Boehringer Ingelheim

Jennifer Bright, MPA
Executive Director
Innovation and Value Initiative

RE: Comment on IVI MDD Model Scope May 13, 2021

Dear Ms. Bright,

Boehringer Ingelheim Pharmaceuticals Inc. ("Boehringer Ingelheim") is a company committed to developing novel treatments for psychiatric diseases and appreciates the opportunity to comment on the Innovation and Value Initiative's (IVI) Open-Source Value Platform (OSVP) model for Major Depressive Disorder (MDD). We commend IVI for conducting primary research with patients to inform the model, and for facilitating an open dialog throughout the development of this model.

Boehringer Ingelheim acknowledges the model strengths such as a customizable model structure allowing for flexibility and the inclusion of patient preferences. We welcome the approach to feature the societal perspective in the base case to reflect the broad impact that MDD can have not only on patients directly, but also on their caregivers, employers and society overall. To allow for further analysis of different stakeholder perspectives, we recommend including the perspectives of different payer types including government payers in the model.

Boehringer Ingelheim offers the following specific recommendations to aid in improving the model scope:

- Given the heterogenous nature of MDD and the broad range of MDD symptoms and impacts, it will be important to ensure that outcome measures used to inform health states can capture improvements that are relevant to patients. IVI may consider including additional instruments such as Patient-reported Outcome instruments to inform the model.
- As an additional treatment sequence, we would suggest inadequate response to antidepressant treatment.
- We would suggest two additional populations:
    - patients aged 65 and older
    - patients covered under Medicaid.
- IVI should consider allowing for a comparison with digital therapy as an adjunct to pharmacotherapy.

- IVI should consider providing guidance on how to utilize psychotherapy as a comparator in combination with pharmacotherapy and how to address differences in access and availability of psychotherapy.
- We recommend to carefully assess and incorporate the implications of delayed onset of action as well as the side effects of current treatments.
- We encourage IVI to carefully address heterogeneity of treatment effects, and guide users in interpreting the potential ramifications.

Boehringer Ingelheim appreciates the opportunity to provide this feedback and welcomes any questions or requests for clarification that IVI may have.

Newell E. McElwee

Newell E. McElwee, PharmD, MSPH
Vice President Health Economics and Outcomes Research
Boehringer Ingelheim Pharmaceuticals, Inc.
E: Newell.McElwee@boehringer-ingelheim.com
C: +1 203 482 9688

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Page 1: Information on Public Comment

Q1

First and Last Name

Debra Lerner

Q2

Title

Professor and Director

Q3

Organization

Tufts Medical Center and Tufts Clinical and Translational Science Institute

Q4

Email Address

dlerner@tuftsmedicalcenter.org

Q5

Please check the stakeholder group(s) with which you identify.

Researcher

Page 2: Overall Feedback and Recommendations

Q6

Please use this space to provide feedback and recommendations on the overall approach outlined in the proposed model scope.

The approach generally reflects the Advisory Group's perspectives and those of the relevant literature. The document itself is overly technical in some areas and uses jargon unnecessarily. I would like to see it written in plain English so it is accessible to more readers. I do not feel that the discrete choice experiment and planned survey merit the amount of space in the document mainly because the work is not completed and therefore any results thus far should be considered preliminary. Also, I am not sure the Advisory Group will consider it foundational to the model until we have the results in hand.

Q7

What factors of patient experience, priorities, costs or outcomes are not currently captured by our proposed model scope or are especially important to include?

Career disruptions have been mentioned in economic models-both for the person with depression and their caregivers.

Page 3: Specific Questions

Q8

The MDD model will consider all care settings in MDD treatment, including primary care, specialty (psychologist/psychiatrist), and telehealth. What are the specific ways that care setting can impact the key clinical and economic outcomes? (Sections 7.2 and 7.13.1)

I saw several issues that require more discussion and resolution. I'm going to load them all in this box. 1) How to handle care for suicide risk and post suicide attempts. This is increasingly regarded as a distinct area of care. 2) How to handle public health interventions such as screening on combination with referral to a system of care, which is consistent with the USPSTF guidelines. 3) How to integrate phases of MDD treatment, which are not even mentioned. 4) How to handle collaborative care (different from stepped care), which is a comprehensive set of interventions. It is not just a context. Why wouldn't collaborative care be a care option? 5) How will you reconcile the many different comparators used in research? Usual care, standard care, treatment as usual, no care are all defined differently in different studies. The approach is not clear to me.

Q9

Respondent skipped this question

From your perspective, how much time is typically required to fully assess a treatment’s effectiveness after its initiation? Are there differences across interventions in time to assess success? (Section 7.6)

Q10

Clinical instruments (e.g., PHQ-9) are often used to evaluate treatment success. In addition to the clinical instruments listed in the model scope document, are there other clinical instruments we should evaluate during the protocol development stage? In addition to clinical instruments, what other outcomes (e.g., specific symptoms such as sleep, adverse clinical events) will be important to consider in evaluating the success of a treatment or intervention? (Section 7.8)

Respondent skipped this question

Q11

In addition to clinical instruments, what other outcomes (e.g., specific symptoms such as sleep, clinical events such as suicide) will be important to consider in evaluating the effectiveness of a treatment or intervention?

The current instruments such as the EQ5D and SF6 do not capture occupational functioning, which is so important to patients, family members and employers. There are data that may help to fill this gap and could be explored further.

Q12

In the scoping document, specific cost items the MDD model may evaluate are described, along with their relevance to various stakeholders (e.g., employers). (Section 7.10 and Appendix 9)

Are the costs described relevant to your decision-making?	**One of the major missing pieces of information about cost is the amount that patients are paying due to incorrect billing. If you have been involved in managing claims related to a major health event, especially one that is chronic, the billing is consistently a problem. People spend countless hours either fixing the claims on the phone or just paying them. Surely we can get an estimate of overbilling.**
Are there other costs the model should evaluate?	**Caregiving.**
Can you point us to data sources that address your suggested cost factors?	**AARP/NAC studies, Lerner et al studies.**

Q13

Do you have suggestions for data sources or literature we can reference that can contribute to MDD model inputs? We are particularly interested in recommendations for: efficacy of various treatment options based on depression measures, especially PHQ-9; efficacy data for digital therapies; productivity gain/loss due to absenteeism and/or presenteeism; and measures of stigma in the workplace due to an MDD diagnosis (Sections 7.8 and 7.13.3)

Productivity, absenteeism and presenteeism especially in relation to PHQ-9 scores.

Q14

Appendix 2 lists a set of stakeholder-specific decision questions.

Do these questions seem relevant from your perspective?	**Yes**

Q15

Do you have any additional recommendations or suggestions?

Distinguish payer and purchaser perspectives when appropriate. It was not clear to me when an employer is considered a payer.

Jennifer Bright & Rick Chapman
Innovation and Value Initiative
917 Prince Street
Alexandria, VA 22314
public.comment@thevalueinitiative.org

May 14, 2021

RE: Public Comments on the IVI-MDD Model Scope Document

As a biopharmaceutical company committed to developing novel therapies with the potential to transform the lives of people with debilitating disorders of the brain, Sage Therapeutics ("Sage") appreciates the Innovation and Value Initiative's (IVI's) efforts in developing open-source value assessment models that are patient-centered. Sage's depression, neurology, and neuropsychiatry franchise programs aim to change how brain disorders are thought about and treated. We aim to improve on the understanding that Major Depressive Disorder (MDD) may be episodic in nature and a condition that should be treated with urgency We are encouraged by IVI's goal of creating a new, transparent, and more holistic approach to value assessment and incorporating the patient perspective. We are committed to providing constructive feedback and support that will help improve the model for Major Depressive Disorder (MDD) and broaden the applicability of the model.

