IVI INNOVATION AND VALUE INITIATIVE

IVI-Major Depressive Disorder (MDD) Model Scope Document

April 7, 2021

Dear Colleague,

On behalf of the Innovation and Value Initiative (IVI), we invite you to provide your insights and recommendations on the initial scope of our major depressive disorder economic model during the public comment period, April 12-May 14, 2021. The model scope outlines our preliminary assumptions for the model design. We ask that you provide recommendations on the most important factors to build into the model as well as insights on how to incorporate novel data elements.

As a laboratory for testing new methods and approaches to value assessment, IVI has launched a multi-year initiative to build and test an open-source model to help evaluate pharmacologic and nonpharmacologic healthcare interventions indicated for major depressive disorder (MDD). Our objective in developing models through the Open-Source Value Platform (OSVP) is not to produce a single model with a specific set of estimates. Rather, it is to explore and test ways to improve how we develop economic models to assess value, improve alignment with real-world decision needs, and advance dialogue about how best to use economic assessments to link value to resource use in healthcare.

After working with a multi-stakeholder advisory group and research partners for the past eight months, we are at the first major milestone, the public comment period for the model scope document. Developed based on discussions with the Advisory Group and literature reviews, the scope describes the overarching model objectives, key assumptions, and preliminary specifications of the IVI-MDD model. It also delineates the specific considerations that will be evaluated and confirmed during the protocol development stage, the next phase of our effort.

Consistent with our firm beliefs in open-source modeling and multi-stakeholder engagement, we are excited to share this document and invite your feedback and comments. The purpose of holding a public comment period at this stage is to obtain feedback in three main areas:

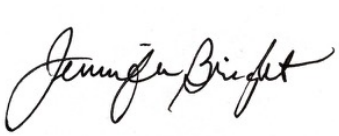
- Assumptions and data elements missing from the initial model design
- Factors most important to include in the model
- Specific use cases to be built into the first edition of the model

Please share the draft model scope and the invitation for feedback with colleagues in the field. IVI will also hold an informational webinar on May 3 at 1:00 PM EDT to share more about the model development process and to answer questions.

To submit comments, either submit them on letterhead in PDF form to public.comment@thevalueinitiative.org, or complete a survey to answer the questions posed within the scoping document. All responses will be made available on our website. Please provide comments by the end of day on Friday, May 14.

Thank you in advance, and we look forward to continuing this dialogue to improve value assessment.

Sincerely,



Jennifer Bright, Executive Director

Rick Chapman, Chief Science Officer

IVI-Major Depressive Disorder Model Development Process

Executive Summary

In 2020, the Innovation and Value Initiative identified major depressive disorder (MDD) as the focus of its next economic model. MDD is a pervasive health condition that includes a wide range of treatment options. IVI is building a flexible, open-source, and patient-centric model that will help inform the decision needs of multiple stakeholders in the health care system, including people living with MDD as well as employers, payers, and clinicians.

Purpose of this Document

Rather than feedback on the general design of the model, we are seeking insights on what we should consider or include in the model. As you review the model scope, please consider these main areas:

- Assumptions and data elements missing from the initial model design
- Factors most important to include in the model
- Specific use cases to be built into the first edition of the model

Model Description

Consistent with previous models developed as part of the OSVP, the MDD model will be an individual-level simulation model allowing comparison of treatment sequences over patients' lifetimes. In addition to conventional health system costs and clinical benefits, the model will include additional variables with bearing on value from the societal and other specific decision perspectives.

We will seek to incorporate as many scientifically defensible assumptions as possible, to allow for both exploration of structural uncertainty and model customization based on user preferences and available data. In addition, the model will incorporate exploratory and alternative methods; for example, we will include a module designed to test the use of multi-criteria decision analysis (MCDA). We are also piloting a new method for eliciting drivers of patient-level value that will be incorporated into the model.

Timeline and Submission Process

We are inviting individuals and organizations from multiple stakeholder groups to submit comments on the model scope. An additional public comment period will be held for the model protocol, which will include more technical questions about the model's specifications and inputs.

A webinar will be held on May 3 at 1:00 PM EDT to present background on the model and to answer questions about the model scope and model development process.

Webinar:	IVI Model Scope on Major Depressive Disorder
Date/Time:	Monday, May 3, 2021 at 1:00 PM EDT
Panelists:	Jessica Kennedy, Chief of Staff, Mental Health America
	Mohannad Kusti, MD, MPH, President and Chief Medical Officer, Optimal Workplace and Environmental Wellness Corporation
	Richard Xie, PhD, HEOR Manager, Innovation and Value Initiative
Moderator:	Rick Chapman, PhD, Chief Science Officer, Innovation and Value Initiative

Public Comment Period for the Model Scope: April 12-May 14, 2021
There are two ways to submit comments: complete the survey on the website to answer specific questions within the scoping document or submit comments on letterhead in PDF form and send to public.comment@thevalueinitiative.org.

Post-Public Comment Period
Following the close of the public comment period on May 14, we will review all comments and prioritize recommendations in partnership with the multi-stakeholder advisory group. All comments and survey responses will be made publicly available on our website within eight weeks after the public comment period closes.

Model Protocol
Following the close of the public comment period, the recommendations will be used to adjust the model scope and develop the model protocol. The model protocol is a technical document that outlines all necessary details for model structure and analyses, including the analytic approaches, assumptions, data inputs, and model output. A public comment period for the model protocol will be held as well.

Invitation to Share with Others
Our objective in developing models through the OSVP is not to produce a single model with a specific set of estimates. Rather, it is to explore and test ways to improve how we develop economic models to assess value, improve alignment with real-world decision needs, and advance dialogue about how best to use economic assessments to link value to resource use in healthcare. With this in mind, please share the draft model scope with your colleagues in the field and encourage them to participate in this effort to advance the science of value assessment.

Table of Contents

1. Introduction

IVI's Objective in Developing Open-Source Models

The objective in developing a model through the Open-Source Value Project (OSVP) is not to produce a single model with a specific set of assumptions and estimates. Rather, it is to explore and test ways to improve how we develop economic models to assess value, improve alignment with real-world decision needs, and advance dialogue about how best to use economic assessments to inform resource allocation in health care.

IVI-MDD Model Description

Consistent with previous models developed as part of the OSVP, the IVI-Major Depressive Disorder (MDD) model will be an individual-level simulation model allowing comparison of treatment sequences indicated for MDD over a lifetime horizon. In addition to capturing the costs and benefits from a health system or private payer perspective, the model will include a more comprehensive assessment of elements of value from the societal perspective, and other decision perspectives such as employers.

Rather than identifying a single set of structural assumptions as the "best" design, the model will incorporate the flexibility to include multiple scientifically defensible assumptions, allowing for exploration of structural uncertainty and customization based on user preferences and available data. In addition, the model will incorporate exploratory alternative methods. For example, a module will be included to test use of multi-criteria decision analysis (MCDA). A new method is being piloted for eliciting patient-informed value attributes for MDD treatments and associated preferences for incorporating into the model.

Purpose of the Scope Document

Developed based on review of prior models and guidance from our multi-stakeholder Advisory Group (AG), this model scope document describes the overarching model objectives, key assumptions, and preliminary specifications of the IVI-MDD model. Initial steps have begun to develop a model protocol. The scope document delineates the specific considerations that will be evaluated and confirmed during the protocol development stage, the next phase of effort.

The goal for the public comment period is to ensure comprehensive feedback on model development and the evaluation of treatment sequences in MDD. Rather than input on whether the suggested scope and design parameters are the best options, we seek

insights into modeling aspects such as these: likely decision contexts and metrics useful to potential users of the model; alternative approaches to modeling transitions between health states; key value factors from an employer's perspective; and robust data sources for burden on familial caregivers.

2. Questions for Public Comment

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)?

    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)?

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?

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?

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?

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?

Specific Questions and Reference Guide

(Feel free to skip questions that are not relevant to you.)

Questions	Section
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. 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. 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?	7.8
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. 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. 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 • Measures of stigma in the workplace due to an MDD diagnosis	7.8, 7.13.3
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?	Appendix 2

3. Background

According to the National Alliance on Mental Illness, over 19 million[a] Americans had at least one major depressive disorder (MDD) episode in the past year. National data has emerged identifying exponential growth in rates of depression related to the COVID-19 pandemic,[b] while simultaneous impacts on the mental health workforce and access to treatment have affected care delivery and patient outcomes.[1]

In 2015, the Patient-Centered Outcomes Research Institute (PCORI) convened a multi-stakeholder panel to consider and prioritize key questions in comparative effectiveness research for MDD treatments.[c] Prioritized questions and subsequent research seek to understand the value of non-pharmacological interventions compared to pharmacologic treatments, treatment strategies for older adults, and the role of pharmacogenomics.

