Charles Cutler, MD, MS, FACP

I am glad to see that major depressive disorder is the focus of the latest model protocol. It is a disorder that had wide ranging effects on the individual, workforce and healthcare system. I have a few comments that generally do not fit into the specific questions outlined in the public comment document.

1. **Major depression adds considerable complexity to the care of chronic physical health conditions** which are very common in people with MDD. Physical health providers often do not have a consistent process to identify major depression, so it often goes undiagnosed and untreated. Looking at the population where MDD is identified could provide useful insights into their physical health care. While I agree with the initial approach to identify cost as the costs directly related to MDD, it would be useful in the future to consider the additional costs and outcomes related to chronic disease in the presence of MDD.
2. Outside the research setting, MDD is often treated without **clear measures of severity** or response. While the studies used for the protocol will likely all have standard measures such well validated questionnaires, it is not clear how often these are used in practice. While standard measures of depression are not a therapy per se, they may be a critical component of management. As the studies are analyzed, comments on the different tools and their use may be valuable.
3. **Identifying psychotherapy use may be challenging.** In some parts of the country, it may be very difficult to obtain psychotherapy. Where it is available, it is not uncommon that the providers do not accept insurance so data from claims files may significantly underestimate the use. An additionally complexity, especially in the current pandemic environment is the use of virtual visits. Do we need to differentiate the data from in-person from virtual visits?
4. Medicaid health plans that have been successful in treating behavioral health disorders often provide additional **community and individual support services**. This includes community outreach workers, peer support specialists (people who have or had behavioral health conditions and are trained in outreach and support), and other social services. Some have found these services to be cost effective by increasing adherence to medical and follow up care. It would be helpful to consider these costs, but will pose a challenge both in measurement and the ability to compare across types of insurance (Medicaid, Medicare, Commercial) and geographies.
5. Finally, one simple measure could be very useful, but will nearly impossible to collect. That is the use of a **formal treatment plan or guideline**. It seems to be more challenging in behavioral health than in other conditions such as oncology, asthma or diabetes to identify the planned course of treatment.

#11

COMPLETE

Collector:	Web Link 1 (Web Link)
Started:	Monday, January 24, 2022 8:10:13 PM
Last Modified:	Monday, January 24, 2022 8:36:06 PM
Time Spent:	00:25:52
IP Address:	159.53.174.247

Page 1: Introduction

Q1

First and Last Name and degrees, if you would like included

Nelly Ganesan, MPH

Q2

Title

Executive Director, Community Engagement and Health Equity

Q3

Organization if Any

Morgan Health, JP Morgan Chase

Q4

Email Address

nelly.ganesan@jpmchase.com

Q5

Phone Number

2404725601

Q6 **Employer**

Please check the stakeholder group(s) that you represent

Page 2: General Questions

Q7

What are potential data sources and partners to address data gaps identified in the draft model protocol?

Patient-Reported Outcomes and Utilities: Noted in draft protocol were focus groups with patients and that this data would be integrated into future versions of the protocol. Potentially increasing patient focus groups that target specific sub populations could be an additional data source to fill gaps noted throughout the protocol.

Q8

What are your recommended data sources or technical approaches when multiple valid approaches exist?

n/a

Q9

What are ways that you envision using the IVI-OSVP model and what are practical applied research questions that you would like the model to address?

Given that race/ethnicity is being collected and generally we know that depression is underdiagnosed among Asians, Hispanics and American Indian/Alaskan Natives; can we look at differences in both treatment as well as access to therapies by race.

Q10

Additional Comments

n/a

Page 3: Specific Questions Referenced by Section

Q11

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? Section 6.1

This may not be the right place for this - but is it possible to also look at geography - I wonder if MDD diagnosis would vary based on location.

Q12

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)? Section 6.1.1

n/a

Q13

Do you have some suggestions on studies/data sources/methods that we can reference in extrapolating the long-term efficacy inputs? Section 6.5/8.2.3We 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?

n/a

Q14

Are there other model outputs that will be of interests to your organization? In what decision contexts will they be useful? Section 6.8

Included this above - but geography may be useful to determine where trials and/or other initiatives can be done as we think about "all healthcare is local."

Q15

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? Section 6.8

Not sure of the ability to extract this data, but conducting a social media scrape may also be a good data source to examine suicide behavior, depression and/or anything linked to mental health.

Q16

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? Section 6.9.3

Yes

Q17

We specified scenarios in which individuals in our simulation will move to a new line of treatment. Section 6.9.3.1Are 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?

If individuals have a negative reaction, are pregnant, and/or may be subject to significant side effects they may consider different lines of treatment.

Q18

Is it reasonable to assume the same sets of model inputs (efficacy and safety) for the first and second lines of treatment? Section 6.9.3.2In 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?

n/a

Q19

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). Section 7.3Is 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?

The first approach. Claims for primary and secondary diagnosis codes should address Rx costs.

Q20

Are there key adverse events that have a significant clinical and economic impact that we should include in the model? Section 7.1.2We 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?

n/a

Q21

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? Section 7.2

n/a

Q22

For psychotherapy, what is a reasonable assumption for the length of a visit and for duration of psychotherapy to include (Table 10 and 11)? Section 7.3

n/a

Q23

Do you have any suggestion on studies or data sources that can inform the calculation of informal caregiving burden or costs? Section 7.3.5.2

RAND Study 2015 The Opportunity Costs of Informal Elder-Care in the United States - http://dx.doi.org/10.1111/1475-6773.12238

integrated burden model of informal caregiving - https://pubmed.ncbi.nlm.nih.gov/17007487/

Q24

Appendix H describes some of the novel questions or research opportunities that the model could help inform. What specific use cases or decision contexts should be prioritized? What are other important use cases or decisions that this model could help inform? Appendix H

Would consider including caregiver burden in the employer subgroup - as caring for a spouse/child with MDD may impact productivity as well.

Q25	**Yes**

May we contact you with follow-up questions if they arise?

#9

COMPLETE

Collector:	Web Link 1 (Web Link)
Started:	Tuesday, January 18, 2022 1:42:17 PM
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Time Spent:	Over a day
IP Address:	72.89.248.222

Page 1: Introduction

Q1

First and Last Name and degrees, if you would like included

Nathaniel Z Counts, JD

Q2

Title

SVP, Behavioral Health Innovation

Q3

Organization if Any

Mental Health America

Q4

Email Address

ncounts@mhanational.org

Q5 **Respondent skipped this question**

Phone Number

Q6 **Patient or Caregiver**

Please check the stakeholder group(s) that you represent

Page 2: General Questions

Q7

What are potential data sources and partners to address data gaps identified in the draft model protocol?

Respondent skipped this question

Q8

What are your recommended data sources or technical approaches when multiple valid approaches exist?

Respondent skipped this question

Q9

What are ways that you envision using the IVI-OSVP model and what are practical applied research questions that you would like the model to address?

We envision using the model to make the case for increased access and investment in mental health services with public and private payers, to examine how different policy options that impact key model parameters might affect health and cost outputs, and to understand how new therapies in the pipeline might impact mental health and the mental health treatment system.

Q10

Additional Comments

Congratulations on creating such an incredible and comprehensive document. It advances the field and sets a critical foundation for future work, while ensuring that the initial model remains feasible. We will be thrilled to see the next stages.

One comment I had was that I was not sure how random remission and response (i.e. partial or complete response that occurs in those not treated or that occurs in those treated but is independent of the treatment) was captured in the model. In my understanding, random remission is quite common (“12.5% of people with untreated depression remitted without treatment within 12 weeks” https://www.sciencedirect.com/science/article/pii/S0165032721010053). Not including random remission in the model may overstate the effects of treatment.

Page 3: Specific Questions Referenced by Section

Q11

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? Section 6.1

Respondent skipped this question

Q12

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)? Section 6.1.1

Respondent skipped this question

Q13

Do you have some suggestions on studies/data sources/methods that we can reference in extrapolating the long-term efficacy inputs? Section 6.5/8.2.3We 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?

Respondent skipped this question

Q14

Are there other model outputs that will be of interests to your organization? In what decision contexts will they be useful? Section 6.8

Respondent skipped this question

Q15

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? Section 6.8

Respondent skipped this question

Q16

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? Section 6.9.3

Respondent skipped this question

Q17

We specified scenarios in which individuals in our simulation will move to a new line of treatment. Section 6.9.3.1Are 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?

Respondent skipped this question

Q18

Is it reasonable to assume the same sets of model inputs (efficacy and safety) for the first and second lines of treatment? Section 6.9.3.2In 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?

Respondent skipped this question

Q19

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). Section 7.3Is 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?

I would recommend the "bottom-up" approach. In a sense, the two approaches ask two different questions. Top-down asks: how efficient is a current treatment pathway now? Bottom-up asks: how efficient would a treatment pathway be, if it was effectively implemented? The second question seems to be the more normatively desirable question for the model.

Along these lines, it may also be good to consider the inclusion of an additional model input: incentives for implementation. Some studies analyze the elasticity of healthcare prices on supply as well as the role of upfront payments in promoting access. Model users could also explore the effect of paying more or offering upfront incentives for implementation on the model outputs, which would be really useful for policy.

Q20

Are there key adverse events that have a significant clinical and economic impact that we should include in the model? Section 7.1.2We 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?

Respondent skipped this question

Q21

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? Section 7.2

Respondent skipped this question

Q22

Respondent skipped this question

For psychotherapy, what is a reasonable assumption for the length of a visit and for duration of psychotherapy to include (Table 10 and 11)? Section 7.3

Q23

Respondent skipped this question

Do you have any suggestion on studies or data sources that can inform the calculation of informal caregiving burden or costs? Section 7.3.5.2

Q24

Appendix H describes some of the novel questions or research opportunities that the model could help inform. What specific use cases or decision contexts should be prioritized? What are other important use cases or decisions that this model could help inform? Appendix H

As noted, the opportunity to model additional incentives that may improve the supply or quality of services would be critical. Theoretically most of these services are “available” today, but there are gaps in understanding about how to increase access to them.

Q25

Respondent skipped this question

May we contact you with follow-up questions if they arise?

PIPC Partnership to Improve Patient Care

January 19, 2022

Jennifer Bright, MPA
Executive Director
Innovation and Value Initiative
2 Bethesda Metro Center #850
Bethesda, MD 20814

Dear Ms. Bright:

The Partnership to Improve Patient Care (PIPC) is pleased to provide feedback on the Innovation and Value Initiative's (IVI) draft model protocol on major depressive disorder (MDD). We appreciate the process you have set forward providing transparency into and encouraging stakeholder feedback on your model and process. This type of transparency and robust stakeholder engagement, particularly from patients and providers, leads to stronger models that more accurately convey value to patients and society.

Upon reviewing the materials, PIPC would suggest you consider the following:

IVI should reframe how it incorporates mortality multipliers into the model to mitigate risk of underestimating the value of successful treatment.

IVI rightly states that there is strong empirical evidence that MDD patients have higher mortality rates than the general population.[1,2] The problem with the sources being used is that they are longitudinal in nature and have a sample of people defined as having been diagnosed with MDD at a single point in time. These estimates will therefore include people who are in any of the three states of response described in the model. As such, there is no distinction for what state a patient was in: non-response, partial or complete response.

This leads us to the more relevant question of how these mortality multipliers are applied in the model. Is the suggestion that the MDD multiplier be applied only to non-responders? If so, the three studies cited by IVI may be inappropriate sources for the requisite mortality multiplier(s) as each likely reports the average effect of MDD on mortality for patients distributed across all three states. The mortality multiplier is likely to be much higher among patients in the no-response state as compared to among patients in the complete or partial response states.

Alternatively, if we apply such an 'average' multiplier to all MDD states rather than to the no-response state alone, the model will observe no survival benefit associated with successful treatment. This would incorrectly imply the same probability of death for patients in the no-response state as for patients in the complete- and partial-response states.

[1] Pratt LA, Druss BG, Manderscheid RW, Walker ER. Excess mortality due to depression and anxiety in the United States: results from a nationally representative survey. General hospital psychiatry. 2016 Mar 1;39:39-45.
[2] Chiu M, Vigod S, Rahman F, Wilton AS, Lebenbaum M, Kurdyak P. Mortality risk associated with psychological distress and major depression: A population-based cohort study. Journal of Affective Disorders. 2018 Jul 1;234:117-23

With this in mind, we are concerned that applying the same 'average' multiplier to all MDD states will lead directly to underestimating the absolute health gain from any successful treatment in the model and would encourage IVI to consider how to appropriately handle this challenge.

The model as designed is unlikely to be able to address the issue of treatment heterogeneity. We would suggest broadening the question of how to estimate the accrual of 'marginal value' from new therapies.

Most treatments are effective for only a reasonable portion of all potential beneficiaries. Unfortunately, most current methods to estimate cost-effectiveness rely heavily on RCT data for estimates of average treatment effect (ATE). RCTs are designed to produce a mean population ATE and not to directly produce estimates of incremental effect of treatment for individuals.[3] As such they provide scarce information on the heterogeneity of treatment effect that is useful for translating what is mean efficacy of a new therapy into what is population specific effectiveness of a new therapy.[4] It is one of the many limitations of RCTs for informing practical health policy, and has been discussed and dissected at length in the literature.[5,6,7,8]

This means if a new treatment, and in particular a new mechanism of action or 'type' of treatment, is more efficacious in populations for which traditional therapies have previously been largely ineffective - even if the ATE across the entire population is no greater than that of current treatments - the model as designed would not allow for such nuances of health benefit for subpopulations to be teased out. As IVI values insight into a broader question of estimating the value of innovation in healthcare it should evolve away from the traditional cost-effectiveness methods' reliance on the RCT and ATE framework and develop approaches that provide insight into the value of introducing new types of therapy at the subpopulation level. This is an area in which IVI could add huge value to the current lexicon of value assessment methodologies.

IVI should not use the quality-adjusted life year (QALY) in its models.

IVI has made some very positive strides towards making value assessment more accurately represent value to patients, not just cost and value to payers. We are thankful for the efforts IVI has put into

[3] Stevens W, Normand C. Optimisation versus certainty: understanding the issue of heterogeneity in economic evaluation. Social science & medicine. 2004 Jan 1;58(2):315-20.
[4] Basu A, Grieve R, Pritchard D, Stevens W. One size does not always fit all in value assessment. Am J Manag Care. 2019 Nov 1;25(11):540-2.
[5] Deaton A, Cartwright N. Understanding and misunderstanding randomized controlled trials. Social Science & Medicine. 2018 Aug 1;210:2-1.
[6] Mustafa FA. Notes on the use of randomised controlled trials to evaluate complex interventions: Community treatment orders as an illustrative case. Journal of evaluation in clinical practice. 2017 Feb;23(1):185-92.
[7] Anjum RL, Copeland S, Rocca E. Medical scientists and philosophers worldwide appeal to EBM to expand the notion of 'evidence'. BMJ evidence-based medicine. 2020 Feb 1;25(1):6-8.
[8] Anjum RL, Copeland S, Rocca E. Rethinking causality, complexity and evidence for the unique patient: a CauseHealth Resource for healthcare professionals and the clinical encounter. Springer Nature; 2020.

moving value assessment in a patient-centered direction, that being said, to be truly patient-centered, IVI must stop using the discriminatory QALY in its models.

