methodology

To ensure the quality and availability of translations of the *SMDDS* across studies, users must follow the approved PRO Consortium Translation Process if the translations needed are not available. The approved process is based on the good practice principles and recommendations for translation, cultural adaptation, and linguistic validation outlined in the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) task force reports (Wild et al. 2005; Wild et al. 2009). To reach agreement on the process, firms within the translation industry were engaged in a consensus development initiative that resulted in the final process. The process includes the following steps: development of an Item Definition Table, multiple forward translations, reconciliation, back-translation, back-translation evaluation and revision of reconciled forward translation, international harmonization, proofreading, cognitive interviewing, post-cognitive interview analysis and review, and final review and documentation. The PRO Consortium process includes in-country affiliate review and feedback prior to linguistic cognitive interviews whenever possible and a back-up plan to fill this role if in-country affiliates are not available.

The PRO Consortium, through its partner, FACIT.org, manages (but does not necessarily conduct) all translations of the measure and maintains the *SMDDS* translation files for distribution.

A critical step in ensuring consistency across translations is the development of an Item Definition Table (Appendix C) which is distributed to all translation firms involved in translating the *SMDDS*. The Item Definition Table provides translators with the instructions, item stems, and item response options, as well as the intended meaning and interpretation of terms in the item/response options. Foreseeable translation issues and points of clarification are also outlined and possible alternative wording and synonyms are provided.

The purpose of following a formal translation process that includes linguistic validation is to obtain translated versions of the *SMDDS* that are both conceptually equivalent to the English source version and easily understood by the target population.

2.2.2 Available translations

A list of available translations is provided on the PRO Consortium's website [INSERT LINK-TBD], and is updated as new translations become available. Translation certificates ensuring good practices in translation and cultural adaptation for each translation are available upon request. Please note that licensing fees may apply for use of existing translations.

When appropriate and feasible, a "universal" approach to translation is preferred by the PRO Consortium. A "universal" translation is intended for use in multiple countries or regions, which helps to minimize the number of translations needed for a single language. As languages are tested in additional countries or other issues arise, modifications can be made to translations based on the results of this new information. The most current versions will be distributed to licensee following execution of the license agreement providing authorization to use the measure and any of the translations available for the measure. Translations are available for *SMDDS* only; translation of mode-specific instructions for electronic data collection is the responsibility of the sponsor and ePRO vendor. See Section 2.3 for information on obtaining available translations and requesting permission to translate the *SMDDS* into new languages, which must follow to the approved translation process addressed above.

2.3 Copyright and licensing

To protect the integrity of the measure, the *SMDDS*, including the User Manual, scoring instructions, and any portions, subsets or versions of the above, any modifications to the above, translations of the above, or derivative works based on the above (regardless of whether made by C-Path, Licensee, or others), together with all intellectual property rights contained in or related to any of the foregoing, are owned by C-Path (© 2015 Critical Path Institute. All rights reserved). The measure may not be used or altered in any way without prior written permission from C-Path. The *SMDDS* is available for use under a formal licensing agreement. Please contact (INSERT EMAIL ADDRESS-TBD) to request permission for use or for additional information.

3.0 ADMINISTRATION PROCEDURES

3.1 Modes of data collection

The *SMDDS* was designed with electronic self-administration in mind. The quantitative pilot study utilized web-based data collection where participants logged into a website remotely to complete the questionnaire battery. This method has both advantages and drawbacks over paper and pencil methods. Advantages over paper data collection include minimizing missing data, minimizing time and potential errors with manual data entry, providing confirmation of when data entry took place (preventing back or forward-filling of data) and implementing safeguards for avoiding missing data and missed completions (e.g., through use of reminders) (Coons et al. 2009). Given the numerous advantages of electronic over paper-based completion, the electronic modes of data collection are recommended over paper for the *SMDDS*. Any planned use of the *SMDDS* in modes of data collection other than the ones for which data are already available will need to be approved. Evidence from a small sample of the target population should be provided that demonstrates respondents are interpreting and responding to each item the same way regardless of the data collection mode.

3.1.1 Paper-and-pencil forms

A US English paper and pencil format of *SMDDS* was used in the cognitive interviewing phase of its development (Appendix B). This format was then migrated to a web-based data collection format, with a single-item per screen. A separate paper to electronic mode equivalence study was conducted to confirm cognitive equivalence between the paper and web-based formats, as described in more detail in Section 3.1.2. The paper format of the *SMDDS* is available under a licensing agreement with C-Path should study sponsors wish to implement the *SMDDS* in this format. The PRO Consortium recommends that a paper format only be considered for a study design which uses site-based assessment of the *SMDDS* at clinic visits; use of the paper format for field-based assessment (e.g., at home, work, school, or other non-clinic location) is not recommended.

3.1.2 Tablet PCs

The *SMDDS* has not yet been implemented on tablet platforms. Given that the use of tablet devices will involve presenting larger font and potentially alternate presentation styles, qualitatively assessing measurement comparability across devices via cognitive interviews is recommended.

3.1.3 Handheld devices

The *SMDDS* has not yet been implemented on a handheld device (e.g., smartphone). Given that the use of handheld devices will involve presenting smaller font and potentially alternate presentation styles, ensuring consistency across device types via cognitive interviews is recommended.

3.1.4 Web-based applications

The more widespread use of the Internet and web-based technologies by potential clinical trial participants suggests that web-based questionnaires may be a viable alternative to conventional paper-and-pencil questionnaires in research studies (Hohwu et al. 2013). The *SMDDS* was developed on paper and tested as a web-based questionnaire in the quantitative pilot study, for which it was programmed by ERT[1] (Appendix A). Prior to the quantitative pilot study, the *SMDDS* was migrated to a web-based format, and a stand-alone paper to electronic mode equivalence study was conducted to confirm cognitive equivalence between the paper and web formats. A total of 16 cognitive interviews were conducted with participants meeting the same inclusion criteria as the qualitative research to evaluate the success of the migration of the draft *SMDDS* from paper to electronic (P-to-E) format. Feedback from participants during the interviews demonstrated that the understanding of the instructions, items, or response options was not affected by the mode of data collection. Therefore, the web format of the *SMDDS* was shown to be cognitively equivalent to the format originally developed and evaluated on paper. Evidence for usability, reliability, and validity of the web-based format of the *SMDDS* have been documented through qualitative (cognitive interviews) and quantitative data analyses. To minimize errors due to variability in *SMDDS* display, participants used a larger-sized display, either a desktop screen or laptop screen, and this larger screen size would be the recommended approach to future web-based implementations.

