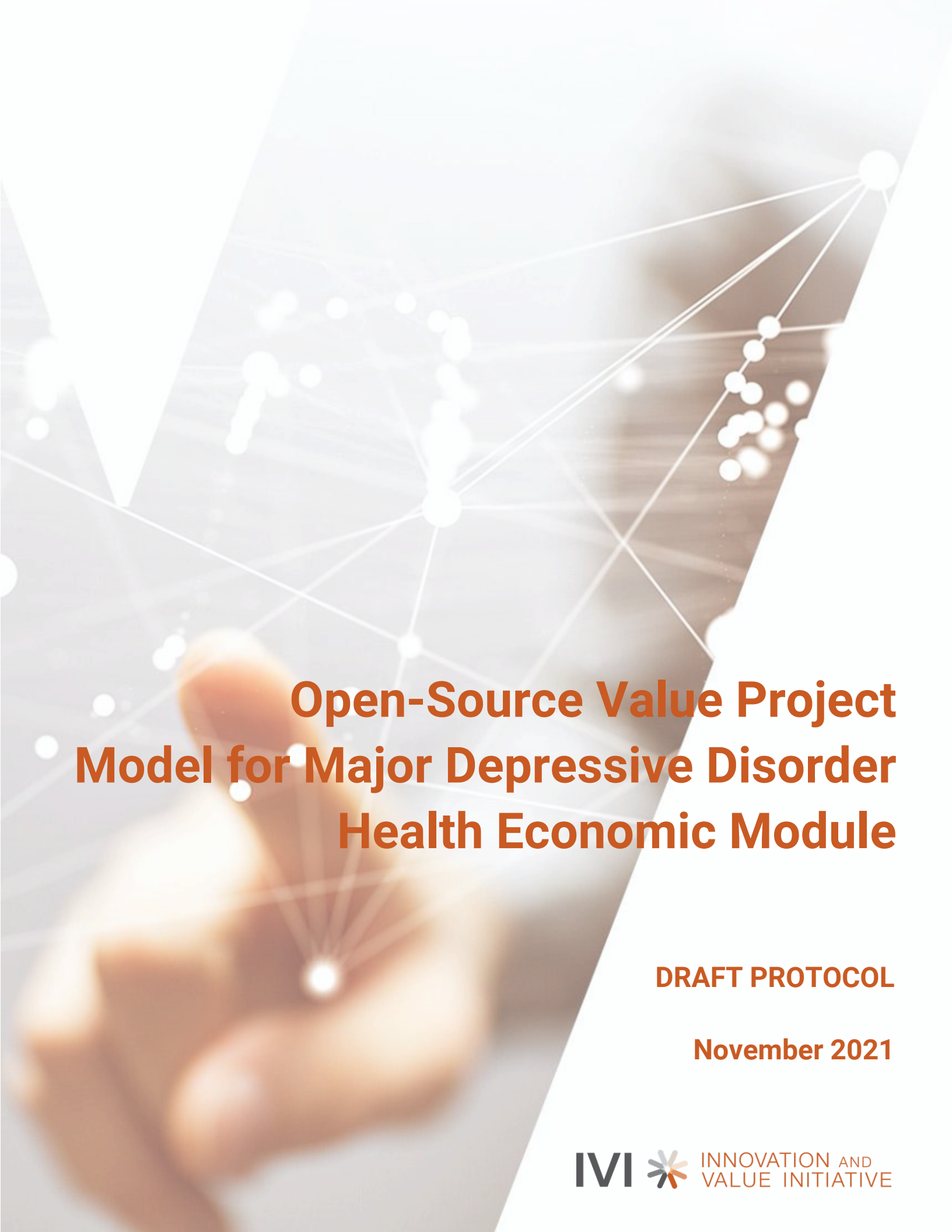

Open-Source Value Project Model for Major Depressive Disorder Health Economic Module

DRAFT PROTOCOL

November 2021

IVI INNOVATION AND VALUE INITIATIVE

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Abbreviations

AD	Anti-depressant
ADT	Anti-depressant therapy
BAT	Behavioral activation therapy
CGI	Clinical Global Impression
CMS	Centers for Medicare and Medicaid Services
CPT	Current Procedural Terminology
DBS	Deep brain stimulation
DRG	Diagnosis-Related Group
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECT	Electro-convulsive therapy
HAM-D/HDRS	Hamilton Depression Rating Scale
HR	Hazard ratio
HRQoL	Health-related quality of life
ICD	International Classification of Diseases
IPT	Interpersonal psychotherapy
IVI	Innovation and Value Initiative
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	Mono-amine oxidase inhibitor
MBCT	Mindfulness-based cognitive therapy
MDD	Major depressive disorder
OSVP	Open-source value project
PHQ	Patient Health Questionnaire
PICO	Population, intervention, comparator, outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PST	Problem-solving therapy
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomized controlled trial
RR	Relative risk
SE	Standard error
SLR	Systematic literature review
SNRI	Selective norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tri-cyclic antidepressant
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
TRD	Treatment-resistant depression
UCR	Usual, customary, and reasonable
VNS	Vagus nerve stimulation

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 assessment 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 for MDD over a lifetime horizon. In addition to capturing the costs and benefits from a health care 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 employer purchasers. 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.

Purpose of the Draft Model Protocol Public Comment Period

The draft model protocol outlines the technical specifications and data sources that will guide model development in subsequent modeling phases. Following the model scope public comment period, IVI has worked with our research partner, OPEN Health, and our multi-stakeholder advisory group[1] to develop this more detailed draft protocol.

In this process, we have strived to ensure that the model design incorporates key feedback from the public, the advisory group, and people with lived experiences, and that the model reflects real-world treatment sequences and key value elements from a societal perspective. We have also identified some additional methodological and data gaps.

An important challenge for us in developing the draft model protocol is to design a "forward-looking" model that reflects the key decision needs of end-users and inputs from people with MDD. Our hope is that such an approach will help us highlight existing data and method gaps to promote conversations across stakeholders and highlight areas for future research. For areas with methodological and data gaps, we have proposed short-term solutions throughout this draft protocol.

In the spirit of our ongoing learning process and to ensure that the model can help address the decision needs of key decision makers in the healthcare system, we are seeking your feedback and

suggestions on how we can navigate these gaps to build a more useful and relevant model for different decision contexts. We are mainly seeking your feedback in the following three areas:

- data gaps in key model assumptions and inputs, as well as potential data sources and partners to address such gaps;
- prioritization of data sources and technical approaches when multiple valid approaches exist; and
- potential use cases, particularly how the MDD model can help inform decisions in your organizations.

We will revise this draft protocol based on feedback from stakeholders and will publish the final model protocol in February 2022. The final model protocol will inform development of the IVI-MDD Model, which we plan to release in the second quarter of 2022.

2 Questions for Public Comment

Below is a list of questions that we are seeking feedback on.

Section	Question
General	Do you have any general comments or feedback for us to consider in finalizing the model protocol?
6.1	Are there any other studies/data sources that will better represent the characteristics of the MDD population based on the target population of the model?
6.1.1	Do you know of any studies/data sources that examine how key model inputs (e.g., effectiveness, safety, costs) vary by subgroups defined by patient characteristics including age, race/ethnicity, and socioeconomic status (e.g., education level, income)?
6.5 and 8.2.3	Do you have some suggestions on studies/data sources/methods that we can reference in extrapolating the long-term efficacy inputs? We have limited data on responses to treatments for some comparators from our literature review of meta-analyses (Table 3). - Should we extract such inputs from clinical trials or observational studies? - If so, do you have any recommendation on data sources?
6.8	Are there other model outputs that will be of interests to your organization? In what decision contexts will they be useful?
6.8	Do you have any suggestions on data sources that examine suicidal behavior or attempts for: (1) the general MDD population, and (2) those that have received different treatment options?
6.9.3	Is it reasonable to assume that somatic therapies (e.g., ECT) will only be offered as 3rd and 4th lines of treatment, given the target population in our model?
6.9.3.1	We specified scenarios in which individuals in our simulation will move to a new line of treatment. Are these scenarios consistent with real-world clinical practice? Are there other scenarios in which individuals might switch to a different line of treatment that we should include in the model?
6.9.3.2	Is it reasonable to assume the same sets of model inputs (efficacy and safety) for the first and second lines of treatment? In the absence of data for the key efficacy inputs for third and fourth lines of treatment, we intend to: (1) first use estimates based on the treatment-resistant depression (TRD) population as model inputs; and (2) if estimates based on TRD population do not exist, use a hazard rate approach where treatment efficacy rates will be proportional to efficacy rates used in the first and second lines. Do these assumptions seem reasonable to you? Do you have any suggestions for sources to derive model estimates for the third- and fourth-line treatments?

7.3	We have proposed two approaches to derive direct medical cost inputs in our model: a "top-down" approach (identify proportion of all-cause medical costs that can be attributed to MDD), or a "bottom-up" approach (identify individual resource requirements and unit costs; and sum across all resource use items). Is there one approach you would recommend over the other? Are you aware of any data sources/studies that we should look into for this issue?
7.1.2	Are there key adverse events that have a significant clinical and economic impact that we should include in the model? We plan to conduct additional literature searches to identify key AEs to include in the model. What sources would you recommend that we prioritize (e.g., prescribing labels, real-world studies, etc.)? One of the challenges is to identify a set of AEs and their frequencies across a drug class. Do you have any suggestions for how to approach this?
7.2	Of the possible data sources for utility inputs listed in Table 8, is there one we should prioritize? Are there other sources we should consider?
7.3	For psychotherapy, what is a reasonable assumption for the length of a visit and for duration of psychotherapy to include (Table 10 and 11)?
7.3.5.2	Do you have any suggestion on studies or data sources that can inform the calculation of informal caregiving burden or costs?
Appendix H	Appendix H describes some of the novel questions or research opportunities that the model could help inform. Are there specific use cases or decision contexts that should be prioritized? Are there other important use cases or decisions that this model could help inform?

3 Clinical Background

3.1 Major Depressive Disorder

Major depressive disorder (MDD) is a common condition that affects patients, families, employers, the health care system, and the community at large. According to the Diagnostic and Statistical Manual (DSM-5), individuals who experience five or more selected symptoms during a 2-week period, with one of those symptoms being either depressed mood or loss of interest or pleasure, can be diagnosed with depression, as long as the symptoms are not the result of another condition or substance abuse.[2] MDD is sometimes also referred to as "unipolar depression" to differentiate it from bipolar depression, a variation of depression that also includes manic states. Treatment-resistant depression (TRD) is typically defined as depression that has not responded to two trials of appropriate therapies of adequate dose and duration.[3]

With more than 19 million adults living in the United States (US) having had at least one episode of MDD and 11 million having had an episode with severe impairment in 2019,[4] the impact of MDD is substantial. Employers bear a large portion of the economic burden, with absenteeism and presenteeism responsible for most of the cost of MDD in the US.[5]

Identifying the appropriate treatment for individuals with MDD can be challenging. More than one-third of adults and more than 60% of adolescents do not receive any treatment at all.[4] Medication and psychotherapy are guideline-approved first-line therapies.[3, 6-9] Combination therapies often yield better results than monotherapy, with incremental benefits for adjunctive therapies for individuals with more severe disease. Side effects can impede adherence with treatment. After the resolution of an acute episode, long-term treatment is often required. An underlying question with MDD is how to define and recognize a meaningful improvement from the perspective of the individual with MDD. A recent qualitative analysis based on interviews with individuals with TRD and caregivers suggests that trials may not be routinely measuring endpoints that matter to individuals with TRD.[10]

3.2 Clinical Treatment Guidelines

As part of the initial model conceptualization, current treatment guidelines in MDD focused on the US were identified.[3, 6-9] The assumptions and structure rely most heavily on guidelines from the American Psychiatric Association and the American Psychological Association.[3, 6, 7] Treatment guidelines in MDD provide insights and recommendations that consider three dimensions in addition to symptomatology: age, treatment resistance, and comorbidities. For example, separate recommendations are available for pediatric and elderly populations, for individuals with treatment-resistant depression versus depression that responds to first- and second-line treatments, and for individuals with comorbid conditions, including postpartum depression, other psychiatric

disorders, and other physical conditions that may be relevant to treatment. We referenced the treatment guidelines specific to our target model population in developing the protocol.

The American Psychiatric Association's recommendations,[6] extensively referenced for the model, suggest that acute treatment for individuals with mild to moderate depression may include medication or psychotherapy and for individuals with moderate to severe depression treatment may also include somatic therapies, light therapy, or a combination of treatments, with the acute phase lasting for at least 6-12 weeks. The guidelines suggest that response should be assessed at 4-8 weeks, with changes such as dose adjustment made as needed, and re-evaluation after a further 4-8 weeks. The guidelines state that there is no evidence to suggest a clinically meaningful difference in response rates across common medication classes (TCAs, SSRIs, SNRIs, MAOIs, and other specified agents) and that the choice of treatment should be guided by safety, cost, preference, tolerability, and prior treatment history. Once achieving response, individuals are monitored during the 4- to 9-month continuation phase and may continue with the treatment to which they responded at the full therapeutic dose, or may initiate psychotherapy. Individuals at considerable risk for relapse then are recommended to continue with pharmacotherapy and psychotherapy, with less frequent sessions. Somatic therapies such as ECT and VNS may be offered to individuals who have inadequate response to pharmacotherapy or psychotherapy.