QALYs are discriminatory in design and implementation. For this reason, in 2019, the National Council on Disability, an independent federal agency advising Congress and the administration on disability policy, issued a report finding that use of the QALY would be contrary to United States civil rights and disability law.[9] The United States has a thirty-year, bipartisan track record of opposing the use of the QALY and similar discriminatory metrics and has established appropriate legal safeguards to mitigate their use. There is currently a ban on use of the QALY or similar metrics in Medicare decision-making.[10] In 1992, the U.S. Department of Health and Human Services established that Oregon's efforts to utilize a cost-effectiveness standard in Medicaid would violate the Americans with Disabilities Act.[11]

PIPC urges IVI to build on this precedent and cease using the QALY in its models. We encourage IVI instead to build on the strides it has made in patient-centric value assessment by investing in alternative metrics.

Additionally, we have compiled answers to several of the specific questions on which you have requested input:

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?

The IVI-MDD model protocol draft indicates that the target population for the model protocol includes adults diagnosed with MDD without diagnosis of other psychiatric and physiological comorbidities. In reality, the majority of MDD patients have comorbidities so limiting the population only to those without comorbidities risks building a model that will only represent a small proportion of the full population of need. Studies suggest that the majority of MDD patients have at least one other psychiatric disorder. With this in mind, in order to replicate a real-world population, we would recommend running the model for both the primary population outlined in the protocol, plus at least one other index patient group with a significantly common comorbidity.

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?

[9] https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf

[10] 111th Congress of the United States of America. (2010). H.R. 3590 The Patient Protection and Affordable Care Act. *Section 1182*. Washington, DC.

[11] https://www.nytimes.com/1992/09/01/opinion/l-oregon-health-plan-is-unfair-to-the-disabled-659492.html

- If so, do you have any recommendation on data sources?

Delayed efficacy has long been a problematic aspect of traditional treatments for MDD, often being seen as a major driver of early discontinuation of treatment.[12] If you choose a cycle length of 3 months, a practical way to link short-term response data with long-term risk of relapse and retreatment would be to differentiate between fast and slow responders.

Several studies have shown that those that respond quickly in the first 2-6 weeks of treatment have significantly improved downstream outcomes, compared to those who are slow to respond to treatment in that early period. Multiple studies have estimated that slow responders in this period are between four to eight times more likely to relapse at multiple stages further into treatment; evidence suggest higher relapses rates at six, twelve, and eighteen months for slower responders.[13,14,15] As such, these two subtypes would have different transition matrices reflecting differing likelihoods of relapse and retreatment over time.

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?

The most common source for efficacy across lines of therapy used in cost-effectiveness modeling in MDD has been the data from the Sequenced Treatment Alternatives to Relieve Depression (STARD) series of studies undertaken by the National Institute of Mental Health.[16,17] This paper has tables estimating rate of response up to four lines of therapy. This is quite old so it may only afford data for a subset of the available therapies you are looking at.

---

[12] Samples H, Mojtabai R. Antidepressant self-discontinuation: results from the collaborative psychiatric epidemiology surveys. Psychiatric Services. 2015 May 1;66(5):455-62.
[13] Lutz W, Stulz N, Köck K. Patterns of early change and their relationship to outcome and follow-up among patients with major depressive disorders. Journal of affective disorders. 2009 Nov 1;118(1-3):60-8.
[14] Roca M, Baca E, Caballero L, de Polavieja PG, Casillas M, Valladares A, Gilaberte I. Early response and remission as predictors of a good outcome of a major depressive episode at 12-month follow-up: a prospective, longitudinal, observational study. The Journal of clinical psychiatry. 2011 Oct 4;72(2):5328.
[15] Schlagert HS, Hiller W. The predictive value of early response in patients with depressive disorders. Psychotherapy Research. 2017 Jul 4;27(4):488-500.
[16] Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR* D report. American Journal of Psychiatry. 2006 Nov;163(11):1905-17.
[17] Ross EL, Zivin K, Maixner DF. Cost-effectiveness of electroconvulsive therapy vs pharmacotherapy/psychotherapy for treatment-resistant depression in the United States. JAMA psychiatry. 2018 Jul 1;75(7):713-22.

One issue with the assumption needed to back up your hazard rate approach outlined above is that it instantly assumes that any new treatment will have the same relationships between initial efficacy and later effectiveness waning, as for other treatments. This distinction is important because two different treatments may have a very different structure to their long-term effectiveness. One may work initially with a high level of efficacy but have a high level of waning so that by the fourth or fifth line of therapy it is barely effective at all, whereas another may start with a lower level of initial efficacy (first line of therapy), but 'maintain' that level of effectiveness without waning over many treatment cycles. Given the importance of a component of long-term maintenance of efficacy, to assume the same rate of waning for all therapies would do a disservice to a treatment that may have a more robust maintenance, and also would discourage innovators from developing new therapies or approaches that achieve higher rates of maintenance of efficacy for long periods of time.

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?

Both top-down and bottom-up costing approaches have their own challenges. Bottom-up tends to be limiting in that you include only the costs you think are relevant. Top-down can include costs that are irrelevant and require more validation from multiple other sources of data. The better solution is to use a top-down source of cost that can allow potential hidden costs to be identified, by design. With this approach, you can simply compare an MDD population to a matched control, and any marginal difference can be allocated to MDD. Greenberg et al. use this method for MDD. These studies look at direct costs and all other healthcare costs as well as indirect costs, such as burden of suicides and work loss per patient.[18,19]

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?

IVI has highlighted three potential sources for health state utility values in its protocol. It is important to try to tease out randomized clinical trial populations when estimating health state utility value (HSUV) in MDD populations, as the population is prone to strong Hawthorne effects,[20] which can lead to

[18] Greenberg PE, Fournier AA, Sisitsky T, Simes M, Berman R, Koenigsberg SH, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2010 and 2018). Pharmacoeconomics. 2021 Jun;39(6):653-65.
[19] Greenberg PE, Fournier AA, Sisitsky T, Pike CT, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). The Journal of clinical psychiatry. 2015 Feb 25;76(2):0-5.
[20] Benedetti F, Carlino E, Piedimonte A. Increasing uncertainty in CNS clinical trials: the role of placebo, nocebo, and Hawthorne effects. The Lancet Neurology. 2016 Jun 1;15(7):736-47.

exaggerated utility values for baseline untreated and non-response states in RCTs.[21] If Brockbank[22] is chosen, any estimate should be limited to non-RCT sources for utility values. Alternatively, Revicki and Wood[23] would be the best source for the United States. Here the utility weight for no-treatment / no-response was 0.30 for example, whereas in RCT studies non-responders / no-treatment states can be artificially high with Brockbank suggesting between 0.5 and 0.7.

Conclusion

We are appreciative of the robust and transparent process you have put forward in which stakeholders may participate. Thank you for considering our input, and we are happy to provide additional comments as helpful.

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care

[21] McCarney R, Warner J, Iliffe S, Van Haselen R, Griffin M, Fisher P. The Hawthorne Effect: a randomised, controlled trial. BMC medical research methodology. 2007 Dec;7(1):1-8.
[22] Brockbank J, Krause T, Moss E, Pedersen AM, Mørup MF, Ahdesmäki O, Vaughan J, Brodtkorb TH. Health state utility values in major depressive disorder treated with pharmacological interventions: a systematic literature review. Health and quality of life outcomes. 2021 Dec;19(1):1-7.
[23] Revicki DA, Wood M. Patient-assigned health state utilities for depression-related outcomes: differences by depression severity and antidepressant medications. Journal of affective disorders. 1998 Feb 1;48(1):25-36.

Society for Women's Health Research

January 25, 2022

Jennifer Bright, MPA
Executive Director
Innovation and Value Initiative
917 Prince Street
Alexandria, VA 22314

Rick Chapman, PhD
Chief Scientific Officer
Innovation and Value Initiative
917 Prince Street
Alexandria, VA 22314

Re: Innovation and Value Initiative Comment Period on the Major Depressive Disorder Draft Model Protocol

Dear Ms. Bright and Dr. Chapman,

On behalf of the Society for Women's Health Research (SWHR), I am writing to provide comments on the Innovation and Value Initaitive (IVI) draft protocol of IVI's economic model for major depressive disorder (MDD). SWHR appreciated the opportunity to provide comments in May on the value model's scope and is glad to now share thoughts on the draft protocol.

For more than 30 years SWHR has been dedicated to promoting research on biological sex differences in disease and improving women's health through science, policy, and education. SWHR has brought attention to diseases and conditions that disproportionately or differently impact women—like MDD. MDD is nearly twice as likely to occur in women than men, with lifetime prevalence rates of 21% and 12%, respectively.[1] This increased prevalence for women emerges around puberty and continues throughout the lifespan.[2] While it is unclear exactly why the gender gap in MDD exists, hormonal changes, inherited traits, and stressful personal life circumstances and experiences have all been associated with a higher risk of depression in women.

Given MDD's prevalence in women, SWHR is pleased to provide the following comments on IVI's economic model for MDD for consideration:

[1] Sloan, DM, & Sandt, AR (2006). Gender differences in depression. *Women's Health, 2*(3), 425-434.
[2] Albert, PR (2015). Why is depression more prevalent in women? *Journal of Psychiatry & Neuroscience, 40*(4), 219-221. doi: 10.1503/jpn.150205

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Target Population

SWHR appreciates IVI's work to ensure that the model design reflects real-world treatment sequences and key value elements from a societal perspective, and we are glad to see that the model design will allow users to specify subgroups, including gender, and/or use subgroup-specific inputs to make comparisons across them. However, we would strongly encourage IVI to ensure that its protocol includes both sex and gender to reveal the biological and environmental and social impacts across pouplations. It is well-known that symptom presentation varies by gender, and the differences in prevalence, presentation, and coping are important to consider in determining the value of treatments. There also exists some evidence that certain treatments may be more effective depending on an individual's biological sex—for example, selective serotonin reuptake inhibitors (SSRIs) may be more effective in the presence of estrogen.[3] Having the ability to disaggregate data based on factors such as sex and gender will be important for answering IVI's prioritized research questions regarding the societal burden of untreated or under-treated MDD, differences in model outcomes across subgroups compared with the overall population, and "low-value" care in real-world treatment sequences.

Of note, SWHR encourages IVI to revisit MDD with respect to preconception, as well as prenatal and postpartum, women. "Pregnancy" is not mentioned once within the draft economic model, and "postpartum" is mentioned just once. SWHR recognizes that separate recommendations are available for postpartum depression, but we suggest IVI explicitly and operationally define postpartum depression within the list of exclusion criteria. There remains a great deal of debate as to whether a depressive episode occuring during the postpartum period is sufficiently different than MDD episodes that occur outside of this life stage. Evidence as to the clarity and certainty of this distinction is mixed and largely depends on how the postpartum period is classified (e.g., depression occuring early in the postpartum period—up to eight weeks postpartum—may be distinct from depression with onset during the later postpartum period, with the latter more similar to typical MDD episodes).[4]

Patient Experience

Women are frequently primary caregivers for their family members; between 53 and 68 percent of caregivers are estimated to be women.[5] These roles can be either informal or formal: hands-on caregiver, case manager, companion, decision-maker, and advocate.

SWHR was pleased to see that IVI's model incorporated caregiving, noting that it "is a concern in the MDD community." Yet, while SWHR was glad to see that factors related to informal caregiving were included in the model, the focus was on individuals with MDD who have a caregiver. SWHR would encourage IVI to revisit its decision that

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[3] Gorman, JM. (2006). Gender differences in depression and response to psychotropic medication. *Gender Medicine, 3*(2), 93-109. doi: 10.1016/s1550-8579(06)80199-3.

[4] Batt, MM, et al. (2020). Is postpartum depression different from depression occurring outside of the perinatal period? A review of the evidence. *Focus.* doi: 10.1176/appi.focus.20190045

[5] Family Caregiver Alliance. Who Are Family Caregivers? https://www.apa.org/pi/about/publications/caregivers/faq/statistics. Accessed 25 January 2022.

"other concerns about caregiving, including that some caregivers have lost work, have changed jobs, or have suffered mentally and/or physically…are not planned to be incorporated in the model." Reports suggest that up to 20% of family caregivers suffer depression—a rate approximately twice that of the general population. In general, women who provide care for family members experience higher rates of depression than men.[6] SWHR strongly recommends the needs and input of individuals who have MDD and who are also caregivers for others be considered when evaluating patient needs and experiences.

Also related to patient experience is the economic burden of MDD, and specifically, the economic burden of MDD on women. A draft economic model such as IVI's could help determine whether insurance coverage and out-of-pocket costs are imbalanced for women and how that economic burden impacts their care. According to findings from the 2020 Kaiser Family Foundation's Women's Health Survey, among women who have been to the doctor in the past two years (93%), uninsured women (55%) are significantly less likely to have discussed mental health issues with their health care provider than women with health insurance (70%)—and further, Black (61%) and Asian (60%) women are less likely to have had this discussion with their provider than white women (72%).[7] SWHR appreciates IVI's comment that studies of the national economic burden tend not to be granular enough to differentiate between treatments, and therefore sees the value of utilizing a bottom-up approach for identifying health costs to capture this information, as it is critical to one's experience.

***

SWHR appreciates the opportunity to comment on this important economic model. If you have questions, please do not hesitate to reach out to me at kathryn@swhr.org.

Kathryn G. Schubert, MPP
President and Chief Executive Officer
Society for Women's Health Research

[6] Family Caregiver Alliance. Caregiver depression: A silent health crisis. https://www.caregiver.org/resource/caregiver-depression-silent-health-crisis/

[7] Long, M, Frederiksen, B, Ranji, U and Salganicoff, A. Women's Health Care Utilization and Costs: Findings from the 2020 KFF Women's Health Survey. Published April 2021, https://www.kff.org/womens-health-policy/issue-brief/womens-health-care-utilization-and-costs-findings-from-the-2020-kff-womens-health-survey/view/footnotes/ Accessed 19 Jan 2022.

#11

COMPLETE

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Time Spent:	00:10:36
IP Address:	100.15.204.68

Page 1: Introduction

Q1

First and Last Name and degrees, if you would like included

Becky Yowell

Q2

Title

Director, Reimbursement Policy and Quality

Q3

Organization if Any

American Psychiatric Association

Q4

Email Address

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Q5

Phone Number

703-399-5580

Q6 **Clinician**

Please check the stakeholder group(s) that you represent

Page 2: General Questions

Q7

Respondent skipped this question

What are potential data sources and partners to address data gaps identified in the draft model protocol?

Q8

Respondent skipped this question

What are your recommended data sources or technical approaches when multiple valid approaches exist?

Q9

What are ways that you envision using the IVI-OSVP model and what are practical applied research questions that you would like the model to address?

It would be interesting to have the capability to compare outcomes and costs for patients seen in primary care and specialty care settings.

Comparison of treatment options based on outcomes and cost would be valuable information. The model could inform the impact of measurement-based care (MBC) through the use of PROMs to measure patient outcomes. Consideration of other evidence-based models of care such as Collaborative Care on outcomes and cost would also be informative. In addition, there is value in understanding the impact care management activities have on the overall cost of care, including length of time in treatment. Some understanding of the impact of tele-mental health on overall costs of care is also something of interest. The model could help inform the development of quality measures focused on improved outcomes.

