IVI INNOVATION AND VALUE INITIATIVE

Dear Colleague,

Thank you for your review and recommendations for the Innovation and Value Initiative's Value Model on Major Depressive Disorder (MDD). We are deeply appreciative of your comments and suggestions during this third public comment period for the MDD model. You can find all materials, including the downloadable version of the R code, on our website here.

IVI, together with our research partners Medicus and OPEN Health, our Advisory Group, and our technical and clinical expert panels, worked to design the model to incorporate information and data sources on patient preferences and experiences. Our goal is to develop models that can allow us and our partners to test new methods and approaches to health technology assessment (HTA).

During this public comment period, IVI is seeking feedback in four main areas:

- The **model design** including the structure, key assumptions made, and input sources (i.e., the internal structure and sources for the model);
- The extent to which the **user interface** (i.e., the front-facing design of the model) is user-friendly and effective in addressing your decision needs;
- Suggested approaches to address some of the **data gaps** identified in the MDD model (e.g., databases or research partners we should consider); and
- **Additional methodological questions or real-world applications** that IVI should prioritize following the launch of the model.

We are also seeking feedback on specific areas. Below is a list of questions that reference specific sections. We recognize that the questions are detailed and invite you to respond to any or all questions in your submission of comments. Please send question responses and comments on letterhead to public.comment@thevalueinitiative.org. We are accepting comments through December 15, 2023. IVI will post all comments on our website and will provide an overview of how we intend to incorporate the recommendations.

MDD Model Design and Code

One of the key reasons we chose to examine major depressive disorder in the IVI learning laboratory was to highlight data gaps, including the mismatch between the data needed for HTA and what is available. Given this known problem, IVI made a series of assumptions to allow stakeholders to use the model. We are seeking your input in case you know of additional data sources, including real world data and other sources, or if you have recommendations to improve our assumptions.

Please refer to the following supporting materials (which can be found via the IVI-MDD Model web page) while reviewing these questions:

Technical Report
Model User Interface
R Code on GitHub

Context	Question	Reference Point in Technical Documentation
Efficacy Rates		
Decrement in efficacy rates by line of therapy is derived from STAR*D and is not treatment- or class-specific in the current version (Rush 2006).	Do you know of other data sources to recommend, especially any data sources that are more treatment-specific or more recent?	Section 4.2 and Table 7
The model applies a decrement to Complete Response for later lines of therapy, but not to Partial Response.	In the absence of data, we currently do not apply a decrement to Partial Response (PR) by line of therapy. Do you know of any data sources to inform this?	Section 4.2
Efficacy rates of combination therapies are based on risk ratios comparing likelihood of response between combination therapy and pharmacologic monotherapy (Cuijpers 2020, Mohamed 2017).	Does this seem reasonable? Do you have any other recommendations for input sources for efficacy rates of combination therapies in the model?	Section 4.2 and Table 4
Efficacy rates of PR are calculated based on a common risk ratio of PR vs. CR for all non-brain stimulation therapies (Koeser 2015, Ross 2019).	Are there any other sources you would recommend, especially any that are more treatment-specific?	Section 4.2, Table 5

Partial Response to Treatment Assumptions		
Spontaneous response leading to Complete Response (CR) is considered in the model, but not spontaneous response leading to PR (i.e., assumed to be 0%).	Do you know any data sources or literature that can help us identify inputs for PR due to spontaneous response?	Section 4.3
Do you have any recommendations for how we should model the impact of early response on long-term clinical outcomes? For example, one way we considered modeling this was through differential relapse rates for early (those that achieved CR within 4 weeks of treatment initiation) vs. late responders in our model (Chitnis 2023).	In the base case, patients who achieve early *complete* response (CR) are assumed to relapse at two-thirds (HR = 0.67) the rate at which patients who achieve late CR relapse. Due to lack of data, we assumed no difference in relapse rates for early *partial* response (PR) vs late PR. Do you have any recommended data sources?	Section 4.4 and Table 8
Data Sources: Real World Data and Representativeness		
The base case of the model relies heavily on efficacy inputs from randomized controlled trials (RCTs). As we continue to update the model, we hope to incorporate data sources that capture the heterogeneous experiences of patients in the real world.	Do you have any recommendations on data sources that estimate the effectiveness of different treatment options in the real world for the overall MDD population and by subgroups?	NA
We are interested in effectiveness data on treatments by line of therapy, and on subgroups that might have difficulties in accessing quality treatment or care (e.g., racial and ethnic minority groups, those living in rural areas, those without insurance).	Are you aware of data sources that might have this information?	Section 3.1
Adverse Events		