Below are the key points that Sage would like to emphasize as the IVI-MDD model scope is finalized:

- The target population should be expanded to include patients (or specifically report outcomes for patients) who have been previously treated and/or are experiencing recurrent episodes.
- We strongly support the proposal that additional modules be built for those over 65 years and for those with specific comorbid conditions.
- Given the heterogeneity of patients with MDD, the IVI-MDD model should focus on stratifying results for specific groups of patients rather than producing results for an "average" MDD patient.
- We would like to propose that IVI consider adding flexibility of a shorter model cycle to account for early decision making and the heterogeneity of disease course.
- IVI's model should reflect the complexity of the disease course of MDD and specifically integrate the heterogeneity of episodes and relapse.
- The IVI-MDD model should consider incorporating the impact of functional impairment, with a focus on activity impairment, on patients' personal lives in addition to work productivity.
- Careful consideration must be taken when measuring health state utility values.
- We strongly support the integration of the impact of caregiver and family in the IVI-MDD model.

The remainder of this letter provides a more detailed discussion of these points.

The target population should be expanded to include patients (or specifically report outcomes for patients) who have been previously treated and/or are experiencing recurrent episodes.

In IVI's model scope document for MDD, the target population for the model is treatment-naïve adults (pg. 14). MDD is characterized by episodes which can occur as a single or recurrent episode (APA 2013). The National Center for Health Statistics (NCHS) data 2017 data brief reported that 12.7% of Americans aged ≥12 used antidepressants in the past month and of all adults taking antidepressants in the US, 68% have been taking them for over 2 years and 25% have been taking them for over 10 years (Pratt 2017). We would suggest that IVI consider expanding the target population to include adults at the start of a new MDD episode diagnosed by a healthcare provider regardless of prior treatment status or alternatively consider modeling adults with MDD with prior treatment experience as a subgroup. This could allow the model to better capture the heterogeneity of patients within their disease course and align with the clinical data available for inputs. The STAR*D study, a commonly used data source for MDD models, enrolled patients with prior treatment experience and who were experiencing a recurrent episode (75%) (Rush 2006). Treatment pattern analyses find that the majority (64%) of new pharmacotherapy treatment decisions within a year were prescribed to patients with prior treatment experience in the last year (Arnaud 2021).

We strongly support the proposal that additional modules be built for those over 65 years and for those with specific comorbid conditions.

Sage supports adding an additional module to examine patients with MDD over 65 years and integrate the unique considerations for this population including more complex comorbid medical conditions (Fiske 2009), different functional impairment considerations, and substantial impact of MDD on family and caregiver burden in this population (Martire 2010).

Sage also supports adding an additional module exploring the effects of MDD on populations with specific comorbid conditions, as comorbidities are common and contribute to significant costs in this population. Of commercial insured patients in the United States (US) with MDD, 85% have at least one other diagnosed health condition (Blue Cross Blue Shield 2018). An economic analysis using national survey and administrative claims data showed that for $1 dollar spent on MDD direct costs, an additional $2.57 was spent on direct comorbidity costs incurred by persons with MDD compared to those without (Greenberg 2021). Research has shown that the presence of depression can worsen the severity of pre-existing comorbid medical conditions including arthritis, diabetes, cardiovascular disease, asthma, dementia and other neurological disorders (Dirmaier 2010, Fan 2014, Moussavi 2007, Raskind 2008, Sawa 2014) and impair people's ability to adhere to medication (Grenard 2011). Studies have also shown that effective treatment of MDD can lead to improvements in the disease course of comorbid conditions (Ell 2011, Kinsinger 2010, Pintor 2006, Stewart 2014).

Given the heterogeneity of patients with MDD, the IVI-MDD model should focus on stratifying results for specific groups of patients rather than producing results for an "average" MDD patient.

There is considerable heterogeneity in the MDD population with regards to patient characteristics, developmental timing, comorbidities, and environmental contexts which impact treatment decisions, adherence to treatment, risk of relapse, impact on quality of life (QoL) and function. As

such, it may be difficult to characterize an "average" patient with MDD and will be more valuable to show the perspective of multiple strata of patients by producing results for specific groups which would better capture the patient perspective and experience with the disease and aid in the interpretation of the findings.

We would like to propose that IVI consider adding flexibility of a shorter model cycle to account for early decision making and the heterogeneity of disease course.

The disease course of MDD should be considered in model design, as the rapidity of symptom improvement, duration of episode, and number of treatments can impact clinical outcomes. The model scope states, "American Psychiatric Association guidelines recommend at least a four-week observation period before treatment effectiveness can be fully assessed, thus a four-week cycle length may be used in the model" (pg. 18). However, to allow flexibility in the model and future model iterations, we would suggest a shorter cycle length such as 2 weeks. Other guidelines commonly referred to in the US suggest reassessing patients for tolerability, safety, and early improvement no more than 2 weeks after starting a medication (Kennedy 2016) which could result in treatment changes namely in the case of adverse events. Additionally, the assessment of a single or recurring episode of MDD requires presence of symptoms for 2 weeks (APA 2013). Data also suggests that early improvement of symptoms can predict positive treatment outcomes and functional improvement (Habert 2016, Szegegi 2009, Kraus 2019). Patients who improve within 2 weeks of therapy are highly likely to achieve stable response and stable remission after continued treatment (Szegegi 2009). Longer episode duration is associated with greater QoL impairment (Reed 2009). We would encourage IVI to consider the added flexibility of a shorter cycle length to allow model users to account for early decision making and broaden the applicability of the model.

IVI's model should reflect the complexity of the disease course of MDD and specifically integrate the heterogeneity of episodes and relapse.

The heterogeneity of relapse is an important concept that should be included in the model. The STAR*D study found that there were increased rates of relapse with each treatment step needed to achieve response or remission, and higher rates of relapse in patients who did not achieve remission prior to entering follow up. The study reported rates of relapse ranging from 33.5% to 83.3% of patients depending on remission status and the number of treatment steps at follow-up entry (Rush 2006). Additionally, even in patients who have achieved remission, the number of residual symptoms has been shown to be predictive of relapse (Nierenberg 2010). As such, we recommend that the additional complexity and factors predictive of relapse be integrated in the model when designing health states and probabilities of relapse or recurrence.

The IVI-MDD model should consider incorporating the impact of functional impairment, with a focus on activity impairment, on patients' personal lives in addition to work productivity.

According to the World Health Organization (WHO) Mental Health Surveys, 57% of patients with MDD reported severe or very severe impairment in at least one of these—home, work, relationships, social situations (Bromet 2018). As MDD can greatly impact a patient's ability to participate in pleasurable activities and important and meaningful life events as well as accomplish daily activities outside of work; we encourage IVI to consider including activity

impairment or a similar concept in the model. We would suggest specifically accounting for this impairment through the utility elicitation work or by other means.

Careful consideration must be taken when measuring health state utility values.