Q10

Additional Comments

We are generally supportive of the model protocol. We encourage more in-depth analyses of racial/ethnic/cultural diversity as we know the treatments and outcomes for minoritized populations are vastly different.
There is a strong evidence-base supporting the use of measurement-based care (MBC) to improve outcomes and reduce costs:
Scott et al. Using Measurement-Based Care to Enhance Any Treatment. Cognitive and Behavioral Practice. 2015;22(1):49-59.
Fortney et al. A Tipping Point for Measurement-Based Care. Psychiatr Serv. 2017 Feb 1;68(2):179-188.
Slade et al. Use of standardised outcome measures in adult mental health services: randomised controlled trial. Br J Psychiatry. 2006 Oct;189:330-6.
Priebe et al. The impact of routine outcome measurement on treatment processes in community mental health care: approach and methods of the MECCA study. Epidemiol Psychiatr Soc. 2002 Jul-Sept;11(3):198-205.
Capturing the impact and importance of MBC within the model would be valuable, as would consideration of care management activities (patient engagement, assistance with social determinants of health, etc.).
It would also be helpful to have more information on ECT, or at least some additional discussion of the lack of data on ECT, as we know that ECT still remains one of the most effective treatments for resistant depression.
Finally, it is important the outcomes measured by the model are based as much as possible on patient-reported outcome measures (PROMs).

Page 3: Specific Questions Referenced by Section

Q11

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? Section 6.1

Respondent skipped this question

Q12

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)? Section 6.1.1

Respondent skipped this question

Q13

Do you have some suggestions on studies/data sources/methods that we can reference in extrapolating the long-term efficacy inputs? Section 6.5/8.2.3We 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?

Respondent skipped this question

Q14

Are there other model outputs that will be of interests to your organization? In what decision contexts will they be useful? Section 6.8

It would be interesting to have the capability to compare outcomes and costs for patients seen in primary care and specialty care settings.

Q15

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? Section 6.8

Respondent skipped this question

Q16

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? Section 6.9.3

No,

Please comment here: :

This depends on the patient and their (medical/psychiatric/family) history. For some patients, ECT (and other neuromodulation treatments) will be used earlier in a treatment course, especially in subsequent episodes if it has been helpful in the past.

Q17

Respondent skipped this question

We specified scenarios in which individuals in our simulation will move to a new line of treatment. Section 6.9.3.1Are 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?

Q18

Is it reasonable to assume the same sets of model inputs (efficacy and safety) for the first and second lines of treatment? Section 6.9.3.2In 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?

We don’t have specific suggestions but if you want to be more comprehensive you will need to look beyond the meta-analyses.

Q19

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). Section 7.3Is 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?

The bottom-up approach seems a more reasonable approach. As noted in the report, this may allow for better representation of the indirect costs associated with MDD and treatments for MDD.

Q20

Are there key adverse events that have a significant clinical and economic impact that we should include in the model? Section 7.1.2We 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?

It is important to consider adverse events broadly, including the impact on income/employment and quality of life, in addition to specific costs tied to side-effects or monitoring requirements of specific medications. For some of these, patient-reported measures will be essential to determining the true impact in populations.

Q21

Respondent skipped this question

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? Section 7.2

Q22

For psychotherapy, what is a reasonable assumption for the length of a visit and for duration of psychotherapy to include (Table 10 and 11)? Section 7.3

Some consideration should be given to the variation in practice patterns across provider groups. PCPs will use primarily E/M codes unless they have a therapist as part of the practice. Psychiatrists would bill E/M codes at each visit, which may also include psychotherapy. Psychologists, social workers, and other therapists would primarily bill psychotherapy services.

The list of CPT codes should include 90791 and 90792, which describe the initial evaluation done by therapists (90791) and psychiatrists* (90792). You may also want to consider including group psychotherapy (90853), which is a modality of care for patients diagnosed with depression.
We support the expansion, when possible, of the range of evidence-based therapeutic interventions.

*psychiatrists can also choose to use the 99202-99205 series codes

Q23

Respondent skipped this question

Do you have any suggestion on studies or data sources that can inform the calculation of informal caregiving burden or costs? Section 7.3.5.2

Q24

Appendix H describes some of the novel questions or research opportunities that the model could help inform. What specific use cases or decision contexts should be prioritized? What are other important use cases or decisions that this model could help inform? Appendix H

Comparison of treatment options based on outcomes and cost would be valuable information. The model could inform the impact of measurement-based care (MBC) through the use of PROMs to measure patient outcomes. Consideration of other evidence-based models of care such as Collaborative Care on outcomes and cost would also be informative. In addition, there is value in understanding the impact care management activities have on the overall cost of care, including length of time in treatment. Some understanding of the impact of tele-mental health on overall costs of care is also something of interest. The model could help inform the development of quality measures focused on improved outcomes.

Q25

Yes

May we contact you with follow-up questions if they arise?

#3

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IP Address:	185.152.72.11

Page 1: Introduction

Q1

First and Last Name and degrees, if you would like included

Shane O'Connor

Q2

Title

Research analyst

Q3

Organization if Any

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Q4

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Q5

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N/A

Q6

Please check the stakeholder group(s) that you represent

Researcher,

Industry

Page 2: General Questions

Q7

What are potential data sources and partners to address data gaps identified in the draft model protocol?

OM1 - Data vendor that has a unique behavioural dataset. Linked EMR and claims data source with 160k MDD patients.

Q8

What are your recommended data sources or technical approaches when multiple valid approaches exist?

N/A

Q9

What are ways that you envision using the IVI-OSVP model and what are practical applied research questions that you would like the model to address?

Understand patient journey in MDD / TRD.

Q10 **Respondent skipped this question**

Additional Comments

Page 3: Specific Questions Referenced by Section

Q11

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? Section 6.1

N/A

Q12

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)? Section 6.1.1

N/A

Q13

Do you have some suggestions on studies/data sources/methods that we can reference in extrapolating the long-term efficacy inputs? Section 6.5/8.2.3We 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?

This was an issue we ran into during our SLR on therapies for treatment-resistant depression. I'm not aware of any robust studies that look at long-term efficacy outputs.

Q14

Are there other model outputs that will be of interests to your organization? In what decision contexts will they be useful? Section 6.8

This seems like a comprehensive list.

Q15

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? Section 6.8

https://www.jmcp.org/doi/10.18553/jmcp.2020.26.8.987?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

Table 2 of this paper illustrates suicidal attempts and ideation in TRD and non-TRD MDD cohorts.

Q16

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? Section 6.9.3

No,

Please comment here: :

ECT is rarely prescribed as a 3rd and 4th line treatment in MDD (TRD) patients. Somatic treatments are usually reserved for later lines.

Q17

We specified scenarios in which individuals in our simulation will move to a new line of treatment. Section 6.9.3.1Are 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?

I'm not a clinician so I can't comment on this.

Q18

Is it reasonable to assume the same sets of model inputs (efficacy and safety) for the first and second lines of treatment? Section 6.9.3.2In 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?

Respondent skipped this question

Q19

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). Section 7.3Is 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?

I would imagine the sources that list the "top-down" costs initially derived the overall cost using a "bottom-up" approach. Using your own bottom-up approach seems like it would be duplication of work.

Q20

Are there key adverse events that have a significant clinical and economic impact that we should include in the model? Section 7.1.2We 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?

Respondent skipped this question

Q21

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? Section 7.2

Simpson KN, Welch MJ, Kozel FA, Demitrack MA,
Nahas Z. Cost-effectiveness of transcranial magnetic stimulation in the treatment of major depression: a health economics analysis. Advances in Therapy. 2009;26(3):346-368. doi:10.1007/s12325-009-0013-x

This is CE model that outlines different utilities based on severity.

Q22

For psychotherapy, what is a reasonable assumption for the length of a visit and for duration of psychotherapy to include (Table 10 and 11)? Section 7.3

N/A

Q23

Do you have any suggestion on studies or data sources that can inform the calculation of informal caregiving burden or costs? Section 7.3.5.2

N/A

Q24

Appendix H describes some of the novel questions or research opportunities that the model could help inform. What specific use cases or decision contexts should be prioritized? What are other important use cases or decisions that this model could help inform? Appendix H

I think this is a comprehensive list.

Q25 **Yes**

May we contact you with follow-up questions if they arise?

Public Comment on the IVI Draft Model Protocol for Major Depressive Disorder

The following comments on the Innovation and Value Initiative (IVI) draft model protocol for major depressive disorder (MDD) were made from the perspective of the health economics consultancy, BresMed.

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General comments

Topic	Comment
Model structure	It is noted that the guidelines state there is no evidence to suggest a clinically meaningful difference in response rates across common medication classes (TCAs, SSRIs, SNRIs, MAOIs, and other specified agents). Have you considered including the option to apply a cost-minimisation model as a simplified approach? In section 6.9.2, it is proposed that the health states will not be linked to a score on clinical measure given there is no consensus on the score that reflects improvement or response. Whilst we agree that this would increase flexibility in usability of the model, users should be cautioned that comparisons informed by multiple efficacy data sets which vary in clinical measurement instrument and event (e.g. response) definition could result in biased and misleading outcomes. Remission is to be captured in the model by tracking individuals who remain in the complete response health state for three consecutive cycles and reducing their treatment to a maintenance dose or to no treatment. Whilst we agree that capturing the reduced treatment costs associated with a patient achieving remission will be an important factor in the model, we believe other impacts such as reduced monitoring costs, and quality-of-life improvements should also be considered for patients, particularly in long-term remission. A further potential weakness associated with microsimulations and treatment sequencing but not yet considered in Section 8.1 is that additional data are typically required to properly inform these

	types of models whereas, as described in Section 7.1.1, limited data were found to be available, particularly following the initial response outcome. We would suggest the model diagram in Figure 2 should be updated to clearly show how remission and no treatment fit in.
Treatments	It is proposed that individuals in the model will be able to receive up to four lines of treatment during the simulation. Given the model will follow individuals with MDD over a lifetime time horizon, modelling a maximum of four lines of treatment appears low. To support plausibility, we would ask that a justification for why a maximum of four treatment lines is appropriate be provided in the first iteration of the model, or that it is clarified if the four lines of treatment is per MDD episode (and so would reset after a recurrence of MDD in the model). According to Section 6.9.2, patients who receive no active treatment are assumed to remain in the no response health state and assigned no benefit. It would be useful if this could be clarified as a simplifying model assumption or if there is clinical evidence to demonstrate that individuals with MDD who do not receive an active treatment will have no improvement across a lifetime horizon then this should be supplied. Alternatively, data showing the trajectory for untreated patients should be used (think similar to the use of natural history data in RA models). We were surprised not to see any evaluation of potential observational data sources for natural history information for any of the model parameters in the model specification. We welcome the plan for future enhancements of the model (Table 10, page 39) to include the ability of the user to populate the model with the specific agent, doses, market shares and costs

Commented [A1]: I would think 'spontaneous' improvements in MDD are possible over time without active treatment so would be interested what this assumption is based on as does not appear to be clinically valid to assume someone will always have MDD symptoms without treatment

	associated with the pharmacotherapies as this will support adaption of the model to investigate future emerging treatments.
Population/included attributes	Insurance coverage type is missing as an included attribute despite being listed as a key consideration in the objectives. Similarly treatment setting / location is described on page 24 as a key factor but is not included within the attribute list and is not clear whether / how this will be taken into account. Whilst we agree that socioeconomic status is likely a factor which prognostically influences MDD, it may also be possible that a diagnosis and progression of MDD could in turn influence an individual's socioeconomic status. With such variability expected over time, and anticipated correlation between MDD severity and socioeconomic status, it will be important to attempt to capture (or caveat the assumptions required if not possible) the meaningful impacts of this patient attribute. Given the importance of socioeconomic status we wonder also if a future model iteration looking at distributional cost-effectiveness analysis would be beneficial. Section 6.1 reports that the baseline population will reflect the following key characteristics from the National Survey on Drug Use and Health analysis. However, if these characteristics are not aligned to the baseline population of the efficacy source informing the model it is misleading to generate outcomes of the model and interpret them as being representative of outcomes of a baseline population based on the National Survey on Drug Use and Health. Given the draft model scope previously described the results of the patient preference study, in which a large proportion (30%) of people who participated in the Phase 1 interviews were aged 65

Commented [A2]:

	years and above, we welcome the intention to explore a population aged 65 and older in future extensions of the model. We also believe that exploration of a population with comorbid conditions would be a valuable consideration.
Model inputs	***Treatment discontinuation*** In addition to no response (the criteria proposed to stop treatment in the model), there are several other factors which can influence treatment discontinuation in MDD including treatment toxicity, patient compliance and treatment guideline recommended time-based stopping rules. As treatment discontinuation can substantially influence costs and efficacy in the model, we believe further consideration of treatment discontinuation would be beneficial to include in the model and is likely to be of vital importance from a payer's perspective. ***Safey*** The difficulties with sourcing adverse event data from meta-analyses (the studies contributing to each meta-analysis often have different definitions and thresholds for reporting adverse events and may aggregate events differently) was described in Section 5.2. However, we would ask if the model developers can be sure that these same difficulties would not also be present in the suggested alternative source; FDA prescribing labels. ***Quality of life*** Though we welcome the consideration of multiple sources of utility values in a model where there is uncertainty in the values, please be aware that a health state value of 0.90 as suggested for the complete response health state based on the Yrondi et al. 2020 source appears to be implausibly

Commented [A3]: I'm assuming these just report the AEs from the pivotal clinical trial(s) so surely still have biases in the reporting of AEs between them for different treatments?

	high for a patient population with MDD versus equivalent age-matched values for a general population. Section 6.9.3.2 describes the intention to use the same utility values throughout the model, with discontinuation as appropriate. We believe this would also ideally include the ability to apply age adjustment of the utility values over time to account for the expected decline in quality of associated with patient aging. This is particularly important for this model which plans to use a lifetime time horizon. Similar to the assumption of remission after three consecutive cycles in the complete response health state, individuals who have two consecutive cycles of no response can be moved to another treatment or can be treated as having discontinued. It is assumed all individuals in the no response health state will have the same utilities assigned, regardless of treatment status but it may be more beneficial to consider different utility inputs for individuals who discontinue treatment versus continue to receive treatment as some treatments may have treatment-related adverse events or other quality of life impacts associated with them. Section 7.2.2 describes that disutility can be applied for the initial cycle(s) of a treatment or for the duration of the treatment, to be informed by literature and clinical guidance. With regards to disutility associated with adverse events, it would be more meaningful to consider applying the disutility for the average duration of the adverse event. As previously discussed in our comments on the draft model scope, whilst we agree that costs associated with caregiving will be an important factor in the model, we believe the quality-of-life

	impacts of caregiver burden should also be considered and may be more important in some markets. ***Costs*** We welcome the inclusion of the bottom-up approach for cost inputs in the model and would also recommend the inputs are designed to be as flexible as possible so that they may be easily adapted by the user, thus supporting use of the model for other country settings and perspectives. In response to the request for input on the mix of resource use by adherence and persistence, we believe the ability to input itemised resource use frequencies and costs per health state is the most useful format. Further splits by adherence and persistence are only useful to consider in the model if they are expected to have a meaningful impact on the associated resource use and costs.
Model outcomes	In addition to those reported in Table 1, other outcomes which may also be of interest to stakeholders include: • Remission • Duration of remission • Recurrence
Targeted literature search	As described in Section 5.2, it appears the literature search was limited to meta-analyses. We expect that additional information to guide the model design would have been available from also searching existing economic evaluations, including the economic models which inform health technology appraisals.

