Dear Colleague,

Thank you for your review and recommendations for the Innovation and Value Initiative's draft model protocol on major depressive disorder (MDD). You can find all materials on our website here.

IVI, together with our research partner OPEN Health, has worked to design the draft model protocol to incorporate information and data sources on patient preferences and experiences and bring them into the mechanics of value assessment models. IVI is seeking feedback on three main areas of the draft protocol:

- Data gaps in key model inputs and potential data sources and partners to address such gaps;
- Prioritization of data sources and technical approaches when multiple valid approaches exist;
- Potential use cases or practical applied research questions, particularly how the MDD model can help inform decisions in specific contexts.

We are also seeking feedback on specific areas throughout the protocol. Below is a list of questions that reference specific sections in the protocol. You may respond to any or all questions in your submission of comments or through an online form.

Please send any questions to public.comment@thevalueinitiative.org. We are accepting comments through January 18, 2022.

Research Questions:

Section	Question
6.1	Are there any other studies/data sources that will better represent the characteristics of the MDD population based on the target population of the model?
6.1.1	Do you know of any studies/data sources that examine how key model inputs (e.g., effectiveness, safety, costs) vary by subgroups defined by patient characteristics including age, race/ethnicity, and socioeconomic status (e.g., education level, income)?
6.5 and 8.2.3	Do you have some suggestions on studies/data sources/methods that we can reference in extrapolating the long-term efficacy inputs? We have limited data on responses to treatments for some comparators from our literature review of meta-analyses (Table 3). - Should we extract such inputs from clinical trials or observational studies? - If so, do you have any recommendation on data sources?
6.8	Are there other model outputs that will be of interests to your organization? In what decision contexts will they be useful? Do you have any suggestions on data sources that examine suicidal behavior or attempts for: (1) the general MDD population, and (2) those that have received different treatment options?

6.9.3	Is it reasonable to assume that somatic therapies (e.g., ECT) will only be offered as 3rd and 4th lines of treatment, given the target population in our model?
6.9.3.1	We specified scenarios in which individuals in our simulation will move to a new line of treatment. - Are these scenarios consistent with real-world clinical practice? - Are there other scenarios in which individuals might switch to a different line of treatment that we should include in the model?
6.9.3.2	Is it reasonable to assume the same sets of model inputs (efficacy and safety) for the first and second lines of treatment? In the absence of data for the key efficacy inputs for third and fourth lines of treatment, we intend to: (1) first use estimates based on the treatment-resistant depression (TRD) population as model inputs; and (2) if estimates based on TRD population do not exist, use a hazard rate approach where treatment efficacy rates will be proportional to efficacy rates used in the first and second lines. - Do these assumptions seem reasonable to you? - Do you have any suggestions for sources to derive model estimates for the third- and fourth-line treatments?
7.3	We have proposed two approaches to derive direct medical cost inputs in our model: a "top-down" approach (identify proportion of all-cause medical costs that can be attributed to MDD), or a "bottom-up" approach (identify individual resource requirements and unit costs; and sum across all resource use items). - Is there one approach you would recommend over the other? - Are you aware of any data sources/studies that we should look into for this issue?
7.1.2	Are there key adverse events that have a significant clinical and economic impact that we should include in the model? We plan to conduct additional literature searches to identify key AEs to include in the model. What sources would you recommend that we prioritize (e.g., prescribing labels, real-world studies, etc.)? One of the challenges is to identify a set of AEs and their frequencies across a drug class. Do you have any suggestions for how to approach this?
7.2	Of the possible data sources for utility inputs listed in Table 8, is there one we should prioritize? Are there other sources we should consider?
7.3	For psychotherapy, what is a reasonable assumption for the length of a visit and for duration of psychotherapy to include (Table 10 and 11)?
7.3.5.2	Do you have any suggestion on studies or data sources that can inform the calculation of informal caregiving burden or costs?
Appendix H	Appendix H describes some of the novel questions or research opportunities that the model could help inform. Are there specific use cases or decision contexts that should be prioritized? Are there other important use cases or decisions that this model could help inform?
General	Do you have any other comments or feedback for us to consider?