It is important that health state utility values represent actual change in quality of life. Although the EuroQol-5 Dimension (EQ-5D) is widely used for calculating quality-adjusted life-years (QALYs) in cost-effectiveness evaluations, it lacks sensitivity to changes in health status in mental health disorders, and particularly, severe depression (Brazier 2010). 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. We would suggest that IVI consider other manners of eliciting health state utility values that are more sensitive to changes in MDD state such as the SF-6D. In addition, utilities should consider the impact of residual symptoms and side effects. For example, residual symptoms of depression, such as insomnia and fatigue as well as residual anxiety and vitality impairment, are common in patients with MDD even in those who have reached remission resulting in varying quality of life and function within patients who have remitted (Nierenberg 2010, Neirenberg 2015, Romera 2013, Habert 2016, IsHak 2013, IsHak 2016). IVI's MDD model should account for residual symptom burden and long-term side effect burden due to the large impact on quality of life, function and probability of relapse by quantifying and tracking these in the model.

We strongly support the integration of the impact of caregiver and family in the IVI-MDD model.

In addition to impacting the patient's quality of life, MDD can also impact the quality of life of caregivers, partners, guardians, and dependents. Research has shown that caregivers of patients who suffer from MDD experience psychological distress, social disability, and role disability (Zendjidjian 2012). Additionally, caregivers and family members of patients with MDD incur higher healthcare costs (Ray 2017). For example, a recent study examining caregivers of patients with treatment-resistant depression showed a significant economic burden on caregivers, mainly due to work productivity loss (Lerner 2020). Sage strongly supports the inclusion of cost and quality of life burden to caregivers and family in the IVI-MDD model.

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,

DocuSigned by:
Stephen Kanes
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Stephen Kanes, MD, PhD
Chief Medical Officer
Sage Therapeutics, Inc

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Janssen Scientific Affairs, LLC

1125 Trenton-Harbourton Rd
Titusville, NJ 08560

May 14, 2021

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

Contact Information	
Submitter	Michelle Han, PharmD
Profession	Associate Director, Payer & Health Systems, Medical Information & Knowledge Integration
Organization	Janssen Scientific Affairs, LLC
City	Titusville
State	NJ
Phone Number	609-720-6293
Email Address	mhan@its.jnj.com

Dear Ms. Bright and Dr. Chapman,

Thank you for the opportunity to comment on the IVI-Major Depressive Disorder (MDD) Model Scope Document. At Janssen Scientific Affairs, a part of the Janssen Pharmaceutical Companies of Johnson & Johnson, we work every day to transform patient lives by supporting access to innovative medicines and ensuring their optimal use.

We support IVI's principles for value assessment in the U.S., which are consonant with the principles outlined in our 2020 Janssen U.S. Transparency Report.

Janssen applauds IVI's efforts to build an open-source, patient-centric MDD model to assist healthcare stakeholders, including employers, clinicians, policy and advocacy organizations and payers, in understanding the value of alternative treatment options. As a member of the MDD model multi-stakeholder Advisory Group, we look forward to further collaboration to develop a model that is flexible and comprehensive enough to enable exploration of a range of value analyses related to delivering care for individuals living with MDD.

Janssen's comments on the scope document are as follows:

Heterogeneity of the Patient Population and Health Care Inequities

MDD is a heterogeneous disease, and Janssen strongly supports IVI's goal to build a model that can accommodate a diverse set of sub-populations, including populations with high unmet need and associated poorer clinical outcomes (APA 2010) (e.g., patients with comorbid anxiety, patients receiving sub-optimal levels of treatment, patients with treatment resistant depression, among others). Considering the importance of continuity of care especially for patients with MDD who are hospitalized, it is also key that the model account for care pathways after discharge.

We agree the model should enable exploration of the impact of health care inequities, given how outcomes vary by race, sex, ethnicity, and an array of geographic and socioeconomic factors. For example, some patients with MDD may not seek treatment due to stigma or other concerns. Furthermore, the health care system may not recognize MDD uniformly across different groups when individuals do seek care.

Also varying across subgroups is the probability of treatment initiation and continuation. For those who do not achieve timely response or remission, progression to additional lines of therapy or initiation or adjustment of psychotherapy can proceed slowly [APA 2010, Henke 2009].

Treatment Strategies

Because MDD impacts each patient differently and each patient responds to treatments in different ways, any model must account for the need to individualize treatment and treatment duration. It should be able to reflect the difference in treatment strategies and durations for those experiencing their first episode or undergoing episodic treatment as well as those receiving care who have a history of severe recurrent MDD. In addition, access to certain treatments varies across the severity spectrum; for example, in the U.S., there may be income-based inequities in access to psychotherapy, a recommended first line therapy for MDD.

The model should also recognize that although clinical trials generally use a four-to-eight-week trial duration, real-world treatment modifications often occur over a longer period of time, and many existing treatment guidelines recognize the need for long-term maintenance treatment.

Treatment Option Comprehensiveness, Granularity and Evidence-Base Evolution

The MDD model should ideally account for all key treatment options. Several new pharmacotherapies were omitted from the scoping document (e.g., vortioxetine, vilazodone). We suggest they be added. Additionally, pharmacotherapy augmentation strategies should also be included in Appendix 8 under second line treatment.

We also recommend that pharmacological treatments be considered at the individual drug product level rather than at a class level due to variations in efficacy, safety and tolerability profiles, as well as potentially in access.

The model should be structured to allow a user to add new treatment options and update key parameters related to existing treatments. In addition, as the timeframe of the model extends up to a lifetime, the model should consider the dynamic nature of the prices of treatments. For example, branded competition among alternative pharmaceutical treatments within and across classes, as well as genericization or changes in the relative price of telehealth vs. office based psychiatric care will alter the results of the simulations. (Neumann et al 2016) Actual transaction prices that different purchasers face should be used as inputs, and ideally, would include patients' out-of-pocket costs.

Use of the QALY

Janssen commends IVI for recognizing the concerns over the use of the cost per quality-adjusted life-year (QALY) and for establishing a model that goes beyond the QALY to include the flexibility to present various economic and clinical outputs to meet the decision needs of multiple stakeholders. However, we are still concerned that the QALY is included in the model, even if just as an outcome metric, as 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 2020).

Outcomes Measurement

In addition to the current proposal to include the PHQ-9 as a patient-reported depression measure, we recommend considering capturing information on level of anxiety symptoms (e.g., GAD-7 [Spitzer et al 2006]), given how prevalent anxiety is with MDD and the associated poorer outcomes. [Fava et al 2008].

To reflect real world clinical practice, we recommend also including a clinical global impression of severity (CGI-S) and adding patient reported measures of function and satisfaction (e.g., the WLQ [Lerner et al 2001], WPAI [Reilly et al 1993], and TSMQ [Atkinson et al 2004]).

The consequences of untreated or under-treated MDD are significant, and came into sharper focus in 2020 amid the pandemic and the invigorated spotlight on systemic racism. We therefore encourage IVI to consider these subgroups as an initial focal point for study. For example, in addition to the impact of depression symptoms and associated health care costs, MDD leads to consequences that affect patients' caregivers and families – consequences such as:family disruption; lost employment, underemployment, decreased skill or educational development; increased mortality for all-causes and suicide; exacerbation of physical health and other mental health comorbidities; increased risk of treatment resistance; and increased stigma. In addition, it will be important to consider the spillover effects of non-optimized treatment on other sectors of the economy and societal programs.

Looking Ahead

Janssen looks forward to continued engagement with IVI. We are confident the model will be a useful tool to improve the lives of those with MDD by enabling better healthcare decisions. Beyond MDD specifically, we also believe that IVI's project will improve stakeholders' understanding of the role of holistic value assessment in informing treatment choices and policy options, and also yield key insights regarding the importance of considering multiple perspectives in value assessments.

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Hi, Rick.