As these guidelines were last updated in 2019, they may not reflect recent clinical developments (e.g., emerging treatment strategies). Therefore, we also relied on findings from a targeted literature review and input from the advisory group and other stakeholders in developing this draft protocol.

4 Model Objectives

4.1 Primary Objective of the Health Economic Model

The primary objective of the health economic model is to allow users to evaluate the lifetime benefits and risks of various treatment sequences in US adults (age 18-64 years) newly diagnosed with MDD by a healthcare provider, from multiple perspectives (i.e., private and public payers, employers, people with MDD, and society).

4.2 Prioritized Research Questions

Based on the feedback from continual advisory group engagement and public comments[11] in the model scope phase, three specific research questions were prioritized to guide the development of the initial version of the model:

- What is the societal burden of untreated or "under-treated" MDD?
- How do key model outcomes vary for certain subgroups (e.g., those with prior treatment experience or lower socioeconomic status) compared with the overall population?
- What is "low-value" care in existing real-world treatment sequences?

These three focus areas are specifically addressed in the model design in this protocol, with the flexibility for users to select specific model populations, assumptions, inputs, and outputs.

- **The societal burden of untreated or under-treated MDD**: This can be explored by the user selecting the societal perspective and assigning "no treatment" as part of the treatment sequence. "Under-treatment" could, for example, be explored by not adjusting treatment strategies appropriately after inadequate response to initial treatment.

- **Subgroup considerations**: The user can specify subgroups and/or use subgroup-specific inputs to make such comparisons; for instance, the user can select the same interventions in the general population versus a subgroup (defined by age, gender, insurance coverage type, etc.) and then compare key outcomes. In many cases, there is currently little evidence available on differences in effectiveness across subgroups. However, the model structure and set-up will allow users the flexibility to incorporate subgroup-specific inputs and produce subgroup-specific outputs (such as productivity/presenteeism by income).

- **The identification of low-value care pathways**: By enabling users to select different treatment pathways (comprising both pharmacologic and nonpharmacologic treatments), the model can provide insights on treatment pathways that may be of lower value, as measured by higher costs and lower projected effectiveness.

5 Model Protocol Development Process

In developing this draft protocol, we first finalized the model scope based on the aggregated public comments and feedback from the MDD model advisory group. Based on the finalized model scope, a targeted literature review was conducted to identify key model inputs and evidence gaps. Findings from these intermediate steps informed the development of the draft protocol.

5.1 Finalized Model Scope

The finalized model scope (summarized in Table 1) guided the development of the draft protocol and was developed based on: (1) review of existing economic models focusing on MDD (Appendix A), (2) feedback from our continual advisory group engagement,[12] (3) synthesis of public comments,[11] received during the draft scope public comment period, and (4) feedback from the advisory group on how to prioritize responses to public comments.

Table 1. MDD Model Scope: Overview of Proposed Model Elements

Model Element	Description
Primary objective	Develop an economic model to assess the value of interventions used in the treatment of major depressive disorder (MDD)
Population	People newly diagnosed with MDD (age 18 to 64 years) without other major psychiatric or chronic conditions (i.e., with no diagnosis of anxiety, bipolar disorder, schizophrenia, substance abuse disorder, cancer, cardiovascular disease, multiple sclerosis, or Parkinson's disease)
Interventions	Treatment options: • No treatment • Pharmacologic therapies, categorized by drug class and individual therapies • Psychotherapy (including behavioral therapy, CBT, MBCT, IPT, psychodynamic therapies, supportive therapies) • Somatic therapies (ECT, TMS, VNS, DBS) • Combination therapies (e.g., CBT plus SSRI) • Additional treatments or enhancements (e.g., digital therapeutics) implemented with a placeholder for impact on efficacy and costs Treatment sequencing: Individuals can receive up to four lines of treatment during the simulation. Available treatment options may vary by line of therapy to reflect real-world clinical practice.
General model structure	Individual-level simulation
Included attributes	• Age • Sex • Ethnicity/Race • Socioeconomic status

Model Element	Description
Costs	• Direct medical costs, including pharmacy and medical • Direct non-medical costs • Productivity costs • Caregiver costs
Outcomes	• Life years • Quality-adjusted life years • Response • Duration of response • Relapse • Suicide attempts and deaths • Psychiatric hospitalizations
Perspectives	• Payer (private/commercial and government) • Societal • Employer • People with MDD

5.2 Targeted Literature Review

Based on the finalized model scope, a targeted literature review (TLR) was conducted to identify existing evidence gaps and guide the model design. Given the wide range of treatment options specified in the model scope and constraints on the evidence and resources available, the first model specification will prioritize treatment sequences and value elements with high-quality evidence, but also include structural placeholders that will support the extension of the model in subsequent versions.

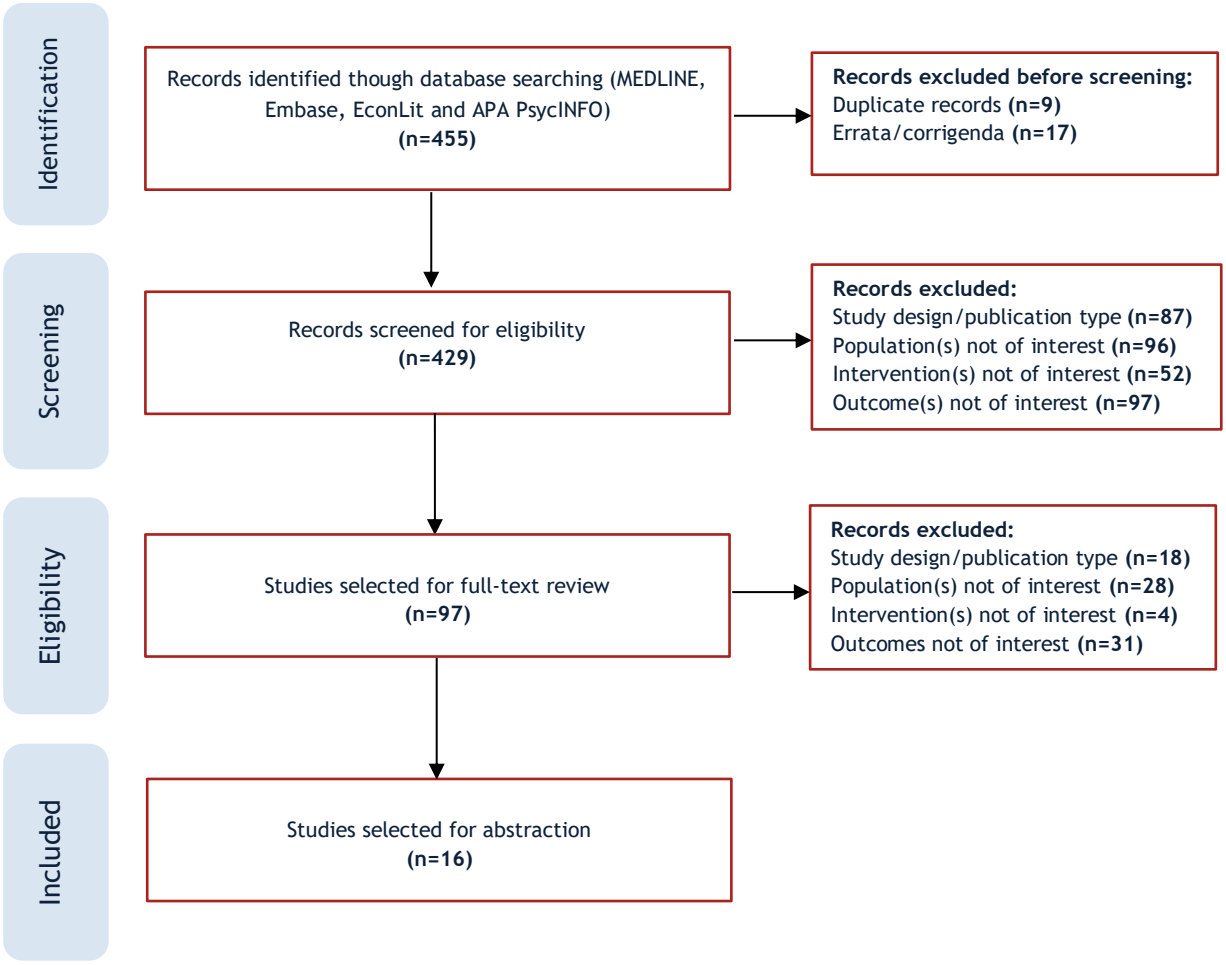
The literature search was conducted in MEDLINE, Embase, EconLit and APA PsycINFO databases to identify meta-analyses investigating safety, efficacy, productivity, health care resource utilization (HCRU), costs, utilities, and patient-centered outcomes in individuals with MDD. The full list of search terms for identification of relevant studies is provided in Appendix B. After initial application of the search strategy, we further limited the search criteria to focus on publications in 2018 and after. As our model follows individuals with MDD over a lifetime horizon and some individuals might develop treatment-resistant depression over time, our search included articles for both general MDD and treatment-resistant populations.

The search strategy identified a total of 455 records. The record review process is depicted in Figure 1. After exclusion of duplicates and errata, 429 records were screened by title and abstract for eligibility. Studies were reviewed and excluded if they did not meet the inclusion criteria (e.g., were commentaries or did not meet PICO criteria). Studies were not excluded based on design (intervention versus observational) or comparators (active versus placebo).

This process was independently completed by two researchers. Reasons for exclusion were tracked and recorded based on the first of the reasons that was identified. The first 10% of records were

reviewed by both researchers to coordinate review. Lack of agreement was resolved through discussion. The remaining records were assigned, with approximately 20% of records being reviewed by both. Following the title and abstract review phase, 97 articles were identified for full-text review. Lack of agreement for those records reviewed by both reviewers was again resolved through discussion. Reasons for exclusion at this phase were also tracked and recorded. Of the 455 records identified, after two rounds of review, 16 studies were eligible for abstraction.

Figure 1. PRISMA Flowchart



The following information was extracted from the included studies when provided: author, publication year, population (i.e., MDD, TRD, or both), number of studies included in the meta-analysis, age, meta-analysis sample size across included studies, interventions and comparators, treatment dose range (where provided), treatment duration range and assessment time points, primary outcome measure(s) and definitions (i.e., response and remission), instruments used to measure outcomes, and estimated effect sizes (i.e., odds ratio (OR), risk ratio (RR) and respective confidence intervals (CIs)).

An overview of key characteristics of the studies identified in the TLR is provided in Table 2. Most studies investigated treatment efficacy, mainly reporting response and remission as the primary outcome measures. Among the 16 included studies, 9 reported response, 10 reported remission, and 3 reported on risk of relapse. Response was defined as a ≥50% reduction in the severity of depression measured by MADRS/HDRS, a 50% reduction in depressive symptomatology according to a standardized rating scale and achieving a CGI-I rating of "1" or "2" post-baseline, across studies. Additionally, remission was defined across studies as a ≥50% reduction from baseline in the depression rating scale, a MADRS score of ≤9 or ≤10, a HDRS-17 score of ≤7 or <8, or an HDRS-24

score of ≤ 10 or ≤7. Rather than reporting absolute response rates, meta-analyses reported a variety of metrics, including risk ratios, risk differences, or effect sizes reporting the comparative effect size of intervention against comparator, thereby limiting the use of these values to populate transition rates in the model. Thus, alternatives to findings from the meta-analyses will be needed for the model inputs. Specific needs are discussed below.

Safety outcomes were reported in 2 articles but were limited to discontinuations or dropouts due to an adverse event (AE). AEs can be challenging to source from meta-analyses, as the studies contributing to each meta-analysis often have different definitions and thresholds for reporting AEs and may aggregate events differently (e.g., what one study reports as a serious adverse event may not be categorized as serious in another study). Because of this inconsistency in study design and reporting, we plan to derive these inputs from other sources, such as FDA prescribing labels, as detailed in Table 7 below.