Existing cost-effectiveness models for assessing the value of MDD treatments typically do not prioritize factors and outcomes important to people with MDD, nor do they feature in their primary analyses the societal perspectives relevant to this highly prevalent condition.[2–4] Moreover, the primary focus in assessing the value of new pharmaceutical interventions overlooks the opportunity to consider the comparative value of multiple interventions for MDD treatment. In addition, current approaches may not fully address the decision-making needs of payers, employers, and clinicians.

Finally, employers have emerged as an increasingly concerned community in value assessment conversations. MDD constitutes a significant burden in productivity and health costs to employers. The National Alliance of Healthcare Purchaser Coalitions (National Alliance), American Psychiatric Association, American Psychiatric Association Foundation Center for Workplace Mental Health, and Meadows Mental Health Policy Institute have launched a major endeavor, Path Forward, aimed at improving local collaboration, service delivery, and coverage, aligning the needs of people with MDD and purchasers. At the same time, the National Alliance seeks to improve value assessment frameworks and methods to better represent the factors (e.g., productivity) that matter to their constituents.

There is increasing convergence of important questions about the comparative value of treatment options, the growing importance of incorporating patient preferences into

---

[a] Source: National Alliance on Mental Health, Mental Health By the Numbers. URL - https://www.nami.org/mhstats

[b] Source: Mental Health America, Mental Health and COVID-19. URL - https://mhanational.org/covid19

[c] Source: https://www.pcori.org/events/2015/prioritizing-comparative-effectiveness-research-questions-treatment-major-depressive

value assessment and data input collection methods, and the emerging leadership among healthcare purchasers. IVI views this confluence as a significant opportunity to influence value assessment research methods and policy conversations.

Value assessment models addressing MDD exist but have varied in their approaches, in their inclusion of pharmacologic and non-pharmacologic interventions, and their inclusion of people living with MDD in methods to define preferences or value factors.[5] As part of the Open-Source Value Project (OSVP), IVI is developing the MDD value model to evaluate relevant pharmacologic and non-pharmacologic interventions for MDD. This initiative will contribute to future model development through more robust analytic tools, and by defining inputs of importance to patient communities that may not be well represented now in the evidence base guiding clinical and cost-effectiveness decision-making.

4. Objective

IVI launched the MDD initiative to build a flexible, open-source, and patient-centric model that will help advance the science of value assessment, facilitate multi-stakeholder conversations, and ultimately inform the decision needs of multiple stakeholders in the health care system including employers, payers, and clinicians.

To guide the model development process, we seek to explore the following questions:

- For people living with MDD, what key factors define the value of an intervention? What is the relative importance of these value factors?
- What are promising methods to develop value assessment models that reflect patient-defined preferences (e.g., patient preference-based health utilities, multi-criteria decision analysis)?
- How can the model support the decision needs of clinicians, care providers, payers, and employers in comparing the value of various interventions? How can we actively engage with stakeholders throughout the modeling process to ensure that key decision needs are reflected in model design?
- What real-world data can be incorporated into value assessment models to provide insights on factors relevant to people with MDD? To employers? To payers?

5. Model Scoping Process

IVI undertook a novel approach to model design and development through continuous engagement with a multi-stakeholder Advisory Group (AG) from the outset. This section describes the preparation work that led to the model scope, including AG engagement, targeted literature review, interviewing people with lived experiences of MDD, and alternative decision-analytic framework.

5.1. Multi-Stakeholder Advisory Group (AG) Engagement

The AG is comprised of key stakeholders in the health system, including people with MDD, employers, payers, clinicians, and HEOR researchers, and meets at least bi-monthly. AG members discuss possible approaches for various model specifications; review and comment on initial findings from contributing research partners; engage in small-group feedback sessions on specific questions (e.g., relevant treatments, clinical instruments); and share specific decision contexts or evidence gaps in their respective organizations. Over 20 highly engaged AG members have participated[d] in this process.

A total of six group meetings, two surveys, and ten small-group discussions were held between July 2020 and March 2021. These engagements yielded important insights and feedback that helped inform the model design, helping meeting IVI's goal to address specific decision needs from various stakeholder perspectives.

27 summarizes the aggregated feedback from the AG by model specification; below contains the key decision needs from the perspectives of various stakeholders.

5.2. Targeted Literature Review

IVI's research partner, Pharmerit, conducted a targeted literature search in MEDLINE and Embase using the ProQuest Dialog database to identify existing economic models and economic analyses for MDD from 2010 through the search date in September 2020. The objective was to identify a subset of representative and high-quality models developed for MDD to understand the range of modeling approaches and develop a foundation for the model scoping. below describes search strategies and number of articles. Data were abstracted based on the fields listed in below; extractions are summarized and presented in Appendix 5.

[d] The list of AG members can be found here: https://www.thevalueinitiative.org/wp-content/uploads/2020/11/2020-11-20.MDD-Advisory-Group.pdf

5.3. Patient Engagement

To augment the patient perspectives and data elements built into the MDD model, IVI launched a patient preference study with researchers from the Patient-Driven Values in Healthcare Evaluation (PAVE) center at the University of Maryland School of Pharmacy. A novel approach to eliciting patient-prioritized value elements in evaluating MDD treatment options was tested, with the goal of subsequently estimating the preference weights associated with these elements using a discrete choice experiment design. The study is based on a set of patient-centered value elements developed by Dr. Susan dosReis and colleagues.[6]

The study has two phases. In the recently completed Phase 1 work, researchers identified a subset of attributes that were the most important selections among alternative treatments, based on interviews with 20 people living with MDD. In Phase 2, a discrete choice experiment survey will be developed based on the value elements identified in Phase 1 and administered to a larger patient sample (N=300) to estimate preference weights for the treatment attributes being considered.[7] below provides additional context on the study, inclusion/exclusion criteria for the patient interviews, and the Phase 1 findings.

The results from the PAVE study will be used in the design and construction of the MDD model in the following ways:

- The patient-prioritized value elements in Phase 1 will be used to inform the selection of clinical instruments, health-related quality of life measures, and additional cost inputs in the MDD model protocol development stage.
- IVI and research partners will explore whether the Phase 2 findings can be used as health utility inputs.
- IVI and research advisors will explore the potential for using alternative decision-analytic frameworks in the model (described in above).

6. IVI-MDD Model

The MDD model includes a health economic (HE) model module and a multi-criteria decision analysis (MCDA) module (described below).

7. Health Economic Model Module

The initial model scoping was informed by the targeted literature review of economics models and clinical guidelines, interviews with people who had lived experiences of MDD, and continuous engagement with the AG. This section describes our conceptual approaches to key model specifications.

7.1. Target Population

At the start of the simulation, the model population will be treatment-naïve adults, 18 to 64 years in age, diagnosed with MDD by a healthcare provider (e.g., primary care provider, psychologist, psychiatrist).

Based on feedback from the AG, the model will also aim to provide flexibility to evaluate outcomes for these subgroups:

- Subgroups defined by age, race/ethnicity, and socioeconomic status (SES)
- People with MDD who did not achieve adequate response after two lines of treatment in the model simulation

IVI is also exploring the feasibility of building additional modules for evaluating these populations:

- Those aged 65 and older
- Those who are Medicaid insured
- Those with a specific comorbid condition (e.g., diabetes or cardiovascular disease)

7.2. Setting and Location

Subject to feasibility assessment, the model will seek to evaluate a wide range of treatment settings including primary care, specialty care (e.g., psychiatrist), and telehealth in the United States. Section 7.13.1 describes how the model specifications will differ by care setting.

7.3. Study Perspective

The model will feature the societal perspective as the base case, capturing a comprehensive set of costs and benefits regardless of who is impacted. The types of societal inputs to be included will be guided by recommendations from the Second

Panel on Cost-Effectiveness in Health and Medicine (below).[4] The societal perspective will allow various stakeholders to select a subset of costs and benefits relevant to them. Such stakeholders include:

- U.S. third-party payers (i.e., health care sector)
- Fully or partially self-funded[e] employer purchasers
- Fully insured[f] employers
- People with MDD

Appendix 9 includes a list of potential costs from various stakeholder perspectives.

7.4. Model Structure

Model structure is used to simulate the transition of key economic and clinical outcomes over time. Consistent with previous OSVP models and AG members' interest in conducting subgroup-specific analyses, the MDD model will feature an individual-level simulation. This will better account for patient heterogeneity and facilitate user case development for policy interventions targeting a subset of the population. The specific model structure and analytic approaches will be determined during the protocol development stage. below contains potential model structures under consideration.

7.5. Comparators

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[g] and explore clinical and economic outcomes associated with different treatment sequences. Based on AG feedback, a "no active treatment" comparator will also be included (described in section 7.13.2). Potential treatment strategies are listed below.[h]

---

[e] In this arrangement, employers will partner with an insurance carrier or a Third Party Administrator (TPA) to provide the tangible employee coverage, but the employer assumes financial responsibility for members' claims.