Based on literature and clinical expert input, one composite severe adverse event (SAE) was modeled for pharmacotherapy and another one for brain stimulation therapy. It is assumed that psychotherapy will not lead to SAEs (Jakobsen 2017, Overvliet 2021). Individuals experiencing a SAE will experience a one-time disutility decrement (Sullivan 2004).	Are you aware of any sources for a common set of treatment-specific likelihoods of SAE that would provide more granularity in the model? Are you aware of alternative or more recent sources for SAE-related disutility inputs, especially at a treatment or class level?	Section 4.6 and Table 13 Section 4.8 and Table 16
Cost Inputs		
The cost inputs for psychotherapy treatment were calculated assuming individuals receive 2 45-minute CBT sessions per week while on treatment. This is based on guideline recommendations and clinical input.	Are you aware of any evidence estimating the real-world frequency and duration of psychotherapy (e.g., CBT) sessions for MDD or the costs of receiving such treatments in the US?	Section 4.9.1 Table 17
As brain stimulation therapies (e.g., rTMS, ECT) are typically used as one-time treatments to induce response, brain stimulation therapies are modeled as "add-ons" in the fourth line, with cost of the treatment based on a single administration.	Is this a reasonable assumption? If not, why, and what would be a more appropriate assumption in this context?	Section 3.5, Table 2 and Section 4.9.1, Table 17
Caregiver Inputs		
We would like to include relevant caregiver costs in an update of the model.	Do you have any recommendations for data sources on caregiver costs by different health states (CR, PR, and NR) and clinical characteristics (e.g., treated vs untreated, first/second line vs third/fourth line)?	NA
We would like to include relevant caregiver quality of life in an update of the model.	Do you think the model should incorporate caregiver disutility, and if so, how should it be incorporated (e.g., through modifying the model structure)?	NA

	Do you have recommendations on data sources for caregiver utility or quality of life?	
Mortality Inputs		
Currently, the sources for background mortality are US life-tables, stratifying by age and sex, adjusted with mortality multipliers based on the health state and treatment status (i.e., whether treated, and the line of therapy). Sources for mortality multipliers are Oude Voshaar (2021) and Reutfors (2018).	Are you aware of mortality data sources by health state, treatment status, and/or line of treatment (first/second vs third/fourth) that you would recommend?	Section 4.7 and Table 14
Outcomes		
The model provides clinical outcomes (e.g., time-to-event outcomes), economic outcomes (e.g., QALYs gained) and clinical cost-effectiveness outcomes (e.g., NMB).	Are the existing outcomes included in the model effective in addressing the key decision needs you have? If not, are there other key outcomes that you suggest we include in the model? Alternatively, are there different ways that we can present these outcomes to make them more useful for your decision-making?	Section 5.1, Section 5.2, Section 5.3
We tested the model by applying some common scenarios, with results shown in the technical report.	From the results in the technical report and test runs you have done, do the outcomes make sense and seem to have validity to you?	Section 8, technical report
Sensitivity Analyses		
Multiple inputs were built into the model. To simplify the user interface, we currently show only the 10 most impactful inputs.	Are there any other inputs for which we should conduct sensitivity analyses? If so, what are the ranges to use around those? Are there any specific use cases where you would want to apply the model to inform future decisions?	Section 8.2 and User Interface
We included a set of clinical, cost, and cost-effectiveness	Are there any other key outcomes that you would want to examine in sensitivity analyses?	Section 8.2 and User Interface