Table 2. Study Characteristics

Study	Population(s)	Included studies, N	Intervention	Comparator	Sample size across studies	Mean ages across studies	Primary outcome, definition	Measurement scale(s)
Cuijpers 2020 [13]	Both MDD and TRD	101	Psychotherapy [a], Pharmacotherapy [b], Placebo	NA	11,910	NA	**Remission:** number of patients with a score for depressive symptoms below a specific cut-off on a validated rating scale **Response:** 50% reduction in depressive symptomatology according to a standardized rating scale	N/A
Gellersen 2018 [14]	TRD	11	dTMS	NA	282	41 - 54	**Remission:** HDRS≤7 for HDRS-17 and HDRS≤10 for any other version of HDRS **Response:** ≥50% reduction in HDRS scores at the end of daily stimulation phase relative to baseline	HDRS
Gellersen 2019 [15]	TRD	19	dTMS, rTMS	NA	368	39 - 54	**Remission:** HDRS≤7 for HDRS-17 and HDRS≤10 for any other version of HDRS **Response:** ≥50% reduction in HDRS score from baseline	HDRS
Guidi 2021 [16]	MDD	17	CBT/modifications [c]	TAU	2,283	34.8 - 51.7	**Relapse/recurrence:** Reaching a cutoff on any validated rating scale for depression and/or the occurrence of a defined major depressive episode after remission/ recovery	N/A

Study	Population(s)	Included studies, N	Intervention	Comparator	Sample size across studies	Mean ages across studies	Primary outcome, definition	Measurement scale(s)
He 2018 [17]	MDD	22	Vortioxetine, Levomilnacipran, Vilazodone	Placebo	N/A	39.9 - 46.75	**Remission:** MADRS total score ≤10, total score of HAMD-24 ≤7 **Response:** ≥50% reduction in baseline total score of MADRS or HAM-D	MADRS, HAM-D
Hung 2020 [18]	TRD	15	dTMS	Sham, Pre-post treatment	701	40.8 - 65.4	**Remission:** HDRS-17 score of ≤7, or HDRS- 24 score of ≤10 **Response:** ≥50% improvement from baseline according to the study primary depression scale	HDRS
Iovieno 2021 [19]	MDD	17	Vortioxetine (5-20 mg)	Placebo	7,269	N/A	**Response:** N/A **Remission:** N/A	MADRS
Kato 2021 [20]	MDD	40	ADT	Placebo	8,890		**Risk of relapse**, N/A **Dropout due to AEs:** risk of discontinuation due to AE of treatment	CGI-I, HAM-D, MADRS
Li 2018 [21]	TRD	6	CBT, MBCT, RFCBT, Smartphone CBT	TAU, psychoeducation, HEP, medication change	847	39.5 - 50.9	**Remission:** N/A **Response:** N/A	HRDS-17, BDI-II, PHQ-9, HAMD-21
Luan 2018 [22]	TRD	8	Aripiprazole (dose range 2-20 mg/day)	Placebo, Mirtazapine, Mirtazapine + Aripiprazole	2,260	35.15 - 66.4	**Remission:** N/A **Response:** N/A	CGI-I, CGI-S, MADRS, HAMD-17, SDS, IDS-SR
Seshadri 2021 [23]	MDD	4	Aripiprazole (5mg/d - 10mg/d) *augmentation adjunctive to other ADs*	Bupropion augmentation	2,632	38.8 - 54.2	**Remission:** N/A	HDRS, MADRS
van Bronswijk 2019 [24]	TRD	3	Psychotherapy	TAU	293	N/A	**Depression severity change:** N/A	HAM-D, MADRS, BDI-II, IDS

Study	Population(s)	Included studies, N	Intervention	Comparator	Sample size across studies	Mean ages across studies	Primary outcome, definition	Measurement scale(s)
van Bronswijk 2019 [24]	TRD	20	Add-on psychotherapy	TAU	3,539	N/A	**Depression severity change:** N/A	HAM-D, MADRS, BDI-II, IDS
Wang 2019 [25]	MDD	9	tDCS	Sham tDCS, Sham tDCS + ECT, placebo	632	25.5 - 50	Effectiveness of tDCS in improving MADRS and HDRS-17 score compared to control	HDRS-17, MADRS
Zhang 2018 [26]	MDD	20	CBT, MBCT	TAU, wait-list, placebo, maintenance ADT	1,945	43.3- 74	Risk of depression relapse	MADRS, HRSD, DSM-IV/III-R, SCID
Zhang 2020 [27]	TRD	3	VNS + TAU	Sham VNS + TAU, TAU	1,048	46.5 - 50.1	**Response, N/A**	HAM-D, MADRS
Zhou 2018 [28]	TRD	14	DBS	NA	162	40.8 - 55.5	**Remission:** HDRS-17 score <8, HDRS-28 score <10, or a >75% reduction in MADRS **Response:** 50% reduction in the severity of depression as measured by MADRS or HDRS	HDRS, MADRS

AD, antidepressant; ADT: Antidepressant therapy; AE, Adverse event; BDI-II, Beck Depression Inventory-II; BSP, Brief supportive psychotherapy; CBASP, Cognitive behavioral-analysis system of psychotherapy; CBT, Cognitive Behavioral Therapy; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-severity; DBTST, Dialectic Behavior Therapy Skills Training; DBS, deep brain stimulation; DSM-IV/ DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders; dTMS, Deep transcranial magnetic stimulation; ECT, Electroconvulsive Therapy; GBOPT, Group body oriented psychological therapy; HDRS/HAMD, Hamilton Depression Rating Scale; HEP, Health-Enhancement Program; IDS-SR, Inventory of depressive symptomology self-report scare; IPT, Interpersonal therapy; MADRS, Montgomery-Asberg Depression Rating Scale; MBCT; Mindfulness-based cognitive therapy; MDD, major depressive disorder; N/A, not applicable; PHQ-9, Patient Health Questionnaire-9; RFBT: Rumination Focused Cognitive Behavioral Therapy; rTMS, repetitive transcranial magnetic stimulation; SCID, Structured Clinical Interview for DSM Disorders; SDS, Sheehan disability scale; SSRI, Selective serotonin reuptake inhibitor, SNRI, Serotonin–norepinephrine reuptake inhibitor; TAU, treatment as usual; TCA, Tricyclic antidepressants; tDCS, transcranial direct current stimulation; TRD, treatment-resistant depression; Tx, treatment; VNS, Vagus nerve stimulation

[a] CBT, Individual, group/mixed; [b] SSRI, TCA, other; [c] Preventive cognitive therapy, CBT of residual symptoms, well-being therapy, MBCT; [d] CBT, CBASP, IPT, DBTST, BSP, MBCT, IRCBT, PBCT, GBOP

Results of the literature review are summarized in Table 3, grouped by diagnosis, treatment type and outcome measure used.

Table 3. Study Abstraction

	Population	Treatment	No. of studies	Remission	Response	Risk of relapse	Discontinuation/ dropout due to AE	Study
Pharmacotherapy (by drug class)	MDD	SSRI	3	x	x		x (He 2018, Kato 2021)	He 2018 [17], Iovieno 2021 [19], Kato 2021 [20]
		SNRI	1	x	x		x	He 2018 [17]
	Both (MDD, TRD)	SSRI	1	x	x			Cujipers 2020 [13]
		TCA	1	x	x			Cujipers 2020 [13]
Somatic therapies	TRD	VNS	1		x			Zhang 2020 [27]
		rTMS/ dTMS	1	x	x			Gellersen 2019[a] [15]
		dTMS	2	x	x			Gellersen 2018[b] [29], Hung 2020 [18]
		DBS	1	x	x			Zhou 2018 [28]
		tDCS	1					Wang 2018[c] [25]
Psychotherapy	TRD	CBT	3	x	x	x (Zhang 2018)		Li 2018 [21], van Bronswijk 2019[e24] , Zhang 2018 [26]
		MBCT	3	x	x	x (Zhang 2018)		Li 2018 [21], van Bronswijk 2019[d 24] , Zhang 2018 [26]
	MDD	CBT	1	x	x	x		Guidi 2021 [16]
	Both (MDD, TRD)	CBT	1	x	x			Cujipers 2020 [13]
		MBCT	1	x	x			
		BAT	1	x	x			
		PST	1	x	x			
		IPT	2	x	x			Cujipers 2020 [13], van Bronswijk 2019[e 24]

Psychotherapy + ADT	Both (MDD, TRD)	Combination therapy	1	x	x	Cujipers 2020 [13]
Antipsychotics	TRD	Aripiprazole	1	x	x	Luan 2018 [22]
	MDD	Aripiprazole	1	x	x	Seshadri 2021 [23]

[a] Results reported after 10 daily sessions; [b] Results reported after 20 daily sessions; [c] Reports effectiveness in improving MADS/HDRS score; [d] Reports change in depression severity.
ADT: Antidepressant therapy; BAT, Behavioral activation therapy; CBT, Cognitive behavioral therapy; DBS, Deep brain stimulation; dTMS, Deep transcranial magnetic stimulation; IPT, Interpersonal therapy; MBCT; Mindfulness-based cognitive therapy; MDD, Major depressive disorder; PST, Problem solving therapy; rTMS, Repetitive transcranial magnetic stimulation SSRI, Selective serotonin reuptake inhibitor, SNRI, Serotonin–norepinephrine reuptake inhibitor; TCA, Tricyclic antidepressants; tDCS, Transcranial direct current stimulation; TRD, Treatment-resistant depression; VNS, Vagus nerve stimulation.

In drafting this protocol, some additional targeted searches were conducted in cases where insufficient data were identified in the review of meta-analyses to populate the model. This process included first reviewing records that were identified in the initial TLR but were excluded, typically because they were systematic reviews rather than meta-analyses. In the absence of an alternative sources from the TLR, we conducted additional literature searches and consulted experts from the advisory group to make assumptions consistent with real-world clinical practice.

The list below describes some key decisions and assumptions made to simplify and/or to recognize data challenges:

- High priority was given to meta-analyses that describe classes of medications rather than individual medications.
- Due to limited evidence in the literature on effectiveness based on prior treatment history, the effectiveness of a second-line treatment does not vary based on what was provided for first-line therapy, and is assumed to be the same as its effectiveness as first-line therapy. A hazard ratio approach, allowing users to decrement effectiveness by a specified proportion, is a potential alternative to using the same effectiveness for second- as for first-line therapy.
- Effectiveness for first- and second-line treatments was derived from meta-analyses that included patients that were not considered treatment-resistant.
- Effectiveness rates for third- and fourth-line treatments were approximated by meta-analyses of patients identified as difficult to treat or having treatment-resistant depression (TRD). Although the definition of TRD is not universally accepted, it generally refers to patients who have failed two or more trials of different interventions of adequate dosage and duration [30].
- Data gaps were recognized in two ways. Placeholders are used throughout the model to reflect parameters for which there are not suitable data. In addition, we have included a section on limitations and challenges (Section 8) to describe data gaps and concerns about the generalizability of published meta-analyses for the model.

6 Model Specification

The model specifications described in the protocol are developed based on: (1) feedback from the multi-stakeholder advisory group, (2) feedback received during the model draft scope public comment period, and (3) the TLR (described in Section 5.2).

6.1 Target Population

The initial version of the model will focus on treatment-naïve adults, 18 to 64 years in age, diagnosed with MDD by a healthcare provider (e.g., primary care provider, psychologist, psychiatrist) without diagnoses of other psychiatric and non-psychiatric chronic comorbidities (e.g., anxiety, bipolar disorder, schizophrenia, substance abuse disorder, cancer, cardiovascular disease, multiple sclerosis, Parkinson's disease). Individuals who have depressive symptoms but not an MDD diagnosis are not considered in the model (and were excluded from the literature review, as the meta-analyses included patients with diagnosed MDD). Individuals without a diagnosis would not clearly be eligible for the treatments included in the model.

The population characteristics in aggregate will reflect findings from recent analyses of the National Survey on Drug Use and Health [31], which records self-reported experience with depression in the previous year by sex, race/ethnicity and income. The baseline population will reflect the following key characteristics from the National Survey on Drug Use and Health analysis:

- Sex: approximately two-thirds female, one-third male [31]
- Race/ethnicity: reflect US population with MDD [31]
- Income level: prevalence four times higher among adults with income less than 100% of the federal poverty level (FPL) compared to adults with family income 400% or more above the FPL (however, it is not known how other demographic characteristics interact with income and whether the relationship between income and prevalence is linear)

Sources for other baseline characteristics include:

- Age: distribution available from Greenberg et al 2018 [32]
- Education: education level of individuals with depression may be lower than the general population, but no US-based source was identified

Severity level of depression at presentation may also be included in the model, as choice of initial therapy could vary by severity level [3, 6, 7]. No relevant data were identified in the meta-analysis to inform initial severity estimates.

We acknowledge that the exclusion of individuals with other comorbid conditions (e.g., anxiety, bipolar disorder, schizophrenia, substance abuse disorder, cancer, cardiovascular disease, multiple sclerosis, Parkinson's disease), in the initial version of the model might not capture the experiences of a significant portion of people with MDD in the real world, as MDD is a prevalent comorbid condition with other types of psychiatric and non-psychiatric chronic diseases. However, the

framework of the model is designed to support expansion to other segments of the MDD population, including those with other psychiatric and nonpsychiatric comorbid conditions. In future extensions of the model, IVI intends to explore the feasibility of building additional modules for the following populations:

- Those aged 65 and older
- Those who are Medicaid-insured

6.1.1 Subgroup Analyses

The model will provide flexibility to evaluate key 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 (i.e., TRD)

However, it should be noted that our TLR did not specifically search for, nor did it identify any, reports differentiating effectiveness and cost by the key characteristics above, although there are some studies that explore subgroup differences with selected treatments.[33]

6.2 Setting and Location

The model will enable evaluation of treatment sequences in a range of care settings including primary care, specialty care (e.g., psychiatrist), and telehealth.