3.1.5 Interactive voice response (IVR) systems

IVR methodology has been in widespread use for two decades for assessing patient-reported outcomes across a variety of disease states, interventions, and clinical trial designs (Corkrey & Parkinson 2002; Kobak et al. 2001; Piette 2000). It has major advantages in the automation and standardization of data collection in clinical trials (Mundt et al. 1998). IVR formats of questionnaires for self-administration have been used in psychiatry, including the Hamilton Depression Rating Scale (Mundt et al. 1998). An auditory-based format of the *SMDDS* has not yet been implemented on an IVR system. The *SMDDS* is amenable to administration via IVR; however, a change of this magnitude would likely require equivalence testing, including both qualitative and quantitative evidence of measurement comparability (Coons et al. 2009).

3.2 General principles for *SMDDS* completion

The general principles for completion of the *SMDDS* are as follows:

- The *SMDDS* should be administered electronically using a clear and simple interface on a chosen mode outlined in the protocol. The *SMDDS* is designed as a PRO measure and should be completed only by the intended respondent (i.e., a person with depression). Observers, including (but not limited to) clinicians and spouses/caregivers, should not complete the *SMDDS* on behalf of the intended respondent.

[1] ERT is a global company specializing in clinical services and customizable medical devices to biopharmaceutical and healthcare organizations. They assist in collecting, analyzing and distributing electronic patient-reported outcomes (ePRO) in multiple modalities across all phases of clinical research.

- The 16 *SMDDS* items are used to calculate the *SMDDS* Total Score (see Section 4.0).

The final item of the *SMDDS* covers the concept of self-harm/suicide: "Over the last 7 days, how much of the time did you feel that life is not worth living?" with responses of Never, Rarely, Sometimes, Often, and Always. It may be a necessary procedure to have a mechanism in place to contact the respondent's health care provider if his or her response is over a threshold (e.g., "Always"), or to have an algorithm built in to display a suicide prevention website at the conclusion of the *SMDDS* (if a respondent triggers a high response). With a population with MDD, inclusion of an assessment of suicidality (e.g., Columbia-Suicide Severity Rating Scale [Posner et al. 2011]) to enable the proper identification and management of suicidal respondents is recommended.

3.3 Training

In general, no specific training is required to complete the *SMDDS* since the instructions are self-explanatory. This may vary from case to case however depending on the age and ability of the respondent and the particular mode of data collection being used.

No difficulties have been reported among the various respondent groups who have assisted with the preliminary testing using web-based data collection in the studies conducted thus far. The consistently small amounts of missing data (less than 5%) attest to the acceptability of the *SMDDS* to respondents.

3.3.1 Investigator training

Standard considerations for training of investigators and clinic staff who provide the questionnaires to the participants should include the following training:

- Proper completion of the *SMDDS* (including set up and log on to ePRO devices, demonstration of how to register responses and move forward in the questionnaire, and where the respondent is to end and what the procedure is for completion).

- Great care should be taken to avoid messages (verbal or otherwise) that might influence participants to respond to items in a way they feel may be acceptable to the investigator rather than according to their own feeling. Avoid introducing any bias in any interaction that could influence how a participant may respond to an item.

- Investigator should not answer questions of interpretation or clarification for *SMDDS* items. If a respondent asks how he or she is meant to answer a particular item, the investigator/trainer should reply that the respondent should answer the question based on what he or she thinks the question is asking (and say nothing else, no further explanation, etc.) The subjective response of the respondent must be given according to what he or she perceives the item to be asking. Insertion of explanations on meaning and terms from the clinic staff is a source of bias that should be avoided.

Staff members are instructed on how to train respondents on the use of the device or other mode of data collection. With electronic PRO data collection systems, investigators are able to utilize a web-based data management system to monitor respondent compliance. Sites are instructed to contact respondents if they exhibit low compliance. The purpose of this contact is to ask if the respondent if having problems with the device or mode, and to further remind him or her to complete the measure according to the protocol assessment schedule.

A quick reference guide for study investigators should be made available and include details of preparing the device (if applicable) prior to deployment in a study. This guide includes details on how to confirm site specific settings, setting up a new respondent on the device, training the respondent on how to use the device and to complete the *SMDDS*, transmitting/sending data and device deactivation. The reference guide for web-based or IVR modes would be tailored to the mode in question.

3.3.2 Respondent training

Respondent training procedures include a review of the questionnaire, guidance on how and when to complete it, and an opportunity to practice completing it on the data collection mode prior to submitting any data.

Study personnel should ensure that the following general information about the *SMDDS* is provided to respondents:

- Respondents should be informed about the *SMDDS* assessment schedule per protocol.
- Respondents should be informed that when completing the *SMDDS*, they will be asked to reflect on the past 7 days from the day of completion.
- Respondents should be instructed to complete the *SMDDS* on their own without the help of others and should answer the questions based on their own experience of depression.
- Respondents should be instructed to be honest and as accurate as possible in their responses.
- Respondents should complete the *SMDDS* in a quiet place and within a single time period, if possible.
- Finally, please assure respondents that their identity will be kept confidential and their answers will only be used for scientific purposes.