I talked with my psychiatrist colleague, and we have some comments for you:

- Psychiatry is a tough area because it's so subjective. Stakeholder selection at the next stage will be critical:
  - You need input from a lot more patients. (Bob said, "at least 300." Some of that could be done by remote survey, presumably.
  - Subject selection is really important, especially in today's social media world where people hang out in echo chambers. You want a representative sample of patients.
  - I get that you're focusing one 18-64yo because of the employer audience, but remember that employer groups have dependents too. An associate with a teenager that's having serious problems is NOT being fully productive—I guarantee!
  - Don't forget to consider the impact of comorbidities. The interaction between these can be complex, and sometimes it's hard to tell whether the depression is primary or secondary to what's going on medically.
- In general, it looks like your medical advice is coming heavily from academic medical communities. Bob would like to see community psychiatrists from multiple locations represented there.
- A problem with the RCT data is that almost all studies are short term (often as little as 6 wks follow up) and do not have RW endpoints. A 6-week improvement in MADRS doresn't tell me much about the patient. The patient wants to know, will it make me feel better? And will I be able to function better?
- Our input may be more helpful at the next stage, when you have a draft model. At that point we can look at how it's set up and comment on how realistic the framework and assumptions are.

I hope that's some help. You picked a tough place to start, but it's an area that definitely needs help!

Best regards,
John

John Watkins, PharmD, MPH, BCPS
Residency Program Director
Premera Blue Cross MS 432
7001 220th St SW
Mountlake Terrace, WA 98043-2160
Cell: +1 206-321-3568

#13

COMPLETE

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Page 1: Information on Public Comment

Q1

First and Last Name

Michelle Leavy

Q2

Title

Head, Healthcare Research & Policy

Q3

Organization

OM1

Q4

Email Address

mleavy@om1.com

Q5

Please check the stakeholder group(s) with which you identify.

Researcher

Page 2: Overall Feedback and Recommendations

Q6

Please use this space to provide feedback and recommendations on the overall approach outlined in the proposed model scope.

Respondent skipped this question

Q7

What factors of patient experience, priorities, costs or outcomes are not currently captured by our proposed model scope or are especially important to include?

Thank you for the opportunity to comment on the IVI initiative to create an open-source value assessment prototype model to support evaluation of major depressive disorder (MDD) interventions. Improving depression treatments and outcomes is critical given the burden of this condition, and I appreciate IVI's focus on identifying a wide range of outcomes of importance to patients, clinicians, and employers.

In the next phase of this work, I encourage the model developers to use consensus-based, standardized definitions for key outcome measures, such as remission and response. The proposed model currently does not include definitions for these outcomes. Multiple definitions exist for these concepts, which makes it difficult to compare results across studies and across clinical practice settings. The Agency for Healthcare Research and Quality (AHRQ) led a consensus-based effort to harmonize definitions for outcome measures for use in depression research and clinical practice. The measures were developed by a multi-stakeholder panel and are suitable for use in routine clinical practice across care settings (see Gliklich RE, Leavy MB, Cosgrove L, et al. Harmonized Outcome Measures for Use in Depression Patient Registries and Clinical Practice. Ann Intern Med. 2020;172(12):803-809.).

To assess the feasibility of using the measures, AHRQ funded a pilot project to capture the measures in primary care and behavioral health care settings. The measure results were used at the individual patient level to inform clinical decision-making and at the population level for research purposes. Findings from this pilot project will be published in 2021 and made available through the AHRQ website.

These efforts have demonstrated the importance of using consensus-based, harmonized definitions for key outcome measures such as remission and response. I encourage the model developers to consider these definitions in the next phase of this important effort.

Page 3: Specific Questions

Q8

The MDD model will consider all care settings in MDD treatment, including primary care, specialty (psychologist/psychiatrist), and telehealth. What are the specific ways that care setting can impact the key clinical and economic outcomes? (Sections 7.2 and 7.13.1)

Respondent skipped this question

Q9

From your perspective, how much time is typically required to fully assess a treatment's effectiveness after its initiation? Are there differences across interventions in time to assess success? (Section 7.6)

Respondent skipped this question

Q10

Clinical instruments (e.g., PHQ-9) are often used to evaluate treatment success. In addition to the clinical instruments listed in the model scope document, are there other clinical instruments we should evaluate during the protocol development stage? In addition to clinical instruments, what other outcomes (e.g., specific symptoms such as sleep, adverse clinical events) will be important to consider in evaluating the success of a treatment or intervention? (Section 7.8)

Respondent skipped this question

Q11

In addition to clinical instruments, what other outcomes (e.g., specific symptoms such as sleep, clinical events such as suicide) will be important to consider in evaluating the effectiveness of a treatment or intervention?

Respondent skipped this question

Q12

In the scoping document, specific cost items the MDD model may evaluate are described, along with their relevance to various stakeholders (e.g., employers). (Section 7.10 and Appendix 9)

Respondent skipped this question

Q13

Do you have suggestions for data sources or literature we can reference that can contribute to MDD model inputs? We are particularly interested in recommendations for: efficacy of various treatment options based on depression measures, especially PHQ-9; efficacy data for digital therapies; productivity gain/loss due to absenteeism and/or presenteeism; and measures of stigma in the workplace due to an MDD diagnosis (Sections 7.8 and 7.13.3)

Respondent skipped this question

Q14

Appendix 2 lists a set of stakeholder-specific decision questions.

Respondent skipped this question

Q15

Do you have any additional recommendations or suggestions?

Respondent skipped this question

#9

COMPLETE

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Page 1: Information on Public Comment

Q1

First and Last Name

Nathaniel Counts

Q2

Title

SVP, Behavioral Health Innovation

Q3

Organization

Mental Health America

Q4

Email Address

ncounts@mhanational.org

Q5

Please check the stakeholder group(s) with which you identify.

Patient or Family Organization

Page 2: Overall Feedback and Recommendations

Q6

Please use this space to provide feedback and recommendations on the overall approach outlined in the proposed model scope.

Mental Health America (MHA) congratulates the Innovation and Value Initiative (IVI) on completing its Major Depressive Disorder (MDD) Model Scope Document and is grateful for the opportunity to provide comment. The Model Scope is incredibly comprehensive and clearly demonstrates the work that went into incorporating the perspectives and values of patients, offering the opportunity to advance a new paradigm in value for MDD. We offer several recommendations here to further build on this work.

When fitting the model to different perspectives, we recommend that federal and state governmental perspectives be developed as separate from a societal perspective. Because federal and state governments are safety net providers, their cost dynamics are different from other payers. If ongoing poverty and/or disability can be averted through effective MDD treatment, they experience substantial savings in the form of reduced Medicaid and Medicare enrollment along with other public benefit utilization, in addition to reduced healthcare costs from those enrolled in Medicaid and Medicare. Further, federal and state governments experience gains from additional tax revenue associated with increased productivity - which is a financial benefit they directly internalize, as opposed to more abstract productivity benefits in a societal perspective . By modeling the specific perspectives of federal and state governments, public agencies will be better equipped to invest in MDD treatments based on their direct monetary benefits.

We applaud IVI's exploration of including patient-centered value in the utility inputs. Utilities based on individual health state preferences offer one important component of value, but do not encompass other important areas. For example, other individuals, such as family members, may also derive utility from an individual's MDD remission or response, which is not captured by individual health state preferences. Others may derive utility from the availability of effective MDD treatments creating a more equitable society. To the extent that there is evidence in the literature that could be used to enhance the utility determination with domains of value beyond individual health state preferences, we believe that this could enrich the model.

