Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000008: Symptoms of Major Depressive Disorder Scale (SMDDS)
Full Qualification Package

1.0 OVERVIEW OF *SMDDS* FOR QUALIFICATION FOR EXPLORATORY USE

1.1 Introduction and overview

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). It is characterized by depressed mood, loss of interest or pleasure, fatigue, poor concentration, associated feelings of worthlessness and guilt, and suicidal thoughts (Hamilton 1960). Although depression may occur only once during a person's life, multiple episodes of depression is the norm (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).

1.1.1 Clinical trial setting

In clinical trials, efficacy of new treatments for MDD is typically evaluated using clinician-reported outcome (ClinRO) measures like the *Hamilton Depression Rating Scale (HAM-D)* (Hamilton 1960) or *Montgomery-Åsberg Depression Rating Scale (MADRS)* (Montgomery 1979), and a *Global Clinical Impression of Change*. While ClinRO measures capture information not fully evaluable via self-report (e.g., psychomotor retardation, physical agitation), MDD is primarily a subjective experience, with severity of symptoms directly related to the degree of impairment (Foley 2013). Therefore, the assessment of patient-perceived depressive symptoms is an essential endpoint for clinical studies, particularly where the use of clinical indicators will be limited.

Research indicates that patient-reported measures contribute more than ClinRO measures in predicting pharmacological treatment outcome for MDD, suggesting that patient report provides clinically important information not accessible through clinician rating scales (Uhuer 2013). Therefore, the assessment of depressive symptoms from the patient's perspective is essential to fully evaluate treatment risk-benefit profiles in clinical studies and thereby complement traditional ClinRO measures in the assessment of treatment outcomes.

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 2006). As novel therapies continue to be developed, the ability to reliably and validly measure symptom improvement from the patient's perspective becomes imperative. Therefore, the PRO Consortium Depression Working Group at the Critical Path Institute (C-Path) embarked on the development of a new patient-reported outcome (PRO) measure designed to assess key symptoms of MDD as an endpoint measure in clinical trials.

1.1.2 Limitations of existing instruments

In developing a new PRO measure, the Depression Working Group considered the appropriateness and relevance of frequently measured depression-related concepts through a literature review of potential existing instruments. Both literature and input from clinical experts indicated that the depression symptom experience is the concept most proximally related to treatment efficacy. Therefore, the Depression Working Group concluded that depression symptoms experienced and reported by patients represent the most important means of assessing the benefit of drug treatment.

The FDA PRO Guidance (US Food and Drug Administration 2009) emphasized the need for rigorous development of any PRO measure that is intended for use in assessing a clinical trial endpoint. This suggested that the adequacy of symptom inventories developed prior to the Guidance should be carefully reconsidered.

While numerous patient self-administered depression symptom inventories existed, no single measure had been used consistently in clinical development programs. Existing inventories were found to vary greatly with respect to their content, response options, anchors, scoring algorithms, and recall periods. Furthermore, limited information was available in the literature on the developmental history of many of the existing depression symptom inventories, making it unclear whether the inventory items were developed with direct patient input.

For these reasons, along with a thorough qualitative assessment of the concepts relevant to patients and important to clinicians in assessing patient status, plus a cross-reference of concepts contained in existing PRO measures, the Depression Working Group decided that development of a new PRO measure was the best course of action to obtain a measure fit for the assessment of patient-reported depression symptoms in clinical trials.

1.1.3 Brief description of the *SMDDS*

Because the severity of MDD symptoms is directly related to the degree of impairment that patients experience, the PRO assessment of depressive symptoms is an essential endpoint for clinical studies. This new PRO measure, named the *Symptoms of Major Depressive Disorder Scale* (*SMDDS*), was developed for this purpose with consideration of the recommendations and scientific best practices set forth in the FDA PRO Guidance (US Food and Drug Administration 2009) and recent scientific literature (Patrick et al. 2007, Rothman et al. 2009, Patrick et al. 2011a, and Patrick et al. 2011b).