If applicable, study personnel should ensure that the following information about completing the *SMDDS* on an electronic device is provided to respondents:

- The respondent should be reminded that the device should be charged at all times.
- The respondent should be taught how to use the device, including:
    - Turning the device on/off
    - Navigating the device

  - Setting a PIN code to access the device
  - Setting alarms to remind the respondent to enter data at the correct time

- The *SMDDS* will not be available on the device outside of the stated completion time periods. If a respondent is unable to complete the *SMDDS* during these windows, he or she cannot make it up later.
- The respondent should be shown how to access the measure in a practice setting and then should answer all 16 items in order to ensure comprehension of the *SMDDS* and the characteristics of the specific ePRO device.
- If the respondent is required to actively send/transmit data, he or she should be informed of the process to do this and a practice run should be conducted.
- The respondent should be provided with a 24-hour helpdesk number in case of issues with data transmission or use of the device.
- The respondent should be provided with a user guide to take home with instructions on how to use the device.
- The site should monitor data upload in accordance with the study protocol and ensure missing data are within acceptable protocol defined limits.

The electronic device will include a pre-installed training module, which all respondents are instructed to work through. Through this training, any issues with the device functionality should be identified. This training module allows respondents to complete the practice version of the measure until they are sufficiently familiar with the process.

Respondents are instructed to respond to all of the items in one sitting, and to save their responses at the end. Respondents should be encouraged to respond to all items in the *SMDDS*, but sponsors may choose to allow items to be actively skipped, so site staff should be aware of this potential option. If implemented, the following standard skip language is recommended via the inclusion of electronic pop-up edit checks.

- In cases where there is a pop-up heading, the heading and message text would be as follows:

  “No response selected”

  “Do you want to continue without providing a response?”

- In cases where no pop-up heading is used, only the following message text would be shown:

  “No response selected. Do you want to continue without providing a response?”

An audible alarm (on tablets or handheld devices) that sounds at the appropriate time can be used to remind the respondent to complete the *SMDDS* on the assessment date if it has not been completed. For web-based implementations, the reminder may take the form of an email or SMS text message on the due date.

Respondents should be provided with a quick reference guide, which provides instructions on: how to use the ePRO device, how to respond to the items, the time windows for completion, the

alarm that will remind them to provide responses (where applicable), how to transmit their data (where appropriate), and how to report a problem with the device.

3.4 Instructions for administration by study/clinic staff

Administration of the *SMDDS* should be in a quiet place away from the influence of others. The investigator and clinic staff should consider the reading ability required for self-completion before leaving a respondent alone to complete the questionnaire. This can be done by asking if the respondent needs assistance. Persons with low literacy or compromised eyesight should always be provided the assistance of a clinic staff person to read the items for them and record the responses.

Before the respondent is left to complete the questionnaire on his or her own, the investigator and/or clinic staff person should be sure that the respondent is properly logged on, understands how to enter responses and move to the next item on his or her own. Respondents also need to know what they are to do next once they have completed the *SMDDS*.

3.4.1 Interviewer administration

The *SMDDS* was designed to be self-administered by persons with MDD. The quality of the data is predicated on the respondent's subjective response, with no interference or influence by others. However, self-administration is not always possible because the respondent may be too ill, unable to read the screen for some reason (e.g., vision impairment), or uncomfortable using computers or electronic data capture devices. In these extenuating cases, data collection may require the assistance of a staff person or another person with appropriate training to administer the *SMDDS* via interview.

- If a respondent is able to read the items on his or her own but not enter his or her response, a staff person can enter the response for the respondent, but cannot question the response or attempt to influence the response in any way.
- If a respondent cannot read the items or instructions on the screen, a staff person may help him or her by reading exactly what the item on the screen says and what the response options are, but may not alter the language in any way, give explanation or further elaborate any of the text in the *SMDDS* items.
- If a respondent does not read the language provided (e.g., English in the US) sufficiently well to be able to self-administer the *SMDDS*, it is NOT ACCEPTABLE for any other person (family member or clinic staff) to interpret between varying languages. In this case, the *SMDDS* cannot be completed, as the interpretation itself will be biased and outside of the accepted good practices for translation of PRO measures. A formal translation/cross-cultural adaptation process is required to develop any other language version of this standardized instrument, as described in Section 2.2.1.
- If the protocol allows interviewer administration, the mode of administration will need to be indicated in the database for each assessment so that the data from each mode of administration can be identified and analyzed separately.

4.0 SCORING

4.1 Summary of provisional scoring instructions

The *SMDDS* consists of 16 items which were not designed to be scored individually. 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. If one of these two items is missing, the included response is used as the "Eating Behavior" value. The *SMDDS* score is then computed by taking the sum of the 15 items (items 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, "Eating Behavior" value, 13, 14, 15, 16) as shown in Table 1.

Table 1. Scoring the *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 daily 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**

4.2 Interpretation of scores

The *SMDDS* total score ranges between 0 and 60. Higher scores indicate more severe depressive symptomatology, but at this point in time there are no cut-points identified for levels of MDD severity (e.g., mild, moderate, severe). Currently, the measurement properties of the *SMDDS* have only been explored using data from a non-interventional, observational study. Given that little to no change occurred in this sample as no intervention occurred, no analyses associated with the interpretation of change on the *SMDDS* have been conducted thus far. Proposed methods for future analyses (e.g., anchor and distribution-based methods and cumulative distribution functions) should be considered when aiming to assess the meaningfulness of within-patient change on the *SMDDS* total score within a clinical trial. In terms of anchor-based methods, multiple anchors at multiple time-points that include at least a "current" state patient global impression of severity (PGIS) item and a patient global impression of change (PGIC) item (i.e., comparison of current state to the state of an earlier time-point) are recommended.

4.3 Handling of missing data

If it is possible, incorporate ways to avoid missingness before the actual data collection takes place. In addition, it is advised to plan to use data analysis methods that are robust to missingness. An analysis is robust when confidence that mild to moderate violations of the technique's key assumptions will produce little or no bias or distortion in the conclusions drawn about the population.

There are two types of missing data for PRO measures: missing data at the 'form' level and missing data at the 'item' level.

4.3.1 Form-level missing data

If a participant does not complete the *SMDDS*, such as due to attrition in longitudinal studies or due to forgetting to complete an individual assessment, his or her *SMDDS* score should not be computed for that time point.