Based on feedback from the advisory group and our preliminary TLR, the treatment setting can influence the following specifications in the model:

- Treatments prescribed, particularly the use of non-pharmacologic treatments
- Cost inputs
- Demographic characteristics
- Effectiveness (e.g., due to differences in adherence)

6.3 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 [34]. 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[1] employer purchasers
- Fully insured[2] employers
- People with MDD

The specific cost inputs associated with each stakeholder perspective are described in Appendix F. Sources for each type of costs data are further described in Section 7 of the protocol.

6.4 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 (Appendix G) and explore clinical and economic outcomes associated with different treatment sequences. The model comparators include the following, modeled at the Treatment Group/Class level:

Table 4. Modeled Comparators

Treatment Group/Class	Examples of Specific Therapies
Drug class	
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
Atypical antidepressants	bupropion, esketamine, ketamine, mirtazapine
Psychotherapy	cognitive behavioral therapy, interpersonal therapy, problem-solving therapy, psychodynamic therapy, supportive therapy

[1] 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.

[2] 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.

Treatment Group/Class	Examples of Specific Therapies
Somatic therapy	deep brain stimulation (DBS), electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), vagus nerve stimulation (VNS)
Digital therapeutics	prescription digital therapy, non-prescribed digital applications
Combination therapy	pharmacotherapy + psychotherapy, pharmacotherapy + psychotherapy + somatic therapy
No active treatment	standard health care with no specific treatment for MDD

In addition, placeholders will also be included to enable users to model novel treatment options or augmentation strategies/therapies, for which there are insufficient data currently. These placeholders will be designed such that the user can enter specific values for key inputs that is likely to impact the key model outcomes (e.g., efficacy, safety, costs) or specify that the intervention is a specified percentage than a comparator. Inputs for each intervention are detailed in Section 7 below. Examples of augmentation strategies include:

- Combination of two MDD pharmacotherapy treatments[3] (e.g., bupropion and SSRI)
- MDD pharmacotherapy augmented by antipsychotics
- MDD pharmacotherapy augmented by lithium

Augmentation would not be treated as a new line of therapy. To limit the complexity and data requirements for the model, it will be assumed that there can only be one augmentation strategy implemented during a model cycle.

Up to four lines of treatments will be considered in the model (further discussed in Section **6.9.3**).

6.5 Time Horizon

The model horizon is lifetime, with an option to output results at other user-defined time intervals (minimum one year).

The horizon was requested during the model scoping phase. It should be noted, however, that few of the models reviewed in the scoping phase had a duration longer than 2-5 years and that there

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

are limited data on long-term experience in individuals with MDD. There may be substantial uncertainty in results when modeling longer periods. This is discussed in more detail in Section 6.9.2.1.

6.6 Cycle Length

The cycle length is specified to be 3 months in the model based on two key considerations: (1) clinical guidelines, while acknowledging heterogeneity in individual treatment needs, generally recommend 8-12 weeks of treatment and observation period before assessing responses to treatments [2, 3, 7]; (2) the cycle length is also consistent with the efficacy inputs identified in the TLR, which were typically presented in three-month time intervals.

6.7 Discounting

Per best practice in the US [34], costs and benefits will be discounted at 3% per annum. Alternative values can be entered by the user and can be used for sensitivity analysis. Users will be able to specify different rates for costs and benefits.

6.8 Model Outputs

The following outcomes will be tracked and counted to enable reporting and comparison across treatment sequences:

- Number of responses/remissions/relapses/recurrences
- Duration of response (number of cycles/months in response health state)
- Number of MDD-related hospitalizations
- Number of all-cause hospitalizations
- Number of suicide attempts and suicides avoided*

- Life years *(See below. This may be a more meaningful metric if suicide is included in the model.)*
- Quality-adjusted life years (QALYs)

- Costs (by specific category, such as MDD treatment, outpatient, inpatient, indirect, and total)
- Cost per clinical outcome (e.g., cost per response, cost per remission)
- Cost per QALY

Note that the number of suicide attempts and suicides avoided was identified by the advisory group as of interest. However, during the literature search, we were unable to find relevant data in meta-analyses. Also, increased suicide may be associated with certain interventions, although ideally this would be minimized through thoughtful prescribing and monitoring. Should suicide attempts and suicides be added to the model, there would need to be two counters with the depression-related and treatment-related events tracked separately.

6.9 Model Structure

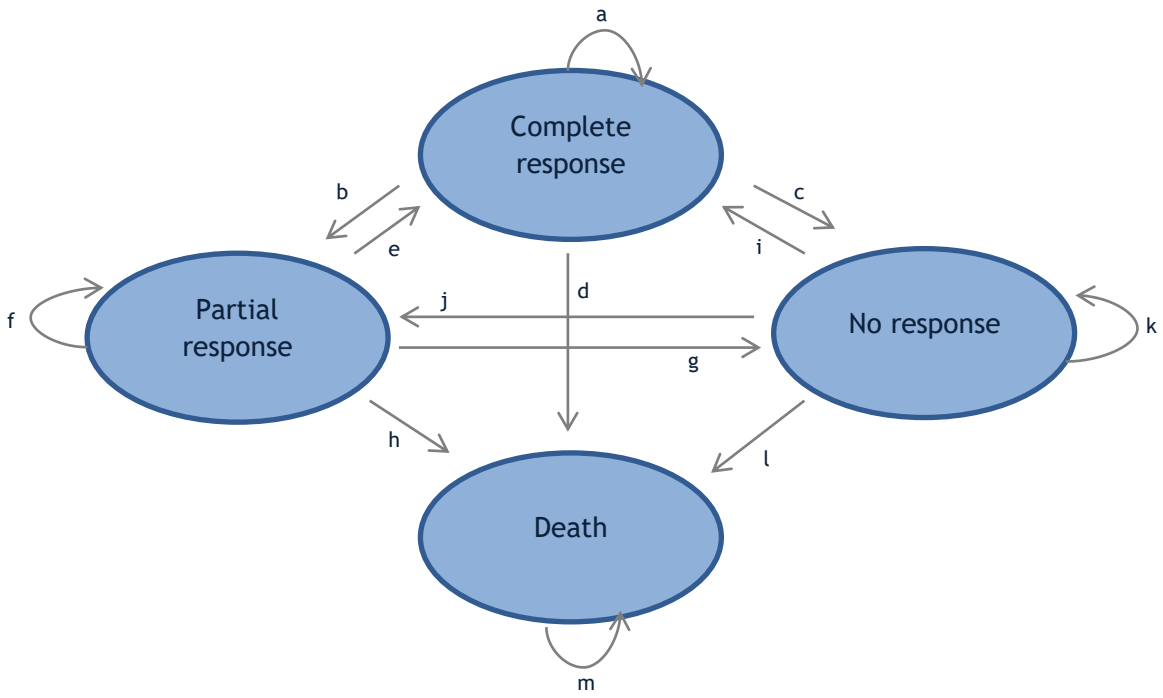
Consistent with the prior OSVP models and based on the key modeling objectives, an individual-level simulation approach has been selected for this model. A microsimulation with a state-transition approach balances the need to address heterogeneity in the population, incorporates the important role of the individual's history in the disease course [35].

This approach was chosen based on at least the following three considerations: (1) it can model the heterogeneous experiences of people living with MDD in terms of key clinical and economic outcomes along the treatment experience, which might vary depending on the key clinical and sociodemographic characteristics of people with MDD; (2) end users of the model (e.g., payers or employers) who are interested in modeling a population that matches theirs (either beneficiaries or employees) may also wish to reflect their population closely (e.g., through re-weighing); (3) it will also allow for the flexibility to model the differential impacts of a specific health intervention or policy on different subgroups and associated health disparities.

The state-transition approach allows the model to leverage what is already known about health states in depression as well as recognize some amount of individual history. Specifically, long-term sustained response (i.e., remission) would typically be associated with a maintenance dose of pharmacotherapy or reduced frequency of psychotherapy session; tracking individual history allows for this to be reflected in model inputs (where data permit). This is also consistent with the approaches used in existing published economic models (Appendix A).

The use of a small number of health states simplifies the model and reflects the practical challenge of having limited data available to populate the key model inputs. It also reflects the structure used by many of the models reviewed during research.

Figure 2. Model Schematic



Each arrow indicates a potential transition in the model. Individuals can move from one health state to another, or they can remain in the same health state for subsequent cycles.

6.9.1 Health States

6.9.2 Health State Descriptions and Parameterization

Following treatment initiation (or no active treatment), individuals in the simulation could be in one of the four possible health states depending on their response to the treatment (Table 5). These states are mutually exclusive, and any individual can only be in one of the states at any time during the simulation. The specifications of the health states are developed based on clinical guidelines, advisory group input, and (by design) the meta-analyses reviewed for this protocol development all described meeting certain clinical thresholds.

The individual studies that were included in the reviewed meta-analyses established a criterion for measuring response to treatment, often using the Hamilton Depression Rating Scale, the Montgomery-Asberg Rating Scale, or the General Health Questionnaire. Table 2 provides details of how responses were categorized for each reviewed study. There is no consensus on the score or change score that reflects improvement or response; therefore, we propose that the model use these health states that were commonly found in previous models and our scoping review, but that there does not need to be direct linkage to a score on a clinical measure. This would permit broader usability of the model and also recognize that the likelihood of being able to populate effectiveness

data for multiple instruments (and multiple versions of some instruments) with several thresholds for change is low.

Each health state will be associated with different clinical and economic benefits/costs, including a measure of patient-centered effectiveness (utility value) and costs (both direct and indirect, as detailed below).

Tracking individual medical history will allow sustained states of complete response to be treated as remission (and thus allow for reduction to maintenance dosing as appropriate) and to recognize when a lack of response should be considered a need to switch treatments versus a recurrence or relapse after a prior response. More detail appears below.

The "no response" health state represents either an ineffective treatment (in which the individual/health state is assigned medical and non-medical cost but no benefit) or the lack of treatment (in which case the individual/health state is assigned non-medical cost and no benefit). Individuals who receive no active treatment are assumed to remain in the "no response" state. It can reflect someone not receiving treatment as well as someone who has received treatment that was completely or partly effective but then failed to generate a response (i.e., recurrence or relapse).

The health states specified also consider state transitions (Section 6.9.2.1) across multiple cycles. Subsequent cycles in the complete response (CR) health state are treated as the same as the CR state but defined as remission. After remission, a transition to no response (NR) is termed recurrence. After a single cycle of CR, a transition to NR is termed relapse. Relapse and recurrence are treated the same as a NR cycle. Cycles in each health state are counted; entering remission, relapse, or recurrence are also counted as specific events.

Specific benefits and costs assigned may be dependent on both the health state and the treatment received.

Table 5. Health State Overview

Health State	General Description	Benefits and Costs
Complete response (CR)	Return to usual functioning and/or absence or near absence of symptoms. Operationalized in reviewed studies as meeting a specific score (e.g., a score of 7 or less on the Hamilton Depression Rating Scale)	Effectiveness, medical and non-medical costs

Health State	General Description	Benefits and Costs
Partial response (PR)	Reduction in symptomatology insufficient to meet definition of responder. Often operationalized in reviewed studies as >50% reduction in score on a validated clinical instrument	Effectiveness, medical and non-medical costs
No response (NR) / no treatment (NT)	Not meeting either definition for complete or partial responder	No response: Medical and non-medical costs No treatment: Medical costs (exclusive of treatment costs, which would not be incurred) and non-medical costs
Death	N/A – Absorbing state	None

6.9.2.1 Health State Transitions

Individuals can transition from any one health state to another, in that they can have a cycle with a complete response and then have a subsequent cycle with only a partial response or no response; similarly, they can begin treatment and the first cycle may yield only a partial response but then their response can improve to a complete response in the next cycle. The only exception is death, which is an absorbing state. Transition probabilities for each possible transition are needed. Probabilities are defined for each possible transition; there will be a distribution around each value; the specification of the distribution is not yet defined.

A sample transition matrix is shown in Section 7.1.1.

6.9.3 Treatment Sequences

An important feature in the model is the ability for the user to specify treatment sequences, that is, to specify the treatments and the order of treatments available to an individual in the model (for a maximum of four treatments during the model horizon) as well as determining when an individual should transition from one treatment to the next. Each of these presents questions that must be addressed before finalizing the model protocol.

The model will assume that treatments have similar effectiveness when offered as first- or second-line therapy, and when offered as third- or fourth-line therapy but that treatments may be less effective as third- or fourth-line therapy compared to first- or second-line therapy. At this stage, we have made the simplifying assumptions that somatic therapies will not be used as first- or second-line therapies; input from the advisory group and public may alter this assumption.

6.9.3.1 Moving to a New Line of Therapy

While in complete response, it is assumed that individuals will continue with the existing treatment(s). In partial response, it is assumed that individuals may continue with the existing treatment, with or without augmentation, or they may switch to a different therapy. The proportion of individuals who would continue with the existing treatment(s) or switch will need to be determined; this may vary by type or line of therapy. In the no response state, it is assumed that individuals would switch to a new line of treatment (unless this is their fourth line of treatment).