[f] Refers to an employer that purchases health coverage from an insurance carrier for a per-member premium. The insurance provider assumes the risk that employees will use their healthcare and pays for that in accordance with their selected plans.

[g] A line of treatment can be monotherapy with a pharmacologic agent or psychotherapy; combination of different pharmacotherapies; or combination of pharmacotherapy and psychotherapy. A treatment is considered a new "line" of therapy if a patient discontinued one treatment regimen and started a different one. Dosing adjustment would not be considered a new line of treatment, while augmenting existing treatment with another would be.

[h] The MDD model will not make recommendations regarding specific treatments or sequences of treatments.

Pharmacotherapy

Modeled at a drug class level:[i]

Drug Class	Examples of Specific Drugs
Tri- and tetra-cyclics (TCA)	amitriptyline, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine
Selective serotonin reuptake inhibitors (SSRI)	citalopram, escitalopram, fluoxetine, paroxetine, sertraline
Monoamine oxidase inhibitors (MAOI)	isocarboxazid, phenelzine, selegiline, tranylcypromine
Serotonin and norepinephrine reuptake inhibitors (SNRI)	venlafaxine, desvenlafaxine, duloxetine
Serotonin modulators	nefazodone, trazodone

Individual drugs ("atypical"):

- Bupropion (Wellbutrin)
- Mirtazapine (Remeron)
- Ketamine (Ketalar)
- Esketamine (Spravato)

Psychotherapy

- Cognitive Behavioral Therapy (CBT)
- Other types of therapy,[j] including:
    - Interpersonal psychotherapy (IPT)
    - Psychodynamic therapy
    - Problem-solving therapy
    - Supportive therapy

[i] These therapies are modeled at a drug class level based on similar efficacy and safety profiles of individual therapies.

[j] This comparator may be represented as the weighted average of the other types of therapy.

Somatic Therapy

- Electroconvulsive therapy (ECT)
- Transcranial magnetic stimulation (TMS)
- Vagus nerve stimulation (VNS)

Digital Therapeutics

- Prescription digital therapy
- Non-prescribed digital applications

Combination Treatments

- Combination of pharmacotherapy + psychotherapy
- Combination of psychotherapy + pharmacotherapy + somatic therapy

Pharmacotherapy Augmentation Treatments

Possible combinations include:

- Combination of two MDD pharmacotherapy treatments[k] (e.g., bupropion and SSRI)
- MDD pharmacotherapy augmented by antipsychotics
- MDD pharmacotherapy augmented by lithium

No Active Treatment which includes standard health care with no specific treatment for MDD.

7.5.1. Treatment Sequences

Based on clinical guidelines and conversations with clinical AG members, the range of treatment options will vary by their order in the treatment sequence. A patient can switch to a different treatment strategy if an adequate response[l] is not achieved (e.g., from one psychotherapy to another, from a pharmacotherapy to a combination of treatment). Consistent with real-world clinical practice for pharmacotherapy, a patient can switch to a different drug within the same drug class, or a different drug class.

[k] The two treatment options can be from the same or differing drug classes.

[l] To be defined during the protocol development stage.

below lists the relevant treatment options by order in the treatment sequence. The list of treatment options along with relevant treatment sequences will be finalized during the protocol development stage.

7.6. Time Horizon

The models found in the literature review typically followed people with MDD for fewer than five years after initiation of treatment. Based on AG feedback, this model will seek to evaluate clinical and economic outcomes over a lifetime horizon, with the flexibility for interim evaluations at user-specified time points.

7.6.1. Cycle Length

Depending on the chosen model structure, a cycle may be specified in the model[m] that describes the required time period before changes in the clinical and economic outcomes can occur. 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.

7.7. Discount Rate

Consistent with best practice in the U.S. and the recommendation from the Second Panel on Cost-Effectiveness in Health and Medicine, costs and benefits will be discounted at 3% per annum. Alternative values may be entered by the user and will be used for sensitivity analysis.[4]

7.8. Effectiveness

Following treatment initiation, clinical instruments and other outcome measures may be used to evaluate the effectiveness or success of treatments.

7.8.1. Clinical Instruments

The MDD model will seek to incorporate flexibility in evaluating treatment effectiveness based on multiple patient- or clinical-reported outcomes including, but not limited to, these instruments:

- Patient Health Questionnaire-9 (PHQ-9)

[m] For example, cycle length will not be required if a discrete event simulation is adopted in the model.

- Hamilton Depression Rating Scale (HAM-D)
- Montgomery-Asberg Depression Rating Scale (MADRS)

The set of clinical instruments used to characterize treatment effectiveness and patient experiences will be finalized during the protocol development stage.

7.9. Health States

Depending on the specific model structure, health states[n] may be specific to capture how the clinical experiences of people with MDD change over time with treatment. Following treatment initiation, people with MDD can transition into one of the health states specified in the model, which are typically associated with varying levels of health resource use and costs, and quality of life (i.e., utility). Possible health states could include complete response, partial response, no response, and death.

Based on review of existing models and AG input, health states may be defined based on the changes in, or the absolute levels of, effectiveness metrics, typically a clinical instrument (e.g., MADRS). Health state definitions will be finalized during the protocol development stage.

7.10. Costs

Three broad categories of costs will be considered in the model:

- ***Direct medical costs*** e.g., receiving treatments, treating adverse events due to treatments, primary or specialist care, emergency room visits
- ***Direct non-medical costs*** e.g., transportation costs to or from MDD care, caregiving support
- ***Indirect costs*** e.g., missed work for treatment, not being fully present at work

Medical costs for specific health procedures or clinical events (e.g., outpatient visits) for a specific evaluation time period will be estimated and included in the model. Some costs could vary based on clinical effectiveness (i.e., measured by health states), while others may not be directly related. The specific inputs and assumptions used to calculate these costs will be finalized during the protocol development stage.

[n] We acknowledge that using a finite number of health states to capture the responses of people with MDD to real-world treatments is a simplification of treatment experiences and outcomes.

The costs will be provided in multiple categories, with insurance-covered and patient co-pays separated to facilitate calculation and presentation of different perspectives (Table 1). Alternative sets of cost inputs may also be used to reflect payers' differential reimbursement rates (e.g., commercial, Medicare, and Medicaid). below provides a more detailed list of costs by different stakeholders.

Table 1: Cost Perspectives

Perspective	Definition
Societal	All direct and productivity costs regardless of the payer/beneficiary
Payer	Costs borne by the payer (i.e., reimbursed to providers)
People with MDD	Costs borne by people with MDD, medical (e.g., co-pays) and non-medical (e.g., day care while receiving treatments)

7.11. Utility

Utility[o] is a measure of people with MDD's preferences for different health states and can be used to measure quality-of-life changes associated with treatments or other clinical events.[8] Utility values, on a scale from 0 (death) to 1 (perfect health), will be assigned to different health states in the simulation, as described in section 7.9. Utility inputs will be derived from published literature but will be user modifiable. Utilities will also reflect adverse events or major clinical events (e.g., hospitalization). Additionally, IVI will work with PAVE researchers to identify ways to incorporate utility estimates from the ongoing patient preference research into the model.

7.12. Model Outputs

Model outcomes can be expressed as costs, effectiveness, and cost-effectiveness. Costs will be summed over the observation period in the model. Effectiveness can be expressed in terms of clinical events, time, or utilities; for example, number of people with MDD in remission/recovery[p]; total months in remission/recovery; or total utilities each over the time period of interest.

[o] [o] Utility values can be used as the basis to calculate quality-adjusted life years (QALY).

[p] To be defined.

Incremental cost-effectiveness between treatments will be expressed as the cost per additional unit of effectiveness metric.

While cost per quality-adjusted life-year ($/QALY) is a common metric in health economic evaluation, there is some controversy over its applicability in MDD. We intend to include it as an outcome metric so that users can compare insights based on different metrics.

The model will include the flexibility to present various economic and clinical outputs to meet the decision needs of multiple stakeholders. Based on the literature review and AG stakeholder input, these model outputs may be included:

- Number of remitters[q]
- Number of responders[r]
- Total costs
- Total life-years (LYs) gained
- Total quality-adjusted life-years (QALYs) gained
- Cost per responder achieved
- Cost per remitter achieved
- Cost per LY gained
- Cost per QALY gained

Outcomes of interest will be finalized in the protocol development phase.

7.13. Other Modeling Considerations

7.13.1. Setting of Care

Care setting (i.e., primary care vs. specialty care vs. telehealth) is a key consideration highlighted by the AG and could influence the following specifications in the model design:

- Treatments prescribed, particularly the use of non-pharmacologic treatments
- Cost inputs

[q] Remitters refer to people with MDD that achieve remission following treatment initiation within a time period and will be based on the remission definition in the model.