4.3.2 Item-level missing data

If data are being collected electronically, sponsors may decide to allow respondents to skip individual items within the *SMDDS*. If patients are allowed to skip items, missing data at the item level may be present. A greater than 50% rule will be employed for missing data at the item level. This is supported both by the data and the literature (Fairclough & Cella 1996). 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* 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).

5.0 *SMDDS*-RELATED PUBLICATIONS

McCarrier KP, Deal LS, Abraham L, Blum SI, Bush EN, Martin M, Thase ME, Coons SJ on behalf of the Patient-Reported Outcome Consortium's Depression Working Group. 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.

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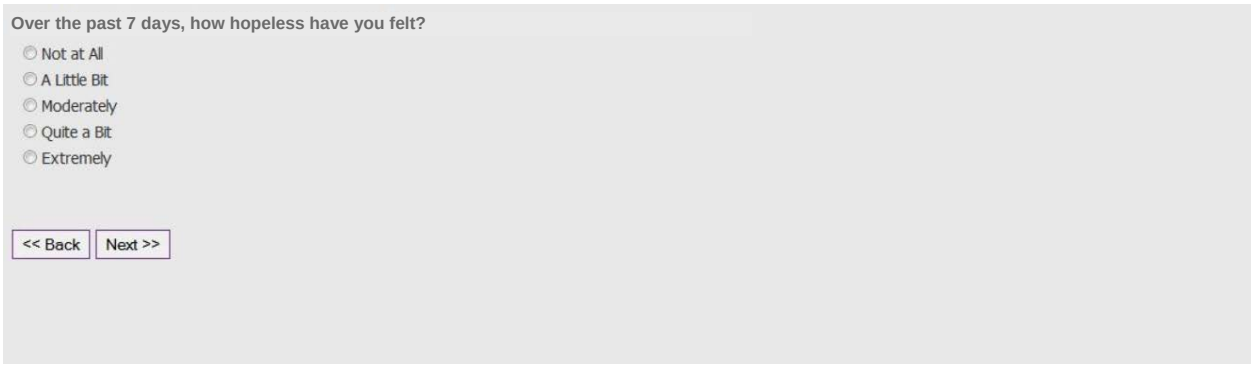
APPENDIX A: SMDDS (v1.0) Web Format Screenshots

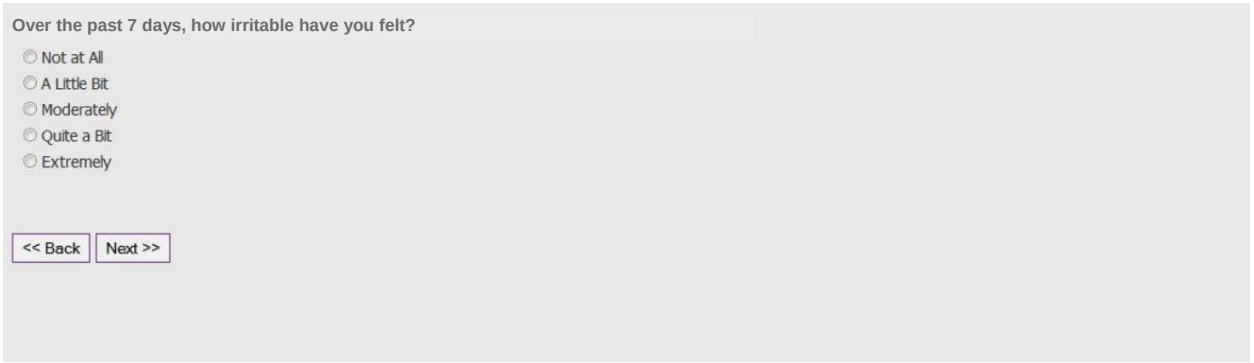
Symptoms of Major Depressive Disorder Scale (SMDDS) Version 1.0