The model will require specification of the number of cycles in each health state (section 6.9.1) that would direct the user to the following treatment sequence. We propose the following assumptions be considered:

- The third consecutive cycle of complete response be considered "remission." Upon reaching remission, the individual's treatment (if it includes pharmacotherapy or psychotherapy) be reduced to a maintenance dose or to no treatment.
- Individuals who have two consecutive cycles of partial response will be moved to a new therapy for the following cycle, with the rationale being that they are interested in receiving treatment and would be willing to start a new treatment.
- Individuals who have two consecutive cycles of no response can be moved to another treatment or can be treated as having discontinued. There are insufficient data from the meta-analyses to determine how to apportion individuals among these options. This health state will have the same utilities assigned, but the proportion of individuals who are assumed to have discontinued will not have treatment costs assigned to them.

6.9.3.2 Inputs Depending on Sequence

The cost of an intervention would not depend on where it falls during the treatment sequence, and while there may be some anecdotal concern that individuals who have longer duration of MDD have different utilities, it is planned to use the same utility values throughout a model (with discounting as appropriate). However, clinical inputs may vary depending on prior treatment experience.

Given challenges in identifying evidence to support different effectiveness inputs for the same treatment based on its placement in a treatment sequence, the model uses effectiveness inputs for general MDD patients to represent first- and second-line therapies and for treatment-resistant/difficult-to-treat patients to represent third- and fourth-line therapies. In cases when there are insufficient data, a hazard ratio can be applied as a crosswalk between first- and second-line and third-and fourth-line therapies, in which the response associated with later line therapies is decremented.

Clinical stakeholders will be consulted for input when assumptions may be required or to confirm whether treatments are of interest. In the absence of data, the application of a hazard rate approach, that is, to assign a proportionally different effectiveness rate in later lines of therapy, may be used.

6.9.3.3 Novel Sequencing Options

While some treatments that are typically offered throughout the treatment experience for MDD can be addressed by applying a hazard ratio, this approach is likely not adequate for all treatments, particularly those for which data are just beginning to emerge on effectiveness when used earlier in the treatment experience. Based on usage patterns when the research included in these meta-analyses was conducted, there were not data on all treatments of interest, some of which may be offered in individuals with different clinical profiles or generate different responses when used early versus late in therapy. For example, there is new interest in offering ECT for individuals with MDD who present with severe symptoms at the time of diagnosis. Their outcomes may be different than for individuals who receive ECT only after multiple previous unsuccessful treatments and simply applying a hazard ratio may be inappropriate.

In addition, there may be some treatment options that should not be available for users to select for a first-line therapy, such as using an antipsychotic as adjunctive therapy.

We recognize that there are multiple interventions or combinations of interest that may, at this time, be offered only to individuals who have certain previous experience but, as with using somatic treatments as first-line therapy, may become more common during the time this model will be used.

We ask for public comment as to whether somatic therapies should be limited to third- and fourth-line therapy and/or how to adjust clinical inputs appropriately for their earlier use.

6.10 Programming/Software

The final decision about the software used to program this structure and the model described herein will be made with consideration to processing speed, usability, and the ability to implement the features of interest in a modular fashion. Several options have been considered.

- Health Economic Evaluation MODeling (heemod) is robust but limited to Markov modeling and cannot be used for patient-level simulations.
- Discretely Integrated Condition Event (DICE) simulation is open source but has a limited user base and support network for troubleshooting and examples.
- R and its Health Economic Simulation Modeling and Decision Analysis (hesim) modeling package can be used to implement microsimulation and will be comfortable for R users but is challenging from an efficiency standpoint.

7 Model Inputs

This section describes our approaches to obtaining key model inputs. As the target population (age 18-64) is more likely to be commercially insured than have government-sponsored insurance [36], the input values included in the tables in this section reflect those for the commercially insured population. However, wherever applicable, we describe our approaches to deriving input values for individuals covered by government-sponsored insurance.

7.1 Clinical Inputs

7.1.1 Efficacy

For each modeled intervention, there will need to be a likelihood of transition to each other health state (with the exception of death, which is an absorbing state). These transitions will be applied to each 3-month cycle through the observed period. The inputs to the model will include the following for each intervention, and theoretically, could include differential response/transition rates by sociodemographic characteristics as well as based on medical history. Based on the limited available data, particularly following the initial response, we propose a set of point estimates and distributions but request input from stakeholders to populate the matrices.

Table 6. Transition Matrix Template Overview

Event	Subsequent Health State			
Initial Health State	**Complete Response**	**Partial Response**	**No Response/ No treatment**	**Death**
Complete Response	X	X	X	X*
Partial Response	X	X	X	X*
No Response / No Treatment	X	X	X	X*
Death	X	X	X	N/A (probability = 1.0)

* Probabilities based on age-adjusted general population mortality data, adjusted to reflect MDD or TRD diagnosis

7.1.2 Safety

Adverse events can be operationalized in the model as rates (and counted), as a decrement to patient-centered outcomes (i.e., utilities), and as a cost in the model. Across the range of

pharmacologic and nonpharmacologic treatment options considered in the model, there is a wide variety of AEs documented in the literature (e.g., pivotal trial results) and in prescribing information.

While our model does not explicitly model the treatment selection process, it should be noted that some of these adverse side effects may influence an individual's willingness to initiate a treatment as well as adherence with treatment once started. Side effects such as weight gain could, in theory, lead to the development of other conditions (e.g., obesity, cardiovascular events) that would complicate the attribution of events to AEs of treatment.

In the TLR, the only safety events reported were all-cause death and discontinuation due to AEs. This is likely due to the different definitions and reporting methods across studies. We intend to conduct targeted literature reviews and review the prescribing information to identify AEs associated with specific drug classes. Placeholders can be included in the model to enable users to add additional types of AEs associated with different treatment strategies, to reflect the rates of AE for each intervention or intervention type, a temporary decrement in utilities associated with each AE, and a cost associated with treatment treating the AEs.

Table 7 below lists some examples of AEs we might consider for the model. There is a wide variety of side effects documented in the literature and in prescribing information although reports are limited in the meta-analyses reviewed. As a result, the current phase of this effort did not yield class-specific adverse events. We propose future iterations conduct a targeted literature search to identify other study types reporting class-specific AEs. A retrospective claims data analysis conducted by Nguyen and colleagues evaluates the incidence and economic impact of serotonin syndrome among patients receiving serotonergic drugs for AE rates and related costs among patients treated with SNRIs and SSRIs [37] (Table 7) is an example of such a study. Placeholders will be set up in the model to enable users to model additional AEs of interest. Other studies shown in Table 7 can be used to apply incidence and cost for other AEs.

Table 7. Adverse Events

Event	Interventions	Incidence	Cost
Serotonin syndrome	SSRI/SNRI	0.09%	Median: $10,792 [37]
Seizures/extrapyramidal symptoms	SSRI/TCA	2-30%, depending on duration of treatment [38]	Lifetime costs: ~$180,000-190,000 [39]
Hyponatremia	SSRI/TCA / venlafaxine	0.06%-70%, depending on agent [40]	$263-$3,441 per patient, depending on treatment setting [41]
TBD	*TBD*	*TBD*	*TBD*

7.1.3 Mortality

Long-term mortality was not reported in any of the papers reviewed in the TLR. A targeted search for relevant data provided an alternative approach: data from the National Vital Statistics System mortality data (see https://www.cdc.gov/nchs/nvss/mortality/gmwk23r.htm for a link to sample data) and additional assumptions from the literature will be used to establish background mortality. These statistics do not exclude patients with MDD.

Mortality for adults with MDD is higher than for the general population. Findings from Pratt and colleagues, which used the National Health Interview Survey to explore the elevated risk of mortality associated with anxiety and depression, found that the adjusted hazard ratio (HR) was 1.6 [42].

Sensitivity analyses can explore a lower HR, which the study found after considering mediators, behaviors, and chronic diseases; the confounders in the initial model were limited to sociodemographic and economic factors. Sensitivity analyses may be considered to address the finding that the HR for mortality decreased with the duration of follow-up, although the data only explored a maximum of five years. Of note, the HR of 1.6 was similar to the HR of 1.57 found in a Canadian study [43].

For mortality for patients who are undergoing third- and fourth-line therapy, we propose a study that identified excess all-cause mortality in patients with TRD compared with non-TRD MDD patients using a large US database [44]. Among patients who started a third antidepressant after two previous regimens were identified as having TRD. After adjustment for sociodemographic characteristics as well as clinical characteristics (comorbidities, substance abuse, other psychiatric comorbidities), patients with TRD had a mortality HR of 1.28 compared to patients with MDD without TRD. Sensitivity analyses can be used to account for concerns that the commercial claims database used for the analysis may not reflect MDD patients covered primarily by government insurance.

7.2 Utilities

7.2.1 Utilities Associated with Health States

Despite the lack of consensus on the importance of health utilities in depression, utilities will be included as outcome metrics in the model. Health states will be assigned to health states as one type of measures utilities to reflect patient-reported (or proxy- or physician-reported) health status. For health states with limited data in the literature, placeholder values will be used. Including health utilities will permit the assessment of cost-utility, which is of interest to selected model users. The review of meta-analyses in our TLR did not identify suitable sources for health state utility values to populate the model fully. Additional targeted literature review identified multiple possible sources for utility inputs (detailed in Table 8). These sources were referred to in the reviewed documents; they do not represent a comprehensive list of possible utility sources.

Given that there is no consensus in the literature reviewed for utilities to map to the health states proposed, we are requesting input to identify which, if any, of these studies are preferred and what other alternatives may be appropriate.

Table 8. Health State Utilities

Health State	Utilities			
Complete response	0.90 ± 0.15	0.70 (95% CI 0.67-0.73)	0.72 to 0.83 "maintenance therapy"	
Partial response	0.80 ± 0.21	0.57 (95% CI 0.54-0.61) "mild depression"	0.64 to 0.73 "mild depression"	0.337 to 0.449 "inadequate treatment response"
No response	0.41 ± 0.29	0.52 (95% CI 0.49-0.56) "moderate depression"	0.55 to 0.63 "moderate depression"	0.33 to 0.544 "major depressive episode"
Death	0		25% of patients rated severe depression as equivalent/worse than death	
Source	Yrondi et al. 2020 [45]	Kolovos et al. 2017 [46]	Revicki and Wood 1998 [47]	Brockbank et al. 2021 [48]

7.2.2 Disutilities Associated with Adverse Events

Adverse events can, theoretically, also be reflected by disutility, i.e., decrements in utility values. Disutility may be applied for the initial cycle(s) of a treatment or for the duration of the treatment; this will be driven by literature and clinical guidance. The literature review did not identify estimates of disutility associated with specific adverse events, with the exception of one study that examined utilities by depression severity and comparing TCAs with newer treatments (that is, introduced in the 1990s) [47]. This study reported disutility associated with the following AEs, with the disutility ranging from 0.12 to 0.01: nervousness, lightheaded/faint, headache, sedation, constipation, dry mouth, and nausea [47]. Additional literature searches will be conducted to identify disutility associated with AEs once we identify a final set of AEs based on feedback from the public comment period.

7.3 Cost Inputs

Except for pricing of pharmaceutical treatments, we considered two approaches for cost inputs in the MDD model—a bottom-up cost developed by identifying likely resources and assigning costs, or a top-down cost developed by using an overall estimate of costs and apportioning a subset of the costs to MDD. Costs for each intervention received will be applied regardless of its effectiveness; total costs and the proportion of costs associated with MDD will vary by health state, with the assumption that individuals with a complete response likely have a lower proportion of all-cause

costs attributable to MDD. Additional targeted searches would be needed to operationalize this assumption.

Summing costs for resources that are expected to be used over the course of three months with a specified treatment would apply best practices to treatment. This approach likely overestimates actual resource use. However, real-world studies may underestimate and are subject to the limitations associated with any claims database or observational analysis. The following sections provide possible inputs for both a bottom-up approach and a top-down approach.

7.3.1 Overview of Costs Included in the Model

Costs in the model will include direct medical costs associated with treatment and adverse events (pharmacotherapy, psychotherapy, somatic therapy, outpatient visits, hospitalizations, laboratory tests, etc. as shown in Table 9), direct non-medical (transportation and patient costs associated with medical care) as well as indirect costs, including lost work productivity (based on absenteeism or mortality) and informal caregiving. The costs will be provided in multiple categories, with insurance-covered and patient co-pays separate to facilitate calculation and presentation of different perspectives. In addition, alternative sets of costs can be available to reflect commercial, Medicare, and Medicaid reimbursement rates.

Table 9. Cost Types Included

Costs	Examples
Direct medical costs	• Pharmacotherapy, psychotherapy, somatic therapy • Laboratory tests required for initiation or monitoring • Primary/specialist care, ER visits, hospitalizations
Direct non-medical costs	• Transportation costs to/from MDD care
Indirect/productivity costs	• Informal/unpaid caregiving • Lower workforce participation • Missed work/time for treatment and hospitalization • Presenteeism

For each cost type, both unit costs and frequencies will be required. Sources for costs for the model will be nationally-representative; users can adjust costs to reflect reimbursement, salary, and co-pay to reflect their research question or situation. Costs will be based on the 75th percentile of the Usual, Customary, and Reasonable fees[49].