[r] Responders refer to people with MDD that achieved complete response to treatment following treatment initiation within a period of time and will be defined based on the corresponding health state definition.

- Patient characteristics
- Effectiveness (e.g., due to differences in adherence)

The final model design will be described in the model protocol stage.

7.13.2. Delay in Receiving Active Treatments Following Diagnoses

Recent research from the National Institute of Mental Health suggested that, in 2017, up to 35% of adults that experienced a depression episode did not receive active treatment.[8] This is also a theme highlighted by the AG. Delayed treatments can result in disease progression and significant clinical events such as suicide attempts. Subject to data availability, the MDD model will seek to evaluate the costs associated with delay in initiating active treatments following an MDD diagnosis by a healthcare provider.

7.13.3. Productivity

The model will highlight various aspects of productivity loss, reflecting feedback from the AG, particularly employer and patient representatives. The types of productivity loss to be evaluated include:

- Absenteeism (time absent from work)
    - Due to receiving treatment
    - Due to MDD symptoms
- Presenteeism (loss of productivity when employees are not fully functioning in the workplace)
- Short- and long-term disability
- Workers' compensation (e.g., for employees that develop MDD while employed)
- Ability to work or "fitness for duty" (e.g., diagnosis of MDD or medication side effects might affect the ability to return to work)

7.13.4. Adherence

Adherence to treatments and the impacts on health and economic outcomes may be assessed in the model, subject to feasibility. Should data allow, suboptimal adherence or discontinuation behavior would be modeled as impacting treatment effectiveness, with subsequent impact on health states and key clinical events (e.g., ER visit).[9]

8. MCDA Module

In addition to the health economic (HE) module, IVI aims to explore the use of multi-criteria decision analysis (MCDA) in the MDD model. MCDA will allow decision-makers to consider a broader set of value elements that may not be captured in traditional health economic modeling such as cost-effectiveness analysis (CEA). Keeney and Raifa (1993) define MCDA as “an extension of decision theory that covers any decision with multiple objectives,” providing “a methodology for appraising alternatives on individual, often conflicting criteria, and combining them into one overall appraisal.”[10]

Quantitative MCDA methodology is a process through which a decision-maker (or group of decision-makers) evaluates the relative value of a set of alternatives by: 1) defining the decision problem; 2) identifying a set of criteria most important to the decision-maker; 3) establishing sources to measure performance and score alternatives by criteria; 4) assigning weights to the criteria included in the analysis; and 5) calculating the aggregate score for alternatives. The results of the analysis then provide a rank order of the decision alternatives.[11,12]

Unlike population-level decision analysis methods such as CEA, MCDA provides insights into the relative value of alternatives specific to a given decision-maker. Conducting an MCDA thus requires decision-makers to undergo an iterative process of reflection and, when conducted in a group setting, discussion and consensus-building.

MCDA is increasingly regarded as a method to support healthcare decision-making, though formal uptake of the approach is limited. This is due in part to the fact that the group process presents complexities and potential challenges. In addition, debate surrounds the methods used in MCDA, including determining the set of attributes, and selection of the most important attributes for analysis, weighting, and subsequent calculation of relative value.

8.1. IVI-MDD Module

Previous OSVP models developed by IVI have incorporated partial MCDA analysis, allowing users to assign weights to a selected set of attributes and outcomes as decision criteria, and then compare treatment sequences based on an aggregated measure of value. Within the MDD model, IVI aims to develop expanded functionality to support the full iterative process of MCDA, including definition, selection, and weighting of criteria, as well as relative value analysis. This function is intended to support the decision-making process, including group processes, but will not include support for group attribute selection.

As with all IVI model development, the goal is to explore and test methods for MCDA while also facilitating use and field testing. Where appropriate, the MCDA function will provide the ability to select between different methods supported by the literature. For example, multiple methods exist for assigning weights; where possible, users will be able to choose among the approaches.

8.2. Development Guidance from MCDA Working Group

To ensure that the MCDA module is scientifically supported and aligned with decision-maker needs, its development has begun during the early scoping phase. To guide it, a small working group of MCDA experts is being convened to advise in working through the process earlier described. This group will provide guidance more broadly, especially in terms of:

1. Identifying and grappling with issues of theory and methodology.
2. Where multiple methodological approaches exist – for example, ways to assign weights for the decision criteria – support IVI in incorporating multiple approaches within the final model.

8.3. Key Steps

MCDA module development will be based on consideration of several key steps in the MCDA process:

1. Defining decision-maker perspectives and the specific decision problem to ensure both are relevant to potential users

2. Selecting and structuring criteria for MCDA

    a. How to structure the select relevant criteria from a list of potential decision factors, and clearly define the final set
    b. Measuring performance of decision criteria alternatives

        i. The specific measure to be used for each criterion
        ii. Determining whether data are available to support parameterization; if not, whether and how to collect needed evidence

3. Methods and mechanics of MCDA module in MDD model

    a. User determination of perspective (if more than one included)
    b. Methods for selecting criteria for MCDA
    c. Methods for assigning weights to set of criteria
    d. Scoring and aggregation methods.

9. References

1. Ettman CK, Abdalla SM, Cohen GH, Sampson L, Vivier PM, Galea S. Prevalence of Depression Symptoms in US Adults Before and During the COVID-19 Pandemic. JAMA Netw Open [Internet]. American Medical Association; 2020 [cited 2020 Sep 15];3:e2019686. Available from: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2770146

2. Kern DM, Cepeda MS, Defalco F, Etropolski M. Treatment patterns and sequences of pharmacotherapy for patients diagnosed with depression in the United States: 2014 through 2019. BMC Psychiatry 2019 201 [Internet]. BioMed Central; 2020 [cited 2020 Dec 16];20:1–10. Available from: https://bmcpsychiatry.biomedcentral.com/articles/10.1186/s12888-019-2418-7

3. 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). J Clin Psychiatry [Internet]. Physicians Postgraduate Press Inc.; 2015 [cited 2020 Sep 15];76:155–62. Available from: https://pubmed.ncbi.nlm.nih.gov/25742202/

4. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second panel on cost-effectiveness in health and medicine. JAMA - J. Am. Med. Assoc. American Medical Association; 2016. p. 1093–103.

5. Kolovos S, Bosmans JE, Riper H, Chevreul K, Coupé VMH, Van Tulder MW. Model-based economic evaluation of treatments for depression: A systematic literature review [Internet]. Pharmacoeconomics. Springer International Publishing; 2017 [cited 2020 Sep 15]. p. 149–65. Available from: https://pubmed.ncbi.nlm.nih.gov/29441493/

6. dosReis S, Butler B, Caicedo J, Kennedy A, Hong YD, Zhang C, et al. Stakeholder-Engaged Derivation of Patient-Informed Value Elements. Patient [Internet]. Adis; 2020 [cited 2020 Sep 14];13:611–21. Available from: https://link.springer.com/article/10.1007/s40271-020-00433-8

7. Wolowacz SE, Briggs A, Belozeroff V, Clarke P, Doward L, Goeree R, et al. Estimating Health-State Utility for Economic Models in Clinical Studies: An ISPOR Good Research

Practices Task Force Report. Value Heal [Internet]. Elsevier Ltd; 2016 [cited 2021 Feb 20];19:704–19. Available from: https://pubmed.ncbi.nlm.nih.gov/27712695/

8. National Institute of Mental Health - Major Depression - Statistics [Internet]. [cited 2021 Mar 9]. Available from: https://www.nimh.nih.gov/health/statistics/major-depression.shtml

9. Ta JT, Sullivan SD, Tung A, Oliveri D, Gillard P, Devine B. Health care resource utilization and costs associated with nonadherence and nonpersistence to antidepressants in major depressive disorder. J Manag Care Spec Pharm [Internet]. Academy of Managed Care Pharmacy ; 2021 [cited 2021 Jan 29];27:223–39. Available from: https://www.jmcp.org/doi/10.18553/jmcp.2021.27.2.223

10. Keeney RL, Raiffa H, Meyer RF. Decisions with multiple objectives: preferences and value trade-offs. Cambridge university press; 1993.