SMDDS Item 1

SMDDS Item 2

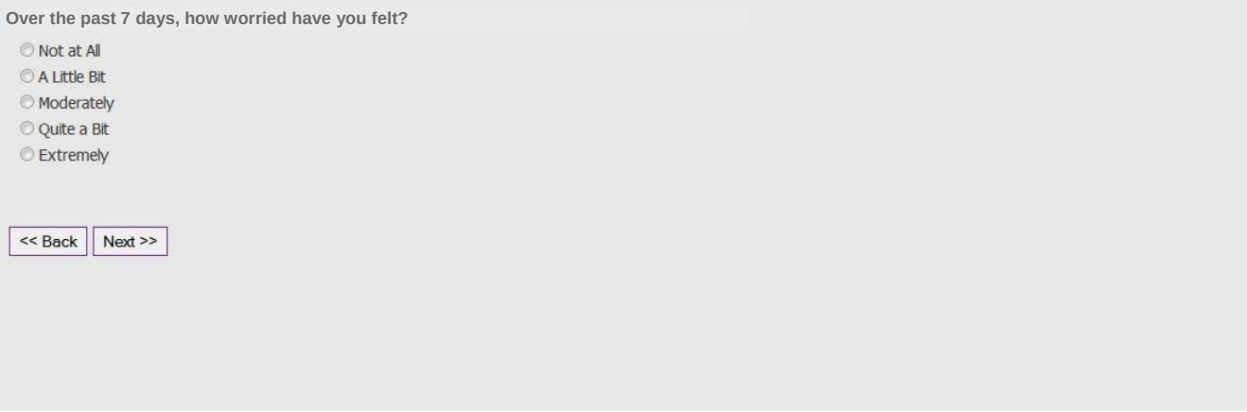


SMDDS Item 3



SMDDS Item 4

SMDDS Item 5



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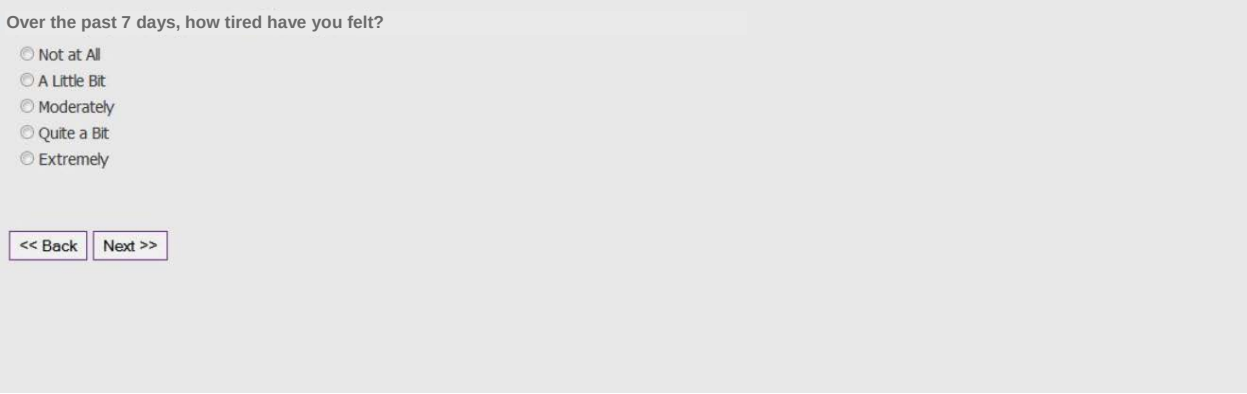

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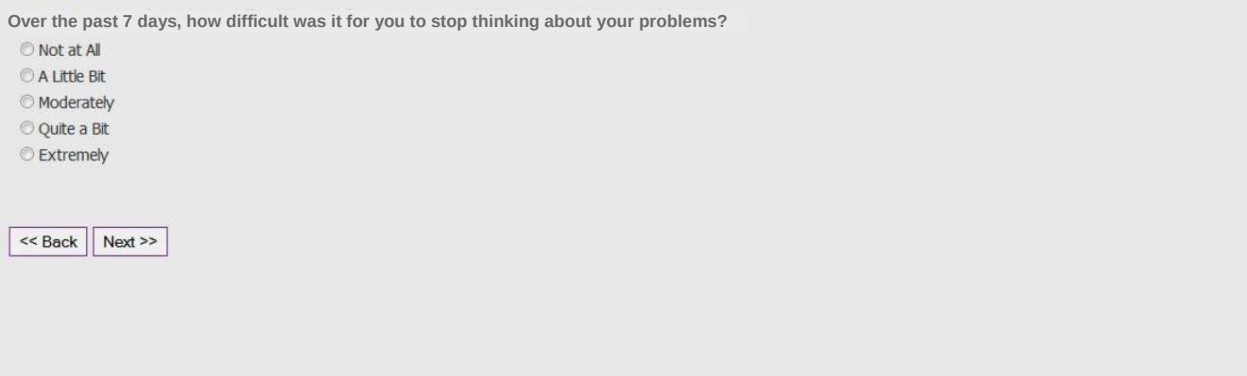
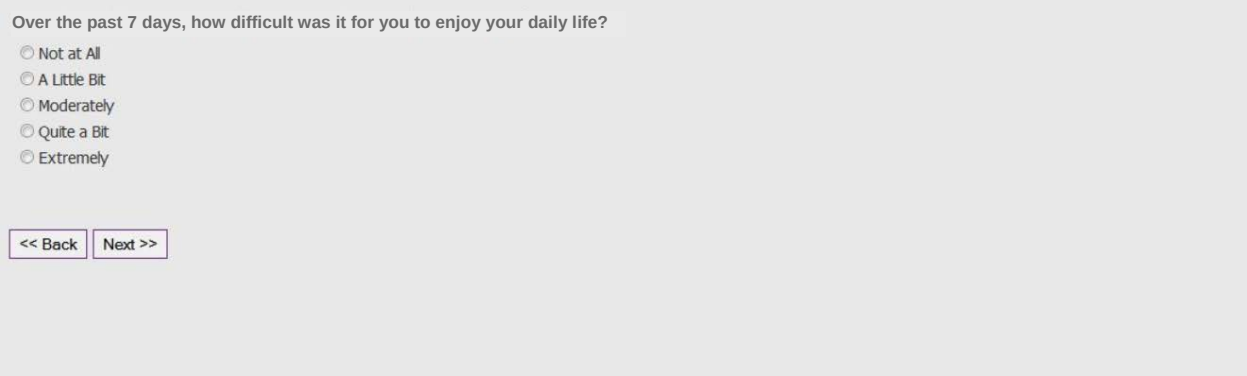
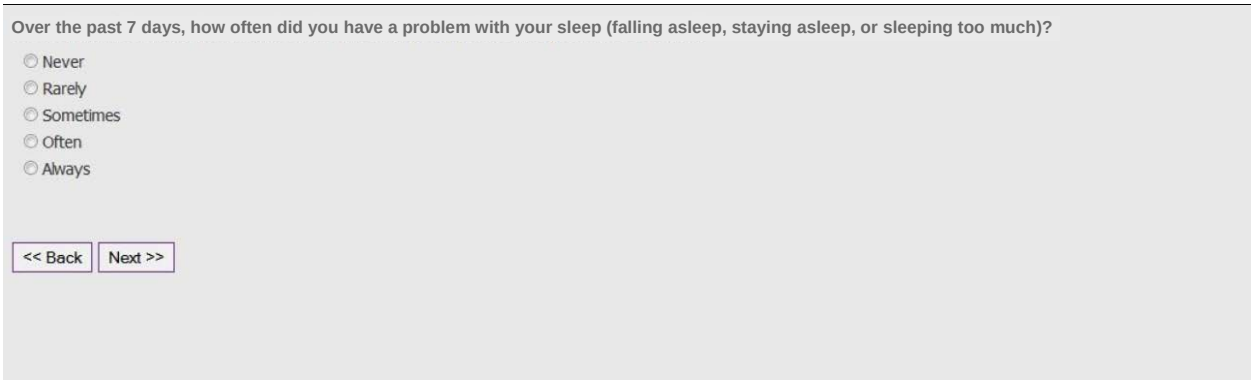