7.3.1.1 Costs by Decision Maker Perspective

Appendix F describes how the cost inputs will differ by decision-maker perspectives.

7.3.2 Healthcare Resource Utilization

The literature review did not identify sources for rates of utilization for the resources of interest. Instead, an analysis of claims by US adults with MDD will be used to populate rates. Ta and colleagues identified more than 224,000 adults with MDD with commercial insurance and report all-cause 12-month use of inpatient hospitalization, emergency room services, and outpatient care for patients by adherence or persistence [50]. Table 2 in the study from Ta and colleagues, reproduced in Appendix 2, provides estimates for resource utilization [50] that could be considered for this model, with consideration needed to whether adherence or persistence with therapy can be aligned with the planned health states.

7.3.3 Direct Medical Costs: Sources and Values

7.3.3.1 Direct medical: Cost of intervention

Given that the data on response rates from the literature are generally reflective of guideline-defined adequate treatment, that is, sufficient duration and dosage for evidence of a response, the costs for intervention are based on approved dosages and recommended number of treatment sessions based on the FDA label and assume adherence to therapy. However, in the real world, not all MDD patients receive adequate treatment.[51] The initial implementation of the model will not address inadequate treatment, but future revisions can include other treatments and either provide alternative response rates or provide a hazard ratio with which to decrement response rates from existing literature.

A list of drug dosages is provided as Appendix E for review. This information will be used to assign pricing. (*If different dosing would be used for acute versus maintenance treatment, this should be noted.)*

Table 10. Costs of Interventions

Intervention	Approach	Initial Implementation	Future enhancements
Pharmacotherapy	Based on weighted average wholesale acquisition cost (WAC) obtained from RED BOOK [52] for the class and a typical dose used in the base case. User can specify a patient co—pay.	Pharmacotherapies will be limited to selected treatment classes (i.e., SSRIs, SNRIs, TCAs, MAOIs, NDRIs, and noncompetitive D-methyl-D-aspartate receptor antagonists, as previously specified), as available in the data.	The user will be able to populate the model with specific agents and doses, as well as allowing the user to insert the market shares within a class to change the distribution of agents and costs.
Somatic therapies	Based on commercial and/or government reimbursement rates for 20 sessions of rTMS (1 initial, 19 subsequent, using CPT codes 90867 and 90868 obtained from medical fee resource [49]). User can specify a patient co—pay.	Inputs for somatic therapies will be parameterized based on data from rTMS, the most thoroughly reported in the literature search. It will be limited to third- and fourth-line treatments (pending public comment about its potential use earlier in treatment).	The user will be able to populate the model with specific therapies (e.g., ECT, rTMS, tDCS, VNS), as well as allowing the user to insert the market share of each therapy to change the distribution of treatments and costs.
Psychotherapy	Based on commercial and/or government reimbursement rates for twice-weekly sessions of psychotherapy. The base case will assume 45-minute sessions, with 1 session per month including an evaluation and management component (e.g., CPT 90836 and 90834 obtained from Medical Fees Directory [49]). User can modify frequency of sessions and specify a patient co—pay.	Treatment will be limited to CBT, as it was the most thoroughly reported in the literature search.	The user will be able to populate the model with specific therapies (e.g., CBT, IPT), as well as allowing the user to insert the duration and frequency of sessions as well as distribution of each type of therapy to change the distribution of treatments and costs.
Combination therapies	Based on the sum of drug price and commercial and/or government reimbursement rates and co-pays for specified treatments.	Only one meta-analysis reported on combination therapy (psychotherapy and pharmacotherapy); suggest using alternative source.	Pending availability of data, specific combinations of two or three interventions that are common treatment options may be built into the model.
Additional / user-defined	User can also enter additional therapy options with associated cost. Will be able to select whether as alternative to existing treatment option or in addition.	User-defined.	User-defined.

7.3.3.2 Direct medical: Cost of hospitalizations

The cost of MDD-related hospitalizations will be based on US reimbursement (DRG 881 -depressive neuroses, includes ICD-10 F329 – major depressive disorder, single episode, unspecified). The 2020 national average allowance was approximately $4721. [53]

7.3.3.3 Direct medical: Cost of outpatient visits

There are two approaches to considering outpatient care. One would make assumptions about the proportion of outpatient visits from real-world studies are associated with MDD and apply costs for MDD and non-MDD care. The second is to build up a regimen of outpatient care based on clinical guidelines and best practices, with consideration for psychotherapy.

Using the first approach, the cost of outpatient visits would be based on the appropriate CPT codes [49], with the assumption that a specified proportion of outpatient visits are for MDD-related care, and that 57% of mental health-related outpatient visits to physicians are to a psychiatrist [54]. Existing national surveys of the proportion of outpatient visits for counseling or anxiety and nervousness suggest that approximately 6% of visits are for these reasons [55]. A full list of available codes will be available for the user to select. Each new treatment course will include a diagnostic evaluation (CPT code 90792). The user will be able to select from a list of outpatient and psychotherapy codes, with examples shown in Table 11. Final decisions on which of the levels (for visit length and complexity and for duration of psychotherapy) to include and the distribution, if appropriate, will be informed by advisory group and clinical input.

The second approach would assume a specific number of visits (for the base case) to a psychiatrist or general practitioner during a model cycle, based on the guideline-recommended treatment patterns [6, 7]. Additional visits would be applied for individuals who are undergoing psychotherapy. The base case would assume bi-weekly visits of 45 minutes, with one visit per month including an evaluation and management (E&M) assessment. The user would be able to vary these assumptions.

Table 11. Outpatient Evaluation and Management and Psychotherapy Codes

CPT	Description	Cost [A]
99202-99205	Office or outpatient visit, new patient, levels based on time and complexity	$184-$525
99211-99215	Office or outpatient visit, established patient, levels based on time and complexity	$59-$363
90832	Psychotherapy, 30 minutes	$130
90834	Psychotherapy, 45 minutes	$181
90837	Psychotherapy, 60 minutes	$202
90833	Evaluation and management and 30 minutes psychotherapy	$147
90836	Evaluation and management and 45 minutes psychotherapy	$205
90838	Evaluation and management and 60 minutes psychotherapy	$258

[A] Costs will be based on the 75th percentile of the Usual, Customary, and Reasonable (UCR) fees or the Medicare National Average allowance as a proxy for state-specific Medicaid reimbursement rates. The commercial rates are shown here. The user will be able to select from within a range (50th UCR to 90th UCR).
Cost Source: Medical Fees 2021[49]

7.3.3.4 Direct medical: Laboratory

Laboratory costs are included for somatic therapies and some pharmacotherapies, as shown below.

Table 12. Laboratory Codes and Costs

Resource	When applied	Cost [A]
Electrocardiogram (CPT 93000)	Applied for x% of patients who initiated treatment with TCA, and are 45 years and older; prior to ECT	$87
Comprehensive physical exam (evaluation and management code, level TBD)	Prior to use of somatic therapies	TBD
General health panel (CPT 80050)	Prior to use of somatic therapies	$250

[A] Costs will be based on the 75th percentile of the Usual, Customary, and Reasonable fees or the Medicare National Average allowance as a proxy for state-specific Medicaid reimbursement rates. The commercial rates are shown here. The user will be able to select from within a range (50th UCR to 90th UCR).
Cost Source: Medical Fees 2021[49]

No other laboratory utilization is included.

7.3.3.5 Direct medical: Adverse events

As discussed in section 7.1.2, safety data were limited in the literature review; there was no information available on resource utilization related to adverse events (AE). Other data sources may be available, for example, an estimate of costs associated with experiencing serotonin syndrome was identified [37]. Once the final list of key AEs of interest for the initial implementation of the model are identified, cost and patient burden (i.e., disutility) associated with these AEs will be sought in other published literature.

7.3.4 Direct Non-medical Costs

7.3.4.1 Direct non-medical: Transportation

No estimates of transportation were available in the MDD literature that was reviewed. Time for transportation and waiting for medical care were identified and appear under indirect costs. However, neither mileage/gas nor parking costs are included in the base case of the model. There will be a placeholder such that the user can enter a value to be applied to visits to reflect these costs.

7.3.5 Indirect Costs

Indirect costs were not reported in the meta-analyses, but studies of the national economic burden of MDD include these costs. These tend not to report at a granular enough level to differentiate between treatments, as is required for this model. If a bottom-up approach is used for identifying healthcare costs, then indirect costs can be attached to each visit, for example.

7.3.5.1 Indirect: Lost time

Waiting times associated with health care will be incorporated in the model. An analysis of the American Time User Survey identified that on days on which respondents reported receiving health care services, they reported 45 minutes for traveling and waiting [56]. For each day with an outpatient medical encounter (i.e., psychotherapy session, somatic therapy session, laboratory test, or routine visit), an additional cost will be assigned based on the expected wages for the individual. (This cost will be included in the societal and patient perspectives.)

7.3.5.2 Indirect: Informal caregiving

The targeted meta-analysis review was not designed to explore estimates of caregiving for individuals with MDD and it was not mentioned in any of the studies identified. Caregiving, however, is a concern in the MDD community and can be incorporated into the model.

The following approach can be applied:

- There will need to be an assumption about the proportion of individuals with MDD who have a caregiver, that is someone who provides supportive care without compensation. (Note: this proportion is to be determined based on additional literature.)
- There will be a conservative assumption for the base case that the hourly wage ranges between the value for a certified nurse assistant and the average hourly wage in the US (at present, these values are ~$16 and $26 according to the Bureau of Labor Statistics, but will be updated as appropriate).
- The default value for the number of hours spent weekly (multiplied by 13 to be relevant for a 3-month cycle) will be set at 32, which reflects the number of hours that caregivers for individuals with mental health disorders reported in a recent survey.[57]

Rather than being tied to treatments, caregiving can be tied to response, in that there can be an assumption that individuals who have a complete response to therapy have lower caregiving needs than those with partial or no response. *(Insight from the public and advisory group will be necessary for these estimates. In addition, if caregiver support is required for somatic therapies, this can be added but the literature review did not identify studies suggesting how much may be needed.)*

There are other concerns about caregiving, including that some caregivers have lost work, have changed jobs, or have suffered mentally and/or physically,[57] but these are not planned to be incorporated in the model.

7.3.5.3 Indirect: Lost productivity / presenteeism

Employers reported indirect costs of $6,885 over two years for employees with MDD and $12,765 for employees with TRD [58]. These costs will be inflated to the current year and applied as employer costs associated with MDD and TRD, divided by 8 to reflect the cycle length of 3 months.

7.3.5.4 Indirect: Future earnings

The lost value of future earnings associated with premature mortality will be estimated by calculating the excess mortality for individuals with MDD and calculating the expected income for each lost model cycle until the model-selected retirement age. The default will be set at 65, but the user can enter an alternative value. Similar to other costs, earnings will be discounted at 3% per annum.

7.4 Other Planned Functionality

An important feature in the model is the ability for the user to select treatment sequences, that is, to specify the treatments and the order of treatments available to an individual in the model (for a maximum of four treatments during the model horizon) as well as determining when an individual should transition from one treatment to the next. How individuals progress and whether certain treatments are limited (other than somatic therapies not being available as first- or second-line therapy) is important to the model's objective but input values were not identified in the literature reviewed to the point. The cost of an intervention would not depend on its order in the treatment sequence.

Clinical stakeholders will be consulted for input when assumptions may be required or to confirm whether treatments are of interest. In the absence of data, the application of a hazard rate approach, that is, to assign a proportionally different effectiveness rate in later lines of therapy, may be used.

7.5 User-Driven Approach

The model structure will drive the scope of input requirements. To recognize the many research questions that have not been prioritized at this initial stage of development as well as to allow users to answer research questions using their own data or assumptions, almost all of the inputs (including response rates and transitions, utilities, costs and resource utilization) can be varied by the user.
During this phase of reviewing the structure and proposed model inputs, additional features that are of interest, whether in the short-term or in the long-term, should be discussed. While there may not be data available to enable the features, it may be more efficient to build the model with functionality, or to design with the expectation of specific modules or enhancements.

8 Data Gaps and Suggested Short-Term Solutions

The literature review was designed to identify published data on effectiveness, safety, utilities, costs, and productivity for specific treatment classes of interest in MDD. However, the objective of the modeling effort is to develop a model that answers questions that should be asked in MDD, not necessarily those that have already been asked.

8.1 General Strengths and Weaknesses

As with all population-level models, while the microsimulation approach tries to reflect the heterogenous experiences of people with this condition, ultimately the model does not represent the experience of a single individual.

The structure of the model is dependent on the definition of the health states and that they have unique and meaningfully different costs and benefits to patients, as well as that they can be measured accurately in the studies from which inputs are drawn. Given the findings from the targeted literature review and the construction of other models, it is expected that the health states can be differentiated in terms of patient reported outcomes, clinical effectiveness, and cost, even if the data to support all the interventions of interest are not readily available. At this time, the model can incorporate these research questions by allowing the user to increase or decrease effectiveness by a set rate and by offering alternative costs. That said, it is important to recognize that the proliferation of assumptions, each of which is reasonable on its own, increases the amount of uncertainty around results.