11. Thokala P, Devlin N, Marsh K, Baltussen R, Boysen M, Kalo Z, et al. Multiple criteria decision analysis for health care decision making - An introduction: Report 1 of the ISPOR MCDA Emerging Good Practices Task Force. Value Heal [Internet]. Elsevier Ltd; 2016 [cited 2020 Nov 2];19:1–13. Available from: http://dx.doi.org/10.1016/j.jval.2015.12.003

12. Phelps CE, Lakdawalla DN, Basu A, Drummond MF, Towse A, Danzon PM. Approaches to Aggregation and Decision Making—A Health Economics Approach: An ISPOR Special Task Force Report [5]. Value Heal [Internet]. Elsevier Ltd; 2018 [cited 2020 Nov 2];21:146–54. Available from: https://pubmed.ncbi.nlm.nih.gov/29477392/

10. Appendix

Appendix 1. Summary of Feedback from the AG on Model Specifications

Model Specification	Aggregated Feedback
Objective	Instead of simply comparing the value of treatment A vs. treatment B, the model should be a holistic modeling exercise that examines the treatment pathway of MDD.
Treatment Settings	A significant proportion of people with MDD were diagnosed and treated in the primary care setting. The model should explore how key clinical and economic outcomes vary by treatment settings (primary care, specialty, and telehealth). The factors that are likely to vary across settings include: • Treatments prescribed, particularly the use of pharmacologic and non-pharmacologic agents[s] • Patient characteristics • Effectiveness • Insurance coverage of the people with MDD
Target Population	The model should primarily focus on the general or broader MDD population, but exclude people with MDD with the following conditions: • Pediatric depression • Post-partum depression • Terminal illnesses and depression • People with cognitive impairments • Substance use disorder • A diagnosis of bipolar or other psychiatric conditions
Subgroups of Interest	The model may consider the following patient subgroups in evaluation: • Low socioeconomic status (SES) • Racial/ethnic minority • Those with certain comorbidities (e.g., diabetes, cardiovascular diseases) • Newly diagnosed versus those with years of treatment • Prison population • Insurance type The model should try to incorporate subgroup-specific inputs and allow for examining model outputs for specific subgroups.

[s] Non-pharmacologic treatments were less commonly prescribed in the primary care setting.

Model Specification	Aggregated Feedback
Subgroups of Interest (cont.)	In existing literature, treatment-resistant depression was noted as a subpopulation associated with significant humanistic burden. However, there is no consensus on the definition of treatment-resistant depression. A more clinically meaningful definition is "people with MDD who did not achieve adequate response after receiving more than two types of interventions." Additionally, "difficult-to-treat" depression is a more patient-centric term and is preferred in direct patient communications.
Time Horizon	Existing CEA models typically focus on shorter time horizon (less than 5 years). In the real world, depression "does not go away." The model should build in flexibility to show both short-term and long-term trajectories, even if such data might not be immediately available.
Comparators	The model could consider offering flexibility to evaluate treatments at broader categories (e.g., pharmacologic vs. non-pharmacologic), therapy classes (e.g., SSRIs), and individual treatments. Additional considerations include: • Increasing use of digital therapy • Post-relapse treatment strategies • Add a "no active treatment" arm
Clinical Instruments	HAM-D and MADRS are commonly represented in clinical trials, but PHQ-9 is more commonly used in clinical practice. It is important to recognize that all clinical instruments have their limitations. They do not fully capture the impacts of treatments on people with MDD. From a payer's perspective, any measures that are clinically validated can be considered.
Inputs	General considerations • Use of subgroup-specific inputs whenever possible, instead of population-average estimates • Consider a mix of data sources (e.g., real-world data) beyond clinical trial data Efficacy • Note the time lag between diagnosis and treatment – many people suffering from MDD episodes were not formally diagnosed • Time to treatment effect (if sufficient evidence supports that)

Model Specification	Aggregated Feedback

Inputs (cont.)	Costs
	
	• Long-term cost offsets from improved mental health
	• Given that MDD is a highly co-morbid condition, it might be worth considering MDD-specific and all-cause costs
	• The model should consider the various nuances of costs due to loss of productivity including:
	
	  ○ Absenteeism (due to treatment, due to symptoms)
	  ○ Presenteeism
	  ○ Prejudice (due to diagnosis of MDD)
	
	• Long-term and short-term disability
	• Caregiver burden

Output	The IVI-MDD model should offer a range of model outputs that will be useful to various decision-makers: • QALY is a commonly used but imperfect measure • Consider clinically based outcome measures such as "# of responders" or "# of remitters"
Other Considerations	As the IVI model seeks to incorporate patient-important value elements in the model design, such elements might change over time through the course of their treatment experiences.

Appendix 2. Decision Needs by Stakeholder Perspectives

Stakeholder	Decision Needs
Payers and Employer Purchasers	• What are optimal treatment sequences across classes of pharmaceutical and non-pharmaceutical treatments for MDD? • Are there differences in health and economic outcomes in first line (1L) and subsequent lines of treatments for defined patient subgroups (e.g., by race/ethnicity, age, severity, gender)? • Are there patient perspectives and input that are not accounted for in existing models but may influence outcomes and cost-effectiveness associated with different treatments (e.g., trust in care provider)? • Can modeling give insight on where benefit structure and strategies like utilization management may need to be better aligned with cost-effective treatment sequencing? With patient-centered factors of value? • Can the model support evaluation of cost-effectiveness based on wider sets of indirect costs, such as costs associated with productivity? • Currently, many people diagnosed with MDD do not initiate any active treatments following the diagnosis, which lead to worsening symptoms and higher healthcare costs from ER visits or suicide. What is the cost to a health plan as a result of delayed or no active treatments? • Many people with MDD are treated in the primary care setting. Are there outcome and cost considerations that might give insight to benefit design or appropriate site of care, for example with certain subgroups?
Researchers (Including Value Assessors)	• Provide open-source prototypes that can be tested and stimulate new thinking and next-generation methods. • Help define data inputs representing diverse patient populations within a disease state community that have bearing on treatment choice, treatment adherence, and both clinical and quality of life outcomes. • Expand and test methods for collecting such data inputs based on patient defined attributes of importance. • Test and compare analytic methods for assessing value, including newer methods in CEA (e.g., DCEA, MCDA). • Demonstrate how to incorporate novel elements such as burden on caregivers or impact on productivity (days of work) into value assessment.
Clinicians and Providers	• Identify factors that may inform clinical pathway design; for example, that improve first line treatment choice based on patient subgroups or prioritized attributes. • Identify sequence optimization and related cost-effectiveness that offer support in VBP dialogues.

Stakeholder	Decision Needs
People with MDD	• Identify and incorporate data inputs that are relevant to patient decision-making, that represent clinical and quality of life outcomes of importance to people with MDD that may not be captured in clinical research. • Give insight to how people with MDD make tradeoffs and the factors that matter most in their recovery and sustained health. • Evaluate whether existing treatment protocols and pathways meet the needs of people with MDD. • Identify optimal treatment sequences or important considerations of subgroups that may contribute to improved access to treatment choices. • Include a patient perspective that summarizes the costs borne by people with MDD associated with treatments. This will help better inform the selection of treatments in the shared decision-making context.

Appendix 3. Literature Search Strategy

Set #	Searched for	Results
S1	mesh.exact("Depressive Disorder, Major") OR emb.exact("depressive disorder, major")	31,212*
S2	MESH.EXACT("Economics" OR "Economics, Dental" OR "Economics, Nursing" OR "Economics, Pharmaceutical" OR "Markov Chains" OR "Monte Carlo Method" OR "Value of Life") OR (MESH.EXPLODE("Cost and Cost Analysis" OR "Economics, Hospital" OR "Fees and Charges" OR "Budgets" OR "Models, Economic" OR "Decision Theory" OR "Economics, Medical" OR "Fees and Charges" OR "Budgets"))	535,016*
S3	EMB.EXACT("Socioeconomics" OR "economic aspect" OR "financial management" OR "health care cost" OR "economics" OR "cost" OR "budget" OR "statistical model" OR "probability" OR "monte carlo method" OR "markov chain" OR "decision theory" OR "decision tree") OR EMB.EXACT.EXPLODE("health economics" OR "economic evaluation")	1,655,395*
S4	TI,AB((budget* OR economic* OR cost OR costs OR costly OR costing OR price OR prices OR pricing OR pharmacoeconomic* OR pharmaco-economic* OR expenditure OR expenditures OR expense OR expenses OR financial OR finance OR finances OR financed) OR (value NEAR/2 (money OR monetary)) OR "economic model*" OR markov OR "monte carlo" OR (decision* NEAR/2 (tree* OR analy* OR model*)))	2,375,703*
S5	s1 and s4	1,239°
S6	s2 or s3	2,190,411*
S7	s5 and s6	411°
S8	(s5 and s6) and (pd(2010-2019))	249°

The 249 articles underwent two rounds of review. The first round focused on titles and abstracts and the second on the full text of records that remained eligible from the first review. To be considered for review, articles must have reported on adult populations with MDD and described an economic assessment. Articles without primary analysis, opinion pieces, protocols, and commentaries were excluded, as were reports that described claims analyses or burden of illness studies. After exclusion criteria were applied, 236 documents were considered for abstraction. This included 32 models, 8 of which were formal, government-sponsored, or developed health technology assessments. These articles are included in the reference list herein. In addition, the report authored by the Institute for Clinical and Economic Review on esketamine for treatment-resistant depression, while not identified in the literature search as it does not appear in the peer-reviewed literature, was of interest and therefore included in the review. No other documents outside the literature review were extracted.