outcomes in our sensitivity analyses.		
Low and high parameter values are produced by adding or subtracting 20% to the base value of the parameter value within the confines of the possible parameter range (e.g., utilities must be within 0 and 1).	Are the value ranges used in the sensitivity analyses plausible? Are there other value ranges you would recommend for any of the parameters?	Section 7 and Table 22
Treatment Gaps and Time from Diagnosis to First Treatment		
Currently, the model considers both probabilities of experiencing a treatment gap following relapse or failure after a line of therapy and the duration of the treatment gap, through rates (in units of patients per day) of initiating the next line of therapy (Rush 2006).	Are you aware of any other data sources for treatment gaps, or how these gaps vary by treatment/treatment class or patient sociodemographic and clinical characteristics (e.g., line of treatment)?	Section 4.5, Table 11
The model currently assumes all patients initiate the first line of therapy at the time of diagnosis at model time 0. However, delayed initiation of first-line therapy is possible via input parameters for likelihood of delaying initial treatment (0% in the base case) and maximum time to first-line therapy given no spontaneous response.	Are you aware of any data sources for likelihood and duration of delayed initiation of first-line therapy?	Section 4.5
R Code		
R code and documentation	Is the code clearly written and easy to follow or adapt? Does it provide sufficient documentation within the codes' comments?	Overall R code package
Computational efficiency	Does the code have sufficient computational efficiency, especially as it	dsa.R

	relates to running the univariate sensitivity analyses?	
Code modification	Does it sufficiently allow you to modify model input values in the R code (e.g., interacting with model inputs through an Excel inputs workbook versus a text file)?	Import_inputs.R Generate_inputs_json.R inputs folder
Clarity and accessibility	Do you have any suggestions to further improve the clarity of the R code and/or to make the open-source code more accessible?	Overall R code package

User Interface (UI)

IVI and its partner OPEN Health designed the user interface based on a series of key informant interviews from different stakeholder groups. We are seeking feedback on whether the front-facing portion of the model makes sense and where we need to add clarity or context.

Question
Overarching question: On a scale of 1 to 10, how would you rate your familiarity with economic evaluation?
Were you able to use the tool to create a new analysis and generate results?
How often do you think you might use the web-based tool?
What are the top three questions you would ideally like the web-based tool to answer?
Were you able to use the tool effectively to answer any of your questions? If not, what problems did you experience?
How might you leverage information provided by the tool specifically in your work or life?
If you could, what aspects of the tool would you change to make it better or more useful?
Is a tutorial needed? If so, what format would be most useful (e.g., text, video)?
Are there any inputs that you wish to vary but that are not currently user-modifiable?
Was anything unclear to you on the treatment selection module? If yes, do you have specific suggestions for improvement of the treatment selection module within the UI?
Are there additional treatment options or functions that you would like to see within the UI?

Do you think laboratory/monitoring costs are important inputs to incorporate in the MDD model and UI?
Would you like to see unpaid caregiving costs included as an editable input in the UI, and if so, in what format?
Overall Outcomes Module
Are there any important outcomes missing from the model (including clinical outcomes, costs, cost per outcome, or cost-effectiveness outcomes)?
Are there other ways you would prefer to see any specific results displayed (e.g., chart or table formats)?
Outcomes - Parameter Sensitivity Module
Do you think listing the top 10 input drivers in the sensitivity analysis shown in the UI is adequate? What would be most informative for you?
The model currently includes specific key outcomes (e.g., QALYs, NMB) for the sensitivity analysis module and its presentation. Are there additional specific outcomes you would like us to include in the sensitivity analyses?
Do you prefer to see sensitivity analyses on individual treatments or pathways (as in the current UI), or on the incremental outcomes comparing specific treatments or pathways? If so, how would you prefer the incremental sensitivity analysis outcomes to be displayed (e.g., selection of any two treatments/treatment pathways to see how the key incremental outcomes change)?
Outcomes – Clinical Cost Effectiveness Module
The model allows multiple treatments and pathways to be compared, with cost-effectiveness results displayed as a table of incremental cost-effectiveness ratios and a chart showing the cost-effectiveness frontier. Are there different approaches to presenting the cost-effectiveness results that you would like to see (e.g., cost-effectiveness acceptability curves)?