Programming/software	Section 6.10 describes the software being considered for development of the model. We believe R to be a suitable consideration given it is freely available to all users. We are uncertain what challenges IVI anticipated to be associated with efficiency as our experience of using R is that it usually improves the overall efficiency and processing speed of models compared to using more traditional programming methods, such as Microsoft Excel and the use of Visual Basic for Applications, particularly for a microsimulation approach. This does require, however, appropriate coding to take advantage of the ability to perform matrix-based calculations in R rather than use of loops (a principle which in general improves simulation speed). We agree that heemod is not an appropriate package (although we would note the rationale given is incorrect as what we are looking at in the model spec is in fact a state transition model repeated across patient profiles not a patient level simulation as such).

Potential data sources

In response to the request for feedback on data gaps in key model assumptions and inputs, as well as potential data sources to address such gaps, please consider the STAR*D trial as a potential source of efficacy data by line of treatment, as well as for validating longer-term extrapolations. Of note, the STAR*D trial:

- Is the largest prospective clinical trial of major depressive disorder ever conducted
- Provided up to 4 treatment steps per patient

Useful sources associated with the STAR*D trial include:

- Rush AJ, Trivedi MH, Wisniewski SR et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006; 163(11): 1905-1917.
- https://clinicaltrials.gov/ct2/show/NCT00021528

Other

The following additional comments are also provided for your consideration:

- Please consider amending Table 6 (in Section 7.1.1, page 33) to demonstrate that probabilities from the initial health state of death to subsequent health states will be zero as death is an absorbing state (i.e. the final row of the transition matrix for movements from death to complete response, partial response or no response / no treatment).
- Please could you clarify the following sentence in Section 7.2.1 (page 35): “Health states will be assigned to health states as one type of measures utilities to reflect patient-reported (or proxy- or physician-reported) health status.”

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UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

January 24, 2022

Innovation and Value Initiative
917 Prince Street
Alexandria, VA 22314

Dear IVI Team,

We are writing in regards to the request for public comments on the IVI Draft Protocol for Major Depressive Disorder (MDD). Your model aims to address many priorities in the area of patient-centered value assessment, an area of mutual interest at the University of Maryland Patient-Driven Values in Healthcare Evaluation (PAVE) Center.

First, we express that we are grateful to be a collaborator on this project and have been eager to explore how the findings of our research may be applied in the open-source model (Section 8.3, page 45). We extend our appreciation to your team for the sustained commitment to advancing open-source models and the incorporation of stakeholder feedback and public comments. We would like to submit the following comments for your team to consider in the next stages of your model protocol development:

Overall Comments on Model Scope:

- The choice of an individual-level model in IVI's established open-source format addresses numerous important priorities for value assessment, in particular the ability to patient subgroups, heterogeneity, and ability to update model as new inputs become available, attributes seldom noted in existing models for treatment of MDD.[1] Importantly, your model includes numerous treatment options across multiple modalities, which aligns with our finding that 'treatment modality' was a priority in our study sample.[2]
- The choice of modeling from multiple perspectives is a key feature. This increases its ability to reflect patient priorities throughout the model. As seen in previous models, those reporting a societal perspective are more likely to include impacts related to productivity and out-of-pocket costs[1], a value element of primary importance for individuals in our study. Along with multiple perspectives are multiple model outputs specified as potential denominator metrics. This allows different stakeholders to output the metrics appropriate for their decision-making context. Further in the protocol, you have outlined your approach for capturing productivity loss. This is important for employer decision makers, and we also found that this is a priority for patients.[2] From their perspective, it may also be useful to explore an alternative denominator measure that reflects productivity.
- The protocol clearly outlines the target populations and acknowledges that excluding individuals with comorbidities may present limitations. In later dissemination of the model, it may be helpful expand on this with examples, so model users may consider how to adapt for their application (e.g. anxiety often goes hand in hand with MDD and may have implications for generalizability). Similarly, it would be worthwhile to discuss the issue of undiagnosed conditions and how they might be intertwined with treatment-resistance (6.9.3.2). For example, individuals being treated for depression may have other contributing factors, such as trauma, that are not disclosed early in treatment that impact progress through treatment. It is encouraging to see potential future model extensions indicated in the protocol, such as to populations including those 65 and older and Medicaid-insured; future studies comparing these populations will be of interest.

Regarding your specific questions for feedback, we have addressed several points below:

7.3 Approaches to derive direct medical cost inputs: "top-down" or "bottom-up"?

- Both approaches to estimating costs attributed to MDD may be found in the literature and each method has advantages and disadvantages to consider. We recommend the team review Larg and Moss (2011) critical evaluation of cost-of-illness study methods[3] prior to determining how to translate existing cost estimates in the literature into appropriate inputs.

7.2 Data sources for utility inputs, Table 8.

- Health state utility estimation is one of the most challenging aspects of modeling, in particular the ability to reflect patient experiences adequately. Moreover, the methods to incorporate patient preferences into utility values, while promising, are only yet emerging, and this remains an area for future research and collaboration. This highlights the importance of model transparency and the ability to update models as additional information becomes available, such as for health state utility inputs. Your utilization of 'placeholders' for this purpose addresses this, and the open-source format of the model would allow update of these utility values by individual users. We have two suggestions for this challenging data issue: 1) Explore whether and how these various utility measures addressed patient relationships with others, as we found this to be an important priority for patients in our study[2]; 2) Use one-way sensitivity analysis (e.g. tornado diagram) to understand whether these utilities are main model drivers. Selecting an appropriate set of 'base case' set of utilities will be enhanced by reflecting the full range of possible values using the sources in Table 8. This range can also be used to inform probabilistic sensitivity analysis.
- While there are currently no established methods for translating stated preferences to health state utilities, reflecting heterogeneity in patient preferences through subgroup analysis is a means for estimating value related to patient priorities.

7.3 For psychotherapy, what is a reasonable assumption for the duration of psychotherapy?

- The choice of Cognitive Behavioral Therapy for psychotherapy is appropriate, as this is evidence-based treatment. Modular treatment consists of 16 sessions, although we believe that many patients are in therapy much longer than this. This could be addressed in sensitivity analysis.

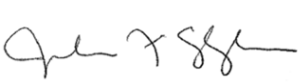
7.3.3.3 Direct medical: Cost of outpatient visits

- Regarding the data that 57% of mental health visits are to a psychiatrist, we have observed that more nurse practitioners have entered the mental health field in response to the recent changes in supply of psychiatrists, and it appears that nurse practitioners are being more widely used for this treatment.

Appendix H outlines numerous research opportunities. Of these, we feel that evidence emerging from both your CEA and MCDA modules will provide key insights on how these two methods may provide complementary evidence for decision making. We would also prioritize work around how to incorporate novel elements such as burden on caregivers or impact on productivity (days of work) into value assessment. This information for employer decision-makers around productivity costs is useful, and productivity was also a key factor for our study participants.[2]

We hope that these comments are helpful as you finalize your Protocol for Major Depressive Disorder. We thank you for your willingness to consider public comments for future iterations of your protocol and look forward to continued collaboration.

Sincerely,

Susan dosReis, PhD	Julia Slejko, PhD	Joey Mattingly, PhD	Beverly Butler, BS
Professor	Associate Professor	Associate Professor	PAVE Patient Stakeholder
Director, PAVE	Co-Director, PAVE	Affiliate Faculty, PAVE	

References

1. Slejko JF, Mattingly TJ, Wilson A, Xie RZ, Chapman RH, dosReis S. Identification of Model Attributes for Patient-Centered Value Assessment of Treatments for Major Depressive Disorder (MDD). Society for Medical Decision Making (SMDM) Virtual Annual Meeting. October 18-20, 2021.
2. dosReis S, Bozzi L, Butler B, Xie RZ, Chapman RH, Bright J, Malik E, Slejko JF. Patient-Informed Value Elements Influencing Preferences for the Treatment of Major Depressive Disorder Among Adults. Society for Medical Decision Making (SMDM) Virtual Annual Meeting. October 18-20, 2021.
3. Larg A, Moss JR. Cost-of-illness studies: A guide to critical evaluation. Pharmacoeconomics. 2011;29(8):653-671.

#12

COMPLETE

Collector:	Web Link 1 (Web Link)
Started:	Thursday, January 20, 2022 9:29:12 AM
Last Modified:	Friday, January 21, 2022 2:09:28 PM
Time Spent:	Over a day
IP Address:	108.5.90.16

Page 1: Introduction

Q1

First and Last Name and degrees, if you would like included

Mousam Parikh, B.Pharm, MS

Q2

Title

Associate Director, HEOR

Q3

Organization if Any

AbbVie

Q4

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Q5

Phone Number

8622618382

Q6

Please check the stakeholder group(s) that you represent

Industry

Page 2: General Questions

Q7

What are potential data sources and partners to address data gaps identified in the draft model protocol?

Respondent skipped this question

Q8

What are your recommended data sources or technical approaches when multiple valid approaches exist?

Respondent skipped this question

Q9

What are ways that you envision using the IVI-OSVP model and what are practical applied research questions that you would like the model to address?

Respondent skipped this question

Q10

Additional Comments

AbbVie appreciates the opportunity to review IVI's MDD economic model protocol. The feedback below reflects key points we want to highlight to IVI and request a teleconference to clarify our comments. We also look forward to seeing the next iteration of the model protocol:

- We recommend IVI to include augmentation therapy option earlier in the treatment sequence, specifically after the first line of therapy, per clinical guidelines1 and published literature2. For patients with partial response to initial monotherapy, literature suggests that augmentation can provide incremental clinical benefits compared to switching. However, the current model protocol only allows for augmentation in the 3+ line of therapy, which is inconsistent with real-world clinical practice.
- Can IVI clarify how benefits and risks of augmentation will be handled in the model? As mentioned above, augmentation could offer incremental benefits to patients, but it is unclear if there is any opportunity to evaluate those incremental benefits in the model.
- Can IVI clarify how the claims study of treatment patterns, presented a couple of months ago, will play a role in deriving inputs for the economic model? It was our assumption that the claims study would provide data inputs for the model; however, the current model protocol does not refer to the claims study.
- Can IVI clarify how switch from one pharmacotherapy to another within the same class will be handled in the model [i.e., as the same line of therapy or a new line]

Reference:

- APA Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts. Feb 2019. https://www.apa.org/depression-guideline/guideline.pdf
- Mohamed S, Johnson GR, Chen P, et al. Effect of Antidepressant Switching vs Augmentation on Remission Among Patients with Major Depressive Disorder Unresponsive to Antidepressant Treatment: The VAST-D Randomized Clinical Trial. JAMA. 2017;318(2):132–145. doi:10.1001/jama.2017.8036

Page 3: Specific Questions Referenced by Section

Q11

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? Section 6.1

Respondent skipped this question

Q12

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)? Section 6.1.1

Respondent skipped this question

Q13

Do you have some suggestions on studies/data sources/methods that we can reference in extrapolating the long-term efficacy inputs? Section 6.5/8.2.3We 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?

Respondent skipped this question

Q14

Are there other model outputs that will be of interests to your organization? In what decision contexts will they be useful? Section 6.8

Respondent skipped this question

Q15

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? Section 6.8

Respondent skipped this question

Q16

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? Section 6.9.3

Respondent skipped this question

Q17

We specified scenarios in which individuals in our simulation will move to a new line of treatment. Section 6.9.3.1Are 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?

Respondent skipped this question

Q18

Is it reasonable to assume the same sets of model inputs (efficacy and safety) for the first and second lines of treatment? Section 6.9.3.2In 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?

Respondent skipped this question

Q19

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). Section 7.3Is 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?

Respondent skipped this question

Q20

Are there key adverse events that have a significant clinical and economic impact that we should include in the model? Section 7.1.2We 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?

Respondent skipped this question

Q21

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? Section 7.2

Respondent skipped this question

Q22

For psychotherapy, what is a reasonable assumption for the length of a visit and for duration of psychotherapy to include (Table 10 and 11)? Section 7.3

Respondent skipped this question

Q23

Do you have any suggestion on studies or data sources that can inform the calculation of informal caregiving burden or costs? Section 7.3.5.2

Respondent skipped this question

Q24

Appendix H describes some of the novel questions or research opportunities that the model could help inform. What specific use cases or decision contexts should be prioritized? What are other important use cases or decisions that this model could help inform? Appendix H

Respondent skipped this question

Q25

May we contact you with follow-up questions if they arise?

Yes

Inspired by patients.
Driven by science.

January 10, 2022

Innovation and Value Initiative
917 Prince Street
Alexandria, VA 22314

RE: Public Comment on the Open Source Development of the IVI-MDD Draft Protocol

Dear IVI-MDD Value Assessment Model Advisory Group,

UCB is a global biopharmaceutical company with U.S. headquarters located in Atlanta, Georgia. With more than 8,000 employees globally, we are inspired by patients and driven by science. Our focus is on innovating new medicines to treat severe, chronic neurological, immunological, and rare conditions. UCB is committed to ensuring that all patients have affordable access to the right medicine at the right time, regardless of age, ethnicity, geography, or economic circumstance. Patients are at the heart of everything we do at UCB, from where we invest our research dollars to how we engage with other stakeholders to bring new therapies to market. Every day, we work to ensure that patients have the best individual experience while promoting access to high-quality, coordinated, affordable care and equitable access to medicines for all patients.

UCB appreciates the opportunity to provide comments on the Innovation and Value Initiative's (IVI) Major Depressive Disorder (MDD) Draft Model Protocol. We are deeply committed to comprehensive value assessments that contribute to meaningful improvements for multiple stakeholders including patients, society, payers, clinicians, and the overall health care system. We share IVI's vision of value assessment principles that are patient-centric, transparent, and adaptive to differing circumstances, and we commend IVI's efforts in facilitating an open source process for estimating the value of health technologies across a broad group of stakeholders.

Although UCB's current therapeutic area focus does not include a targeted therapy for MDD, we understand and recognize that MDD is a devastating disease impacting millions of Americans, particularly when left untreated or undertreated. We also understand under recognition and management of mental health conditions has the ability exacerbate and worsen all underlying health conditions. Our comments are not focused on the detailed technical aspects of the protocol, but rather more general comments and feedback on IVI's request for potential use cases and practical applied research questions, particularly how the MDD model can help inform decisions in specific contexts.

Given MDD is a prevalent comorbid condition with other psychiatric and non-psychiatric chronic diseases, one relevant research question for consideration is, "How do effective and ineffective MDD treatment strategies impact comorbid conditions?" For example, there is evidence individuals with a history of depression are at increased risk of developing autoimmune diseases[1,2] and that individuals with a history of autoimmune diseases are at increased risk for developing depression[3]. Since the initial version of the model excludes individuals with other comorbid conditions, it limits the ability to model real-world MDD patients. This may result in undervaluing the importance of highly effective MDD healthcare solutions. It is important that the model framework is built to support the expansion to other segments of the MDD population to include those with non-psychiatric and psychiatric comorbid conditions.

Additionally, we recommend future extensions of the model include the ability to assess other important patient populations, such as patients aged 65 and older, Medicaid-insured patients, as well as pediatric patients, and women of childbearing age. We appreciate that the model will provide flexibility to evaluate key outcomes for

subgroups defined by age (18-64), race/ethnicity, and socioeconomic status (SES). While available data may be limited related to specific subgroup analyses around effectiveness and cost, it is important to continue to explore ways to model outcomes across a diverse set of subgroups of patients. Value-assessment methods and processes should account for populations typically underrepresented in research and drivers of health disparities. The impact of a treatment on health outcomes and cost differs among patients due to several factors, including those relating to broader drivers of health disparities. Comprehensive value assessment should reflect this aspect.