Appendix 4. Fields Extracted During Literature review

Field	Comments
Citation	--
Study question/treatment addressed	--
Study year	--
Study population	Demographic characteristics; clinical characteristics (e.g., newly-diagnosed or difficult to treat) Subgroup analyses noted
Study design	Decision-analytic or Markov
Country/countries	--
Perspective	Payer, patient, societal As described by authors; noted if not aligned with best practices for the perspective
Duration/horizon	Primary and sensitivity/interim analysis; also cycle length, if appropriate
Discounting	Annual rate, costs and benefits
Costs	Type (medical, non-medical, indirect, etc.)
Resource use	Expressed as units (visits, hospitalizations, prescriptions, etc.)
Health states/events/ quality of life	Unique health states and events in model; questionnaires or evaluations used to assign utilities
Cost-effectiveness outcomes	Incremental cost per quality-adjusted life-year, cost per relapse prevented
Effectiveness metrics	Metrics and thresholds used; any conversions
Data sources	Clinical, cost, utilities, and other as appropriate
Results	High level findings
Comments	As appropriate, limitations, strengths, other notable study characteristics

Appendix 5. Literature Extraction and Summary (Sorted by Year of Publication)

Study (Year)	Population	Treatment	Comparator	Model Type	Health States/Events	Depression Scale and Threshold	Time Horizon	Perspective
Nordström et al. 2010	MDD	Escitalopram	Venlafaxine Duloxetine	DT	Remission – Relapse	MADRS **Remission**: MADRS score ≤12	6 months	Societal (Sweden)
Nordström et al. 2012	MDD	Escitalopram	Venlafaxine XR		Remission – No Remission – Sustained Remission – Relapse – Premature Stop – Switch	MADRS **Remission**: MADRS score ≤12	6 months	Societal (Sweden)
Prukkanone et al. 2012	MDD	CBT Fluoxetine	No treatment	Microsimulation	Sample time to remission/recovery – Sample probability of suicide – Sample time to relapse/recurrent event	RR and effect size estimates from literature	5 years	Health Sector (Thailand)
Taneja et al. 2012	MDD	Aripiprazole + ADT Quetiapine + ADT Olanzapine/Fluoxetine + ADT ADT Monotherapy		DT	Response – Premature discontinuation (unclear on other states)	MADRS **Response:** ≥50% reduction (vs baseline) in MADRS score	6 weeks	US Health care system
Mencacci et al. 2013	MDD	Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline Duloxetine Venlafaxine XR		DT	Remission – Relapse - Suicide attempt after relapse- death due to suicide attempt	HDRS **Remission:** HDRS score of ≤7	1 year	National Health service (NHS) (Italy)
Maniadakis et al. 2013	MDD	Agomelatine	Venlafaxine Fluoxetine Sertraline Escitalopram	Markov	Healthy – Depressive episode on tx - Remission on tx - Depressive episode off tx - remission off tx - Death	HAM-D	2 years	Societal (Greece)
Solomon et al. 2013	Mild to moderate depression	St. John's Wort	Venlafaxine	Markov	Depressive episode – Response – Remission - Dead	HAM-D	72 weeks	National Health Provider (Australia)
Olgiati et al. 2014	MDD (elderly)	Paroxetine high dose	Paroxetine low dose	Markov	Depression - Remission - Relapse - No treatment (discontinuation)	HAM-D	32 weeks	Not specified

Study (Year)	Population	Treatment	Comparator	Model Type	Health States/Events	Depression Scale and Threshold	Time Horizon	Perspective
Annemans et al. 2014	MDD	Citalopram Sertraline Paroxetine Fluoxetine Duloxetine Venlafaxine Mirtazapine Escitalopram		DT	Remission – Relapse - Suicide attempt after relapse- Death after suicide attempt	HAM-D & MADRS **Remission:** HAMD-17 score ≤7 or MADRS score of ≤12	1 year	(2) National Institute of Health and Disability Insurance, Societal (Belgium)
Khoo et al 2015	MDD	Agomelatine Duloxetine Escitalopram Fluvoxamine Mirtazapine Paroxetine Sertraline Trazodone Venlafaxine		DT	Remission – Relapse – Therapeutic change (augmentation and switch therapy)	HAM-D & MADRS **Response:** 50% reduction in HDRS or MADRS score from baseline **Remission:** HDRS-17 score of ≤7 or ≤8 for long HDRS or MADRS score of ≤12	6 months	Societal (Singapore)
Hornberger et al. 2015	TRD	CPGx testing	Treatment as Usual (TAU)	Markov	Alive & responsive –Alive and non-responsive – Died from suicide – Died from other causes	CPGx and TAU effectiveness measure not specified 2nd line tx: HAMD	38 years (base case)	Societal (US)
Nguyen et al. 2015	TRD	rTMS	AD's (tx names not specified)	Markov	Acute tx (HAMD-17 >9) - Full remission (HAMD-17 <8) – Partial remission (HAMD-17 8-19) – relapse (HAMD->19) – Post tx augmentation (HAMD17>19) - Death	HAM-D	3 years	Health system (Australia)
Koeser et al. 2015	MDD	Pharmacotherapy	CBT Combination Therapy	DT	Remission (full response HAMD ≤7) – Response (partial remission HAMD 7-15) - Non-response (HAMD≥15)	HAM-D **Remission:** HAM-D score of ≤7	27 months	Healthcare service (UK)
Health Quality Ontario HTA 2016	TRD	rTMS	Sham rTMS ECT	DT	Response – Full Remission – Response w/o remission – No remission – No response	HAM-D **Remission:** HAMD-17 score <8	6 months	Provincial (Ontario Ministry of Health and Long-term Care)

Study (Year)	Population	Treatment	Comparator	Model Type	Health States/Events	Depression Scale and Threshold	Time Horizon	Perspective
						Response: 50% reduction in HAM-D score		
Ammerman et al 2017	MDD (low-income mothers)	In-home CBT with ongoing home visiting	Home visiting alone	Patient level Markov	MDD – Remission – Death	Not specified in clinical trial abstract	3 years	Payer (US)
Young et al 2017	MDD (pts with inadequate response to 2 ADTs)	Vortioxetine	Duloxetine Venlafaxine Agomelatine	DT + Markov component	**DT:** Remission – Response – No response – Withdrawal due to AE – Relapse – Recovery – Recurrence **Markov:** Remission – No remission-Recovery	HAM-D and MADRS **Response:** 50% or more reduction from baseline in MADRS or HAM-D score **Remission:** MADRS≤10 or HAM-D ≤7	24 months	Not specified
Health Quality Ontario HTA 2017	MDD pts with and without GAD	Individual/group CBT only or in combination with pharmacotherapy	Usual care	Markov probabilistic microsimulation	Acute/mild – Acute/moderate to severe – Continuation/mild – Continuation/moderate to severe – Maintenance/mild – Maintenance/moderate to severe – Recurrent/mild – Recurrent/moderate to severe – Well – Complex TRD - Death	HAM-D	5 years	Provincial (Ontario Ministry of Health and Long-term Care)
Groessl et al 2018	MDD	IDGx testing	Standard of care	Markov	Response – Non response – Survive - Remission – Relapse – Death	HAM-D **Response:** 50% or more in HAM-D score	3 years	Societal (US)
Ross et al 2019	MDD	CBT	2nd generation ADTs	DT	Initiation (1st month of tx) – Remission (Quick Inventory of Depressive Symptomatology ≤5) – Response (≥50% reduction HAM-D) – Nonresponse (initial lack of response or remission) – Relapse (return of depression symptoms after initial response or remission)	**Remission**: (near-complete recovery of depression, defined by score on a validated symptom rating scale (ex.16-item Quick Inventory of Depressive Symptomatology ≤5) **Response**: partial recovery of depression (ex. ≥50%	1-5 years	- Health care - Societal (US)

Study (Year)	Population	Treatment	Comparator	Model Type	Health States/Events	Depression Scale and Threshold	Time Horizon	Perspective
						reduction in HAM-D score)		
ICER 2019	TRD	Esketamine (nasal spray)	Ketamine ECT TMS Oral ADTs	DT	Remission – Response – No response	MADRS **Remission:** MADRS≤12 **Response**: ≥ 50% reduction in MADRS score	Lifetime	Health care sector (US)

ADT: Antidepressant therapy rTMS: repetitive transcranial magnetic stimulation CPGx: Multi-gene combinational pharmacogenetic test DT: Decision Tree; IDGx: IDgenetix test; GAD: Generalized Anxiety Disorder; MADRS: Montgomery Åsberg Depression Rating Scale; HDRS/HAM-D: Hamilton Depression Rating Scale; RR: Relative risk SJW: St. John's wort; HTA: Health Technology Assessment; ICER: Institute for Clinical and Economic Review; NHS; The National Health Service; XR: Extended Release

Models Reviewed and Extracted

Ammerman RT, Mallow PJ, Rizzo JA, Putnam FW, Van Ginkel JB. Cost-effectiveness of in-home cognitive behavioral therapy for low-income depressed mothers participating in early childhood prevention programs. Journal of Affective Disorders. 2017;208:475-82.

