Cost-effectiveness model for evaluation of treatment pathways in the treatment of major depressive disorder (MDD) in the United States

Technical report

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Presented to Innovation and Value Initiative

MEDICUS ECONOMICS

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Abbreviations

ACER	Average cost-effectiveness ratio
AE	Adverse event
CR	Complete Response
CT-IPS	Continuous-time individual-patient simulation
D	Dominated
EQ-5D	EuroQol five-dimension
ED	Extended dominated
DBS	Deep brain stimulation
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECT	Electro-convulsive therapy
HAM-D	Hamilton Depression Rating Scale
HR	Hazard ratio
HSUV	Health state utility value
ICER	Incremental cost-effectiveness ratio
IVI	Innovation and Value Initiative
MADRS	Montgomery–Åsberg Depression Rating Scale
MDD	Major Depressive Disorder
ND	Non-dominated
NMA	Network meta-analysis
NMB	Net monetary benefit
NR	No Response
PR	Partial Response
QALY	Quality-adjusted life year
OSVP	Open-Source Value Project
RCT	Randomized controlled trial
RR	Risk Ratio or relative risk
SA	Sensitivity analysis
SAE	Serious adverse event
SES	Socioeconomic status
SNRI	Serotonin-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
UI	User interface
USD	United States Dollars
WAC	Wholesale acquisition cost
WTP	Willingness-to-pay

1 Executive summary

The IVI-Major Depressive Disorder (MDD) Value Model is an open-source tool that simulates individualized patient journeys for adults in the US newly diagnosed with MDD by a healthcare provider (e.g., primary care providers). Built upon continual multistakeholder engagement and novel patient-centered research, the model enables decision-makers such as payers and employer purchasers to evaluate the benefits and risks of various treatments and treatment pathways to achieve more equitable and patient-centered care for this target population.

A continuous-time individual-patient simulation (CT-IPS) model was developed in R to better represent the complex and dynamic nature of the disease and the myriad of available treatment pathways, as well as to incorporate the flexibility to address clear issues of heterogeneity in the population of need.

The main technical features that differentiate the IVI model from existing MDD models are described below. Firstly, it does not use the more common health-state transition model Markov cohort method as it is believed that the inability of downstream effects to vary as a function of upstream events is a limitation both in how treatments work in MDD and in how a model that is aiming to evaluate a sequence of treatments (vs. a single treatment) is likely to work. Secondly, most previous MDD models evaluating treatment pathways have relied on a simplifying assumption that when a patient relapses or suffers a treatment failure, the patient then moves directly to the next line of therapy with no actual period of non-treatment (what is referred to in this report as a treatment gap). This is also a simplification of real-world practice, in which treatment gaps cannot only exist but may drastically vary by patient type, treatment type, and line of therapy. The IVI-MDD model allows users to consider such gaps in care as both an input and as an outcome, so we can ascertain to what degree reducing these gaps may improve benefits to patients.

The model contains four core treatment classes (selective serotonin reuptake inhibitor [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], atypical antidepressants, and psychotherapy), as well as an additional treatment class (atypical antipsychotics) utilized in combination therapy, and an add-on treatment class (brain stimulation therapies). The options

available for each line of therapy are informed by treatment guidelines of the American Psychological Association and American Psychiatric Association, real-world database studies, and input from a Clinical Expert Panel. Users can specify treatment options in up to four separate lines of therapy. Each treatment by line of therapy may include only a single treatment class (monotherapy) or select combinations of two distinct treatment classes (e.g., "SSRI + psychotherapy"). In addition, brain stimulation therapy may be included as an "add-on" to fourth-line therapy.

The model produces an array of clinical outcomes, categorized as time-to event outcomes (such as time to first response), event-rate outcomes (such as number of relapses), proportional outcomes (such as percent of patients who achieve remission), and quality of life outcomes (such as quality-adjusted life years/QALYs gained). Beyond these, the model also produces a series of economic and clinical cost-effectiveness outcomes for each pathway, including net monetary benefit (NMB) and average cost-effectiveness ratio (ACER). It also identifies pathways on the efficiency frontier and estimates an incremental cost-effectiveness ratio (ICER) for each pathway on the frontier relative to the next-most costly pathway on the frontier. A univariate sensitivity analysis (SA) is also included to examine the impact to results of varying key model parameters.

Given the highly customizable nature of the model by the end user, we feature a sample application in this report for five example pathways utilizing base case input values. These example treatment pathways were selected based on real-world evidence and input from multistakeholder advisors. Depending on the choice of input values and treatment pathways selected by the end user, results produced by the model may notably differ from those contained in this report.