And finally, UCB recommends IVI continue to aggressively pursue methods that incorporate novel measures of patient-reported outcomes. There is an understood challenge that the microsimulation model type proposed requires tremendous data inputs for MDD patients, simulating many years, through many treatment sequences, attempting to reflect the many different experiences these patients face in the real world. Given the lack of available data regarding patient reported outcomes in the MDD patient population, it will be important to explore the feasibility of incorporating the topics and concerns identified by the Patient-Driven Values in Healthcare Evaluation Center (PAVE) from interviews with MDD patients that do not currently exist in the literature. This may help populate the model with additional elements to enhance the patient-centricity aspect IVI strives to represent.

UCB offers IVI our support and continued partnership to advance the evolving field of value assessment. We hope our recommendations and comments contribute to improving future iterations of the IVI-MDD model and we look forward to further discussions.

Sincerely,

Patricia A. Fritz
Vice President, U.S. Corporate Affairs
UCB, Inc.
770.970.8585 office
678.907.5867 mobile

References:

1. Anderson NW, Gustafsson LN, Okkels N, et al. Depression and the risk of autoimmune disease: A nationally representative, prospective longitudinal study. *Psychol Med*. 2015; 45:3559-3569.
2. Liu X, Nudel R, Thompson WK, et al. Genetic factors underlying the bidirectional relationship between autoimmune and mental disorders – Findings from a Danish population-based study. *Brain Behav Immuno*. 2021: 91;10-23.
3. Benros ME, Waltoft BL, Nordentoft M, et al. Autoimmune diseases and severe infections as risk factors for mood disorders: A nationwide study. *JAMA Psychiatry*. 2013: 70;812-820.

Janssen Scientific Affairs, LLC

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January 25, 2022

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Dear Ms. Bright and Dr. Chapman,

Thank you for the opportunity to comment on the IVI-Major Depressive Disorder (MDD) Model Protocol. 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's comments on the protocol document are as follows:

General Comments and Feedback

- Major depressive disorder (MDD) is a highly heterogeneous disease and hence individualization of treatment is essential. Outcomes may vary among different subgroups of individuals with MDD, so it is important that the patient populations considered be clearly defined and the model allow for customization of data inputs and transition probabilities. For example, within the "newly diagnosed population," a distinction should be made between patients with and without a history of MDD since it has been shown that patients with a prior major depressive episode (MDE) have different outcomes, including a shorter time to recurrence, than patients with newly diagnosed first-episode MDD (Hardevelde et al. 2013). In this way, the model can evaluate patients with first-episode MDD as well as patients with recurrent MDD since these two unique sub-groups would likely have different treatment and health trajectories.
- In section 6.1.1, it is noted that the model is intended to have the capability to examine outcomes for subgroups defined by age, race/ethnicity, and socioeconomic status (SES) as well as those with TRD. We agree that these subgroups will likely have different treatment pathways and outcomes which warrant focused consideration. However, we suggest that in this version of the model, TRD be parameterized at the population level by applying a mean total cost rather than explicitly modeling 3rd and 4th line treatment and micro-costing. This type of approach has been used in other models (e.g., type 2 diabetes models focused on the newly diagnosed population parameterize micro- and macro-vascular complications at the population level) and will allow for the capture of the economic burden of developing TRD from poorly or inadequately treated newly diagnosed MDD. Appropriately modeling TRD is a complicated undertaking in its own right, and as noted in the protocol as well as confirmed in literature (Rush et al. 2006a, Gelenberg et al. 2010), reliable input data for many of the later lines of therapy is currently lacking and would require estimation based upon assumptions. Moreover, real world data estimates the prevalence of TRD to be 9.1% amongst all adult patients with MDD (Harsh et al. 2019), suggesting only a small percentage of *newly diagnosed* MDD patients progress to TRD within an episode. Future work could focus on building an appropriately tailored TRD model. Also, for clarity, please update the protocol text and add "within the current episode" to the

definition of TRD.

- Importantly, regarding the structure of treatment lines and parameterization of pharmacotherapy efficacy, we recommend that IVI leverage the seminal STAR*D study (Rush et al. 2006a). In this study, augmentation was considered a new treatment line. In guidelines, use of an augmentation strategy is considered more appropriate for patients with evidence of at least a partial response, while switching to a new antidepressant may be considered as more appropriate for those with non-response (Gelenberg et al. 2010, EMA 2013). Note, augmentation therapy is common in the treatment of MDD. For example, in a real-world evidence claim study, ~15% of patients received augmentation therapy as first-line therapy in a MDE and ~28% of patients received augmentation as second-line (Wu et al. 2019). Also, the STAR*D study documented that response and remission rates dropped with subsequent lines of therapy (Rush 2006a). We suggest that STAR*D be used to adjust the effectiveness of second-line treatment in cases where data is missing rather than assume efficacy is the same as first-line therapy.
- In regard to IVI's question "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?":
  - While these treatments may be used earlier for patients with MDD and acute suicidal ideation or behavior given its rapid onset of effect (Gelenberg et al. 2010), we agree that these treatments are usually reserved for more refractory cases in later lines of treatment and not common for newly diagnosed patient with MDD in earlier lines of therapy.
- In addition, based on available literature (Nierenberg et al. 2001, Rush et al. 2006b) and clinical practice, we recommend the inclusion of a "partial response" health state, even though currently data may be sparse (see below example), as this would help further delineate the levels of response one might see among individual patients. As noted above, use of an augmentation strategy is typically considered more appropriate for patients with evidence of a partial response, while switching to a new antidepressant may be considered as more appropriate for those with non-response (EMA 2013, Gelenberg et al. 2010).
  - Remission
  - Response
  - Partial response
  - Non-response
- The decision of which comorbid conditions to include must balance the generalizability of the model with available data inputs and the model's focus.
  - Specifically, comorbidities such as anxiety and cardiovascular disease are common among patients with MDD and should be included in the model (Zhdanava et al. 2020, Zhdanava et al. 2021). These conditions can contribute substantially to the burden of MDD; therefore, inclusion of these comorbidities would make the model more generalizable to the real world MDD population. Additionally, clinical trials and in real world evidence studies in MDD typically include patients with anxiety and controlled hypertension, so these datasets will already include patients with these comorbidities.
  - In contrast, *moderate to severe* substance or alcohol use disorder is often excluded from trials in MDD, so we agree with this exclusion in the initial model. We agree also that patients with schizophrenia or bipolar disorder should be excluded, as per

DSM-5 they would not meet the criteria for an MDD diagnosis.

- While we understand that the literature search was limited to meta-analyses for pragmatic reasons; however, we are concerned this approach may lead to flawed model inputs and require more assumptions.
  - For example, the focus on meta-analyses in the literature review likely excluded available information on newer antidepressant agents (e.g., vilazodone, vortioxetine) or studies with unique trial designs that would not support inclusion into meta-analyses. This would limit the ability of the model to be used to inform analyses of current MDD treatments.
  - Data from the pivotal trials outlined in the labels for approved medications, as well as any publications providing longer term data should be considered in the evidence review.
  - Limiting to literature from 2018 and afterwards likely excludes evidence on established treatments.
  - Owing to different safety/tolerability and efficacy profiles and outcomes of same-class medications (Cipriani et al. 2018), clinical trials of individual medications should also be considered vs only medication classes.
- As written, the protocol does not include a good rationale for why some therapies were included and others were excluded. Including off-label treatments for MDD is very challenging, given these treatments lack quality data on efficacy and safety outcomes as compared to approved treatments, which have established efficacy and safety/tolerability profiles. For example, we recommend ketamine be removed since it is not an FDA-approved treatment for patients with MDD nor is it typically used in newly diagnosed patients. As per guidelines, the American Psychiatric Association (APA) specifically states that, "major gaps…remain in our knowledge about the longer-term efficacy and safety of ketamine infusions" (Sanacora et al. 2017). In addition, ketamine is not typically used in the first- or second-line of treatment for newly-diagnosed patients with MDD. Moreover, there are many additional non approved, off-label treatments for MDD that were not included (e.g., anticonvulsants, St. John's wort, topiramate, modafinil, methylphenidate, etc.). The inclusion of one off-label treatment and not others presents a difficult design to defend and the inclusion of additional non-approved, off-label treatments would inevitably be subjective.
- In regard to IVI's question "Are there key adverse events that have a significant clinical and economic impact that we should include in the model?"
  - Key treatment emergent adverse events (AEs) that have been documented to have significant clinical and economic impact to consider include: metabolic related AEs (e.g., increased BMI, weight gain, metabolic syndrome, treatment emergent DM), cardiovascular disease, somnolence, and sexual dysfunction.
- We strongly recommend IVI use net prices in the model as they capture rebates and discounting and thus reflect true transaction prices for institutional payers. In addition, as financial outlays from the patient may influence whether or not a particular treatment is used, and a stated focus is on socio-economic status and disparities, we urge IVI to consider reflecting patient out-of-pocket costs in the model. As such, we recommend also including list prices in the model. We appreciate the attention to the employer perspective despite the current lack of data available.

- We especially appreciate IVI's commitment to ensure diverse perspectives and disease specific outcomes, clinical as well as patient -centric, are ultimately represented in the model. We continue to be wary about users relying on the QALY as an outcome measurement in an open-source model. The QALYs rate the value of human life relative to a subjective standard of perfect health and their use may discriminate against populations such as the elderly, chronically ill and disabled. QALY-based frameworks place a lower value on treatments that extend and improve the lives of people who may never have perfect health (Janssen Transparency Report 2020, Nord et al. 2009, Pettitt et al. 2016, Brock 2009).

Additional Comments and Feedback for Specific Protocol Sections:

Section 4.2: Prioritized Research Questions

- Regarding "The societal burden of untreated or under-treated MDD" focus area, data from the NSDUH survey can be used to estimate the proportion of patients with a major depressive episode in the prior year who did not receive treatment.

Section 5.1 Finalized Model Scope (Table 1)

- Cost inputs in the model should include tolerability and safety costs related to AEs of the treatment itself.
- Recommend "Remission" be added to the Outcomes
- A suggested reference to quantify suicide attempts and deaths risk: Holma et al. Incidence and predictors of suicide attempts in DSM-IV major depressive disorder: a five-year prospective study. *Am J Psychiatry*. 2010. 167(7):801-808.

Section 6.2 Setting and Location

- Suggest clarifying whether treatment care settings will include emergency room and/or inpatient and outpatient care

Section 6.4 Comparators

- Suggest to clarify how combination treatments will be addressed in the model (e.g., combination of 2 ADs simultaneously in the current line of therapy, both given at an adequate dose and for an adequate duration)
- Several antidepressant therapies and adjunctive atypical antipsychotics are missing from Table 4: Model Comparators (e.g., Clomipramine (TCA), fluvoxamine (SSRI), vortioxetine, vilazodone).

Section 6.9.2 Health State Descriptions and Parameterization

- With regards to IVI's statement that "there is no consensus on the score or change score that reflects improvement or response" for measures of treatment response (e.g., Montgomery-Asberg Depression Rating Scale [MADRS], Patient Health Questionnaire-9 [PHQ-9]), it is noted that there is some available literature that would be worthwhile to consider.
    - For example, a clinically meaningful within-group change from baseline on the MADRS has been reported to range between a 6- to 9-point reduction in total score (Leucht et al. 2017, Turkoz et al. 2018). When treatment groups are compared to each other, a 2-point difference in MADRS between groups has been found to be clinically meaningful (Montgomery et al. 2009, Montgomery et

al. 2014).
    - For PHQ-9, scores of 5, 10, 15, and 20 represent the thresholds for mild, moderate, moderately severe, and severe depression, respectively, and a 5-point decline represents a clinically significant improvement (Löwe et al. 2004, Kroenke et al. 2002, Kroenke et al. 2010).
- Suggest noting a the "non response" health state (see above)

Section 6.9.3.1: Moving to a New Line of Therapy

- Currently, IVI's protocol states that "While in complete response, it is assumed that individuals will continue with the existing treatment(s)." We suggest noting that patients who continue in remission for a significant period of time, especially if this is their first episode may consider stopping or discontinuing treatment after a period of time without symptoms (Baldessarini et al. 2015). For those patients with recurrent MDD, guidelines typically recommend maintenance treatment to avoid a relapse or recurrence (Gelenberg et al. 2010).

Section 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)?

- While the optimal frequency of psychotherapy has not been rigorously studied in controlled trials, in many trials, psychotherapy sessions have been delivered in approximately 12-16 weekly sessions (Gelenberg et al. 2010). It is also recommended session take place once a week or every other week for 30 to 60 minutes (Mayo Clinic, NHS 2019)

Additional Suggested References:

- Cochrane Reviews
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January 25, 2022

RE: Public Comments on the Innovation and Value Initiative-Major Depressive Disorder Model Draft Protocol

Sage Therapeutics, Inc. ("Sage") and Biogen Inc. ("Biogen") are committed to developing innovative therapies with the potential to transform the lives of people living with debilitating disorders of the brain. We appreciate the Innovation and Value Initiative's (IVI's) efforts to develop an open-source and patient-centered value assessment model for patients with major depressive disorder (MDD). Sage and Biogen value the opportunity to provide constructive feedback and support to help improve and broaden the applicability of the model for this population of high unmet need.

Below are the key themes that Sage and Biogen would like to emphasize as the IVI-MDD model draft protocol is finalized:

1. Measuring the impact of early response and early remission to accurately model the impact of rapid-acting agents and other therapies for the treatment of MDD
2. Incorporating additional key subgroups to capture the effect that MDD has on key patient populations
3. Ensuring that the model accurately captures the full health benefit and impact of treatments for MDD to improve the scientific validity of the model

The remainder of this letter provides a more detailed discussion of the points related to these themes. In addition, we have provided feedback on certain questions posed by IVI related to the MDD model draft protocol.

1. Measuring the Impact of Early Response and Early Remission

The proposed model cycle length of 3 months does not allow the model to capture the effects of early response and early remission or the early benefits of rapid-acting treatments, so we recommend incorporating shorter model cycle lengths to capture the impact of early response/remission.

In Section 6.6, IVI states that the model's cycle length will be 3 months based on clinical treatment guidelines and efficacy inputs identified by its targeted literature review. However, IVI's proposed justification for the model's cycle length contradicts the treatment guidelines of the American Psychiatric Association, which recommend that response be assessed at 4 to 8 weeks, with changes

made as needed, and then re-evaluation after another 4 to 8 weeks (American Psychiatric Association 2010).