Annemans L, Brignone M, Druais S, De Pauw A, Gauthier A, Demyttenaere K. Cost-effectiveness analysis of pharmaceutical treatment options in the first-line management of major depressive disorder in Belgium. PharmacoEconomics. 2014;32(5):479-93.

Groessl EJ, Tally SR, Hillery N, Maciel A, Garces JA. Cost-effectiveness of a pharmacogenetic test to guide treatment for major depressive disorder. Journal of Managed Care & Specialty Pharmacy. 2018;24(8):726-34.

Health Quality Ontario. Repetitive transcranial magnetic stimulation for treatment-resistant depression: an economic analysis. Ontario Health Technology Assessment Series. 2016;16(6):1-51.

Health Quality Ontario. Psychotherapy for Major Depressive Disorder and Generalized Anxiety Disorder: A Health Technology Assessment. Ontario Health Technology Assessment Series. 2017;17(15):1-167.

Hornberger J, Li Q, Quinn B. Cost-effectiveness of combinatorial pharmacogenomic testing for treatment-resistant major depressive disorder individuals with MDD. The American Journal of Managed Care. 2015;21(6):e357-e65.

Institute for Clinical and Economic Review. Eskatamine for the treatment of treatment-resistant depression: effectiveness and value. Evidence Report. Institute for Clinical and Economic Review; 2019.

Khoo AL, Zhou HJ, Teng M, Lin L, Zhao YJ, Soh LB, et al. Network meta-analysis and cost-effectiveness analysis of new generation antidepressants. CNS Drugs. 2015;29(8):695-712.

Koeser L, Donisi V, Goldberg DP, McCrone P. Modelling the cost-effectiveness of pharmacotherapy compared with cognitive-behavioural therapy and combination therapy for the treatment of moderate to severe depression in the UK. Psychological Medicine. 2015;45(14):3019-31.

Maniadakis N, Kourlaba G, Mougiakos T, Chatzimanolis I, Jonsson L. Economic evaluation of agomelatine relative to other antidepressants for treatment of major depressive disorders in Greece. BMC Health Services Research. 2013;13:173.

Mencacci C, Aguglia E, Biggio G, Cappellari L, Di Sciascio G, Fagiolini A, et al. C-QUALITY: cost and quality-of-life pharmacoeconomic analysis of antidepressants in major depressive disorder in Italy. Advances in Therapy. 2013;30(7):697-712.

Nguyen K-H, Gordon LG. Cost-effectiveness of repetitive transcranial magnetic stimulation versus antidepressant therapy for treatment-resistant depression. Value in Health. 2015;18(5):597-604.

Nordström G, Danchenko N, Despiegel N, Marteau F. Cost-effectiveness evaluation in Sweden of escitalopram compared with venlafaxine extended-release as first-line treatment in major depressive disorder. Value in Health. 2012;15(2):231-9.

Nordström G, Despiegel N, Marteau F, Danchenko N, Maman K. Cost effectiveness of escitalopram versus SNRIs in second-step treatment of major depressive disorder in Sweden. Journal of Medical Economics. 2010;13(3):516-26.

Olgiati P, Bajo E, Serretti A. Benefit of slow titration of paroxetine to treat depression in the elderly. Human Psychopharmacology. 2014;29(6):544-51.

Prukkanone B, Vos T, Bertram M, Lim S. Cost-effectiveness analysis for antidepressants and cognitive behavioral therapy for major depression in Thailand. Value in Health. 2012;15(1 Suppl):S3-8.

Ross EL, Vijan S, Miller EM, Valenstein M, Zivin K. The cost-effectiveness of cognitive behavioral therapy versus second-generation antidepressants for initial treatment of major depressive disorder in the United States: a decision analytic model. Annals of Internal Medicine. 2019;171(11):785-95.

Solomon D, Adams J, Graves N. Economic evaluation of St. John's wort (Hypericum perforatum) for the treatment of mild to moderate depression. Journal of Affective Disorders. 2013;148(2-3):228-34.

Taneja C, Papakostas GI, Jing Y, Baker RA, Forbes RA, Oster G. Cost-effectiveness of adjunctive therapy with atypical antipsychotics for acute treatment of major depressive disorder. The Annals of Pharmacotherapy. 2012;46(5):642-9.

Young AH, Evitt L, Brignone M, Diamand F, Atsou K, Campbell R, et al. Cost-utility evaluation of vortioxetine in individuals with MDD with major depressive disorder experiencing inadequate response to alternative antidepressants in the United Kingdom. Journal of Affective Disorders. 2017;218:291-8.

Appendix 6. Patient Preference Study

People with MDD were recruited based on the following inclusion/exclusion criteria.

Inclusion Criteria

- Age 18 or older
- Diagnosed with MDD
- Speak/Read English

Exclusion Criteria

- Bipolar or psychotic depression
- Living in a residential or institutional setting
- Post-partum depression

Part 1: Descriptive summary of people who participated in the Phase 1 interviews (N=20)

Age Group	n	%
25-34	2	10%
35-44	3	15%
45-54	2	10%
55-64	7	35%
65+	6	30%
Sex		
Female	14	70%
Male	6	30%
Race		
African American	4	20%
Caucasian	14	70%
Hispanic	2	10%
Marital Status		
Married	8	40%
Divorced/Separated	7	35%
Never Married	5	25%
Education		
High School/GED	2	10%
Some College	4	20%
2-Year Degree	1	5%
Bachelor's Degree	7	35%
Graduate Degree	6	30%
Household Income		
Less than $10,000	3	15%
$10,000-$24,999	3	15%
$25,000-$49,999	1	5%
$50,000-$74,000	5	25%
$75,000-$99,999	3	15%
More than $100,000	5	25%
Employment Status		
Full time	7	35%
Part time	1	5%
Retired	4	20%
Unemployed; not looking for work	2	10%
Disabled	6	30%

Healthcare Insurance Type		
Private Insurance	10	50%
Public Insurance (Medicare/Medicaid/VA)	4	20%
No Insurance	1	5%
Other Insurance	1	5%
Public Insurance and Private Insurance	4	20%
U.S. Region		
Northeast	6	30%
Midwest	4	20%
South	7	35%
West	2	10%
Mid-Atlantic	1	5%
Residential Community		
Suburban	12	60%
Urban	7	35%
Rural	1	5%
Medication Treatment		
Yes	17	85%
No	3	15%
Non-Medication Treatments		
Electroconvulsive Therapy (ECT)	5	25%
Transcranial Magnetic Stimulation (TMS)	3	15%
Deep Brain Stimulation (DBS)	1	5%
Therapy (unspecified)	13	65%
Cognitive behavioral therapy (CBT)	4	2%
Mindfulness-Based Cognitive Therapy (MBCT)	1	5%
Eye Movement Desensitization and Reprocessing (EMDR) therapy	1	5%
Group Therapy	2	1%
Other Interventions		
Exercise	3	15%
Light Box	1	5%
Diet	1	5%
Meditation	1	5%
Prayer	1	5%
Hospitalized in past year for MDD		
Yes	1	5%
No	19	95%

Part 2: Summary of the value element importance selections

From the PAVE value element set, respondents were asked to identify the important value elements and the most important value elements. The table below provides a summary by domains.

Treatment Effects Element	Important	Top Importance
Medication Frequency	4	4
Length of Treatment	9	3
Side Effects	17	13
Age of Onset	2	1
Symptom Importance	18	14
Surrogate/Intermediate Outcomes	11	6
Impact on Education	9	3
impact on Career	17	7
Predictable Healthcare Costs	13	5
Inability to Plan	12	6
Life Expectancy	11	9

Treatment Access Element	Important	Top Importance
New Therapeutic Option	11	5
Available Treatment	17	11
Provider Willing to Deliver Care	14	8
Proximity to Care Location	14	4
Appropriateness of Care	14	7
System Navigation	13	6
Provider Relationship & Trust	19	16
Care Transitions	10	3
Consistency of Care	17	10
Explanation of Treatment (Benefits & Risks)	17	10

Treatment Costs Element	Important	Top Importance
Affordability	18	15
Cost of Treatment-related Side Effects	13	5
Long-term Costs	15	9
Reimbursed Care	10	9
Sibling Costs	5	2
Long-term Effects on the Family	14	11
Relocation Costs	8	1
Autonomy/Independence	15	12

Life Impact Element	Important	Top Importance
Fatigue	18	11
Ability to Work	18	10
Physical Abilities	16	8
Emotional Status	19	17
Embarrassment/Self-Conscious	9	3
Rejection by Family	10	5
Rejection by Society	10	5

