2024

IVI – MDD Value Model (beta version)

CONSOLIDATED PUBLIC COMMENTS

AMERICAN PSYCHOLOGICAL ASSOCIATION

December 15, 2023

Innovation and Value Initiative (IVI)
917 Prince Street
Alexandria, VA 22314
SENT VIA EMAIL: public.comment@thevalueinitiative.org

Dear IVI-MDD Value Assessment Model Advisory Group,

We are writing regarding the request for public comments on the IVI Draft Model Design and Code for Major Depressive Disorder (MDD). The following comments were developed by members and staff of the American Psychological Association (APA) who have expertise on the topic, but they are not an official statement of the APA.

- In the population characteristics, please include and differentiate between sex and gender identity. In the report and use of this model please include discussion on the importance of shared decision-making between the patient and the provider. Please see this website for related shared decision-making resources: https://www.ahrq.gov/health-literacy/professional-training/shared-decision/index.html
- Please include Patient-Centered outcomes that are important to patients among outcomes examined by the model.
- Please consider issues of equity, diversity, and inclusion throughout the model and associated reports. Related, please refer to the American Psychological Association's *Inclusive Language Guidelines* for guidance on ensuring inclusive language, available here: https://www.apa.org/about/apa/equity-diversity-inclusion/language-guidelines
- A video tutorial would be helpful for individuals who may be less familiar with economic evaluations of treatments.

Thank you for the opportunity to provide feedback on the IVI's draft model design and code for MDD.

Sincerely,

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COMPASS Pathways

From: Shane O'Connor <shane.oconnor@compasspathways.com>
Sent: Monday, December 18, 2023 2:18 AM
To: Public Comment
Cc: Lucinda Orsini; Jason Lerner; Daniel Sutcliffe; Vicki Wing; Trish McAdoo
Subject: Public comments on MDD model
Attachments: Public-Comment-Questions-20231025 (1).docx

Hi there,

I hope this message finds you well. I'm Shane O'Connor, the HEOR Manager at COMPASS Pathways. As you may know, we're advancing in phase III trials for psilocybin therapy, targeting treatment-resistant depression (TRD). Additionally, we're developing a preliminary health economic model for this intervention in TRD.

Enclosed is a document responding to some of your inquiries. Unfortunately, we share similar challenges in addressing the evidence gaps highlighted.

I'd like to pose an additional question concerning our model: For most treatments, outcomes are populated from short-term (e.g., < 6 month clinical trials), and failures comprise patients who have failed to respond or remit. For patients who have positive outcomes (based on trial data), what assumptions have been made regarding long-term adherence to treatment, and do these assumptions vary by therapeutic class (e.g., SSRI vs. atypical antipsychotics)?

We anticipate completing our model by the end of Q1 / beginning of Q2 next year. Upon completion, a collaboration with IVI could be mutually beneficial to exchange insights. Please let us know if you are open to this.

Lastly, we'd like to commend your team on the current simulation model. Its design adeptly navigates many of the common limitations associated with Markov models. We eagerly await the updated version.

Regards,

Shane O'Connor

COMPASS Pathways

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? N/A	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? N/A	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? Not sure if combination therapy means pharmacologic + pharmacologic or pharmacologic + psychological in this context.	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? N/A	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? N/A	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? As I'm sure you're aware, efficacy measures for depression are uncommon in real-world data sources. However, there are some datasets that include PHQ-9 scores in Electronic Medical Records (EMR) for MDD populations. These can be used to assess outcomes such as partial and complete response and potentially to level of different treatment options. Vendors like Holmusk and OM1 have access to unique secondary care data, including patient-reported outcomes. They both report PHQ-9 coverage and have experience working with MDD populations. The main challenge is identifying a patient group with adequate baseline and follow-up PHQ-9 scores for effective efficacy analysis.	NA