SMDDS Item 8

SMDDS Item 9

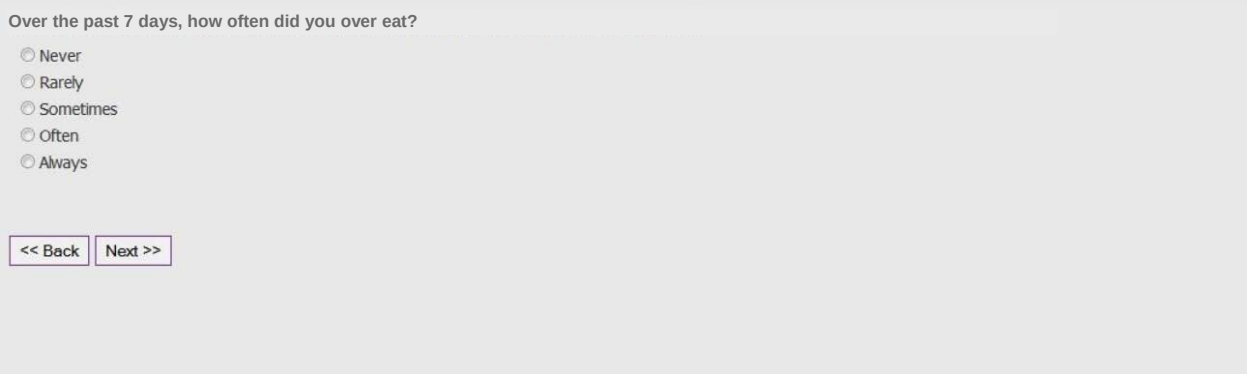


SMDDS Item 10

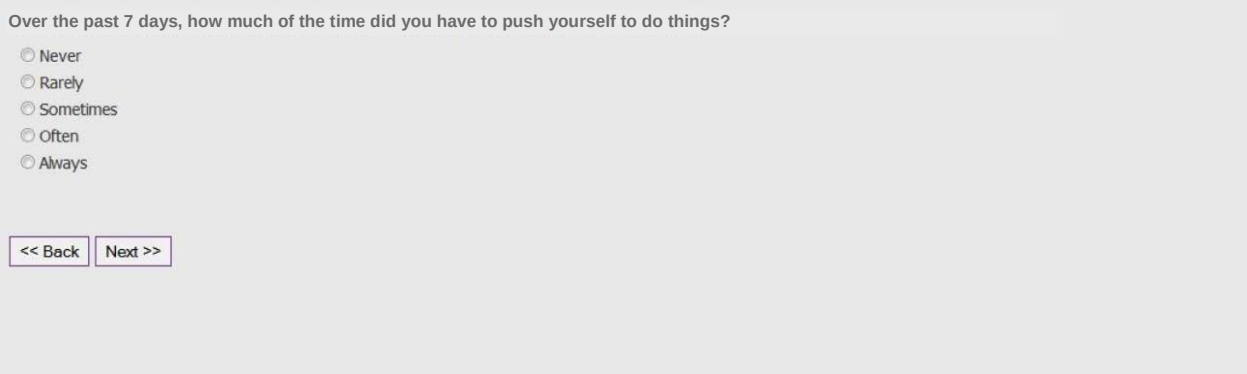


SMDDS Item 11

SMDDS Item 12



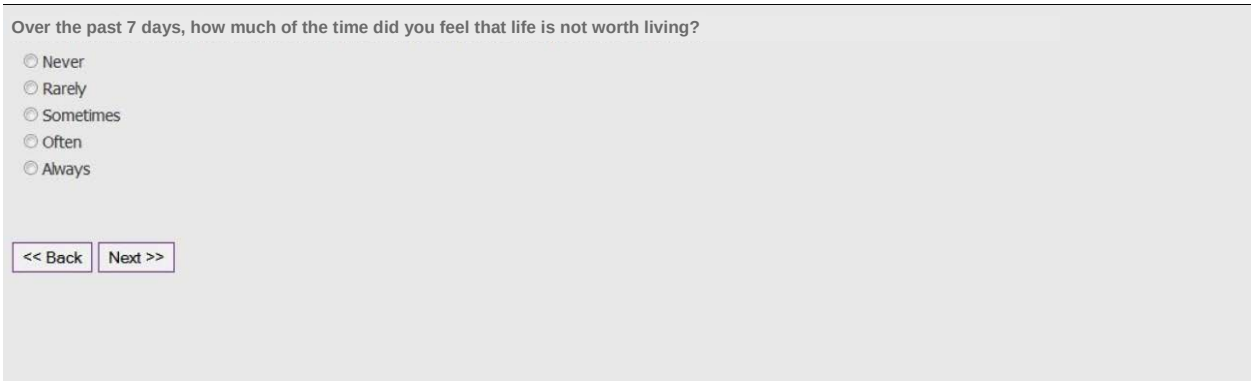
SMDDS Item 13



SMDDS Item 14

SMDDS Item 15

SMDDS Item 16



APPENDIX B: *SMDDS* (V1.0) PAPER FORMAT

Symptoms of Major Depressive Disorder Scale (SMDDS) v1.0

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 sad have you felt?

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

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

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

3. Over the past 7 days, how irritable have you felt?

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

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

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

Symptoms of Major Depressive Disorder Scale (SMDDS) **Version 1.0**

Symptoms of Major Depressive Disorder Scale (SMDDS) v1.0

5. Over the past 7 days, how worried have you felt?

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

6. Over the past 7 days, how tired have you felt?

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

7. Over the past 7 days, how difficult was it for you to stop thinking about your problems?

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

8. Over the past 7 days, how difficult was it for you to concentrate?

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

Symptoms of Major Depressive Disorder Scale (SMDDS) v1.0

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

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

11. Over the past 7 days, how often did you have a poor appetite?

- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Always

12. Over the past 7 days, how often did you over eat?

- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Always

Symptoms of Major Depressive Disorder Scale (SMDDS) v1.0

13. Over the past 7 days, how much of the time did you have to push yourself to do things?

- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Always

14. Over the past 7 days, how much of the time did you feel like doing nothing?

- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Always

15. Over the past 7 days, how much of the time did you blame yourself when bad things happened?

- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Always

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

- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Always

APPENDIX C: *SMDDS* ITEM DEFINITION TABLE

Item Definition Table for the *Symptoms of Major Depressive Disorder Scale* (*SMDDS*)

Note to the translator: This Item Definition Table is designed to provide you with detailed information about the intended concept of each item in the document. The second column contains an explanation of the key terms and ideas, and the third column contains *possible* rewordings and alternatives for some key terms in English. Please note that you are in no way limited to those possibilities, they are simply provided to give you as much information about the concept being asked about as is possible in English. This way, you can decide on the most appropriate wording in your language to fit that concept. Questions and comments regarding this Item Definition Table are welcome at any time.