There have been various studies demonstrating the importance of and the differentiation caused by earlier improvement of MDD symptoms, and it would be a missed opportunity if the model did not capture this value. Research has shown that improvements in depressive symptoms experienced within 3 months of treatment are associated with positive treatment outcomes and functional improvements. Experiencing early improvement (defined as ≥20%–30% reduction in depressive symptoms in the first 2 weeks of treatment) led to an 8-fold higher likelihood of achieving response and a 6-fold higher likelihood of achieving remission after 5 to 12 weeks of treatment (Wagner 2017). Moreover, patients who experienced early remission within the first 6 weeks of being treated with an antidepressant showed average normal functioning after 6 weeks, whereas those who did not remit within 6 weeks needed a whole year to regain average normal functioning (Ciudad 2012) and may have increased residual symptoms of MDD (Nierenberg 2010). Similarly, patients with MDD who responded early to treatment (defined as a 50% decrease from baseline in the 17-item Hamilton Depression Rating Scale score after 6 weeks) had more than a 4-fold greater chance of achieving clinical remission within the first 6 months of treatment than do those who did not achieve an early response (Ciudad 2012). Several studies have shown that individuals who experienced shorter depressive episode durations had improved short- and long-term outcomes, including symptomatic and functional outcomes (Habert 2016, Kraus 2019, Ciudad 2012).

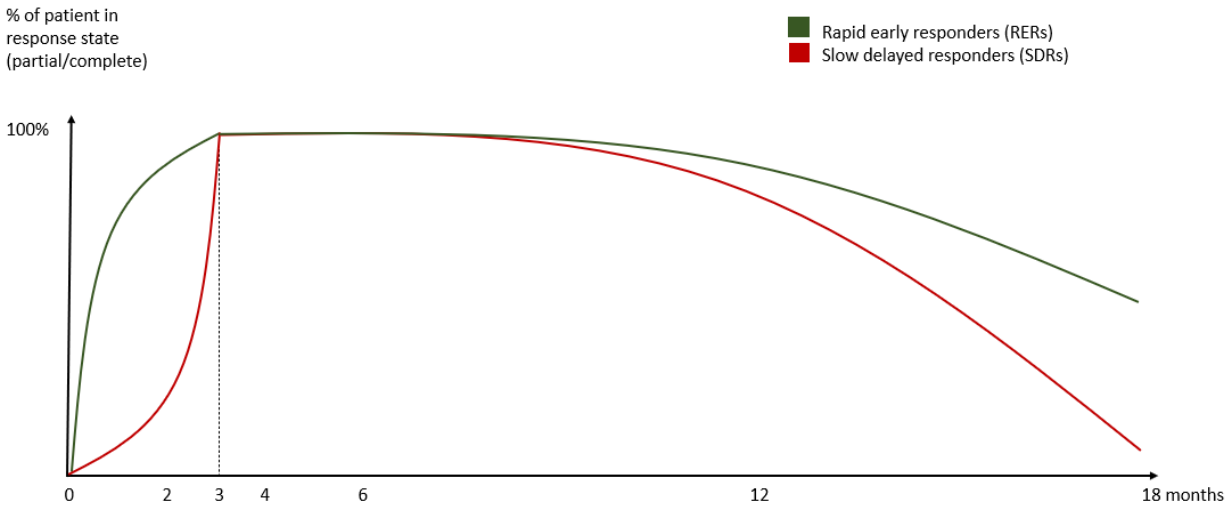
Additionally, ketamine is a rapid-acting agent that was recently approved by the United States (US) Food and Drug Administration for the treatment of treatment-resistant depression, and there are several rapid-acting agents under investigation for the treatment of MDD (Li 2021). To capture the effect of these novel, rapid-acting treatments, we recommend that the model include shorter cycle lengths.

To incorporate an initial shorter model cycle length, results from the STAR*D trial provide information on treatment prognosis (likelihood of response and remission) after 2 and 4 weeks of treatment with a selective serotonin reuptake inhibitor (SSRI) (Jakubovski 2014).

Given the short- and long-term impact of early response and remission, the IVI-MDD model should incorporate a shorter model cycle length, such as 4 weeks, or at the very least, the *initial* model cycle length should be shorter than 3 months.

Introducing responder subtypes into the model is a potential solution to capture the impact of early response and remission, enabling the model to more accurately extrapolate long-term efficacy outcomes for these patient populations.

Given the importance of early response and remission (discussed above), if the model cycle length remains at 3 months and IVI is looking for a way to more effectively link short-term efficacy data with long-term effectiveness outcomes, it may be sensible to consider splitting responders (both partial and full) into 2 groups: rapid early responders (RERs) and slow delayed responders (SDRs). Below is an illustrative figure showing the hypothetical association between subtype response status over time.



As highlighted above, several studies have shown that RERs have markedly different longer-term outcomes than SDRs. Lutz (2009) showed RERs had nearly double the response rates at 6, 12, and 18 months than SDRs. Ciudad (2012) reported that RERs had a 4 times higher chance of achieving remission by 6 months and remaining in remission until the end of the 12-month follow-up period. Wagner (2017) confirmed these findings in a more recent study.

These subtypes would likely have the same utilities (and costs) per cycle by state but would have different transition matrices, reflecting differing likelihoods of improved longer-term outcomes. For example, RER partial responders would have higher transition probabilities of remaining in an RER partial response state and progressing to a complete response state each cycle, as well as a lower probability of transitioning to a no-response state at each cycle (i.e. relapse).

It is possible to operationalize the different longer-term prognoses of RERs and SDRs using data from one of the aforementioned published studies to estimate the relative probability of transitioning from response to no response at the end of each cycle for the RER and SDR subtypes. For instance, Lutz (2009) reports shares of patients "who were reliably improved in the BDI [Beck Depression Inventory] at [treatment] termination" and at 6, 12, and 18 months post-termination, separately for RERs and SDRs. If "reliable improvement" is used to approximate complete response/partial response, these results can be used to estimate the relative single-cycle probability of relapse for RERs vs SDRs in as few as 3 steps.

First, the 6-month conditional probability of relapse given complete/partial response can be approximated for each cohort by dividing the proportion of patients exhibiting reliable improvement at month 6 by the proportion of patients exhibiting reliable improvement at termination and subtracting the resulting quotient from one. These 6-month probabilities can then be converted into 3-month probabilities of relapse for responders (i.e. transition probabilities for a single 3-month cycle) by first converting to rates and then to 3-month probabilities under the assumption that time to relapse is exponentially distributed. Finally, the relative 3-month risk of relapse among RERs compared to SDRs can then be estimated as the ratio of the converted 3-month probabilities for RERs and SDRs. Using this method, the results from Lutz (2009) indicate that patients in an SDR state are approximately 5 times as likely to transition to the no-response state (i.e. relapse) in any given cycle than are patients in an RER state.

Finally, each treatment group (e.g. SSRIs, selective serotonin norepinephrine inhibitors [SNRIs], cognitive therapy) would need to be split into percent of RERs and SDRs. In this way, each treatment class will have its own unique relationship to the accrual of longer-term effectiveness.

While this method does not directly address discontinuation as a driver of long-term effectiveness, it does so indirectly, as one of the reasons that RERs have better long-term outcomes is that RERs discontinue treatment less frequently. RERs may have lower discontinuation rates because lack of initial efficacy is one the major drivers of discontinuation, potentially accounting for more discontinuations than adverse events in MDD (Nantz 2009).

2. Incorporating Additional Key Subgroups

Because individuals with MDD and no comorbidities represent a minor portion of the MDD population, we recommend incorporating subgroups for comorbid MDD and anxiety disorders and comorbid MDD and hypertension, as these represent the most common psychiatric and non-psychiatric comorbidities.

The IVI-MDD model draft protocol states that the target population includes adults diagnosed with MDD without a diagnosis of other psychiatric and non-psychiatric chronic comorbidities, such as anxiety, bipolar disorder, schizophrenia, substance abuse disorder, cancer, cardiovascular disease, multiple sclerosis, and Parkinson's disease. Almost all commercially insured patients with MDD in the US (85%) have at least 1 other health condition (Blue Cross Blue Shield 2018). Approximately two-thirds (64%) of individuals who met criteria for an MDD diagnosis in the past year also met criteria for at least 1 other 12-month psychiatric disorder (Kessler 2003). Additionally, non-psychiatric comorbidities are quite common in individuals with MDD, as almost one-quarter of individuals with MDD also suffer from hypertension (23.0%) and 9.2% from hypothyroidism (Greenberg 2015). Given that only ~15% of individuals suffer from MDD with no comorbidity, this target population would not result in a model representative of the vast majority of individuals experiencing MDD, thereby minimizing its utility for real-word application by patients, physicians, payers, and employers.

Another important reason to examine comorbidities is that MDD and/or MDD treatment can worsen the course of comorbid conditions and make comorbidities more difficult to manage and vice versa (Druss 2011). Additionally, effective treatment of MDD can decrease the risk and severity of certain comorbid conditions (Baumeister 2014, Dobkin 2014). Comorbid conditions associated with MDD can also have a significant impact on cost, as treating both MDD and an individual's comorbidities leads to additional costs (Greenberg 2015). An economic analysis using national survey and administrative claims data showed that for every dollar spent on MDD direct costs, an additional $5.61 was spent on direct and indirect comorbidity costs incurred by individuals with MDD (Greenberg 2021).

Although we recognize the practical infeasibility of including subgroups for every single psychiatric and non-psychiatric disease in the initial version of the model, given the high prevalence of both psychiatric and non-psychiatric diseases, we believe demonstrating the potential impact certain comorbidities may have on MDD treatment outcomes and costs is imperative for the model's continued success. As anxiety disorders are the most common 12-month comorbidity, and over half of individuals diagnosed with MDD also have a diagnosed anxiety disorder (57.5%; Kessler 2003), there should at least be a subgroup analysis focused on

comorbid MDD and anxiety disorder. Similarly, given that hypertension is the most common physical comorbidity (23.0%; Greenberg 2015), there should be a subgroup analysis focused on comorbid MDD and hypertension. By incorporating subgroup analyses for comorbid MDD and anxiety disorders and comorbid MDD and hypertension, the model will be able to demonstrate the potential impact of a psychiatric disorder and a non-psychiatric disorder on treatment outcomes.

The IVI-MDD model should include subgroups defined by gender.

The IVI-MDD model draft protocol indicates that subgroups will be defined by age, race/ethnicity, and socioeconomic status; however, we believe that gender is another important subgroup that should be specified in the model protocol. In 2019, 12.2 million adult females experienced a major depressive episode (MDE) compared to 7.1 million adult males (NSDUH 2019). Studies have consistently shown gender differences in the developmental course of MDD (Birmaher 2004, Essau 2010, Petersen 1991). In addition to higher incidence rates of MDD, females also have a more chronic MDD course than males and tend to have longer depressive episodes (Essau 2010). Research has shown that females with MDD experience poorer quality of life, more severe depression, and increased sexual dysfunction compared to males (Lai 2011). Furthermore, gender greatly impacts the likelihood of comorbidities, which may affect treatment response and symptom presentation (Marcus 2005).

3. Ensuring That the Model Accurately Captures the Full Health Benefit and Impact of Treatments for MDD

We recommend that different mortality multipliers be applied to each of the model's health states, given differences in mortality between responders and non-responders.

The model does not have states explicitly defined by the absence of MDD and treatment-resistant depression (TRD); rather, it has MDD no response, MDD partial response, and MDD complete response. However, the 3 studies cited by IVI as evidence that MDD and TRD patients have higher mortality rates than the general population may be inappropriate sources for the requisite mortality multiplier(s) if the MDD multiplier is to only be applied to non-responders, as each study likely reports the average effect of MDD on mortality for patients distributed across all 3 states. Because mortality is likely much higher among patients in the no-response state compared to mortality among patients in the complete response state, if an "average" multiplier is applied to all MDD states rather than to the no-response state alone, the model will underestimate a patient's lifespan, thereby failing to capture changes in total accrued utility that arise from the underlying differences in state-specific utility multipliers and total years spent in alternate health states. Thus, no survival benefit would be associated with successful treatment.

For example, Pratt 2016 shows an overall mean mortality multiplier of anxiety/depression of 1.6 but also highlights other similar studies in the literature that have resulted in multipliers for MDD as high as 3.1 (Zheng 1997). Differences in these multipliers may be caused by the length of study follow-up and inclusion/exclusion of individuals either previously diagnosed with MDD or with self-reported depression. Similarly, with Li 2019, the categorization of TRD (≥2 previous treatments for MDD) was for all patients who received a third treatment during a 7-year follow-up period. As such, these studies do not account for the impact of each state (non-response, response, remission) or the time spent in each state on mortality.

The problem of variance across states can be seen in Table 4 in Pratt 2016. This analysis separates patients suffering from depression into those who have received treatment in the last year (pharmacological and non-pharmacological) and those who have not, and it provides 4 sets of hazard ratios (range: 1.37–1.57) from 4 distinct mortality models among treated vs. untreated patients. The results of a study by Cuijpers and colleagues (2014) add further evidence that mortality risk is a function of level of response or severity of MDD and should therefore vary by state in the model. That study compared mortality risk for patients with each of major and sub-threshold depression to mortality risk for patients without depression. Relative risk of mortality compared to patients without depression was 1.58 for those with major depression. While these examples are imperfect proxies for responders and non-responders, the analytical underpinnings of these studies should be used to further refine the model's mortality multipliers.

The effect of residual disease is an important element that should be captured in the model or mentioned as a model limitation.

Even when in remission, most individuals with MDD still experience impairment due to residual symptoms or the long-term effects of MDD, including blunted affect, anxiety, sleep disturbances, and fatigue/loss of energy (Nierenberg 2010, Nierenberg 2015, Romera 2013). With current treatments for MDD, more than 90% of patients experience mild to moderate residual symptoms (Nierenberg 2010). Individuals with MDD who remit but have residual symptoms have a higher risk of relapse and recurrence than those without residual symptoms (Nierenberg 2010, Nierenberg 2015, Paykel 2008, Rush 2006). Given the impact of residual symptoms on treatment outcomes, the effect of residual disease should be captured in the IVI-MDD model. Additionally, given the high rates of bothersome side effects (e.g. sexual dysfunction, fatigue) and that the majority of MDD patients aged 12 years and older from 2011 to 2014 receiving antidepressant therapy remained on therapy for at least 2 years, the residual effect of treatment adverse events should be considered (Pratt 2017, Kelly 2008). If it is not feasible to incorporate the effect of residual disease in this iteration of the model, it should be described as a limitation of the model, and future model updates should attempt to include this concept.

IVI should clearly differentiate between MDD and TRD, as these represent very different patient populations.

MDD and TRD represent very different patient populations, as TRD episodes persist about twice as long as non-TRD episodes (Kubitz 2013). TRD is associated with worse health-related quality of life and functioning compared to treatment-responsive MDD (DiBernardo 2018, Jaffe 2019, Mrazek 2014). Additionally, there is an increased economic burden for TRD patients compared to MDD patients, as studies have found TRD patients to be associated with significantly higher healthcare costs and healthcare resource utilization (Arnaud 2021, Olchanski 2013, Sussman 2019). In light of the differences between MDD and TRD populations, IVI should clearly differentiate between MDD and TRD in its model structure and data inputs. Additionally, studies examining populations that include both MDD and TRD should not be included (e.g. Cuijpers 2020).

The IVI model as designed does not estimate the potential benefits of introducing new types of therapies for MDD at the population level.

The current IVI model does not capture the potential benefits that MDD patient populations would accrue from increasing the number of available treatment options. As such, a wider "set" of available treatment options should provide a greater potential population-wide absolute level of

health gain. No treatment is effective for everyone; most treatments are effective for a proportion of all potential patients. For illustrative purposes, let us assume that, on average, each treatment class is fully effective in 50% of the potential target population but did not work or did not work optimally for the other 50%. The chance that the 50% in which treatment A is effective was the exact same group of patients that treatment B is effective for is highly unlikely. Consequently, each new treatment, and in particular each new mechanism of action or treatment type, is likely to enhance the overall population-level health benefit that could be accrued across a diverse population of need.