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 web-based version was then used in a quantitative pilot study to complete the development and establish the initial measurement properties.

This document summarizes key details from the development process for the *SMDDS*, the evidence for content validity, details from its early quantitative testing, and descriptions of its subsequent refinement. The intent of this document is to present the *SMDDS* for qualification as an exploratory endpoint measure in clinical trials for MDD.

1.2 Concept of interest for meaningful treatment benefit

The *SMDDS* is intended to be used as a co-primary or secondary endpoint measure in depression clinical trials to assess self-reported depression symptom severity in adults. The targeted concepts of interest are 16 key signs and symptoms of MDD (see Figure 1). The specific individual symptom-concepts included in the *SMDDS* measure are those identified in the MDD literature, supported by clinical experts, and relevant to patients who have been diagnosed with and treated for this condition. More product-specific labeling language will be defined by the clinical trial sponsor in discussion with the FDA.

Potential language for targeted language claims might include statements such as:

- **Based on group comparison using mean values:**

Patients treated with XX reported clinically significant reductions in depression symptoms compared with treatment YY.

- **Based on group comparison using responder analysis:**

Compared with YY, significantly more patients treated with XX reported clinically meaningful reduction in depression symptoms.

- **Based on group comparison of time spent without symptoms**

Compared with YY, patients treated with XX reported spending significantly less time experiencing depression symptoms.

- **Based on group comparison of time to meaningful clinical response**

Compared with YY, patients treated with XX reported faster reduction of depression symptoms.

1.3 Context of use

The *SMDDS* assesses changes in depressive symptom severity for adults (aged 18 years or older) who have been diagnosed and are being treated in an ambulatory setting for MDD. Because the

symptom experience of MDD is chronic, the *SMDDS* measure asks respondents to report on the status of their MDD symptoms over the past seven days.

The characteristics of the study population participating in the development of the *SMDDS* mirrored those commonly used in clinical treatment trials for MDD. Participants who were included had a major depressive episode within the previous 6 months, had a HAM-D score >18, and met the DSM-IV and later the DSM-V criteria for MDD. Recruitment efforts also targeted diversity in age, gender, ethnicity, race, educational level, marital status, and severity.

Participants were excluded if they had a past history of a personality, bipolar, schizophrenic or other psychotic disorder or confounding mental condition such as retardation or dementia. They were also excluded if they were deemed to be a significant risk for suicide or had evidence of drug or alcohol abuse.

It is expected that the resulting endpoint (change in symptom severity) may be used as a primary or co-primary endpoint to establish treatment benefit or as a secondary endpoint to support labeling claims from data produced in randomized controlled clinical trials where an experimental treatment for MDD is being tested. Comparisons can be made to both placebo groups and comparator drug groups depending on the number of arms in the clinical trial. 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 patient-perceived 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.

