IVI INNOVATION AND VALUE INITIATIVE

IVI-MDD Value Model – Draft Protocol

IVI Response to Public Comments

April 5, 2022

The Innovation and Value Initiative held a public comment period on its draft model protocol for Major Depressive Disorder (MDD) Model from December 12, 2021, through January 25, 2022. The draft model protocol outlines the technical specifications and data sources that will guide the model development. This document summarizes the general themes from the comments received during the public comment period and IVI's response to those comments.

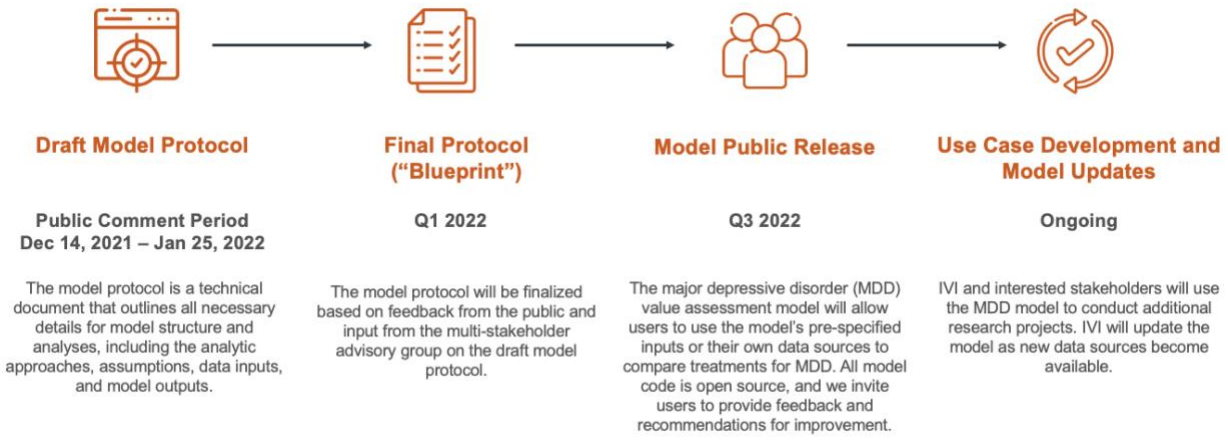
Stakeholder Perspectives Represented

IVI received seventeen comments from individuals and organizations during the public comment period for the draft model protocol, five of which came from members of the MDD multi-stakeholder advisory group. A total of thirty-four stakeholders representing various perspectives have contributed to the development of the draft model protocol. Table 1 below shows the breakdown by stakeholder group.

Table 1. Number of Stakeholders that Have Contributed to IVI-MDD Model Protocol Development

	Advisory Group	Public Comment	Total
Industry	3	4	7
Patient	5	2	7
Researcher	2	2	4
Clinician	5	1	6
Employer & Payer	7	3	10

Overall Model Development Timeline



Summary of Comments Received

The rest of this document summarizes the key themes received, in general and by model specification, and the action steps we propose to take to address or incorporate these suggestions into the final model protocol. If you have additional recommendations or data sources, please send them to public.comment@thevalueinitiative.org.

General Themes

IVI was encouraged to broaden the scope of the evidence review and consider using real-world data (RWD) and real-world evidence (RWE) in finalizing the key assumptions and inputs for the MDD model. Various specific data sources and studies were also recommended.

We agree that RWE should be considered in finalizing the key model assumptions and inputs, to ensure that the MDD model can generate insights consistent with real-world treatment pathways and patient experiences.

As we finalize the model protocol with our research partners and advisors, the research team intends to: (1) review the RWE sources suggested in the public comments received, and (2) broaden our literature search to include relevant RWD studies in determining the key model assumptions and inputs.

We are also conducting a retrospective claims data analysis in collaboration with researchers from HealthCore, to understand treatment patterns and outcomes for commercially-insured individuals following diagnosis of MDD. This study was launched with the specific goal of filling in some key data gaps, and will explore ways in which the results can inform the model's inputs and assumptions. (Please refer to Page 76 to 81 of the Consolidated Comments Document for additional information from our research partner, HealthCore.)

In addition, the MDD model user interface will include the capability for users to modify key model inputs (e.g., efficacy) using their own RWE or other sources.

Stakeholders were interested in learning more specific details about how the model will incorporate patient input (e.g., findings on patient preference from the IVI-PAVE collaboration) to ensure patient-centered HTA.

Patient-centricity is one of the key principles IVI believes should guide value assessment. A specific objective in developing the IVI-MDD model was also to test novel approaches to incorporate direct patient input in the methods to inform HTA (e.g., economic modeling, MCDA). IVI and our research partners have worked to ensure that patient inputs are incorporated in both the process and methods used to develop the model.