The model as designed does not allow for the estimation of such benefits. IVI should consider how to overcome this limitation. Although this may have little effect on the relative net benefit of individual therapies on individual patients, it does provide insight into the value of introducing new types of therapy at the population level. In a heterogeneous disease such as MDD, this wider public health value from innovation should not be underestimated.

Feedback on Certain Questions Posed by IVI

Section 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?

See the above response titled, "Introducing responder subtypes into the model is one solution to capturing the impact of early response and remission and to extrapolating long-term efficacy outcomes."

Section 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?

The data sources for the utility inputs suggested by IVI in Table 8 of the model draft protocol show variable outcomes, as they have quite different populations. It should also be noted that randomized controlled trial (RCT) populations in MDD have been prone to Hawthorne effects. This term is used in clinical research to describe changes in behavioral, clinical, and physiological variables that occur in response to a participant's awareness of being under study. Improvements that occur after recruitment, but before the start of treatment, could be attributable to several factors, including more attention from clinicians, better observation, improved care, and increased expectations of health benefits (Benedetti 2016). These effects have been shown to heavily influence quality of life estimates in RCT populations (McCarney 2007, Bouchet 1996).

It is no surprise then that reviews including a mix of both RCT and observational (non-interventional) studies have high variation. We suggest that the best sources for utility metrics are either the Revicki and Woods (1998) or the Brockbank (2021) review, but we would suggest limiting the inclusion criteria from Brockbank to non-RCT sources for utility values. For example, Revicki and Woods (1998) was the only observational study undertaken in the US in the list of studies included in Brockbank 2021. Here, the utility weight for no treatment was 0.30. The other observational cohort studies that estimated a utility weight for untreated/no-response patients were Sapin 2004 (0.33), and Garcia-Cebrian 2008 and Reed 2009 (0.44). As such, weights between 0.3 and 0.4 should be acceptable for MDD non-response or prolonged treatment failure.

There is a tendency for reviewers of models to critique the use of health utility weights of below 0.5. Utilities of 0.3 and 0.4 are anecdotally believed to be exaggerated, especially in central nervous system (CNS) disorders, where there is less evidence of physical disability or risk of death. This

is a common example of bias against the severity of mental health disorders compared to physical disorders. Given that MDE is the condition most closely associated with suicide ideation and suicide attempts (Hoertel 2015), it should be understandable that the range of utilities for severe or uncontrolled MDD includes utilities below 0 (studies suggest up to 25%). As such, a low mean utility for non-response or prolonged treatment failure should be expected.

Section 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?

Both top-down and bottom-up costing approaches pose challenges. Bottom-up tends to be over-prescriptive in that only costs directly relevant to the disease/treatment at hand are included, resulting in an estimate that may not include any hidden costs. To attempt to capture these hidden costs, researchers rely on a top-down costs approach. With this approach, the researcher does not need to enumerate the relevant categories of costs but attributes any excess costs to the condition in question by comparing costs to a matched control. In fact, Greenberg et al. (2021) is a relevant publication that does just this for MDD and warrants your further attention.

In Table 2 of Greenberg 2021, the direct costs are helpfully broken out into those related to MDD treatment and those related to other conditions, such that the components of costs can be observed but no cost categories are inadvertently left out. This table allows for the incremental cost burden of MDD to be calculated. Another benefit of using Greenberg is that the authors try to value the indirect costs of depression, in addition to direct healthcare costs. The authors report the incremental burden of suicides and work loss per patient, which are costly non-medical outcomes of MDD that should be considered.

Section 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?

A recent study published by Kuvadia and colleagues (2021) examined direct and indirect costs among caregivers of individuals with MDD. Ray et al. (2017) also compared healthcare costs and utilization for family members of individuals with MDD in the years before the MDD diagnosis date and in the years after the MDD diagnosis date with non-MDD family members. This article also reports the likelihood of family members being diagnosed with various healthcare conditions, which could be incorporated into the model using disutilities and/or costs. For TRD, there is a recent published study (Lerner 2020) that estimates direct and indirect costs for caregivers of individuals with TRD compared to caregivers assisting those with other diagnoses.

We appreciate the opportunity to provide comments for this assessment and believe that consideration should be given to these points to ensure a robust model development.

Sincerely,

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January 25, 2022

SUBMITTED ELECTRONICALLY

Jennifer Bright, Executive Director

Rick Chapman, Chief Science Officer

Innovation and Value Initiative Foundation

917 Prince Street

Alexandria, VA 22314

Re: IVI-MDD Model Draft Protocol: Public Comment Period

Dear Jennifer and Rick:

Takeda appreciates the opportunity to provide the below comments to the Innovation and Value Initiative (IVI), in response to IVI's request for feedback on the draft protocol for the open-source model to help evaluate pharmacologic and nonpharmacologic healthcare interventions indicated for major depressive disorder (MDD). Takeda is a global, values-based, R&D-driven biopharmaceutical leader committed to discovering and delivering life-transforming treatments, guided by our commitment to patients, our people and the planet. Takeda focuses its R&D efforts on four therapeutic areas: Oncology, Rare Genetics and Hematology, Neuroscience, and Gastroenterology.

General Do you have any other comments or feedback for us to consider?

Takeda applauds IVI's efforts in attempting to take the broader societal perspective, the patient perspective, and for the willingness to incorporate more novel elements of value in the MDD economic model. To ensure that the model will reflect real-world treatment sequences and consequences and incorporate key value elements from patient and societal perspectives, we recommend the following:

1. Ensuring the incorporation of patient-centric outcomes in the model to truly capture the patient perspective.
    a. The current model inputs include efficacy (based on clinical trial evidence and not real-world effectiveness), safety, mortality, utilities, costs (direct and

indirect/productivity loss), and healthcare resource utilization, but do not directly include outcomes most important to patients (e.g. re-establishing premorbid functioning, social interactions with family, functioning in social settings, at work or school, etc.).[1] While the QALY approach attempts to incorporate quality of life, its limitations are well-documented.[2,3]

b. The 16 studies included in the targeted literature review (TLR) are primarily clinical trial studies and do not reflect real-world MDD treatment, effectiveness, tolerability, or adherence. We recommend that IVI expand the TLR beyond current meta-analyses/reviews to include available high-quality individual observational/real-world studies, patient-reported outcome (PRO) studies that better capture a more complete picture of MDD patients' lived experience.

2. Ensuring that the target population, treatment sequences, cost inputs, and outcomes reflect real-world epidemiology, MDD treatment paradigm, and real-world costs and outcomes.
    a. The current model focuses on treatment-naïve patients 18-64 years without comorbidities (e.g. anxiety, other psychiatric comorbidities) and does not reflect the real-world MDD population (or even clinical trial population) where comorbidities are the standard, not exception.[4] The selection of MDD treatment may be influenced by patient comorbidities. This approach also limits the applicability of the model to decision-makers. We recommend a broader target population that is more reflective of the epidemiology of MDD.
    b. MDD is a complex disease and patient treatments and goals are highly individualized and heterogeneous and the current model structure and inputs do not reflect this. For example, the ability to achieve individualized goals in depression has been studied and recently published.[5] As discussed in 1b, the TLR should be expanded to include such studies.
    c. The current assumptions around drug costs may not reflect real-world costs of drug therapy. The model uses Redbook WAC, which overestimates the true cost of drug therapy.[6] Additionally, the model does not account for genericization, the allowance for future generic drug entry and subsequent drug price decline, which may lead to misinterpretation of long-term opportunity costs for drug, important for a lifetime model.[7]

3. Expanding beyond the traditional cost per QALY approach and prioritizing newer methods for value assessments such as augmented value frameworks and multi-criteria decision analysis approaches,[8,9] as noted in Appendix H. For example, novel MDD therapies with new mechanisms are innovative and could bring renewed hope for patients who fail current treatments, and including "value of innovation" and "value of hope" could be a consideration.[8,10]

Takeda hopes our comments are useful to IVI, and welcome the opportunity to answer any questions. Please do not hesitate to contact Jill Erickson at 773-343-3363 or jill.erickson@takeda.com to discuss further.

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HealthCore Responses to Questions on the IVI Open-Source Value Project Model for Major Depressive Disorder – Draft Protocol

Submitted by HealthCore on 31 January 2022. We appreciate the opportunity to comment on the draft model protocol. Please contact Michael Grabner, Principal Scientist, at mgrabner@healthcore.com should further discussion of our comments be desired.

DISCLAIMER: The responses and comments stated herein are the opinions of HealthCore, Inc. and its Principal Scientist team and are the result of a collaborative effort with Innovation and Value Initiative to develop and draft a study protocol. HealthCore makes no representations or warranties, express or implied, with respect to the use or reliance on the opinions stated herein.

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?

- The National Survey on Drug Use and Health (NSDUH) cited by the authors offers a unique and rigorous source of information about the incidence of untreated Major Depressive Episodes and related impairments in the general US population. The NSDUH data also includes information on health insurance coverage, veteran status, self-reported health status, treatment, and co-occurring mental and physical disorders.
    - Authors might use these data to provide a more comprehensive description of the burden of MDD on individuals, households, and payers, and provide guidance to model users on parameter selection
    - The NSDUH is cross-sectional and easy to use, so additional analyses specifically conducted for the model may be considered
- The ongoing HealthCore/IVI study will provide information about population characteristics relevant for a commercially insured US population and can be a source of input data for scenarios looking at this type of population
    - Population characteristics include age, sex, race/ethnicity, income level, and education level (the last two at a neighborhood level)
    - HealthCore/IVI study extensions may be able to inform population characteristics for the planned model expansions to those aged 65 and older and those who are Medicaid-insured
    - The data environment available to HealthCore can also distinguish between the primary insured and young dependents under age 26, which could be another population of interest in the future
- The ongoing HealthCore/IVI study will also provide information on MDD severity level (for those with specified severity as per ICD-10-CM codes recorded on medical claims)
- We note that patients with other major psychiatric or chronic conditions (anxiety, bipolar disorder, schizophrenia, substance abuse disorder, cancer, cardiovascular disease, multiple sclerosis, or Parkinson's disease) are excluded from the population of interest for the model. How exactly is this incorporated into the model? For example, will the efficacy inputs be limited

to studies that excluded these patients? It will be helpful to provide more clarity in the protocol. MDD without other chronic physical and psychological conditions is probably rare.

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)?

- The ongoing HealthCore/IVI study will provide cost outcomes stratified by treatment behaviors. Study extensions could consider stratification of cost outcomes along other domains, such as demographics and SDOH, to examine the presence and extent of any differences.

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?

- This longitudinal epi study may be useful: https://www.niaaa.nih.gov/research/nesarc-iii

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?

- Taking a private payer perspective, HealthCore notes the following:
    - We appreciate the inclusion of psychiatric hospitalizations (as noted in the protocol) as this is a marker for poor outcomes; MDD is among the most common conditions associated with inpatient care and suicide[1]
    - We appreciate the (planned/attempted) inclusion of suicide attempts (as noted in the protocol) as these are costly and not always associated with appropriate follow-up care
    - Impact of different treatments and treatment sequences on the volume of MDD-related outpatient utilization would be of interest as an additional outcome, particularly with respect to involvement of primary care vs specialty providers in care management, and use of telehealth
    - Section 6.9.2. mentions that generalized health states will be used, in preference to "direct linkage to a score on a clinical measure". It is not clear how the model will channel the efficacy inputs into these health states in the absence of a common clinical measure. Could this be clarified?
        - Moreover, practical application of the model in the health care sector will involve review by clinicians and for this purpose it would be helpful to have

[1] https://pubmed.ncbi.nlm.nih.gov/31171451/, https://pubmed.ncbi.nlm.nih.gov/31171452/

summary-level information on how typical clinical measures map into the model health states (e.g. "complete response is similar to a score of 7 or less on the Hamilton Depression Rating Scale")

- Given the mutual association/pathways between depression and physical health[2], a future version of the model may benefit from further extending the outcomes to include non-MDD resource use and cost (beyond the number of all-cause hospitalizations currently listed in the protocol)

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?

- The ongoing HealthCore/IVI study will look at the prevalence of suicide attempts/ideation pre- and post-MDD diagnosis (using ICD-10-CM codes) for the general MDD population. This can be extended to examine outcomes among subgroups, such as those defined by types and lines of treatment
- HealthCore data can be linked to external sources including the National Death Index. The NDI provides information on cause of death, which could be used to better estimate the incidence of suicide death by capturing suicide deaths that occurred outside of the hospital setting.

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?

- The ongoing HealthCore/IVI study will look at prevalence of somatic therapies by treatment line

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?

[2] https://www.nimh.nih.gov/health/publications/chronic-illness-mental-health

- Yes, this seems reasonable.

- 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?

- The protocol is not clear to us exactly how these two approaches would be used for costing. We would recommend using the bottom-up approach as a main analysis and top-down as sensitivity analysis, since the bottom-up approach typically implies a more granular approach that allows more customization for different stakeholder needs.

- Are you aware of any data sources/studies that we should look into for this issue?

- The ongoing HealthCore/IVI study will provide a "top-down" approach of direct medical costs (private payer allowed amounts) stratified by various treatment parameters (e.g. line of therapy). Additional cost data can be generated as study extensions to help populate model inputs as needed (e.g. costs per all-cause and MDD-related hospitalization)
- It is important for the model to include the "total cost of care" perspective, i.e. to estimate the impact of different treatments not only on MDD-related medical and Rx costs, but on non-MDD-related costs as well. The current protocol is not clear on if/how this is being considered.

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?

- The ongoing HealthCore/IVI study can be augmented to look for AEs identified in claims. HealthCore is a member of the FDA's Sentinel Initiative which uses electronic healthcare databases to look for safety signals[3]; as such we have deep experience in the identification of AEs using claims.

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?

[3] https://www.fda.gov/safety/fdas-sentinel-initiative

- In the absence of literature consensus, we would recommend creating a weighted average of the identified options as the main input, as well as constructing the model front end in such a way that alternative values can be easily chosen and/or supplied by the user (e.g. a drop down menu that allows selection of values from each published paper used in creation of the weighted average)
- Also please consider reformatting Table 8, by putting the last row (with the sources) as the first row instead, so that it is clearer what each column contains.

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)?

- The base case assumptions from Table 10 look reasonable.

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?

- HealthCore would be happy to discuss how a de novo study using direct-to-patient approaches within our research environment could be used to inform these inputs.
- It may also be possible to use emergency room visits and hospitalizations of dependent adults (as identified in the claims) to estimate time off work and travel costs for family caregivers.

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?

- The decision needs listed under "Payers and Employer Purchasers" are all relevant from HealthCore's perspective, with a particular emphasis on optimal treatment sequencing and how to align benefit designs in such a way to encourage this
    - There is a knowledge gap around the best use of psychotherapy (alone or in combination, frequency of visits, etc.) and we hope this model can help close some of these gaps
- In addition, we wonder if the model could inform the following items:
    - Evaluating the economic/QOL impact of quality measures for depression care (e.g. HEDIS AMM[4] and STARS measures for depression screening that involve drug adherence)
    - Establishing the value of new "personalized medicine" approaches such as genetic testing (e.g. genomind, genesight) to inform choice of antidepressant medications

[4] https://www.ncqa.org/hedis/measures/antidepressant-medication-management/

General: Do you have any other comments or feedback for us to consider?