Results from the base-case simulations show that all sequences of solo or combination treatments are superior to no active treatment in terms of total QALYs accrued and net monetary benefit, whether including or excluding indirect costs. For example, we compared five sequences:

1) 4 * no active treatment;

2) 4 * SSRI;

3) SSRI followed by 3 * SSRI + psychotherapy;

4) 2 * SSRI, followed by 2 * SSRI + psychotherapy, with add-on brain stimulation therapy included in the fourth line; and

5) 2 * SSRI, followed by SSRI + atypical antidepressant, followed by SSRI + antipsychotic.

QALYs gained over a five-year time horizon are: 1.93, 2.78. 2.91, 2.89 and 2.91 respectively, with direct-cost ACERs of $33,165, $17,959, $26,887, $38,406, and $18,407 respectively.

2 Objectives

The primary objective of the health economic model was to allow users to evaluate the benefits and costs associated with various treatment sequences in adults (age 18-64 years) in the United States newly diagnosed with MDD by a healthcare provider, from multiple perspectives (i.e., private and public payers, employers, people with MDD, and society) and over various time horizons.

Consistent with previous models developed as part of IVI's Open-Source Value Project (OSVP), the IVI-MDD model is an individual-level simulation model that compares treatment sequences for MDD over a pre-selected time period. In addition to capturing the costs and benefits from a healthcare system or private payer perspective, the model includes 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, the model incorporates the flexibility of including multiple scientifically defensible assumptions, allowing for exploration of structural uncertainty and customization based on user preferences and available data. The intention was that such an approach would help highlight existing data and method gaps to promote conversations across stakeholders and underline areas for future research.

3 Methods

3.1 Patient population

The patient population for the model is individuals of age 18 to 64 years newly diagnosed with MDD by a healthcare provider. As an individual-level simulation, the model is structured to provide users with the flexibility to evaluate outcomes for subgroups of individuals defined by age, race/ethnicity, gender, and socioeconomic status.

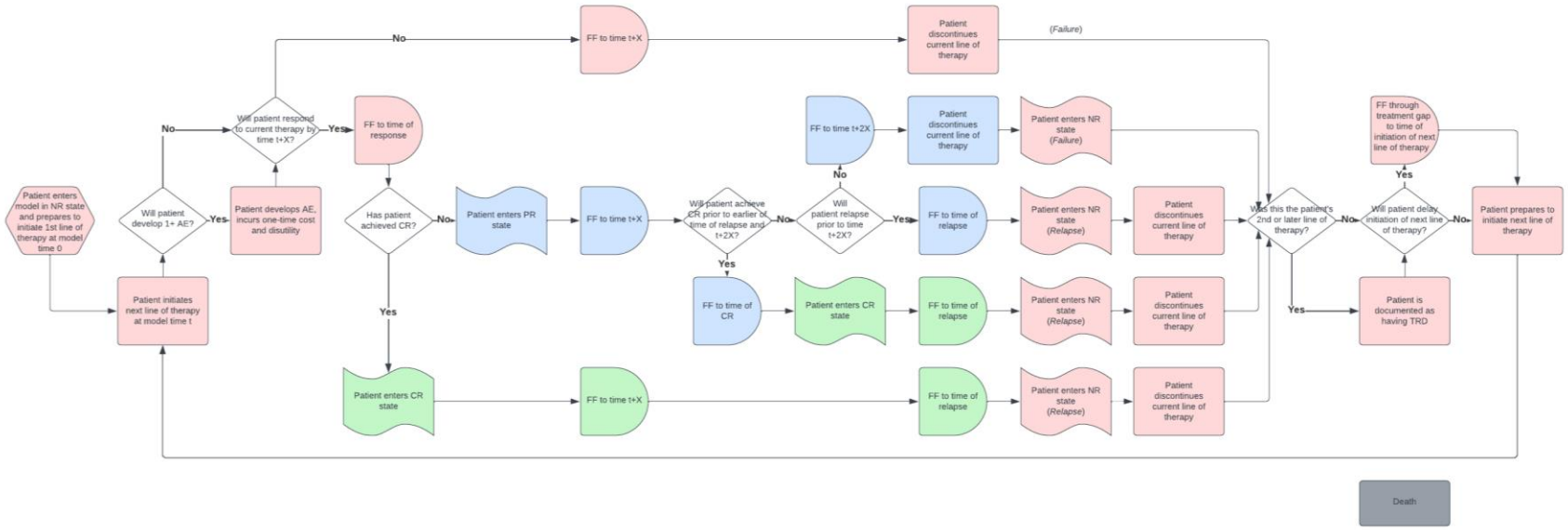
In future versions of the model, IVI plans to work with our research partners and stakeholders to evaluate the feasibility of modeling outcomes for individuals that are: (1) aged 65 and older, (2) insured by Medicaid, and (3) those with specific comorbid conditions (e.g., diabetes).