	For an open-source approach, I recommend contacting The Observational Health Data Sciences and Informatics (OHDSI). OHDSI is an interdisciplinary, multi-stakeholder collaborative focused on extracting value from health data through large-scale analytics. They have conducted research on patient journeys in MDD, analyzing data across various markets. (see here).	
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? Again, I would refer to the above mentioned vendors (OM1 and Holmusk) and also a vendor called clarify that are looking into the impact of Social and Behavioral Determinants of Health (SBDoH).	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? It's important to consider that the initial assumption regarding brain stimulation therapies like rTMS and ECT might benefit from some reconsideration. The idea that these therapies are used as one-time treatments, thus modeled as "add-ons" with costs based on a single administration, may not align fully with the typical treatment protocols. Here's an alternative approach: **ECT** • **ECT Treatment Frequency and Duration**: Typically, ECT is not a one-time treatment. It's usually administered two to three times a week, spanning six to twelve sessions. The average number of	Section 3.5, Table 2 and Section 4.9.1, Table 17

	sessions, as per the ECTAS (Electroconvulsive Therapy Accreditation Service) dataset, is around 10. This suggests a more extended treatment period than a single session. (source) • **Maintenance ECT**: Additionally, the maintenance phase of ECT often involves ongoing treatments, usually one session per month, indicating a long-term treatment strategy. **rTMS** • **rTMS Treatment Frequency and Duration**: Similarly, rTMS treatments are usually more frequent and extended than a single session. Patients typically receive rTMS five days a week, with a standard course lasting 4 to 6 weeks, varying based on individual responses. For conditions like depression, a course might involve about 20 sessions. (source) • **rTMS Maintenance**: The maintenance phase for rTMS often includes treatments once every two weeks, further emphasizing its recurring nature. In light of these treatment regimens, it might be more accurate and insightful to model these therapies as involving multiple sessions. This perspective would more closely reflect their real-world clinical application and the associated costs over time, providing a more comprehensive understanding of their effectiveness and financial implications.	
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)? Yes, caregiver burden should be incorporated into the model as it's mentioned in ICER's updated value framework for 2023. If no caregiver data is available, ICER will assume that "assume that caregiver time spent is proportional to 75% of patient formal labor time.	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? This may not be of help but we already created a summary of how mortality was captured in different HE models for depression interventions. Summary: Cost-effectiveness models for depression that considered mortality did not attribute reduced mortality to specific treatments. Typically, excess mortality risk would be seen at the health state level, by attributing a higher risk to depressed states. For example, Jannsen assigned additional mortality from suicide attempts for the major depressive episode and response health states. **Vortioxetine NICE** No evidence available to support extrapolation to recurrent MDEs or longer-term outcomes, or for mortality differences. **Esketamine TRD NICE** In model, accounted for all-cause mortality risk as well as an excess annual mortality for TRD, associated with suicide, of 0.47% (Bergfeld et al. 2018) linked to the MDE health state. It was assumed that half the excess mortality risk associated with suicide would still be present in the response state. Excess mortality is assigned to patients who	Section 4.7 and Table 14

	remain in the MDE health state and the response health state, independent of treatment arm. While having MDD or TRD may increase a person's risk for suicide, ESK-NS is not assumed to be linked to reducing or preventing suicidality. Additional mortality from suicide attempts was also explicitly modeled: first, for patients in each health state, the number of suicide attempts was calculated, then a proportion of these suicide attempts were considered fatal, giving the total of patients who died from suicide. As the trials in the ESK-NS clinical development programme do not provide comparative efficacy on completed suicide between ESK+AD and PBO+AD, there is no direct link between ESK-NS and mortality. Aligned to the available evidence, it was assumed that additional mortality from completed suicide is per health state and not by treatment arms ICER report of esketamine Assumed treatment does not directly affect mortality. Gender and age-specific all-cause mortality was sourced from the US tables of the Human Mortality Database. Mortality rates were adjusted to reflect increased all-cause mortality for patients with untreated TRD, smoothed using a moving average approach. **Cost-Effectiveness of Repetitive Transcranial Magnetic Stimulation versus Antidepressant Therapy for Treatment-Resistant Depression (Nguyen et al. 2015)** Mortality risk was assumed to be higher for patients in acute depression or in mild/moderate depression than in the general population.	