- We appreciate the inclusion of flexible time horizons in the model (section 6.5) as the payer planning horizon tends to be limited to a few years based on contract renewals. It will be interesting to compare outcomes over a few years vs. assuming a lifetime horizon
- A similar economic model for anxiety would be of interest given that it is another highly prevalent behavioral health condition that can have debilitating consequences
- Additional "settings and locations" (section 6.2) that would be of interest to examine include employee assistance programs, urgent care, and retail clinics
- Given growing alternatives to traditional office visits, such as computerized CBT[5], it would be interesting to include this in future versions of the model to understand their effectiveness, cost impact, and patient satisfaction
- It would be interesting to select a certain small number of use cases that IVI will investigate once the model is complete, and to describe in detail how the inputs and parameters will be set to implement those use cases, together with the suggested sensitivity analyses. This will help future (external) users of the model better understand how to work with the model themselves

[5] https://pubmed.ncbi.nlm.nih.gov/32673212/

Otsuka

Otsuka-people creating new products for better health worldwide

26 January 2022

Innovation and Value Initiative
917 Prince Street
Alexandria, VA 22314

Re: Feedback on the Innovation and Value Initiative's draft model protocol on major depressive disorder (MDD)

Dear Madam or Sir:

Otsuka Pharmaceutical Development & Commercialization, Inc. ("Otsuka") is pleased to submit comments to the **Innovation and Value Initiative** (IVI) in response to the call for public comment of 14 December 2022, on *Innovation and Value Initiative's draft model protocol on major depressive disorder (MDD)*.

Otsuka is an indirect subsidiary of Otsuka Pharmaceutical Company, Ltd. (Otsuka Pharmaceutical). Established in 1964, Otsuka Pharmaceutical is a total healthcare company. In keeping with the corporate philosophy of "Otsuka-people creating new products for better health worldwide," Otsuka Pharmaceutical and its affiliates worldwide aim to treat illness and sustain day-to-day well-being. With a pharmaceutical business that provides breakthrough treatments for patients around the world, and a nutraceutical business that helps healthy people get even healthier, Otsuka Pharmaceutical researches, develops, produces, and sells highly innovative and creative products.

Otsuka would like to acknowledge efforts put forth by the IVI to develop transparent, accessible, and user-friendly economic models in several disease states, including major depression disorder. We have provided comments in response to the draft protocol.

Sincerely,

Shuvayu Sen

Shuvayu Sen, Ph.D.
Vice President, Global Value and Real World Evidence
Global Value and Real-World Evidence
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Otsuka

Otsuka-people creating new products for better health worldwide

Section	Areas/Questions	Comments
I. GENERAL FEEDBACK		
Otsuka congratulates the IVI) on the completion of Model protocol for Major Depressive Disorder (MDD) and appreciates the opportunity to provide comments. The draft model protocol on MDD is detailed and discusses major aspects of the economic model clearly.		
6.1	*The initial version of the model will focus on treatment-naïve adults, 18 to 64 years in age, diagnosed with MDD by a healthcare provider (e.g., primary care provider, psychologist, psychiatrist) without diagnoses of other psychiatric and non-psychiatric chronic comorbidities (e.g., anxiety, bipolar disorder, schizophrenia, substance abuse disorder, cancer, cardiovascular disease, multiple sclerosis, Parkinson's disease)*	Otsuka recommends that the patient population included to be included in the model be expanded to treatment-experienced patients and patients aged 65 years and older. In addition, attention deficit hyperactivity disorder (ADHD) is a prevalent comorbidity in MDD, which should be considered in the exclusion criteria.
6.2	*The model will enable evaluation of treatment sequences in a range of care settings including primary care, specialty care (e.g., psychiatrist), and telehealth.*	Otsuka deems the location and setting appropriate.

Section	**Areas/Questions**	**Comments**
6.3	*The societal perspective will allow various stakeholders to select a subset of costs and benefits relevant to them.*	Otsuka deems the perspective to be comprehensive and flexible.
6.4	*A list of treatment options and strategies will be considered as comparators in the model, based on clinical guidelines, literature review, available data, and input from the AG. The MDD model will give users the flexibility to specify up to four sequential treatments (Appendix G) and explore clinical and economic outcomes associated with different treatment sequences.*	Otsuka deems the list of comparators to be comprehensive. Otsuka recommends using market shares for the comparators when modeling them at the Group/Class level.
6.5	*The model horizon is lifetime, with an option to output results at other user-defined time intervals (minimum one year).*	Otsuka agrees with the idea of modeling effects and costs associated with MDD treatments over a time horizon sufficient to capture these outcomes. However, in MDD, clinical trials are usually very short in duration, preventing proper measurement of the full impact of treatments on predefined outcomes. Modeling the costs and effects of MDD treatment over a lifetime horizon would add significant uncertainty to the ICER estimate. Besides, from a real-world perspective, patients may discontinue their treatments after a short-term period. Otsuka recommends considering two temporal horizons: 1) short term (1 year) and 2) long-term (1+ years). Appropriate data sources to support the long-term modeling efforts will need to be identified, including electronic health records, registries and claims data (recommendations on data sources made in section II of this document).

Section	**Areas/Questions**	**Comments**
6.6	*The cycle length is specified to be 3 months in the model based on two key considerations…*	Otsuka deems the cycle length to be reasonable.
6.7	*Per best practice in the US, costs and benefits will be discounted at 3% per annum.*	Otsuka recommends providing clarifications on how the annual discount rate will be converted into model cycle discount rate
6.8	*The following outcomes will be tracked and counted to enable reporting and comparison across treatment sequences…*	Otsuka recommends including disability adjusted life years (DALYs) as an output in the model to capture the societal burden of MDD.
6.9.2	*There is no consensus on the score or change score that reflects improvement or response; therefore, we propose that the model use these health states that were commonly found in previous models and our scoping review, but that there does not need to be direct linkage to a score on a clinical measure. This would permit broader usability of the model and also recognize that the likelihood of being able to populate effectiveness*	It is Otsuka understanding that using health states commonly found in previous models with no direct linkage to a score on a clinical measure (i.e., HAM-D, MADRS or PHQ-9) is appealing and makes modeling these states easier. However, patient categorization in clinical trials is based on scores on depression rating scales. As a result, the economic model will not truly simulate patients with MDD per typical trial definition (i.e., inconsistencies in definitions of health states used in the clinical trials). Otsuka recommends considering alternative model structure linking thresholds of clinical effectiveness measures (e.g., HAM-D, MADRS) to membership in a health state, specifically. This could be done as part of testing the structural uncertainty of the model and increase the robustness of the analysis.

Section	Areas/Questions	Comments
6.9.2/Appendix B	*Health utility instrument*	Given that the EQ-5D captures information in only 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), areas of functioning and quality of life may not be captured from the EQ-5D, such as vitality, energy or fatigue, and insomnia. Otsuka recommends including utilities obtained from other types of health state utility instruments such as SF-36 (could be mapped onto SF-6D to get health utilities).
6.9.3.2	*The protocol stipulates that "In the absence of data, the application of a hazard rate approach, that is, to assign a proportionally different effectiveness rate in later lines of therapy, may be used."*	It is Otsuka understanding that the application of hazard rate for effectiveness estimation in later lines of therapy is appropriate if the corresponding proportional hazard (PH) assumptions hold. Otsuka recommends formally testing the PH assumptions (e.g., Schoenfeld residuals). In case of violation of the PH assumptions, consider using time-varying hazard ratios to address the non-proportionality of hazards.
II. FEEDBACK ON THE THREE MAIN AREAS		
	Potential data sources and partners to address data gaps	Otsuka recommends exploring the use of electronic health records and claims databases to supplement limited data obtained from clinical trials. For example, "relapse" is an important health state that needs to be captured in modelling MDD. However, clinical trials in this space are of short duration, thus do not allow proper capture of relapse. Partners to address this data gap include Holmusk (https://www.holmusk.com/), a data analytics company that aspires to be world's largest real-world evidence platform for behavioral health.

Section	Areas/Questions	Comments
	Prioritization of data sources when multiple valid approaches exist; and	Otsuka recommends prioritizing data sources as follows: electronic health records (EHR) -> registries -> claims databases.
	Recommendations on how the MDD model can help inform decisions in your organizations	Otsuka believes that the completed IVI open source MDD model could complement the tools used to inform the development of clinical trials for MDD treatments. Specifically, the model could help identify realistic endpoints and effect sizes needed for trials of MDD assets early in their development. This would ensure that these assets return economic value to health technology assessment (HTA) bodies at the time of product launch. In a sense, the model could assist manufacturers in informing go/no go decisions in an iterative fashion. The MDD model could further be used at the time of product launch to support HTA submissions.
III. RESPONSES TO RESEARCH QUESTIONS		
6.1 and 6.1.1	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? 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	Otsuka recommends using real-world data (EHR and claims) for a better representation of the characteristics of the MDD patient population. Otsuka recommends partnering with Holmusk Partners to address this data gap include Holmusk to achieve this objective.

Section	Areas/Questions	Comments
	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?	Otsuka recommends using observational data to estimate long-term efficacy inputs. There are tutorials illustrating how to create a transition matrix based on administrative data (e.g. https://www.sciencedirect.com/science/article/pii/S1098301520301546) and electronic health records (https://journals.sagepub.com/doi/abs/10.1177/0272989X20985752).
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?	Otsuka believes that the completed IVI open source MDD model could complement the tools used to inform the development of clinical trials for MDD treatments. Specifically, the model could help identify realistic endpoints and effect sizes needed for trials of MDD assets early in their development. This would ensure that these assets return economic value to health technology assessment (HTA) bodies at the time of product launch. In a sense, the model could assist manufacturers in informing go/no go decisions in an iterative fashion. The MDD model could further be used at the time of product launch to support HTA submissions.

Section	Areas/Questions	Comments
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?	It is Otsuka belief that assuming the same sets of model inputs may not be reasonable. Failure rates for first, second and treatment resistant have been shown to be different in *Rush et al. 2006* (Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report - PubMed (nih.gov) and *Akram et al.* 2020 (the-clinical-economic-burden.pdf (iqvia.com). For the third and fourth lines, the application of hazard rate seems appropriate. Nonetheless, the PH assumptions would need to hold for the hazard rate to be used appropriately.
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	It is Otsuka understanding that the bottom-up approach would work best if the required data (resource use and unit costs) was captured as part of a trial-based economic evaluation. Otsuka is not aware of a data set that would support such calculations. Otsuka recommends the top-down approach that could be applied in retrospective cohort studies using administrative claims data, allowing longer follow-up and better cost

Section	Areas/Questions	Comments
	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?	capture for outcomes not typically studied in clinical trials (e.g., Relapse).
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?	Otsuka recommends consulting the study by *Jakobsen et al. 2017*: Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and Trial Sequential Analysis | BMC Psychiatry | Full Text (biomedcentral.com)
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 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	To inform the calculation of informal caregiving burden or costs, Otsuka recommends the study by *Kuvadia et al. 2021* available at: https://www.psychiatrist.com/pcc/depression/direct-indirect-costs-among-caregivers-patients-major-depressive-disorder-suicidal-ideation-suicidal-attempt/

Section	Areas/Questions	Comments
	model could help inform?	

#14

COMPLETE

Collector:	Web Link 1 (Web Link)
Started:	Tuesday, January 25, 2022 5:00:19 PM
Last Modified:	Tuesday, January 25, 2022 5:34:23 PM
Time Spent:	00:34:04
IP Address:	72.83.147.168

Page 1: Introduction

Q1

First and Last Name and degrees, if you would like included

Raquel Halfond, PhD

Q2 **Respondent skipped this question**

Title

Q3

Organization if Any

American Psychological Association

Q4

Email Address

rhalfond@apa.org

Q5 **Respondent skipped this question**

Phone Number

Q6 **Clinician**

Please check the stakeholder group(s) that you represent

Page 2: General Questions

Q7 **Respondent skipped this question**

What are potential data sources and partners to address data gaps identified in the draft model protocol?

Q8

Respondent skipped this question

What are your recommended data sources or technical approaches when multiple valid approaches exist?

Q9

Respondent skipped this question

What are ways that you envision using the IVI-OSVP model and what are practical applied research questions that you would like the model to address?

Q10

Additional Comments

- Section 3.2 In intro/background- this section references guidelines from both the American Psychological Association and the American Psychiatric Association. Suggest double checking these references throughout to ensure referring to the correct guideline. For example, it notes the most recent update of Psychiatry's (ref #6) guideline is 2019 but the reference is listed as 2010, whereas the American Psychological Association's guideline (ref #7) is 2019.

- Outcomes- please consider including patient centered outcomes in the model, outcomes that are important to patients (e.g., quality of life).

- For psychological treatments, please consider also listing Cognitive therapy in addition to the therapies listed, consistent with the differentiations made in the American Psychological Association's (2019) clinical practice guideline on depression.

- Great that the model allows for subgroup considerations. I am a little confused by part of section 6.1.1. It mentions that you can search by subgroups but also notes no reports differentiated by the key characteristics. Can additional information be provided to clarify this point, particularly exploration of any subgroup effects by race/ethnicity?

- Section 6.5 Great that allowing for effects over longer periods of time as medication and psychotherapy can have differential effects over time after discontinuation.

- 6.9.3.1 I am unclear about the assumption of discontinuation for patients for which there is no response after two cycles, can this be clarified? Does this refer to patients who have chosen to discontinue treatment?

Page 3: Specific Questions Referenced by Section

Q11

Respondent skipped this question

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? Section 6.1

Q12

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)? Section 6.1.1

Respondent skipped this question

Q13

Do you have some suggestions on studies/data sources/methods that we can reference in extrapolating the long-term efficacy inputs? Section 6.5/8.2.3We 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?

Respondent skipped this question

Q14

Are there other model outputs that will be of interests to your organization? In what decision contexts will they be useful? Section 6.8

Please consider including patient centered outcomes in the model, outcomes that are important to patients (e.g., quality of life).

Q15

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? Section 6.8

Respondent skipped this question

Q16

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? Section 6.9.3

Yes

Q17

We specified scenarios in which individuals in our simulation will move to a new line of treatment. Section 6.9.3.1Are 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?

Respondent skipped this question

Q18

Is it reasonable to assume the same sets of model inputs (efficacy and safety) for the first and second lines of treatment? Section 6.9.3.2In 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?

Respondent skipped this question

Q19

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). Section 7.3Is 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?

Respondent skipped this question

Q20

Are there key adverse events that have a significant clinical and economic impact that we should include in the model? Section 7.1.2We 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?

Suicidal ideation and attempt. If you include discontinuation, please specify the reason (e.g., discontinuation due to adverse event or due to other reason)

Q21

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? Section 7.2

Respondent skipped this question

Q22

For psychotherapy, what is a reasonable assumption for the length of a visit and for duration of psychotherapy to include (Table 10 and 11)? Section 7.3

Respondent skipped this question

Q23

Do you have any suggestion on studies or data sources that can inform the calculation of informal caregiving burden or costs? Section 7.3.5.2

Respondent skipped this question

Q24

Appendix H describes some of the novel questions or research opportunities that the model could help inform. What specific use cases or decision contexts should be prioritized? What are other important use cases or decisions that this model could help inform? Appendix H

Respondent skipped this question

Q25

May we contact you with follow-up questions if they arise?

Yes