3.2 Model structure

The model structure is a continuous-time individual-patient simulation model. Each simulated patient enters the model at time 0 as a newly-diagnosed MDD patient – i.e., one who is currently experiencing a major depressive episode – and as such, begins each model run in the "no response" (NR) state. Based on the type of treatment each patient receives and the values of the associated efficacy inputs, patients may move at various times throughout each model run among NR and two other health states: complete response (CR) and partial response (PR). As summarized in Section 6.9.2 of the draft model protocol document, the definitions of the health states were informed by clinical guidelines, input from the MDD Advisory Group, and our targeted literature review of past economic models and real-world effectiveness studies. Responses to treatments were operationalized based on score changes in established clinical instruments such as the Hamilton Depression Rating Scale, Montgomery–Åsberg Depression Rating Scale (MADRS), or the General Health Questionnaire. For example, CR can be defined as achieving a MADRS score of <= 10, and PR with a >=50% reduction in MADRS score but not an absolute score <=10.

The patient journey following diagnosis of MDD in the simulation is described in detail below and visually summarized in **Figure 1**.

Figure 1: CT-IPS model



AE, adverse event; CR, complete response; FF, fast forward; NR, no response; PR, partial response; TRD, treatment-resistant depression; X, the time allotted to each of the initiation and initiation extension phases.

The model relies on the following assumptions based on considerations of feasibility and computational efficiency, which may be simplifications of real-world clinical practice and patient journeys. We consulted with clinical experts to ensure that for economic modeling purposes, these assumptions would adequately represent the disease, treatment impacts, and the actions taken by patients and their providers of care in this disease space. We welcome feedback/suggestions on these assumptions in the public comment period. Major assumptions in the model include the following:

- All patients start in the NR health state at the first MDD episode. In the base case, patients are assumed to immediately enter the first "initiation phase" and initiate the first line of therapy, if applicable, in the given pathway.
- For each line of therapy, the duration of the initiation phase is fixed and governed by treatment-specific, user-modifiable input parameters. In the base case, the initiation phase is assumed to last for eight weeks for each treatment based on treatment guidelines, real-world database studies, and feedback from the multi-stakeholder advisory group.
- Patients may transition from NR to either the CR or PR health state at any point in time during the initiation phase. They may also remain in the NR health state for the duration of the initiation phase.
- Surviving patients who transition to CR and PR will remain in these states for the duration of the given initiation phase.
- At the conclusion of the initiation phase, patients remaining in NR immediately discontinue the current line of therapy and initiate the next line of therapy, if applicable, at the start of a new initiation phase, except under the conditions that qualify them to experience a treatment gap.
- At the conclusion of the initiation phase, patients in CR enter the maintenance phase while patients in PR enter a separate "initiation extension" phase.
- The maximum duration of the initiation extension phase is fixed and governed by treatment-specific, user-modifiable input parameters. In the base case, to be consistent with the initiation phase, the initiation extension phase is assumed to last for at most eight weeks for each treatment.
- Direct transitions from PR to CR may only occur during the initiation extension phase. During the initiation extension phase, patients may either remain in the PR state for the duration of the phase or transition to either NR (via relapse) or CR.
- Patients who achieve CR or PR during the early response period, defined in the base case as the first four[1] weeks of treatment with a given line of therapy, are considered "early" responders.

[1] Users may experiment with alternative values via a user-modifiable input governing duration of the early response period.