Social Impact Element	Important	Top Importance
Social Network	12	6
Relationship with Family	16	14
Relationship with Peers	14	9
Maintain Social Activities	16	10
Cultural Barrier	4	2
Religious Barrier	4	1

Appendix 7. Potential Cost Components to Consider in the Societal Perspective

Cost Components
Formal Healthcare Sector • Costs paid by third-party payers • Costs paid out-of-pocket by people with MDD
Informal Healthcare Sector • Patient-time costs • Unpaid caregiver-time costs • Transportation costs
Non-healthcare Sector • Productivity • Consumption • Social services • Education • Housing • Other impacts (e.g., environmental, legal, or criminal justice)

Appendix 8. Treatment Options by Sequences of Treatment

Order	First (potential, options)	Second	Third	Fourth
Treatments	Start with: Pharmacotherapy - SSRI - SNRI - Atypical - Mirtazapine - Bupropion - TCAs - Serotonin modulators - MAOI Psychotherapy - CBT - IPT - Psychodynamic therapy Combination – Psychotherapy + pharmacotherapy	Switch to a different treatment option listed below: *(Note – for pharmacotherapy, people with MDD can switch from one medication to another medication in the same class or a different class)* Pharmacotherapy - SSRI - SNRI - Mirtazapine - Bupropion - TCAs - Serotonin modulators - MAOI Psychotherapy - CBT - IPT - Psychodynamic therapy Combination – Psychotherapy + pharmacotherapy	Switch to a different treatment option listed below: Pharmacotherapy - SSRI - SNRI - Mirtazapine - Bupropion - TCAs - Serotonin modulators - MAOI - Ketamine - Esketamine Psychotherapy - CBT - IPT - Psychodynamic therapy Combination of treatments – Psychotherapy + Pharmacotherapy Somatic Therapy - ECT - TMS Pharmacotherapy augmentation strategies	Switch to a different treatment option listed below: Pharmacotherapy - SSRI - SNRI - Mirtazapine - Bupropion - TCAs - Serotonin modulators - MAOI - Ketamine - Esketamine Psychotherapy - CBT - IPT - Psychodynamic therapy Combination of treatments – Psychotherapy + pharmacotherapy – Psychotherapy + somatic therapy + pharmacotherapy Somatic Therapy - ECT - TMS - VNS Pharmacotherapy augmentation strategies

Appendix 9. Costs by Perspective

Costs	Self-funded Employer[t] (fully or partially)	Fully-insured Employer	People with MDD (co-pay or personal expense)	Societal
Insurance premium		X	X	X
Category 1 – Medical Costs Related to MDD Treatments				
Pharmacotherapy	X		X	X
Outpatient visit (any provider type, includes psychotherapy, can include MDD treatment as well as adverse event monitoring or treatment)	X		X	X
Laboratory/radiology	X		X	X
Inpatient care due to receiving treatments	X		X	X
Surgical/procedural	X		X	X
Durable medical equipment (e.g., for light therapy)	X		X	X
Home health care	X		X	X
Emergency care	X		X	X
Future (potential) medical costs	X		X	X
Over-the-counter (e.g., alternative and complementary medicine)			X	X
Non-covered therapeutic services[u] (yoga, meditation, other wellness services/benefits, digital therapies benefits)	X	X	X	X
Category 2 – Non-Medical Costs Related to MDD Treatments				
Transportation to/from medical care			X	X
Patient time costs			X	X
Day care (not explicitly medical)			X	X
Child care			X	X
Social services				
Educational achievement			X	X
Workers' compensation	X	X		X
Disability benefits (short- and long-term)	X	X	X	X
Category 3 – Other Costs Not Directly Related to MDD Treatments				
Presenteeism	X	X	X	X
Absenteeism	X	X	X	X
Lack of workforce participation			X	X
Mortality			X	X
Unpaid leave due to caregiving for family members	X	X	X	X

[t] The costs relevant to a self-funded employer are similar to those from the perspective of a third-party payer.

[u] Some employers might provide subsidy for wellness programs such as gym membership or fitness classes.

Appendix 10. Brief Discussion of Potential Model Structures

Potential approaches for simulation include cohort-based models and microsimulation models. A brief discussion on the merits of each approach is outlined below.

As suggested by their name, cohort-based models simulate the progression of disease and treatment effect based on assumed population averages. The most common approach used in the setting of MDD has been through the use of Markov models, which feature distinct health states corresponding to different levels of response to treatment.

A distinct feature of Markov models is the memoryless feature of such models, which thereby does not readily allow for tracking of disease history over time. Furthermore, these models typically do not easily allow for the contemporaneous incorporation of various patient and clinical characteristics that may modify future outcomes. Various approaches can be taken to overcome these limitations; however, these approaches can render the model increasingly complex, especially where many different types of subgroups and patient characteristics are required for consideration. Notwithstanding, Markov cohort models are typically sufficient in most scenarios where heterogeneity is less likely to impact the interpretation of results and where disease history is not anticipated to impact future outcomes.

Individual-level simulation models, or microsimulation models, simulate each patient individually over time, allowing for tracking of individual patient histories through time and the simultaneous incorporation of a patient characteristics, which will better account for patient to account for heterogeneity. Individual patient histories and incorporation of prognostic factors may be especially important in MDD, where effectiveness of treatment can differ as people with MDD experience recurrence or multiple relapses and where other individual patient-level factors may simultaneously impact prognosis.

Appendix 11. Glossary of Terms

General

Terms	Definition
Health technology assessment (HTA)	A multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. A health technology is the application of organized knowledge and skills in the form of devices, medicines, vaccines, procedures, and systems developed to solve a health problem and improve quality of lives for individuals affected.
Value assessment (VA)	Comparison of the relative benefits to the costs of a given technology or service for a specific person or population.
Health economic modeling	A set of analytic approaches in health economic analysis that synthesize clinical, epidemiological, and economic evidence from different data sources into an evaluation framework that enables researchers or decision makers to generate estimates for specific outcomes of interest. Models are simplified representations of the real world to inform decision-making.
Cost effectiveness analysis	A method to examine both the costs and health outcomes of one or more interventions. An intervention is compared to another intervention (or the status quo) by estimating how much it costs to gain an additional unit of a health outcome, such as a life year gained or a case prevented.
Value element	Refers to specific aspects or components that stakeholders may consider as part of an overall assessment of value (e.g., different mode of administration, reduced risk, lower cost).
Patient inputs	A wide range of information and perspectives from patients including but not limited to informal comments; patient opinions expressed publicly, including through social media; patient responses to qualitative surveys; and quantitative measurements of patient-reported outcomes.
Patient perspective	A specific type of patient input describing patients' experience with a disease or condition and its management.
Patient preference	Qualitative or quantitative assessment of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among health interventions.

Modeling Specific

Terms	Definition
Model scope	Document describing key model objectives, assumptions, and specifications on a conceptual level, including population, treatments, outcomes, and settings. This document also describes the specific considerations to be evaluated and confirmed during the protocol development stage.
Model protocol	Detailed technical document that includes the necessary details to build the model and conduct analyses, including the analytic approaches, key assumptions, data inputs, and model output.
Health state	Some models categorize patients into discrete states of health based on patients' symptoms, clinical experiences or treatments (e.g., mild, moderate, or severe disease; pre- vs. post-transplant).
Utilities	A measure of patients' preferences for different health states, which are often used to estimate changes in quality of life associated with treatments or other clinical events. Utility values are typically measured on a scale from 0 (representing death) to 1 (representing "perfect health").
Perspective	Refers to the point of view adopted when deciding which types of costs, health, and economic benefits are to be included in an economic model (e.g., health care sector vs. societal).
Time horizon	The time period during which clinical and economic outcomes will be simulated/evaluated in the model.
Cycle length	The time interval used in a model to track changes in clinical and economic outcomes that occur in the simulation.
Comparator	Different treatment options or sequences of treatments that the model will assess.
Effectiveness	The ability of an intervention (drug, device, treatment, test, pathway) to provide the desired outcomes in the relevant patient population.
Treatment sequence	The time-ordered series of treatments for a given patient or group of patients. Treatment sequences may include monotherapy with a pharmacologic or non-pharmacologic agent, combinations of different pharmacologic agents, or combinations of pharmacologic and non-pharmacologic agents in any given order for specific periods during the treatment process.

References:

Glossary – Health Economics [online]. (2016). York; York Health Economics Consortium; 2016. https://yhec.co.uk/glossary/

O'Rourke, Brian, Wija Oortwijn, and Tara Schuller. "Announcing the New Definition of Health Technology Assessment." Value in Health 23.6 (2020): 824-825.

ISPOR-FDA Summit 2020: Using Patient-Preference Information in Medical Device Regulatory Decisions: Benefit-Risk and Beyond [Internet]. Available from: https://www.ispor.org/conferences-education/conferences/past-conferences/ispor-fda-summit-2020