First, our multi-stakeholder advisory group includes patient representatives from the broad MDD population. They provided insights from the outset in the overall MDD model development process and the component research projects providing inputs for the mode. For example, the patient advisors were instrumental in helping us interpret and prioritize input from people with lived experiences in designing the discrete choice experiment for Phase 2 of the PAVE study. Additionally, in the current model design, we have referenced the results from Phase 1 of the PAVE study to ensure that key model inputs and simulation outcomes reflect as much as possible those of importance to patients in managing their MDD.

For Phase 2 of the study, we are using a DCE study design to derive quantitative estimates of how patients make trade-offs among different attributes of pharmaceutical and non-pharmaceutical treatment options. A deliberate effort is being made to recruit patients from under-represented patient subgroups (i.e., those of non-white race and ethnicity background, and those from lower socioeconomic status). Upon the completion of data collection, we will test a few ways to incorporate these estimates into the MDD model, including to understand model uncertainty and patient heterogeneity in preferences. The final model blueprint will describe in more detail the specific approaches we plan to test. (Please refer to Page 42 to 43 of the Consolidated Comments Document for additional information from our research partner, PAVE Center at the University of Maryland.)

We were asked to further clarify/elaborate how settings of care (e.g., primary care, specialty) will impact the model.

Setting of care (e.g., primary care or specialty) has been known to affect treatment pathways and associated outcomes for people diagnosed with MDD. It was a key consideration emphasized by our MDD Advisory Group, and one emphasized in the public comments we received for the draft MDD model protocol. Currently, subject to evidence availability, we envision that the settings of care will impact the model design in the following ways:

- Treatment options or treatment sequences more likely to be available
- Efficacy inputs (e.g., duration of remission)
- Cost inputs (e.g., number of outpatient visits, healthcare resource utilization frequencies and costs)

The final model protocol will provide more specifics on how settings of care will impact the key model inputs and output. A targeted literature search or retrospective data analyses may also be conducted to understand how settings of care could impact treatment patterns and outcomes.

By Model Specification

Target Patient Population

IVI was asked to confirm the list of comorbid conditions for the target patient population.

MDD is a highly prevalent chronic condition that is often comorbid with other psychiatric (e.g., anxiety) and non-psychiatric conditions (e.g., diabetes). The target patient population of the model will be individuals of age 18 to 64 years newly diagnosed with MDD by a healthcare provider (e.g., psychiatrist, psychologists, primary care physician). Individuals with certain comorbid conditions will be excluded, as they might have different treatment pathways and outcomes compared with the general MDD population.

At this stage, we are confirming the final list of comorbid conditions to be excluded for the target patient population. For example, we are still evaluating whether to exclude individuals diagnosed with substance use disorder (SUD). SUD can impact treatment strategies and outcomes for MDD and vice versa. The final decision will depend on suggestions from our advisory group and the inclusion/exclusion criteria in the studies used to inform model inputs

(i.e., whether SUD is a commonly excluded condition in the selection of patient cohorts).

Stakeholders emphasized the importance of deriving model inputs from study populations that are consistent with the target patient population.

IVI agrees with this suggestion and intends to make sure that the key model inputs and assumptions are based on studies or estimates consistent with the target population of the model, to the extent possible. Wherever we cannot find studies that exactly match the target patient population of the model, we will clearly state the patient population the data inputs were derived from and note this as a limitation. Inputs based on the general MDD and TRD populations will be clearly distinguished, with some patients with MDD going on to develop TRD within the model. The user interfaces will also include the capability for users to change key model inputs and examine how key model outcomes and insights will vary.

Subgroup Analysis

It was suggested that IVI should consider including subgroup analyses by: (1) gender, and (2) disease severity (e.g., those that developed TRD).

As a microsimulation, the IVI-MDD model will provide flexibility to incorporate subgroup-specific inputs (subject to data availability) and examine the differential impacts of healthcare interventions on different subgroups of the MDD population. The draft model protocol included some examples of the subgroups that we intend to incorporate (e.g., race, socioeconomic status, insurance status). We also intend to incorporate the ability to generate output by gender and by disease severity.

Treatment Pathways/Sequences

Stakeholders provided additional input on the scenarios or reasons for which people with MDD switch and discontinue treatments.

We appreciate the perspectives from the comments on the reasons why patients could switch or discontinue treatments. We acknowledge that there are a multitude of reasons in real-world clinical situations, including the following:

- Adverse reactions or side effects
- Lack of efficacy (e.g., not achieving a response)
- Preferences for treatment attributes (e.g., mode of administration)
- Affordability
- Access to treatments

In finalizing our model protocol, we will conduct additional literature searches to attempt to derive estimates for the probability of switching to different treatments or discontinuing, based on the different reasons stated above. We will also seek input from clinician and patient advisors on these issues.

Several stakeholders noted that augmentation should be considered earlier in the treatment pathway, based on real-world evidence and clinical guidelines.

After consulting our clinician advisors and revisiting the treatment guidelines, we agree that augmentation strategies should be made available from the second line in the sequence of treatments. In the model, individuals with a partial response to prior treatment may be prescribed augmentation therapy (e.g., with antipsychotic medication) following the first line of treatment.