Microsimulations typically require more processing power than many other types of models. The programming and implementation team will need to be cognizant of system constraints, but it is possible that certain features may need to be balanced with computational time and power limitations.

8.2 Effectiveness

Overall, there was interest in populating the model with primary data on effectiveness of selected interventions with a common metric (i.e., MADRS or HAM-D score thresholds). The literature review was unable to resolve certain challenges, described below. As the review was focused on meta-analyses, which require that several published relevant studies are available, there may be a bias toward availability of studies on older therapies. This may be addressed through willingness to use individual studies to populate effectiveness matrices. Further, it should be noted that the input values suggested for this implementation of the model often reflect clinical trials, which may not reflect real-world effectiveness and/or lower real-world adherence with treatment.

8.2.1 Effectiveness Metrics

The initial search considered the HAM-D (any version), the MADRS, the PHQ-9, and the GHQ. Meta-analyses typically required that the studies included use a validated measure, but they rarely reported on the thresholds or change scores for each metric, instead assuming appropriate use by the authors of individual studies. Due to resource constraints, our TLR did not review each individual study that contributed to a meta-analysis. Thus, while there was initially discussion about building into the preliminary model the ability for the user to select the instrument and the score threshold to drive effectiveness, this preliminary version is limited to levels of effectiveness but is not tied to individual measures.

8.2.2 Effectiveness in Third- and Fourth-Line Treatments

It was expected that studies would not report on treatments and describe them as being provided as third- or fourth-line therapies; this was confirmed in the literature review. However, given the common definition of TRD being non-responsive to two or more adequate trials of different treatments, it was determined in consultation with IVI that studies on third- and fourth-line treatments could be populated by findings from studies on individuals with TRD.

In the absence of published data on effectiveness of a given intervention in individuals with TRD, such that the data could be used as a proxy for third- or fourth-line therapy, the model will direct the user to effectiveness data from first- and second-line therapy and allow the user to specify a percentage change from those values to represent an increased or decreased effectiveness when used later in the treatment sequence. There will be no constraints; the user will be able to indicate that a given intervention's effectiveness in third- or fourth-line therapy is +/- x% from its effectiveness in first- and second-line treatment.

8.2.3 Long-term Efficacy Rates

The model does not incorporate long-term efficacy directly but rather estimates it from effectiveness during each cycle. Outcomes should be validated against studies that have reported on long-term outcomes.

8.3 Patient-Reported Outcomes and Utilities

The model was envisioned to include novel measures of patient-reported outcomes, beyond the often-used utilities. These measures were not identified in the meta-analyses. The Patient-Driven Values in Healthcare Evaluation Center (PAVE), a multi-stakeholder effort affiliated with the University of Maryland School of Pharmacy, conducted interviews with adults with experience with depression and identified several topics and concerns that do not present in existing literature. In the future, findings from this effort may be able to help populate the model and/or to add new elements.

8.4 Medical Costs and Resource Utilization

There were no meta-analyses that met eligibility criteria, nor were there many that were identified in the literature search. Values proposed for the model are derived from alternative sources or developed based on best practices as described in guidelines. Either a bottom-up or a top-down (attributing a portion of resource use and costs to MDD) can be used. We would be interested in getting public comment on this question.

8.5 Non-medical Costs

There are qualitative reports of caregiving provided to individuals with MDD but it was not included in studies reviewed for model scope and it was not included in the meta-analyses reviewed. The topic has been raised by the advisory group and stakeholders; the model should include the capability to estimate caregiver costs, even if the inputs are assumption-driven.

Other costs associated with getting to and from care can be estimated but a real-world survey study gathering information on travel time, wait time, and costs associated with transportation, as well as whether individuals require caregiver assistance for visits, would be informative.

8.6 Income and Workplace Effects

Multiple studies have reported increasing improvements with self-reported workplace productivity associated with small responses (for example, Beck et al. [59]). However, the crosswalk between productivity and income is challenging to implement and will require additional assumptions. In addition, there are studies suggesting that cognitive impairment associated with treatments may contribute to productivity loss, but the data to fully populate that in a model are not available. Additional granularity, such as average wages earned by individual with MDD and/or whether they are working full or part time, and whether they are excluded from the workplace by choice or as a result of their condition is unknown. Finally, there are reports that depression may affect educational attainment and thus earning capacity. While adding this level of granularity would be welcome, further research would be needed to identify necessary inputs.

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10 Appendices

Appendix A. Scoping Phase – Literature Review of Existing Economic Models

The scoping phase of this modeling effort included a targeted literature search and review conducted using Embase and MEDLINE databases to identify economic models published on MDD from 2010 to the search date (September 2020). A total of 249 articles were identified in the search. Inclusion was restricted to economic evaluation studies in the English language reporting on adult populations with MDD. Study designs such as commentaries, protocols, opinion pieces, burden of illness or claims analyses were excluded. Following these exclusions, 236 studies were eligible for title/abstract and full text review. Subsequently, 20 models were selected for inclusion, shown in **Table 1**. Of these, 2 models were produced for or by government entities [60, 61] as well as 18 produced privately.[62-77] The Institute for Clinical and Economic Review (ICER) study on esketamine for treatment-resistant depression was also of interest and was included in the review despite not being captured in the literature search.[78]

Adults aged 18-64 years with a variety of treatment experiences (i.e., newly diagnosed, treatment-resistant) were used as model target populations. Markov and decision trees models were most frequently used with 2 studies employing a microsimulation model. Model time horizons varied across studies, ranging from a duration of 6 weeks to a lifetime. A majority of the models adopted a societal and health care perspective, with one study employing a payer perspective. Model interventions included somatic therapies, pharmacotherapy, combination therapy, pharmacogenetic testing and psychotherapy.

Response/remission and relapse/no response were included as model health states, with a few models indicating partial response. The Montgomery-Asberg Depression Rating Scale (MADRS) and the Hamilton Depression Rating Scale (HAM-D) were primarily used to measure treatment effectiveness and define health state thresholds. Remission thresholds were mainly defined as a HAM-D score of ≤7 and/or a MADRS score of ≤12 and ≤10. Thresholds for response were consistent across models, defined as a ≥50% reduction in MADRS and/or HAM-D score from baseline. The threshold for partial response and no response varied across studies, ranging from a HAM-D score of 7-15 to 8-19 and HAMD score of >19 to ≥15, respectively.

Table 13. Characteristics of Identified Economic Models

Study, country	Population	Intervention(s)	Comparator(s)	Model Type	Health States /Events	Depression Scale, Threshold	Time Horizon	Perspective
Nordström et al. 2010, Sweden [72]	MDD	Venlafaxine	TCA and SSRIs	DT	Remission - relapse	MADRS, **Remission**: MADRS score ≤12	6 months	Societal
Nordström et al. 2012, Sweden [71]	MDD	Escitalopram	Venlafaxine	DT	Remission - sustained remission – relapse - premature stop - switch	MADRS, **Remission**: MADRS score ≤12	6 months	Societal
Prukkanone et al. 2012, Thailand [74]	MDD	CBT	Fluoxetine	Micro-simulation	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
Taneja et al. 2012, US [77]	MDD	Aripiprazole + ADT Quetiapine + ADT Olanzapine/ Fluoxetine + ADT	ADT monotherapy	DT	Response – non-response – premature discontinuation due to lack of efficacy, AE or other unknown reason	MADRS, **Response**: ≥50% reduction (vs baseline) in MADRS score	6 weeks	US health care system; not specified if government or third-party payer
Mencacci et al. 2013, Italy [69]	MDD	Escitalopram	Citalopram Sertraline Paroxetine	DT	Remission – no remission – relapse – no relapse – maintenance tx after no relapse – suicide attempt after relapse – no suicide attempt after relapse – death due to suicide attempt – survive suicide attempt	HDRS **Remission:** HDRS score of ≤7	1 year	National Health Service (NHS)
Maniadakis et al. 2013, Greece [68]	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 Not specified	2 years	Societal
Solomon et al. 2013, Australia [76]	Mild to moderate depression	SJW	Venlafaxine	Markov	Depressive episode – response – remission - dead	HAM-D Not specified	72 weeks	National Health Provider
Olgiati et al. 2014, Italy [73]	MDD (elderly population)	Paroxetine (high dose)	Paroxetine (low dose)	Markov	Depression - remission - relapse - no treatment (discontinuation)	HAM-D Not specified	32 weeks	Not specified
Annemans et al. 2014, Belgium [63]	MDD	Citalopram Sertraline Paroxetine Fluoxetine Duloxetine	NA	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	- National Institute of Health and Disability Insurance

Study, country	Population	Intervention(s)	Comparator(s)	Model Type	Health States /Events	Depression Scale, Threshold	Time Horizon	Perspective
		Venlafaxine Mirtazapine Escitalopram						- Societal
Khoo et al 2015, Singapore [66]	MDD	Agomelatine Duloxetine Escitalopram Fluvoxamine Fluoxetine Mirtazapine Paroxetine Sertraline Trazodone Venlafaxine	NA	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
Hornberger et al. 2015, US [65]	TRD	CPGx testing	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
Nguyen et al. 2015, Australia [70]	TRD	rTMS	Pharmacotherapy	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, NA	3 years	Health system
Koeser et al. 2015, UK [67]	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
Health Quality Ontario HTA 2016, Canada[10]	TRD	Brexpiprazole		DT	Response – full remission – response w/o remission – no remission – no response	HAM-D **Remission:** HAMD-17 score <8 **Response:** 50% reduction in HAM-D score	6 months	Provincial (Ontario Ministry of Health and Long-term Care)
Ammerman et al 2017, US [62]	MDD (low-income mothers)	In-home CBT	Standard home visitation	Patient level Markov	MDD – Remission – Death	Not specified in clinical trial abstract	3 years	Payer

Study, country	Population	Intervention(s)	Comparator(s)	Model Type	Health States /Events	Depression Scale, Threshold	Time Horizon	Perspective
Young et al 2017, UK [79]	MDD (patients 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, Canada[11]	MDD pts with and without GAD	rTMS	ADT	Markov probabilistic microsimulation	11 health states (includes acute phase – response – relapse)	HAM-D	5 years	Provincial (Ontario Ministry of Health and Long-term Care)
Groessl et al 2018, US [64]	MDD	IDGx testing	SoC	Markov	Response – non-response – survive - remission – relapse – death	HAM-D **Response:** 50% or more in HAM-D score	3 years	Societal
Ross et al 2019, US [75]	MDD	ECT	Pharmacotherapy /psychotherapy	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% reduction in HAM-D score)	1-5 years	- Health care - Societal
ICER 2019, US [78]	TRD	CBT	Second generation ADTs	DT	Remission – response – no response	MADRS **Remission:** MADRS≤12 **Response:** ≥ 50% reduction in MADRS score	Lifetime	Health care sector

ADT, Antidepressant Therapy; AE, Adverse event; CBT, Cognitive Behavioral Therapy; CPGx, Combinatorial Pharmacogenomic Testing; DT, Decision Tree; ECT, Electroconvulsive Therapy; GAD, Generalized anxiety disorder; ICER, Institute for Clinical and Economic Review; IDGx, IDgenetic Testing; MDD, Major Depressive Disorder; RR, relative risk; rTMS, Repetitive Transcranial Magnetic Stimulation; SJW, Saint John's Wort; SoC, Standard of Care, SSRI, Selective Serotonin Reuptake Inhibitor; TAU, Treatment as Usual; TCA, Tricyclic antidepressant; TRD, Treatment-resistant depression; Tx, treatment; UK, United Kingdom; US, United States

Appendix B. Search Strategy (all topics combined)