We also encourage the inclusion of peer support interventions as treatment options. Peer support can be both formal, through the use of paid peer support specialists, or informal, through support groups and other mechanisms. Peer support is quickly becoming a critical component of a continuum of mental health services, and we think valuing it in the model would offer an important contribution to ensuring access to peer support services.

Thank you again for your incredible work and for the opportunity to comment on the model. We are excited to see future iterations and support this initiative!

Q7

Respondent skipped this question

What factors of patient experience, priorities, costs or outcomes are not currently captured by our proposed model scope or are especially important to include?

Page 3: Specific Questions

Q8

Respondent skipped this question

The MDD model will consider all care settings in MDD treatment, including primary care, specialty (psychologist/psychiatrist), and telehealth. What are the specific ways that care setting can impact the key clinical and economic outcomes? (Sections 7.2 and 7.13.1)

Q9

From your perspective, how much time is typically required to fully assess a treatment's effectiveness after its initiation? Are there differences across interventions in time to assess success? (Section 7.6)

Respondent skipped this question

Q10

Clinical instruments (e.g., PHQ-9) are often used to evaluate treatment success. In addition to the clinical instruments listed in the model scope document, are there other clinical instruments we should evaluate during the protocol development stage? In addition to clinical instruments, what other outcomes (e.g., specific symptoms such as sleep, adverse clinical events) will be important to consider in evaluating the success of a treatment or intervention? (Section 7.8)

We hope that it will be possible to capture broader domains, such as hope and quality of life, in the utility input so that it can be integrated into the main model outputs.

Q11

In addition to clinical instruments, what other outcomes (e.g., specific symptoms such as sleep, clinical events such as suicide) will be important to consider in evaluating the effectiveness of a treatment or intervention?

Respondent skipped this question

Q12

In the scoping document, specific cost items the MDD model may evaluate are described, along with their relevance to various stakeholders (e.g., employers). (Section 7.10 and Appendix 9)

Are the costs described relevant to your decision-making?

See previous response.

Q13

Do you have suggestions for data sources or literature we can reference that can contribute to MDD model inputs? We are particularly interested in recommendations for: efficacy of various treatment options based on depression measures, especially PHQ-9; efficacy data for digital therapies; productivity gain/loss due to absenteeism and/or presenteeism; and measures of stigma in the workplace due to an MDD diagnosis (Sections 7.8 and 7.13.3)

Respondent skipped this question

Q14

Appendix 2 lists a set of stakeholder-specific decision questions.

Respondent skipped this question

Q15

Do you have any additional recommendations or suggestions?

Respondent skipped this question

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

Decision questions

From our perspective (health economics consultancy), the stake-holder specific decision questions listed in Appendix 2 which are most relevant are those attributed to researchers (including value assessors).

Though we understand the practicalities of specifying the setting and location of the model to be developed to the United States, please also be aware of the interest in the Innovation and Value Initiative major depressive disorder (IVI-MDD) model from outside of the US and consider this within the model scope wherever possible.

We also believe a valuable consideration for the model is how comorbid conditions and the quality of/capacity for self-care can impact people living with MDD and treatment decisions.

Target population

According to the results of the patient preference study in Appendix 6, a large proportion (30%) of people who participated in the Phase 1 interviews were aged 65 years and above. It therefore appears that the intention to use a target population of adults, 18 to 64 years in age will exclude a sizable group of patients. We would ask that if the exclusion of patients aged 65 years and above cannot be clearly justified it would be beneficial to consider including them in the target population. This is particularly relevant as a lifetime horizon is being used which means that the model will eventually include these patients anyway.

Although the target population being considered is treatment-naïve adults, it would be beneficial to also explore the feasibility of evaluating treatment-exposed patients by restricting the analysis to generate results for the later stages of the treatment pathway/later treatment sequences.

e: info@bresmed.com t: +44 (0)114 309 4372 w: bresmed.com
Steel City House, West Street, Sheffield, S1 2GQ, United Kingdom

Treatments

In addition to the combinations of pharmacotherapy augmentation treatments that are expected to be possible within the model, we believe it will also be important to model treatments given in addition.

Time horizon

As discussed in the model scope document, a limitation of many existing models in patient with MDD is the short time horizons (less than 5 years) though the disorder can have longer-term impacts. We therefore welcome the proposed use of a lifetime horizon, with the flexibility for interim evaluations at user-specified time points.

Model conceptualisation

Though the model scope document describes that health states are being considered, we would recommend thinking beyond a health state-based structure given the clinical instruments for MDD typically use a continuous scale and the use of an individual-level simulation model is planned.

Model inputs

Caregiver burden is listed in Appendix I as a cost input for consideration for the model. Whilst we agree that caregiver burden will be an important factor in the model, we believe the quality-of-life impacts of caregiver burden should also be considered in addition to the costs.

Model outputs

We believe outcomes such as job loss and personal relationship impacts are key to include in the model and are likely to be of vital importance from a patient's perspective but have not yet been considered as part of the model scope document.

We welcome the use of both a health economic module and a multi-criteria decision analysis (MCDA) module within the MDD model and that the MCDA module will provide expanded functionality versus previous Open-Source Value Platform models developed by IVI to support the full iterative process of MCDA.

Model validation and critical evaluation

To allow the user to easily evaluate the robustness of the model, it would be useful if there was functionality within the model to describe the robustness of the underlying data input and assumptions being applied.

Other

The following additional queries are also provided for your consideration:

- What, if any, modelling guidelines will be adhered to during development of the model?
- How will comparability across the proposed patient subgroups and treatment sequence combinations be maintained if data is unlikely to be available in the same outcome measures?
- Are both generic and/or disease-specific quality of life measurements to be considered in the model? It may be useful for some stakeholders to be able to compare outcomes for both approaches
- Will the impacts of MDD treatment on adherence for co-morbid conditions be included?

AMERICAN PSYCHOLOGICAL ASSOCIATION

Comment on IVI-Major Depressive Disorder (MDD)
Model Scope Document

May 2021

These comments were developed by members and staff of the American Psychological Association (APA) who have expertise on the topic, but they are not an official statement of the APA.

Thank you for the opportunity to provide feedback on this thoughtfully constructed model scope document. Several comments are included below:

- Recommend including additional psychotherapy treatments in the model that include the range of treatments recommended for the general adult population (Table 3) in the American Psychological Association's (APA's) *Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts* (APA, 2019). These include:

  - Behavioral therapy
  - Cognitive, cognitive behavioral (CBT), and mindfulness-based cognitive-therapy (MBCT)
  - Interpersonal psychotherapy (IPT)
  - Psychodynamic therapies
  - Supportive therapy

Currently the model includes several but not all of the above psychotherapy treatments. The APA guideline can be found here: https://www.apa.org/depression-guideline/guideline.pdf

- Regarding the question, "Are there differences across interventions in time to assess success?"- Consider including effectiveness/comparative effectiveness of interventions after discontinuation- for example lasting effectiveness over time of psychotherapy versus medication after treatment with the psychotherapy or medication has ended.

- Regarding question #5, "what factors might impact an individual's decision to initiate and continue with a treatment regimen?"- Stigma and treatment burden can impact an individual's decision to initiate and continue a treatment regimen.

- Please include outcomes that are important to patients in the model such as quality of life. It will also be important to assess for adverse outcomes and suicidal ideation, plans, intent, and attempts.

- Please consider barriers to access such as language barriers, availability of childcare, and internet/phone access with telehealth.