	Cost-effectiveness of Electroconvulsive Therapy vs Pharmacotherapy/Psychotherapy for Treatment-Resistant Depression in the United States (Ross et al. 2018) Did not assign excess mortality in base case, but did in scenario analysis. Base case: "We apply 2013 CDC life table data to this age/sex distribution, along with a relative mortality rate of 1.58 (95% CI, 1.47-1.70) for individuals with depression compared with the general population, from a 2014 meta-analysis. Combining these data yields an overall annual mortality probability of 0.00479." "Although some observational studies suggest that depression treatment may reduce suicide risk, 7 randomized studies have not found a significant effect. Hence, we make the conservative assumption that treatment does not affect mortality rates." In a scenario analysis, assessed incorporating an absolute mortality reduction of 0.07% for patients with remission/response of depression, reflecting 1 estimate of the reduction in suicide mortality with effective treatment. Results of the scenario analysis did not markedly change results.	
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? Equal value life years gained 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

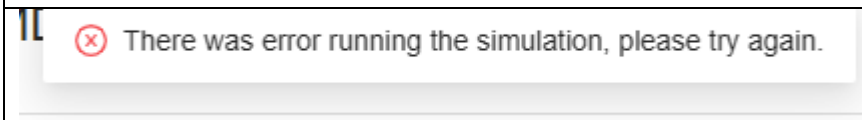
We tested the model by applying some common scenarios, with results shown in the technical report.	From the results in the technical report and test runs you have done, do the outcomes make sense and seem to have validity to you?	Section 8, technical report
Sensitivity Analyses		
Multiple inputs were 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? Yes, they seem plausible.	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? 7
 an error message.
How often do you think you might use the web-based tool? In 2024, we will likely use the tool frequently.
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? No – unfortunately I got an error message (through human error I'm sure!)
How might you leverage information provided by the tool specifically in your work or life? To understand the benefit of rapid-acting antidepressants when compared to conventional antidepressant use. To understand the cost-effectiveness of novel treatments for TRD, I.e. psychedelic therapy.
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)? Yes, a text based tutorial would be useful.
Are there any inputs that you wish to vary but that are not currently user-modifiable? Caregiver / family member costs
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? No, this is clear.
Are there additional treatment options or functions that you would like to see within the UI? Inclusion of novel, rapid acting anti-depressants such as esketamine or psilocybin treatment

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)? Equal value life years gained
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? This seems like an adequate approach
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)?

December 15, 2023

RE: Innovation and Value Initiative (IVI) Major Depressive Order (MDD) Model Technical Report - Response to Request for Public Comments

Contact Information	
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Dear members of the IVI MDD Value Model Committee,

Thank you for the opportunity to comment on the IVI-Major Depressive Disorder (MDD) Model Technical Report. At Janssen, we are supportive of a holistic approach to value assessment that is based first and foremost on the meaningful clinical benefits and health outcomes delivered to patients.

Janssen supports IVI's work on an open-source, patient-centric MDD model. This model can be helpful to inform key healthcare stakeholders, including patient advocates, clinicians, employers, policymakers, and payers, about the value of alternative treatment pathways. As a member of the MDD model multi-stakeholder Advisory Group, we have appreciated the level of collaboration to date and hope to continue further engagement on improving the model. We share IVI's goal of creating a flexible and comprehensive model for value analyses designed to inform the provision of care pathways for those with MDD.