Efficacy

Some stakeholders suggested IVI further examine heterogeneity in time to respond to treatments, which might require a shorter cycle length to capture such differences.

We agree that time to response following treatment initiation is an important aspect of the patient heterogeneity in MDD. As shown in various studies, time to response varies greatly in the real world for most antidepressants (range: 2-8 weeks). Treatment guidelines typically recommend at least a 4- to 8-week observation period before being able to fully assess response to treatments. As a next step, we intend to review the references shared in public comments to examine how earlier responders might have different treatment pathways and outcomes than those that were not early responders (e.g., duration of remission, inpatient hospitalization outcomes). We will then evaluate whether to adjust cycle length based on this literature review and modeling constraints.

It might not be reasonable to assume the same efficacy rates for first- and second-line treatments.

IVI will further examine the references provided in the public comments and conduct additional literature review to determine whether differential inputs or assumptions need to be made for efficacy of the first- and second-line treatments. This will depend on availability of evidence for different treatment options, and whether the evidence is derived based on populations similar to the target patient populations.

The efficacy inputs and assumptions for "no treatment" should be informed by real-world evidence.

Similarly, we will examine the data sources and references shared in the public comments to help derive the efficacy inputs for individuals with "no treatment". Additional literature searches may also be conducted. The model will also recognize that some patients might achieve remission with no active treatments.

Cost Inputs

Both top-down and bottom-up approaches to deriving cost inputs have their strengths and limitations.

We appreciate the input from different stakeholders on comparison of the two approaches and agree that there is not always a preferred approach between the two. One possible approach that we are considering is to feature one approach in the base case, while including other

approaches as sensitivity analyses.

In finalizing the model protocol, we intend to evaluate the articles shared in the public comments and plan to reach out to different stakeholders for feedback on key questions in implementing these approaches (e.g., what are the specific healthcare resource items that should be included in a "bottom-up" approach).

In calculating the costs of pharmaceutical treatments, the use of wholesale acquisition costs (WAC) might overestimate the costs of treatments in the real world.

We agree that WAC could overestimate the costs of pharmaceutical treatments due to reasons such as rebates. We intend to conduct searches to identify inputs for more realistic estimates of costs for pharmaceutical treatments in the real world (e.g., Federal Supply Schedule or FSS). The MDD model user interface will also allow users to modify unit costs.

Utility Inputs

Stakeholders commented on the strengths and limitations of the studies identified through literature searches and provided additional sources for utility inputs.

We intend to evaluate the additional resources shared in the public comments. The choice of utility inputs will take into consideration the following: (1) whether it is estimated from a trial (vs. real-world) setting, (2) whether it is aligned with the model target patient population, (3) populations' geographic location, and (4) face validity. The model interface will also provide users with the flexibility of using different sets of utility inputs or to input their own value sets.

Data Sources

Various data sources have been suggested as inputs for modeling suicide, caregiver burden, and adverse events. Some stakeholders also recommend data partners that IVI can work with to fill in data gaps for the model.

We will review the suggested data inputs and sources to identify possible inputs that align with the model's target population, and additional literature searches may be conducted. We will also contact potential and existing data partners to identify opportunities for collaboration. IVI would like to thank respondents for their helpful suggestions in this area.

Output

Stakeholders cautioned against reliance on the use of quality-adjusted life years (QALYs) and the potential discriminatory consequences for patient subgroups such as those with disabilities.

While we acknowledge that many stakeholder groups see the use of the QALY as problematic for traditional economic models, we want to clarify why we have chosen to include it within IVI's value assessment laboratory. Including QALY as an output of the model, along with several other key outcomes, will allow the flexibility to understand and evaluate the importance of looking at a wide range of clinical and economic outcomes, and will allow comparison with prior economic evaluations that have used this metric. The model's user interface and the open-

source nature of the underlying programming code will provide users the flexibility to output different decision metrics of interest to decision-makers.

While the QALY is a commonly used metric in existing economic evaluations, it has limitations and is considered to be potentially discriminatory to certain patient subgroups (e.g., those with disabilities). Since any metric will have strengths and limitations, IVI believes that it is important that decision-makers not base decisions on any single metric (such as cost per QALY), but that they consider a broad set of diverse clinical and economic outcomes for decision-making.

The purpose of IVI's economic model is to demonstrate the strengths and weaknesses of different methods. We cannot do that without a basis of comparison.
IVI was encouraged to include more clinical outcomes (e.g., duration of remission) in the key model output.

IVI does intend to include a range of clinical and economic outcomes of importance to diverse decision-makers. The draft model protocol describes some examples output that end users can track through the simulations. The ultimate set of clinical outcomes to be included in the model will be informed by our further discussions and outreach to stakeholders. The user interface will allow users to choose among multiple output options. In addition, as the underlying programming code will be open source, advanced users will have the option to customize the output most relevant to their decision-making.