750 First Street, NE
Washington, DC 20002-4242
(202) 336-5500
(202) 336-6123 TDD
www.apa.org

1. It looks as though you will be working with treatment-naive consumers only. Is this correct? I can understand wanting to map out a longitudinal model that can predict treatment choice and efficacy from the start. However, we know depression is a chronic illness with a relatively early age of onset for many people. There is almost certainly something different about consumers with a first depressive episode at age 20 versus 45, and in fact, these may really be two relatively distinct populations. So, simply put, just because you know a treatment-naive consumer at age 45 would prefer psychotherapy to medication does not mean someone who has had MDD all their life would make the same choice at 45. In fact, it is very likely that past experiences (good or bad) with different treatments will affect consumers' choice of treatment at a given timepoint.

   Rather than recruit only treatment-naive consumers, I wonder if you could include those with and without a treatment history. This would mean recruiting more subjects but it would allow you to consider the importance of other variables (e.g., treatment history, number of episodes) in your model.

2. You mention the importance of different subpopulations with different comorbidities, but you do not specifically call out consumers with multiple psychiatric comorbidities, which may be more common than patients with depression alone. How do you intend to account for the combination of depression plus PTSD or OCD or a severe anxiety disorder? In particular, do you intend to exclude consumers with a comorbid substance use disorder from the analyses? Not only might different interventions be efficacious for this population but different interventions may be available in substance use disorder treatment settings than in standard BH settings.

3. As implied above, I imagine you have already thought of this, but it seems treatment setting will be an important variable in the model. For example, many consumers receive antidepressants through a PCP, but a PCP may be very unlikely to prescribe an atypical antipsychotic as an adjunctive treatment, even though they are legally permitted to do so. So, it is not only what treatments are available in a particular setting that's important, but also which treatments are typically prescribed.

4. Will you be looking at measures of consumer functioning in different domains? It sounds like productivity is a variable you will consider; what about relationship functioning (even change in marital status or relationship status could be interesting)? Might also be interesting to look at other work-related variables, like promotions or raises. Will you also be looking at clinical significance or clinically significant improvement in depression, rather than just statistically significant changes from point A to B?

5. I think I would look at the cost of non-BH medical treatment for those with and without controlled MDD. In reality, there are very few situations in which something is purely medical or purely psychiatric. For example, we know that even when a BH diagnosis is not the listed reason for an ER visit (e.g., migraine, asthma, GI distress, cardiac

problems), the presence of a BH problem increases the likelihood of going to the ER. Similarly, given the somatic symptoms associated with depression, I would imagine that consumers with uncontrolled MDD will have more non-psychiatric visits to their PCPs and specialists than consumers whose depression is better managed.

6. What is supportive therapy? Will this be a treatment as usual psychotherapy condition?

From:

Renee Schneider, PhD

Vice President of Clinical Service Design
Octave

#7

COMPLETE

Collector:	Web Link 1 (Web Link)
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Page 1: Information on Public Comment

Q1

First and Last Name

Stephen Nawotniak

Q2 **Respondent skipped this question**

Title

Q3

Organization

Compass Recovery Coaching

Q4

Email Address

sjn81575@gmail.com

Q5 **Patient or Family Organization,**

Please check the stakeholder group(s) with which you identify. **Clinician**

Page 2: Overall Feedback and Recommendations

Q6

Please use this space to provide feedback and recommendations on the overall approach outlined in the proposed model scope.

I am a licensed Occupational Therapist, NYS Certified Peer Specialist and I am successfully living with a bipolar condition. While I have fount the skills and tools of psychological flexibility taught in traditional counseling important, it was Occupational Therapy that taught me how to modify my lifestyle activities to be successful. Things like energy conservation techniques to support me in gettingdressed in the morningwhen I am exhausted with depression, sensory input to help sooth the internal pain and chaos, developing a schedule and routine to allow me to work on auto pilot when I can't think clearly, a focus on meaningful activities to help find hope in a desolate mental landscape. Occupational therapy is what helped me shift my life from focusing on coping with symptoms to managing a condition and living a fulfilling life.

Q7

What factors of patient experience, priorities, costs or outcomes are not currently captured by our proposed model scope or are especially important to include?

From a patient perspective, it is especially important to provide activities and language to normalize the experience. When I was hospitalized for severe depression I felt alone, broken and hopeless. Groups were good, but they didn't show me how normal professionals were successfully living with a condition. All I saw were people struggling and trying to quality for SSI. Famous people were talked about, but they live a lifestyle that I can't relate to.

Page 3: Specific Questions

Q8

The MDD model will consider all care settings in MDD treatment, including primary care, specialty (psychologist/psychiatrist), and telehealth. What are the specific ways that care setting can impact the key clinical and economic outcomes? (Sections 7.2 and 7.13.1)

One setting I done see is an in home setting. Home health outreach could be beneficial, especially for an Occupational Therapist, as 1) this can decrease the amount of missed sessions and 2) can work with the clients real world needs (ie, help client get Bills on autopay to make sure Bills are paid buring this time period).

Q9

From your perspective, how much time is typically required to fully assess a treatment’s effectiveness after its initiation? Are there differences across interventions in time to assess success? (Section 7.6)

It took me 4 weeks for my depression meds to get to a therapeutic level. Then came the task of trying to climb out of the hole my lack of actions caused. I would say a 10 week horizon would be good as one needs to develop a lifestyle that addresses approach and that doesn't happen on its own. Again I advocate for the role of the Occupational Therapist and I would recommend 1 session a week for 10 weeks to start.

Q10

Clinical instruments (e.g., PHQ-9) are often used to evaluate treatment success. In addition to the clinical instruments listed in the model scope document, are there other clinical instruments we should evaluate during the protocol development stage? In addition to clinical instruments, what other outcomes (e.g., specific symptoms such as sleep, adverse clinical events) will be important to consider in evaluating the success of a treatment or intervention? (Section 7.8)

Life satisfaction, not just symptom management, is required for success. The Canadian Occupational Performance Measure (COPM) is an assessment that supports the client in determining that.

Q11

In addition to clinical instruments, what other outcomes (e.g., specific symptoms such as sleep, clinical events such as suicide) will be important to consider in evaluating the effectiveness of a treatment or intervention?

Sleep is very important as are decreases in symptoms, but life satisfaction and fulfillment needs to be the context. Otherwise, nothing sticks.

Q12

In the scoping document, specific cost items the MDD model may evaluate are described, along with their relevance to various stakeholders (e.g., employers). (Section 7.10 and Appendix 9)

Are the costs described relevant to your decision-making?	**Yes**
Are there other costs the model should evaluate?	**Not at this time**
Can you point us to data sources that address your suggested cost factors?	**No**

Q13

Do you have suggestions for data sources or literature we can reference that can contribute to MDD model inputs? We are particularly interested in recommendations for: efficacy of various treatment options based on depression measures, especially PHQ-9; efficacy data for digital therapies; productivity gain/loss due to absenteeism and/or presenteeism; and measures of stigma in the workplace due to an MDD diagnosis (Sections 7.8 and 7.13.3)

I would refer you to the American Occupational Therapy Association (AOTA) for resources on Occupational Therapy's impact.

Q14

Appendix 2 lists a set of stakeholder-specific decision questions.

Do these questions seem relevant from your perspective?	**Yed**
Are there one or more questions that should be prioritized?	**Patient centerdness is key**
What are the key model outputs that could help inform these decisions?	**Conversations with People with MDD**

Q15

Do you have any additional recommendations or suggestions?

I didn't see anything in the document referring to peer specialists...people successfully living with a condition that can share hope, normalize the process, and share practical ways approaches can be applied.