Janssen's comments on the technical report are as follows:

General Comments and Feedback:

MDD- Focused Model

- Janssen commends IVI for creating a comprehensive patient-centric value model for adults with newly diagnosed MDD. We recommend parametrizing the MDD model to allow for specific symptom domains linked to underlying pathophysiology as precision psychiatry is developing to allow for more individualized treatment for MDD. Janssen is committed to ensuring access to the right drug for the right patient at the right time to allow patients and their families the chance to live a life without the burden of MDD. We also recommend the PHQ-9, a brief patient-reported, symptom-based severity questionnaire and important quality measure, be included in the model (Korenke et al 2000).
- Additionally, we recognize that the intent is to continuously improve the model, however given the major differences in clinical characteristics and treatment patterns for patients with TRD and newly diagnosed patients with MDD, we continue to recommend a separate model for TRD. In this version of the model if TRD is to be included, we recommend a mean total cost approach to parameterize TRD at the

population level instead of modeling individual treatments. This approach is preferred due to the lack of reliable input data for later lines of therapy. Future work could focus on building a tailored TRD model.

Redefine "Atypical Antidepressant" Treatment Group/Class

- The grouping of "atypical antidepressants" with bupropion, esketamine, ketamine, and mirtazapine is ambiguous since this term is not commonly used clinically nor classified in the treatment practice guidelines as a drug class (APA 2010). These drugs are mechanistically different from each other and should be distinguished. All therapies should be considered at the individual product level rather than at a class level due to differences in efficacy, safety and tolerability profiles, and potentially access. While we appreciate the difficulties in acquiring these data, differences between drugs within a class can be very important to patients and providers.
- The "atypical antidepressant" class is also described as available to be used for any line of treatment in the model. However, not all drugs in this grouping are recommended to be used first line (Gautam et al 2017, APA 2010). Some are infrequently used as first line in clinical practice. If this version of the model remains at the class level, we strongly urge IVI to correct this group/class (both name and drugs) before broader release of the model. Additionally, drugs that have been only studied in a subtype of MDD should not be included in this model.
- We continue to recommend excluding off-label treatments because of the lack of rigorous efficacy and safety data like that available for FDA-approved treatments. Simulation results including off-label treatments may be misleading.

Comorbidities

- When deciding which comorbid conditions to include in a model for patients with MDD, it is important to balance generalizability with available data inputs and the model's focus. We agree with the importance of including key comorbidities such as anxiety, as it is common and contributes substantially to the burden of MDD (Zhou et al 2017). Also, other comorbidities such as obesity, cardiovascular disease and metabolic conditions, which are common in the US, are important to consider when selecting treatment. Substance and alcohol use disorders are highly prevalent comorbidities among patients with MDD (Hunt et al 2020). We previously agreed with IVI to exclude moderate to severe substance and alcohol use disorders from the first version due to the complexity of modeling these comorbidities. However, given its importance, future work should focus on how to include these in the model.

Adverse Events Inputs:

- Serious adverse events (SAEs) are unlikely to occur with first line therapies in newly diagnosed MDD (Edinoff et al 2021, Yang 2010). SAEs may occur in therapies used later line. Due to the major differences in patient characteristics and treatment patterns with TRD who may require these later line therapies, we continue to recommend a separate TRD model.

Cost Inputs:

- The cost of cognitive behavioral therapy (CBT) can be estimated from a claims-based analysis among the MDD population. However, this will not capture the cost for patients receiving CBT without insurance, which may be substantial. To better capture the out-of-pocket costs of CBT for patients, we recommend survey research or reaching out to patient and clinician groups.
- We recommend reserving brain stimulation therapies for a separate TRD specific model as each of these non-pharmacological interventional therapies differ greatly from each other based on efficacy, safety, dosing, costs, site of administration and stigma/invasiveness. Additionally, brain stimulation therapies are typically reserved for patients with TRD (Mutz et al 2019).

Caregiver Inputs:

- We are unaware of any caregiver burden data for the newly diagnosed MDD patient population. Research on this issue is warranted given that MDD often affects not only the individual patient but also those closest to them. In the near-term, the caregiver burden for general mental health may possibly serve as a proxy estimate.

Use of QALYs:

- Janssen applauds IVI for creating a model that goes beyond the cost per quality-adjusted life-year (QALY) and considers different economic and clinical outcomes relevant to meet the needs of various stakeholders. However, Janssen is still concerned that the QALY is included in the model, as it is a discriminatory metric (Pettitt et al 2016). Janssen appreciates IVI's commitment to patient-centricity and health equity. We are very concerned that including the QALY in the open-source model will facilitate the use of this flawed metric.