*****IMPORTANT INFORMATION ABOUT COLUMN THREE: Please keep in mind that these alternatives are simply conceptually equivalent ways to state these ideas *in English.* Our intent is that you should use this column to get a deeper understanding of the concept of that item, in order to develop the most appropriate way of phrasing the item in the target language-- We do not want to imply that literal translations of these wordings/alternatives are requested; each language must be handled independently. Please always remember that for our purposes, the ideal translation is the one that matches the *concept* of the original English yet reads naturally and fluently in the target language.**

Original English Item	Key Concepts and Explanations	Possible Wordings and Synonyms
Title ***Symptoms of Major Depressive Disorder Scale* (*SMDDS*)**	This is the title of the questionnaire. The target language should utilize the most common medical terms for this condition.	The acronym of the title of the questionnaire should be retained in English as it is and should not be translated. This will facilitate the identification of the measure by search engines when translated versions are published. If necessary, the phrase "by its English acronym" can be added with the acronym in parentheses.
Instruction Sentence 1 For each of the following questions, please choose the one response that best describes your experience over the past 7 days.	This sentence specifies that the respondent should consider only the immediate past 7 days when reporting the major depressive disorder (MDD) symptoms. If the respondent is completing the questionnaire on a Wednesday, he/she should consider the time starting from the previous Thursday up through the current day (one week back).	**over the past 7 days** could also be "during the previous 7 days," "during the last 7 days," "in the last 7 days," etc. **the last 7 days** should *not* be translated as "the past week"

Original English Item	**Key Concepts and Explanations**	**Possible Wordings and Synonyms**
Item 1 Over the past 7 days, how sad have you felt?	This asks the respondent to evaluate the intensity of this symptom during the last 7 days. Feeling **sad** refers to being sorrowful.	**how sad have you felt** could be "to what extent did you feel sad" feeling "low" or "down" might also be acceptable if it is commonly used to convey the concept of "sad" **sad** should *not* be translated as "depressed" since there is a qualitative difference. Feeling sad may be a component of feeling depressed, but they are not synonyms. In some cultures, the word "depressed" carries a very strong negative connotation and is not used as casually as in the US, and for that reason it is not appropriate for this item.
Response Scale for Items 1-9 Not at All A Little Bit Moderately Quite a Bit Extremely	**Not at all** indicates the respondent did not experience the symptom at all. **A little bit** indicates the respondent experienced the symptom slightly. **Moderately** indicates the respondent experienced the symptom with medium intensity. **Quite a bit** indicates the respondent experienced the symptom to a considerable extent. (Note: A word or phrase should be used that reflects the midpoint between moderately and extremely.) **Extremely** indicates the respondent experienced the symptom tremendously.	When translating, each of the response options should increase in equal degrees, such that each option is evenly spaced as intensity increases.
Item 2 Over the past 7 days, how hopeless have you felt?	This asks the respondent to evaluate the intensity of this symptom during the last 7 days. Feeling **hopeless** means the respondent is experiencing feelings of despair and has a bleak outlook. Being without hope, or being "hopeless" implies feeling like nothing will get better and that there is nothing he/she can do to improve his/her situation.	**how hopeless have you felt** could be "to what extent did you feel hopeless" (or without hope) **hopeless** could also be "disheartened" or "despondent"

Original English Item	**Key Concepts and Explanations**	**Possible Wordings and Synonyms**
Item 3 Over the past 7 days, how irritable have you felt?	This asks the respondent to evaluate the intensity of this symptom during the last 7 days. Feeling **irritable** refers to feeling easily annoyed or quick to anger.	**how irritable have you felt** could be "to what extent did you feel irritable"
Item 4 Over the past 7 days, how overwhelmed have you felt?	This asks the respondent to evaluate the intensity of this symptom during the last 7 days. Feeling **overwhelmed** refers to a state of stress. A person who is overwhelmed may feel excessively burdened and have difficulty coping.	**how overwhelmed have you felt** could be "to what extent did you feel overwhelmed"
Item 5 Over the past 7 days, how worried have you felt?	This asks the respondent to evaluate the intensity of this symptom during the last 7 days. Feeling **worried** refers to feeling concerned, troubled about something that might happen	**how worried have you felt** could be "to what extent did you feel **worried**"
Item 6 Over the past 7 days, how tired have you felt?	This asks the respondent to evaluate the intensity of this symptom during the last 7 days. Feeling **tired** refers to feeling sluggish or physically drained. This implies a decreased energy level.	**how tired have you felt** could be "to what extent did you feel **tired**" **tired** should *not* be translated as "sleep" or "fatigued" or "weak"
Item 7 Over the past 7 days, how difficult was it for you to stop thinking about your problems?	This refers to how much difficulty the respondent experienced with not thinking about his/her problems during the last 7 days. This item refers to an inability to control negative thoughts.	**how difficult was it for you** could be "how much trouble" or "how much difficulty" did you have *During the last 7 days, how much difficulty did you have avoiding thinking about your problems?*
Item 8 Over the past 7 days, how difficult was it for you to concentrate?	This refers to how much difficulty the respondent experienced with his/her ability to concentrate during the last 7 days. To **concentrate** refers to focusing one's attention on something. This item refers to impaired concentration.	**how difficult** could be "how much trouble" or "how much difficulty" **to concentrate** could be "to focus" *During the last 7 days, how much difficulty did you have concentrating?*