1.4 *SMDDS* conceptual framework

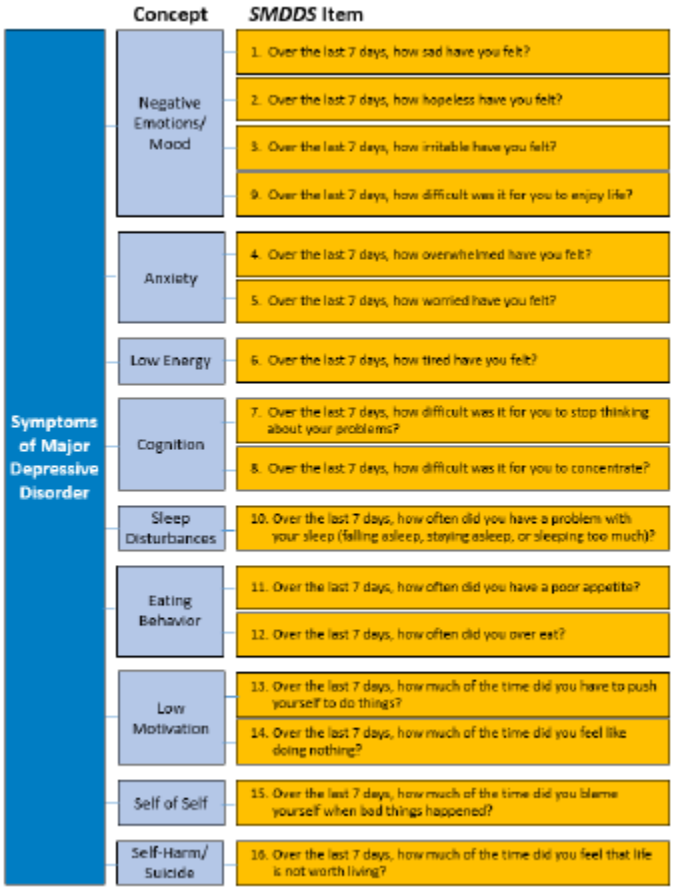
The final 16 items of the *SMDDS* address nine different domains of MDD symptoms: negative emotions/mood (four items), anxiety (two items), low energy (one item), cognition (two items), sleep disturbances (one item), self-harm/suicide (one item), sense-of-self (one item) and eating behavior (two items - scored as a single item). Figure 1 provides an overview of the relationship of the 16 items and nine domains of the *SMDDS*.

Figure 1: Conceptual Framework for the 16-Item *SMDDS*

1.5 Critical details describing the *SMDDS*

The *SMDDS* is a 16-item patient-reported outcome measure that reflects patient-perceived severity of key symptoms of MDD. The final item content is outlined in detail in Figure 2. The mode of administration is patient self-report, with data collection by web-based entry for the development and testing of the measure and ability to be programmed onto other electronic platforms as needed.

Figure 2: Detailed Conceptual Framework for the 16-Item *SMDDS*



1.6 Overview of the developmental status 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 a panel of clinical and methodological experts to provide advice during the development process
- Completion of qualitative concept elicitation interviews conducted to identify the depression 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 participants 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 versions
- 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.

All key documents from each of these stages have been provided to the FDA QRT previously, and four separate consultation and advice exchanges have occurred and resulted in various revisions to the *SMDDS* item content.

Future development work will seek to further explore the measurement properties of the *SMDDS* in the context of interventional studies. In particular, generation of evidence regarding the ability of *SMDDS* scores to detect meaningful within-patient change with treatment or to assess the effect of treatment on the presence/severity of depression symptoms is planned.

1.7 Description of involvement of external expertise, scientific communities or other agencies

Three external clinical experts were engaged throughout the development process, participating at key points with the Development Team (see Table 2). They reviewed the literature review, instrument review summary, and study protocol. Their comments were incorporated into the study design and were addressed by revisions to the study protocol before it was finalized. The external clinical experts took part in the item generation process and assisted with the decisions on important concepts to select for assessment of patients being treated for MDD.

The Expert Panel reviewed the final content of the *SMDDS* before it went to the field for cognitive interviews. Following revisions made by the team based on the cognitive interview and translatability assessment results, a teleconference was held with the expert panel to review and discuss the preliminary measure, its design and its contents. A brief summary of the steps that had been undertaken, the main results, and rationale for changes was provided as a pre-read document along with the preliminary measure.

Table 2: List of Expert Consultants

Name	Title and Affiliation
Madhukar Trivedi, MD	Professor, Betty Jo Hay Distinguished Chair in Mental Health Dept. of Psychiatry University of Texas Southwestern Medical Center
Linda Carpenter, MD	Chief, Mood Disorders Program Director, Neuromodulation Clinic Butler Hospital Professor, Dept. of Psychiatry & Human Behavior Warren Alpert Medical School Brown University
Michael Thase, MD	Professor, Mood and Anxiety Disorders Treatment and Research Program Dept. of Psychiatry University of Pennsylvania

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