Databases – MEDLINE, Embase, EconLit and APA PsycINFO

Search	Topic	Search terms	Number of hits
S1	Indication	TI,AB("major depressive disorder" OR "clinical depression" OR "treatment resistant depression" OR (depression AND (treatment NEAR/4 resist*)) OR (major NEAR/4 depress*)) OR MESH.EXACT("Depressive Disorder, Major") OR EMB.EXACT.EXPLODE("Depressive Disorder, Major") OR EMB.EXACT.EXPLODE("treatment resistant depression") OR MESH.EXACT.EXPLODE("Depressive Disorder, Treatment-Resistant")	206919*
S2	Efficacy outcomes	TI,AB("efficacy" OR "effectiveness" OR "response" OR "responded" OR "responder" OR "remission" " relapse" OR "recurrence" OR "symptom-free" OR "symptom free" OR "hamilton depression rating scale" OR "montgomery asberg depression rating scale" OR "patient health questionnaire" OR "beck depression inventory" OR HAMD OR HAM-D OR HAM-D17 OR HAMD17 OR "HAMD 17" OR HDRS OR HDRS17 OR HDRS21 OR HDRS29 OR HDRS29 OR HDRS8 OR HDRS6 OR HDRS24 OR HDRS7 OR MADRS OR PHQ-9 OR PHQ9 OR "PHQ 9" OR PHQ OR PH-Q OR BDI OR BD-I) OR EMB.EXACT("hamilton depression rating scale" OR "montgomery asberg depression rating scale" OR "patient health questionnaire 9" OR "beck depression inventory") OR MESH.EXACT("Patient Health Questionnaire")	9771448*
S3	Safety outcomes	TI,AB("mortality" OR "safety" OR "adverse" OR "reactions" OR "AE" OR "AES" OR "SAE" OR "SAES" OR "TEAE" OR "TEAEs" OR "TRAE" OR "TRAEs" OR "complications" OR "side effect*" OR "reaction*") OR EMB.EXACT("drug safety") OR EMB.EXACT.EXPLODE("adverse drug reaction" OR "Drug-Related Side Effects and Adverse Reactions") OR MESH.EXACT("Drug-Related Side Effects and Adverse Reactions")	9914702*
S4	Utility/PCO outcomes	TI,AB("quality adjusted" OR "life year*" OR "quality of life" OR hrqol OR hrql OR hql OR hqol OR "hr qol" OR "h qol" OR EQ5D OR "EQ 5D" OR EQ OR EUROQOL OR "EURO QOL" OR EUROQUAL OR "EURO QUAL") OR TI,AB((" short form" OR shortform OR SF) NEAR/1 (six OR 6 OR eight OR 8 OR twelve OR 12 OR sixteen OR 16 OR twenty OR 20 OR "thirty six" OR 36)) OR ((quality OR disability) NEAR/1 adjusted) OR "quality of life" OR qol OR hrqol OR qaly OR qalys OR daly OR dalys OR "life year" OR "life years" OR ((health OR healthy) NEAR/1 (year OR years OR status OR indicator OR indicators)) OR utility OR utilities OR disutility OR "willingness to pay" OR WTP OR "standard gambl[*4] " OR "trade off" OR tradeoff OR "trade-off" OR hui1 OR hui2 OR hui3 OR (European NEAR/1 (qol OR quality)) OR EMB.EXACT("socioeconomics" OR "quality-adjusted life year" OR "patient satisfaction" OR "attitude to health" OR "patient-reported outcome" OR "outcome assessment") OR EMB.EXACT.EXPLODE("health status indicator" OR "quality of life") OR MESH.EXACT("Value of Life" OR "Quality of Life" OR "Quality-Adjusted Life Years" OR "Attitude to Health" OR "Patient Reported Outcome Measures" OR "Patient Outcome Assessment") OR MESH.EXACT.EXPLODE("Health Status Indicators" OR "Patient Satisfaction") OR TI,AB("patient reported outcome" OR "self reported outcome" OR "patient preference" OR "questionnaire*") OR EMB.EXACT("patient-reported outcome" OR "patient preference" OR "questionnaire") OR MESH.EXACT("Patient Preference" OR "Questionnaires") OR TI,AB(impact NEAR/3 (caregiver OR family OR families OR society OR societal or patient	5361634*

		OR person)) OR EMB.EXACT("caregiver burden") OR MESH.EXACT("Caregiver Burden")	
S5	Productivity	TI,AB(("work loss" OR "job loss") OR absenteeism OR presenteeism OR "sick day" OR "sick leave" OR "work absence" OR "work incapacity" OR "sickness absence" OR "disability absence" OR "work leave" OR (burden NEAR/3 (employee OR employer) OR (impact NEAR/3 (employee OR employer))) OR TI,AB(los*) AND TI,AB(work) AND TI,AB(day) OR MESH.EXACT("Employer Health Costs" OR "Efficiency" OR "Presenteeism" OR "Absenteeism") OR MESH.EXACT.EXPLODE("Salaries and Fringe Benefits") OR EMB.EXACT("productivity" OR "medical leave" OR "presenteeism" OR "absenteeism"))	1432895*
S6	Combination of topics	S2 OR S3 OR S4 OR S5	21889255*
S7	Combination of topics and indication	S1 AND S6	116932*
S8	Study design of interest	TI,AB("meta analysis" OR "meta-analysis") OR EMB.EXACT("meta-analysis as topic" OR "meta analysis") OR MESH.EXACT("Meta-Analysis as Topic") OR RTYPE("meta-analysis")	561599*
S9	Study design not of interest	EMB.EXACT("case study" OR "case report" OR "abstract report" OR "letter" OR "note" OR "conference abstract") OR TI,AB("case study" OR "case studies" OR "case report*" OR "case series") OR RTYPE("case reports" OR "letter" OR "historical article" OR "note" OR "editorial" OR "conference abstract") OR PSTYPE("Conference proceedings") OR DTYPE("Letter" OR "Historical Article" OR "Editorial" OR "Note" OR "Comment" OR "News" OR "Newspaper Article" OR "Review" OR "Conference review" OR "Conference abstract" OR "Conference Paper") OR TI,AB("non-human" OR "non human")	21554932*
S10	Meta-analyses studies only	S8 NOT S9	254630*
S11	Combination of study design of inerest, indication and topics	S7 AND S10	1462°
S12	English articles published in 2018 or later	S11 AND (PD(>20171231)) AND LA(English)	455°^╪

* Duplicates are removed from the search, but included in the result count.
° Duplicates are removed from the search and from the result count.
^ Search hits as of Septermber 24 2021

Appendix C. Table 2 from Ta et al. [50]

This table can be used to guide resource utilization estimates for health care resource utilization for individuals with MDD. Costs will be inflated from 2019 (as presented) to current year. Definitions were as follows:

- Adherence: proportion of days covered ≥ 80%
- Persistence: continuous antidepressant therapy without a gap of 30 days or more

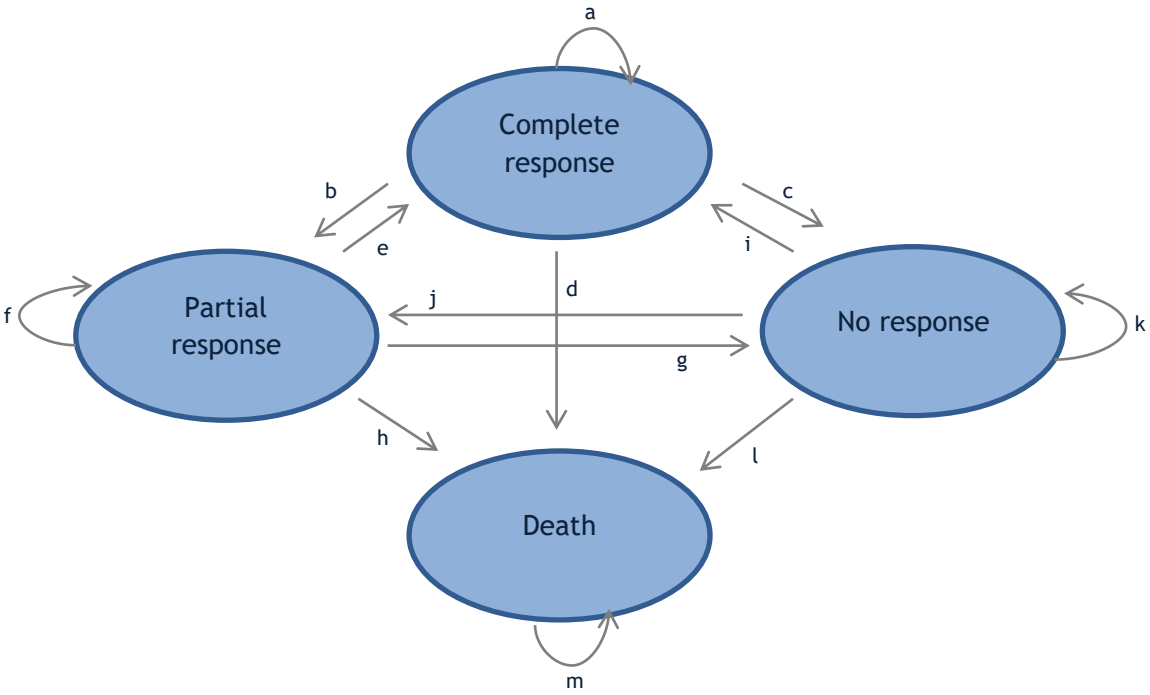
TABLE 2 12-Month All-Cause Health Care Resource Utilization

	Commercial Population					
	Adherent (n=108,777)	Nonadherent (n=100,645)	Incidence Rate Ratio (95% CI)	Persistent (n=105,919)	Nonpersistent (n=103,503)	Incidence Rate Ratio (95% CI)
Unadjusted HCRU, mean [SD]						
Inpatient hospitalizations	0.08 [0.39]	0.11 [0.50][a]	1.36 (1.31 to 1.41)	0.08 [0.40]	0.11 [0.48][a]	1.33 (1.28 to 1.38)
Emergency room	0.29 [0.83]	0.42 [1.20][a]	1.45 (1.42 to 1.48)	0.29 [0.84]	0.42 [1.19][a]	1.44 (1.41 to 1.47)
Outpatient (all)	19.39 [18.48]	17.22 [17.95][a]	0.89 (0.88 to 0.89)	19.46 [18.58]	17.21 [17.85][a]	0.88 (0.88 to 0.89)
Physician office	14.45 [13.52]	12.21 [12.18][a]	0.85 (0.84 to 0.85)	14.51 [13.56]	12.22 [12.17][a]	0.84 (0.84 to 0.85)
Other	4.94 [9.98]	5.01 [10.73]	1.01 (1.00 to 1.03)	4.96 [10.10]	4.99 [10.59]	1.01 (1.00 to 1.02)
Pharmacy	27.22 [19.60]	18.30 [17.15][a]	0.67 (0.67 to 0.68)	27.57 [19.64]	18.19 [17.05][a]	0.66 (0.66 to 0.66)
Adjusted HCRU, mean[c]						
Inpatient hospitalizations	0.07	0.10[a]	1.34 (1.29 to 1.39)	0.07	0.10[a]	1.32 (1.27 to 1.36)
Emergency room	0.28	0.40[a]	1.43 (1.40 to 1.45)	0.28	0.40[a]	1.41 (1.38 to 1.44)
Outpatient (all)	19.21	17.14[a]	0.89 (0.89 to 0.90)	19.27	17.13[a]	0.89 (0.88 to 0.90)
Physician office	14.51	12.35[a]	0.85 (0.85 to 0.86)	14.55	12.36[a]	0.85 (0.84 to 0.86)
Other	4.51	4.65[a]	1.03 (1.02 to 1.04)	4.52	4.64[a]	1.03 (1.01 to 1.04)
Pharmacy	25.73	17.24[a]	0.67 (0.67 to 0.67)	26.03	17.15[a]	0.66 (0.66 to 0.66)

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. 2021 Feb;27(2):223-239. doi: 10.18553/jmcp.2021.27.2.223. PMID: 33506730.

[Input welcome on mix of adherent/nonadherent, persistent/nonpersistent to use – also reports actual costs, but suggest not sufficient for model; would prefer to be allow more granular input]

Appendix D. Transition Matrices by Intervention



	Complete response	Partial response	No Response	Death
Complete response	a	b	c	d
Partial response	e	f	g	h
No Response	i	j	k	l
Death	0	0	0	m=1

Appendix E. Drug Dosages of Pharmaceutical Treatments

Class	Generic	Trade	Usual dose (mg)* (Acute Treatment)
SSRI	Citalopram	Celexa	30
	Escitalopram	Lexapro	15
	Fluoxetine	Prozac	40
	Fluvoxamine	Luvox	100
	Fluvoxamine CR	Luvox CR	150
	Paroxetine	Paxil	30
	Paroxetine CR	Paxil CR	25
	Sertraline	Zoloft	100
SNRI	Desvenlafaxine	Pristiq	50
	Duloxetine	Cymbalta	60
	Levomilnacipran	Fetzima	60
	Milnacipran		150
	Venlafaxine	Effexor	300
	Venlafaxine XR	Effexor XR	150
TCA (tri- and tetra-cyclics)	Amitriptyline	Elavil	200
	Amoxapine	Asendin	150
	Clomipramine	Anafranil	200
	Desipramine	Norpramin	200
	Doxepin	Silenor	200
	Imipramine	Tofranil	200
	Maprotiline	Ludiomil	175
	Nortriptyline	Pamelor	100
	Protriptyline	Vivactil	30
	Trimipramine	Surmontil	200
MAOI	Isocarboxazid	Marplan	30
	Phenelzine	Nardil	45
	Selegiline transdermal	Esmam	6
	Tranylcypromine	Parnate	40
Atypical agents	Bupropion	Wellbutrin	200
	Bupropion SR (12 hr)	Wellbutrin SR	200
	Bupropion XL (24 hr)	Wellbutrin XL	300
	Bupropion hydrobromide (24 hr)	Aplenzin	348
	Mirtazapine	Remeron	30
Serotonin modulators	Trazodone	Oleptro	300
	Vilazodone	Viibryd	40
	Vortioxetine	Brintellix	20

Appendix F. Costs by Perspectives

Costs	Self-funded Employer[4] (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[5] (yoga, meditation, other wellness services/benefits, digital therapies benefits)			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				X
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	X	X	X	X

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

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

Appendix G. Treatment Options by Sequences of Treatments

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 H. Novel Questions or Opportunities by Stakeholder Perspective

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.