Efficacy Rates and Data sources:

- OM1, Osmind, or Komodo can be used to estimate the effectiveness (PHQ-9) of different treatment options in the real world for the overall MDD population and by subgroups.

Treatment Gaps and Time from Diagnosis to First Treatment:

- Please see below suggested references:
    - Jain R, Laliberté F, Germain G, et al. Treatment patterns, health care resource utilization, and costs associated with use of atypical antipsychotics as first vs subsequent adjunctive treatment in major depressive disorder. *J Manag Care Spec Pharm*. 2023;29(8):896-906. doi:10.18553/jmcp.2023.29.8.896
    - Arnaud A, Suthoff E, Tavares RM, et al. The Increasing Economic Burden with Additional Steps of Pharmacotherapy in Major Depressive Disorder. *Pharmacoeconomics*. 2021;39(6):691-706. doi:10.1007/s40273-021-01021-w
    - McIntyre RS, Prieto R, Schepman P, et al. Healthcare resource use and cost associated with timing of pharmacological treatment for major depressive

disorder in the United States: a real-world study. *Curr Med Res Opin*. 2019;35(12):2169-2177. doi:10.1080/03007995.2019.1652053

- Seetasith A, Greene M, Hartry A, et al. Changes in healthcare resource use and costs associated with early versus delayed initiation of atypical antipsychotic adjunctive treatment in major depressive disorder. *J Med Econ*. 2018;21(9):888-901. doi:10.1080/13696998.2018.1484373

In-Text References:

American Psychiatric Association Work Group on Major Depressive Disorder. Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. October 2010. Available at: https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf

Edinoff AN, Akuly HA, Hanna TA, et al. Selective Serotonin Reuptake Inhibitors and Adverse Effects: A Narrative Review. *Neurology International.* 2021;13(3):387-401.

Gautam S, Jain A, Gautam M, et al. Clinical Practice Guidelines for the management of Depression. *Indian J Psychiatry*. 2017;59(1):S34-S50.

Hunt GE, Malhi GS, Lai HMX, et al. Prevalence of comorbid substance use in major depressive disorder in community and clinical settings, 1990-2019: Systematic review and meta-analysis. *J Affect Disord*. 2020;266:288-304. doi:10.1016/j.jad.2020.01.141

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Neurotech Network

From: Jen French <jfrench@neurotechnetwork.org>
Sent: Tuesday, December 5, 2023 3:23 PM
To: Public Comment
Subject: Public Comment on the IVI Model for MDD
Attachments: Neurotech Network_devices for depressionDec2023.pdf

Hello,
First, thank you for building the IVI-MDD Value Model. Working with organizations that represent people with lived experience, I appreciate a model like this to help with decision making. It is my understanding that this model is currently open for public comment. I hope you have received some valuable feedback at this point.

Here are a few points for your consideration with this model:
a. Your model provides a variety of treatment pathways. As you describe, they are pharma and non-pharma based treatments. However, the only technology option is rTMS. For Major Depression Disorders, there are other technology options. I have attached a listing from our neurotechnology directory. Understanding that some are not approved at this time. However, the concern I would like to raise with you is the following: the way that the IVI-MDD model is currently designed, it does not have the flexibility to add new devices in the future. This skews your model toward pharma and therapy-based treatments and away from technology based treatments.
b. In the choice of treatment pathways, the user may only choose rTMS after line 4 and there are no options to only choose brain stimulation. To this point, your model already does not allow for the flexibility for technology to be within the treatment ladder earlier in the pathway paradigm.
c. The Economic inputs for your model should be applauded. It appears that you have included many of the key cost considerations and burdens of MDD. The design in this area is well suited for this.
I hope you will take this feedback into consideration for your model.
Thank you again for the opportunity.
Best,
Jen

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