Please consider me a resource if my personal or professional experiences can help. My cell is xxx-xxx-xxxx .

Society for Women's Health Research

May 11, 2021

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
Major Depressive Disorder Value Model Scope, Public Comment Period

Submitted electronically via
public.comment@thevalueinitiative.org

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 Initiative (IVI) Major Depressive Disorder (MDD) Value Model Scope.

SWHR is dedicated to promoting research on biological sex differences in disease and improving women's health through science, policy, and education. For over 30 years, SWHR has brought attention to diseases and conditions that disproportionately or differently impact women.

MDD is nearly twice as likely 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

[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

personal life circumstances and experiences are all associated with a higher risk of depression in women.

In October 2019, SWHR launched our first-ever set of value assessment principles,[3] conceived to help ensure value frameworks and value assessments 1) account for patient population diversity, including sex and gender, and 2) have the infrastructure and analytic capability to evaluate data that matter to women. Grounded in these principles, SWHR is pleased to provide the following information and guidance to inform IVI's model scope on MDD:

Target Population

SWHR recommends the model population simulate gender differences observed in real-world populations, i.e., designed to capture the observed higher rates of depression in women versus men. Gender disparities in MDD prevalence may be related to reproductive differences (such as those associated with the menstrual cycle, pregnancy, or menopause), prevalence of stressful life events (which women report occuring more frequently, on average), and behavioral genetics (e.g., the diathesis-stress model).[4]

In considering how reproductive changes may contribute to differing experiences of MDD, we recommend careful consideration of how pregnancy affects the definition of depression. SWHR suggests 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).[5] Therefore, it will be important to carefully examine the evidence base when creating criteria for inclusion and exclusion in the model.

We additionally encourage IVI to take into account the impact of gender identity and notably higher rates of depression in transgender individuals. For example, lifetime prevalence of MDD is up to 62% among transgender women, compared to almost 17% in the population at large.[6]

Finally, SWHR recommends using gender to define subgroups for further examination. It is well-known that symptom presentation varies by gender. For example, women with

[3] Society for Women's Health Research. Health Care Value Assessment Principles. Retrieved from: https://swhr.org/swhr_resource/swhrs-health-care-value-assessment-principles/
[4] Sloan, DM, & Sandt, AR (2006). Gender differences in depression. *Women's Health, 2*(3), 425-434.
[5] 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
[6] Hoffman, B. (2014). An overview of depression among transgender women. *Depression Research and Treatment, 2014*. doi: https://doi.org/10.1155/2014/394283

MDD are more likely to report prototypical symptoms of depression, including depressed mood, feelings of worthlessness, anxiety, psychomotor retardation, somatic concerns, and increases in appetite and weight gain. Men with MDD are more likely to report symptoms more commonly assocated with anger, such as loss of appetite, weight loss, insomnia, and irritability. They are also more likely to engage in alcohol and substance abuse than depressed women.[7]

The clear differences in prevalence, presentation, and coping are important to consider in determining value of treatments. There 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.[8] Therefore, we strongly recommend IVI work to consider the influence of sex and gender throughout its MDD value model, in addition to subgroups already identified (age, race/ethnicity, socioeconomic status, etc.).

Time Horizon

SWHR appreciates IVI's understanding that time horizon is important to consider and that long-term outcomes may be equally relevant as short-term. Across the board, SWHR recommends value assessments take into consideration both short- and long-term benefits to ensure models account for the full value of a therapy or intervention, especially considering that the benefits of some therapies may continue to accumulate over time. This is particularly important to consider when attempting to understand the effects of emotional or behavioral interventions, such as those reviewed in the scoping document.

Patient Input & Experience

As outlined in SWHR's value assessment principles,[9] women are frequently primary caregivers for their family members. Nearly 70% of caregivers are women.[10] Women serve multiple roles while caregiving: Hands-on caregiver, case manager, companion, decision-maker, and advocate.

Caregivers may tend to those suffering from mental health conditions, and they may also experience their own episodes of MDD. Reports suggest that up to 20% of family caregivers suffer from 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.[11] SWHR strongly recommends the needs and input of caregivers be considered when evaluating patient needs and experience. We are

[7] Ibid.
[8] 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.
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pleased to see IVI's attention to this within the model scope, and we recommend this continue to be a priority.

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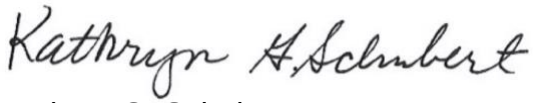
SWHR appreciates the opportunity to comment on this important model scope. If you have any questions, please do not hesitate to reach out to me at kathryn@swhr.org.

Sincerely,



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

1025 Connecticut Ave NW, Suite 1104
Washington, DC 20036
T 202.223.8224
F 202.833.3472
W swhr.org

The below comments are being provided to the Innovation and Value Initiative (IVI) reactively, in response to IVI's request for feedback during the public comment period (April 12-May 14, 2021) on the initial scope of its open-source model to help evaluate pharmacologic and nonpharmacologic healthcare interventions indicated for major depressive disorder (MDD).

General Questions We are seeking overall feedback on the assumption for the MDD model. We are particularly looking for feedback on factors not currently captured in the proposed model scope.

1. Target Population: We intend to simulate the clinical and economic outcomes of treatment-naïve adults, 18 to 64 years in age, diagnosed with MDD by a healthcare provider (e.g., primary care provider, psychologist, psychiatrist) in the MDD model. Would you suggest any changes to the target population (i.e., is the focus on the right segment of the MDD patient population)?

With respect to the target population, would consider extending the upper limit of the age range and/or identifying older adults as a subpopulation of special interest. The traditional cut-off between younger and older adults at 65 years of age is arbitrary. MDD certainly persists into late life, during which most episodes of MDD are recurrent, and older adults are as responsive to treatment as younger patients with SSRIs being the accepted first-line treatment.[1] Real-world and naturalistic studies often include older adults so that the results can be more generalizable to everyday practice, such as the seminal STAR*D study which included patients up to age 75.[2]

1.1. Subgroups: Are there subgroups of particular interest in your decision-making? If so, what are they and why? What makes these subgroups different from others from a modeling perspective (e.g., disease progression, treatment effects)?

The subgroup of patients with at least one antidepressant failure, due to lack of efficacy or side effect issues, is of particular interest as this patient type more closely reflects the patient with Major Depressive disorder seen in real world treatment settings.[3] Healthcare economic costs increase significantly for this patient group, and antidepressant switching is associated with markers of illness severity.[4,5] Additionally, patients who have encountered multiple episodes or multiple lines of treatment are at a greater risk of suicide attempts, hospital admissions, and impaired work productivity.[4-7]

Similarly, subgroups of patients with psychiatric comorbidities (e.g. anxiety disorders) as well as those with medical comorbidities, reflective of real-world clinical practice, are of particular interest from the standpoint of treatment efficacy, sensitivity to side effects, and health economic outcomes.

2. Treatments: The MDD model will offer users the flexibility to evaluate both specific treatments and sequences of treatments (Section 7.5 and Appendix 8). Are there other treatments important to include? Are there specific treatment sequences of special interest?