Original English Item	**Key Concepts and Explanations**	**Possible Wordings and Synonyms**
Item 9 Over the past 7 days, how difficult was it for you to enjoy your daily life?	This refers to how much difficulty the respondent experienced with his/her ability to enjoy daily life during the last 7 days. This item refers to a decreased ability to experience pleasure or amusement in things that would otherwise be enjoyable. Clinically, this condition is often referred to as anhedonia.	**how difficult** could be "how much trouble" or "how much difficulty" **daily life** could be "everyday life" *During the last 7 days, how much difficulty did you have being able to enjoy your daily life?*
Item 10 Over the past 7 days, how often did you have a problem with your sleep (falling asleep, staying asleep, or sleeping too much)?	This refers to how frequently the respondent experienced sleep difficulties during the last 7 days. Having a **problem with your sleep** refers to experiencing changes in sleeping habits such as difficulty falling asleep, difficulty remaining asleep or sleeping in excess. Difficulty **staying asleep** may refer to waking up several times during a sleep cycle or waking up earlier than you wanted to and not being able to return to sleep.	**how often** could be "how frequently" **a problem with your sleep** could be "sleep problems" or "sleep difficulties" When translating, there should be a clear difference between the phrases "falling asleep" and "staying asleep." *During the last 7 days, how frequently did you have sleep problems (difficulty falling asleep or staying asleep, or sleeping in excess)?*
Response Scale for Items 10-16 Never Rarely Sometimes Often Always	**Never** indicates the respondent did not experience this symptom at all (none of the time or 0% of the time). **Rarely** indicates hardly ever, a little of the time, a little bit, infrequently (about 25% of the time). **Sometimes** indicates with some frequency but not with great regularity. This response option is the middle of the response scale (about 50% of the time). **Often** indicates frequently and with some regularity, most of the time (about 75% of the time). **Always** indicates the respondent has experienced the feeling or encountered the situation all the time (100% of the time).	When translating, each of the response options should increase in equal degrees, such that each option is evenly spaced as frequency increases.

Original English Item	**Key Concepts and Explanations**	**Possible Wordings and Synonyms**
Item 11 Over the past 7 days, how often did you have a poor appetite?	This refers to how frequently the respondent had little, or small, or diminished appetite during the last 7 days. Having **poor appetite** refers to experiencing a reduced desire to eat.	**how often** could be "how frequently" or "with what frequency"
Item 12 Over the past 7 days, how often did you over eat?	This refers to how frequently the respondent over ate during the last 7 days. To **over eat** refers to eating in excess or gorging on food.	**how often** could be "how frequently" or "with what frequency" **over eat** could be "eat in excess" or "eat too much"
Item 13 Over the past 7 days, how much of the time did you have to push yourself to do things?	This refers to how much of the time during the past 7 days the respondent struggled with motivation to do things. This item implies that the respondent feels little motivation and has difficulty pushing himself/herself to carry out an activity/task. **To push yourself** refers to exerting yourself or forcing yourself to make an effort when you have little motivation to start an activity - or- fighting through an urge to quit an activity (such as a work task, household chore, or social engagement) prematurely before its natural point of completion.	**to push yourself** could be "to force yourself" For languages where the phrase **push yourself to do things** is considered an incomplete statement, **to do things** could be "to carry out activities" or "to do activities." *During the last 7 days, how much of the time did you have to make an effort to do things?* **how much of the time:** We do not want to ask this item (or any of the following items) in a way that makes a respondent think of how many episodes in a day. It is a chronic condition, so we want to find out about how much of the day was spent in this state. If "how much of the time" cannot be used in a specific language, then a rendering must be found that avoids structuring the item to be asking about frequency of episodes, as that will be an incorrect rendering. Alternatives "how frequently" or "how often" are not preferred and should only be used as a last resort if it is impossible to render the item along the lines of "how much of the time" without using unnatural language. While the literal translation may say "how frequently," the patient interpretation of these alternatives needs to reflect how much of the day and not the number of episodes.

Original English Item	Key Concepts and Explanations	Possible Wordings and Synonyms
Item 14 Over the past 7 days, how much of the time did you feel like doing nothing?	This refers to how much of the time during the last 7 days the respondent felt like doing nothing. This item refers to a loss of interest in activities.	**how much of the time:** Alternatives "how frequently" or "how often" are not preferred and should only be used as a last resort if it is impossible to render the item along the lines of "how much of the time" without using unnatural language. While the literal translation may say "how frequently," the patient interpretation of these alternatives needs to reflect how much of the day and not the number of episodes. See note above on restriction.
Item 15 Over the past 7 days, how much of the time did you blame yourself when bad things happened?	This refers to how much of the time during the last 7 days the respondent blamed himself or herself when bad things happened. This item refers to feelings of guilt.	**how much of the time:** Alternatives "how frequently" or "how often" are not preferred and should only be used as a last resort if it is impossible to render the item along the lines of "how much of the time" without using unnatural language. While the literal translation may say "how frequently," the patient interpretation of these alternatives needs to reflect how much of the day and not the number of episodes. See note above on restriction.
Item 16 Over the past 7 days, how much of the time did you feel that life is not worth living?	This refers to how much of the time during the last 7 days the respondent felt that his/her life was not worth living This item refers to thoughts that the respondent has little reason to continue living, and can also include thoughts of death or suicide. These feelings can be mild/passive thoughts about one's own death ("it would be okay if I were to die" or "sometimes I wish I would die") or can appear as more severe/active suicidal ideation, such as thinking about the specific ways in which one might take one's own life.	**how much of the time:** Alternatives "how frequently" or "how often" are not preferred and should only be used as a last resort if it is impossible to render the item along the lines of "how much of the time" without using unnatural language. While the literal translation may say "how frequently," the patient interpretation of these alternatives needs to reflect how much of the day and not the number of episodes. See note above on restriction.