Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000122: Telemedicine-based Administration of the Montgomery-Asberg Depression Rating Scale (MADRS)
Letter of Intent

Administrative Structure:

Description of the submitter including, but not limited to, principal investigator(s), working group member(s), institutions, and contact information not contained within the cover letter.

Science 37, the submitter of this Letter of Intent (LoI), is a clinical site that has developed a decentralized clinical trial model. Science 37 works with sponsor pharmaceutical and biotechnology companies (and/or their CROs as needed) to execute decentralized clinical studies in which remote clinical outcome assessments are often performed. The principal investigator associated with this LOI is Ben Furst, M.D., Medical Director of Psychiatry and Behavioral Sciences at Science 37. Working with Dr. Furst on qualification of drug development tools described herein are the following individuals, all employees of Science 37:

- Kevin Bruhn, PhD, Vice President, Strategic Operations
- Todd Adamson, PsyD, Associate Medical Director, Psychiatry and Behavioral Sciences
- Volkan Coskun, MD, PhD, Senior Clinical Research Scientist
- Lisa DiMolfetto, PhD, Vice President, Regulatory Affairs

Concept(s) of Interest (COI) for Meaningful Treatment Benefit:

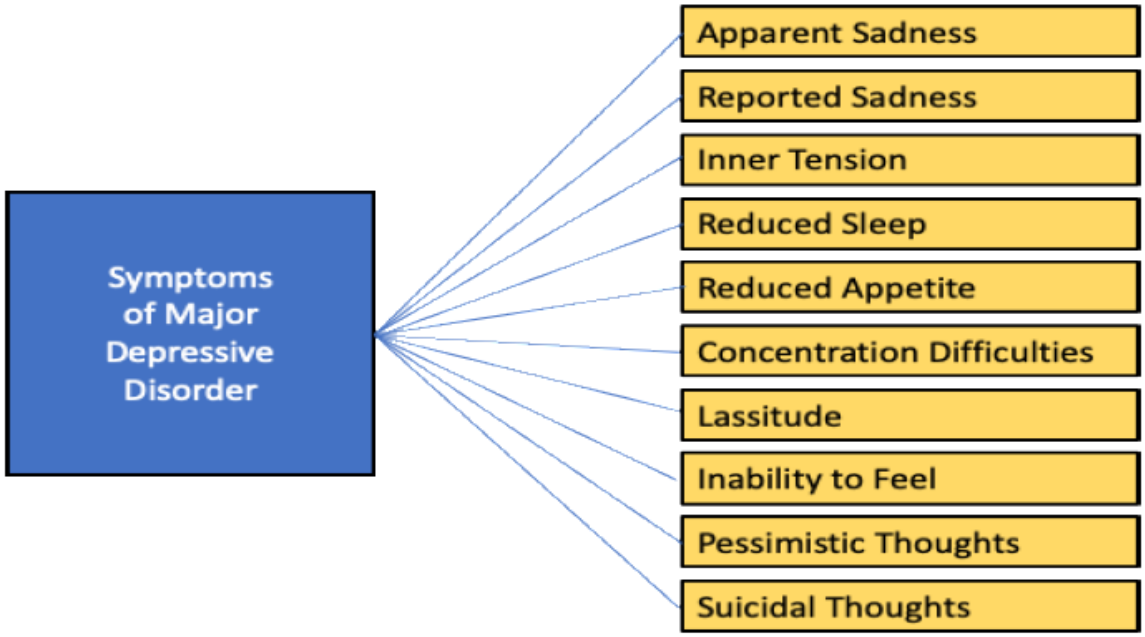
A description of the meaningful aspect of patient experience that will represent the intended benefit of treatment (e.g., presence/severity of symptoms, limitations in performance of daily activities).

Science 37 is pursuing qualification of a telemedicine-based implementation of the Montgomery-Asberg Depression Rating Scale (MADRS), an existing clinician-reported outcome (ClinRO) instrument that is well-established as a reliable measure of depression signs and symptoms when administered in-person.

The targeted concepts of interest for the MADRS are core signs and symptoms of depression. These concepts of interest are identical in the telemedicine-based implementation of this ClinRO. The only difference is that the core signs and symptoms of depression are evaluated by a clinician or study investigator via telemedicine-based (videoconference) assessments of adult patients with depression rather than in-person.

Provide a conceptual framework for the COA(s)

The MADRS has 10 domains interrogated by the clinician to query the patient about the following symptoms of depression:



Context of Use for COA Qualification:

Targeted study population including a definition of the disease and selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, comorbidities, language/culture groups).

The telemedicine-based MADRS (hereafter referred to as the TM-MADRS) is intended to assess changes in depression severity for adults who have been diagnosed with major depressive disorder (MDD). The target population includes adults aged 18 to 65 years of age with a clinical diagnosis of MDD who are treated in an ambulatory setting and who have experienced a major depressive episode within the previous 6 months. The use of the TM-MADRS has no limitations with respect to gender, racial, or ethnic status.

***Targeted study design and statistical analysis plan (includes the role of the planned COA in future drug development clinical trials, including the planned set of primary and secondary endpoints with hierarchy, if appropriate*).**

The primary goal with respect to qualification of the TM-MADRS is to enable its use as a reliable instrument for assessment of outcomes in clinical trials. The use of the TM-MADRS enables investigators (raters) to assess the severity of depression in patients who are not physically present in the room with the rater. Remote administration of this (and other) COA(s) will facilitate new approaches to clinical research (e.g. decentralized clinical trials).

The traditional in-person MADRS has been used extensively in ongoing industry-sponsored trials in MDD as both a primary and a secondary efficacy endpoint. This extensive history of use of the traditional MADRS should provide insights into potential study designs and appropriate contexts for the TM-MADRS, as the role of this ClinRO would not be expected to change based on the setting in which it is administered. Qualification of the TM-MADRS would allow for its use as either a primary

or secondary endpoint in studies that would generally employ the MADRS as a primary or secondary endpoint.

Applicable study settings for future clinical trials

- ***Geographic location with language/culture groups***
  The development of a qualified TM-MADRS should allow for generalized adaptation of this telemedicine-based ClinRO in any language for which the traditional MADRS has previously been developed. Assuming both clinician and patient speak the same language, the TM-MADRS could be translated for use outside the U.S. and could be used in multinational trials or trials within a single country in which multiple language and culture groups may be enrolled.

- ***Other study setting specifics (e.g., inpatient versus outpatient)***
  Acceptance of telemedicine-based COAs in general will allow investigators (raters) to evaluate patients using qualified COAs even when they are not physically in the same room as the patient. This capability will open the potential for the collection of data from patients regardless of their geographic location and allows for the decentralization of clinical trials.

COA Type: ClinRO

The TM-MADRS is a ClinRO instrument that relies on patient responses to questions asked by the clinician via videoconference. The clinician must be appropriately trained on the application of the MADRS and be familiar with telemedicine techniques and best practices.