Consider expanding the comparator list as there are several antidepressant medications not included. By way of reference, a recent meta-analysis of antidepressant trials, the largest conducted to date for the acute treatment of adults with major depressive disorder, evaluated 21 antidepressants.[8]

Regarding treatment sequence, a common approach in the search for the optimal treatment strategy involves considering multiple criteria in medication choice at the individual level such as specific depressive symptoms, side-effect profile, and mechanism of action.[9,10]

Additionally, the current treatment options by sequence of treatment (Appendix 8) do not bring in augmentation until the third line of treatment. This is inconsistent with general practice as reflected in the STAR*D study which allowed pharmacotherapy augmentation at step 2.[2] Evaluating the impact of augmentation vs. switching at step 2 in the model, will be important in guiding HCP's and payers since for patients facing efficacy and tolerability concerns, there is currently limited guidance with respect to antidepressant switching or augmentation.[11,12,13]

3. Time Horizon: The MDD model will simulate the key outcomes of the target population over a lifetime horizon, with the flexibility for users to examine outputs at different time points (e.g., 1 year or 5 year). What time horizons are relevant to your decision-making?

Most patients with MDD suffer from chronic or intermittent illness, and therefore, in our view, a longer timeframe – at least 1 to 2 years – is important to decision-making in order to allow for an adequate understanding of the course of illness as well as of medication efficacy, side effects, and adherence.[14] A recent longitudinal study performed in collaboration with the Sleep-EVAL Database assessed individuals with MDD in two waves two years apart. 41.8% of participants with an MDD diagnosis in Wave 1 still reported depressive symptoms in Wave 2, two years later.[15]

The goal of antidepressant therapy is to achieve symptomatic remission with functional recovery – and to maintain that remission for as long as possible. However, eventually symptoms recur in the majority of patients, with rates of recurrence being reported as high as 85% within 10 years following the first depressive episode. Recurrence is more common and develop earlier in patients who continue to experience residual symptoms than in patients who have achieved full remission. Studies

have shown that long-term use of antidepressants can protect against relapse and recurrence.[16-18] Patients who experience recurrence are likely to have a more complex disease profile due to an increased risk of suicidality and the presence of other comorbidities such as substance abuse, anxiety, and additional depressive disorders that require intensive healthcare resource utilization (HRU).[19] As a result, the increased HRU is likely to increase the economic burden in this patient population.[20] Quality and availability of long-term data, including maintenance (relapse prevention) studies must be considered within the model.

4. Decision Questions: What specific decision questions would you like the model to inform? What model outputs (both clinical and non-clinical) would be most useful in answering these questions?

One important decision question we would like the model to inform is whether there are triggers that suggest specific treatment approaches outside of the general sequence, e.g. for patients with suicidality, adverse sexual reactions. Certain agents may have data, including superiority data, supporting specific benefit with certain complexes of symptoms or side effects.

5. Patient Input: What factors of patient experience are currently missing or are important to include in the proposed model scope. For example, what factors might impact an individual's decision to initiate and continue with a treatment regimen?

The patient's voice must be included in the MDD model scope to ensure that treatment decisions are patient centric. The model should encourage the collection of data with respect to the value and importance of shared decision-making. One way to accomplish this is through the setting of treatment goals by the patient in collaboration with the healthcare provider. A study which adapted the Goal Attainment Scale for depression demonstrated that treatment goals that were most meaningful to the patients improved during antidepressant treatment along with more commonly used measure such as the PHQ-9 and that improvement in patient identified treatment goals is associated with functional recovery.[21,22]

Side effects and residual symptoms, such as sleep disturbance, weight gain, treatment emergent sexual dysfunction, cognitive symptoms of MDD, and emotional blunting are also important factors that can impact a patient's treatment experience including individual decisions to initiate or continue treatment.[23-32]

6. The MDD model will consider all care settings in MDD treatment, including primary care, specialty (psychologist/psychiatrist), and telehealth. What are the specific ways that care setting can impact the key clinical and economic outcomes? 7.2 and 7.13.1 7.

Since up to about 60% of mental health treatment occurs within the primary care setting, primary care providers have a crucial role in recognizing and managing depression.[33] Almost 10% of all primary care office visits are related to depression, and over 70% of antidepressant prescriptions are written by general medical providers.[34,35] However, primary care clinicians feel that limited knowledge and training as well as system issues challenge their ability to manage more complex mental health patients.[36]

7. From your perspective, how much time is typically required to fully assess a treatment's effectiveness after its initiation? Are there differences across interventions in time to assess success? 7.6 8.

We agree with the general consensus that 4-6 weeks of treatment with antidepressant medication at an adequate dose is required before treatment effectiveness can be fully assessed.[13,37]

8. Clinical instruments (e.g., PHQ-9) are often used to evaluate treatment success. In addition to the clinical instruments listed in the model scope document, are there other clinical instruments we should evaluate during the protocol development stage? In addition to clinical instruments, what other outcomes (e.g., specific symptoms such as sleep, adverse clinical events) will be important to consider in evaluating the success of a treatment or intervention?

Antidepressant clinical trials have been utilizing the HAM-D and MADRS as primary endpoints for decades despite both having limitations. Studies need to include other scales in order to strengthen patient assessment as well as the use of new technologies to improve patient self-reporting.[38] Scales to be considered include patient reported outcome measures like the Perceived Deficits Questionnaire (PDQ) for cognitive dysfunction, the Arizona Sexual Experience Scale (ASEX) for treatment-emergent sexual dysfunction (TESD), the Patient Rated Inventory of Side Effects (PRISE) for side effects, the Insomnia Severity Index (ISI) for sleep, the Oxford Depression Questionnaire (ODQ) for emotional blunting, and the Work and Social Adjustment Scale (WSAS) for functioning. Digital tools for data gathering and to enhance shared decision-making between healthcare providers and patients. Digital platforms, such as apps, can facilitate frequent completion of patient reported outcome measures and can allow patients to set and monitor individualized treatment goals and have been well-received by patients and care providers.[39]

9. In addition to clinical instruments, what other outcomes (e.g., specific symptoms such as sleep, clinical events such as suicide) will be important to consider in evaluating the effectiveness of a treatment or intervention? 7.8 10.

As noted above (see response to question 5), residual symptoms such as cognitive symptoms of MDD and emotional blunting, and medication side effects, including TESD, weight gain, and sleep disturbance, are important to monitor, and various scales and tools, including digital platforms, are available for this purpose.

10. In the scoping document, specific cost items the MDD model may evaluate are described, along with their relevance to various stakeholders (e.g., employers). Based on your perspective: • Are the costs described relevant to your decision-making? • Are there other costs the model should evaluate? • Can you point us to data sources that address your suggested cost factors? 7.10 and Appendix 9 11.

The costs associated with presenteeism need to be captured as it has been demonstrated to be a significant issue and which is more associated with MDD than absenteeism.[3] Would also include number needed to treat (NNT) and number needed to harm (NNH) analyses in modeling, for example the work of Leslie Citrome.[40]

11. Do you have suggestions for data sources or literature we can reference that can contribute to MDD model inputs? We are particularly interested in recommendations for:

• Efficacy of various treatment options based on depression measures, especially PHQ-9

Please see references 41 and 42.

• Efficacy data for digital therapies

• Productivity gain/loss due to absenteeism and/or presenteeism

Please see references 43 and 44.

• Measures of stigma in the workplace due to an MDD diagnosis

12. Appendix 2 listed a set of stakeholder-specific decision questions.

• Do these questions seem relevant from your perspective?

• Are there one or more questions that should be prioritized?

• What are the key model outputs that could help inform these decisions?

Racial and ethnic minority populations initiate antidepressant medication treatment at a much lower rate than whites and are more likely to discontinue depression treatment without consulting their physician.[45] Persons with MDD need to be asked about their experience of care to help identify systemic issues that may impede adequate care or an adequate treatment experience.

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