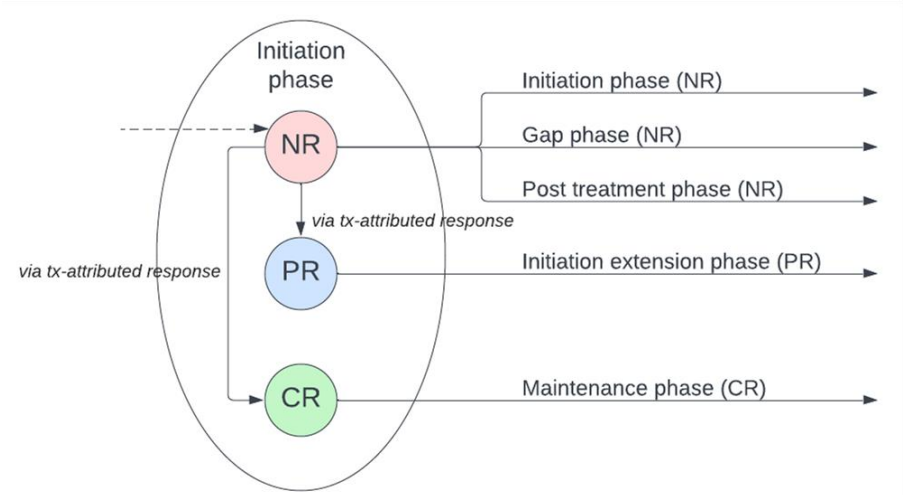
- Patients who achieve sustained CR during the initiation extension phase move to standard maintenance at phase end and remain in CR until experiencing relapse.
- In the base case, patients who remain in PR at the end of the initiation extension phase and those who experience relapse from either PR or CR prior to end of this phase immediately discontinue the current line of therapy, return to NR, and initiate the next line of therapy, if applicable, starting a new initiation phase (except under conditions that qualify them to experience a treatment gap).
- Patients entering the maintenance phase in CR remain in CR until they experience relapse.
- Time to relapse from treatment-attributed response depends on state (PR or CR), time to best response (early vs. late), and line of therapy.
- Following relapse, patients immediately discontinue treatment, return to NR, and either initiate the next line of therapy at the start of a new initiation phase or experience a treatment gap, if applicable.
- All patients initiating treatment are assumed to remain on treatment throughout the initiation, initiation extension, and maintenance phases.
- Adverse events (AEs) will occur at an incident rate for each therapy class and will have associated disutility (but no associated AE-related cost).
- Once a patient has completed all available lines of therapy in a pathway, the patient moves to a "post-treatment" phase for the remaining duration of the modeled time horizon.
- Patients do not receive treatment while in the pre-treatment, gap, and post-treatment phases, but they may achieve spontaneous response.
- Patients who achieve spontaneous response during the pre-treatment or gap phase are assumed to remain untreated and in the given phase until they experience relapse from spontaneous response.
- Patients who achieve spontaneous response are assumed to relapse at a rate proportional to the maximum of relapse rates applicable to patients in treatment-attributed CR or PR.
- In the post-treatment phase, there is no restriction on the number of times patients may achieve spontaneous response and subsequent relapse.

Figure 2 and **Figure 3** below focus on the first phase of the base-case model journey, the treatment initiation phase (also referred to simply as the "initiation phase"), defined in the base case as the first eight weeks (shown as "X" weeks in **Figure 2**) of treatment with a given line of therapy. During each initiation phase, surviving patients may change state at most once, moving from NR to PR or NR to CR. Adverse events are evaluated, and associated utility decrements applied, at the time of initiation of each line of therapy.

Figure 2: Treatment initiation phase process map

AE, adverse event; CR, complete response; FF, fast forward; PR, partial response; X, initiation phase duration and maximum duration of initiation extension phase.

Figure 3: Treatment initiation phase simplified flow diagram



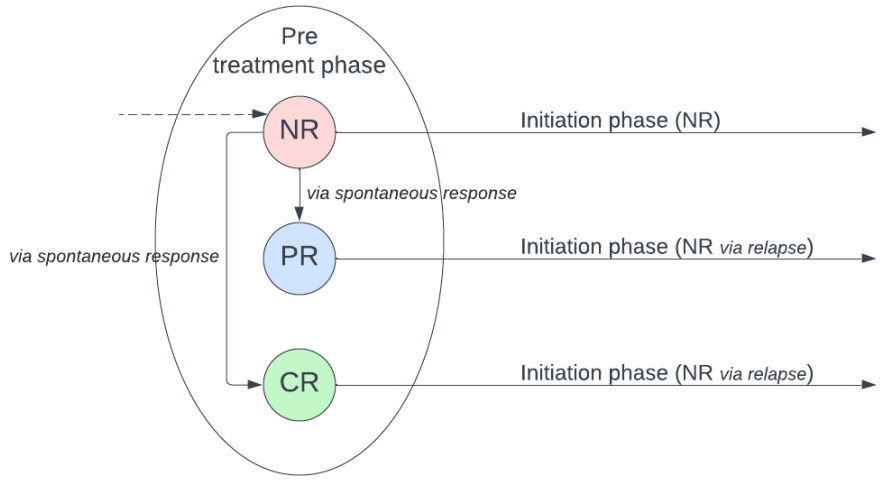
CR, complete response; NR, no response; PR, partial response; tx, treatment.

Outside the base case, for pathways containing at least one[2] therapeutic option, positive values of the user-modifiable input for proportion of patients who delay initial treatment allows some patients to alternatively begin their journeys in a "pre-treatment" phase preceding the first initiation phase (Error! Not a valid bookmark self-reference.). During this and other phases during which patients do not actively receive treatment, patients may experience spontaneous response and transition to either PR[3] or CR. The duration of the delay is preliminarily estimated for each patient based on the values of two user-modifiable input parameters: probability of delayed initiation of first-line therapy and maximum time to initiation of first-line therapy assuming no spontaneous response. At the end of the period given by this patient-specific preliminary estimate, each patient who has not yet achieved spontaneous response exits the phase and proceeds to the first initiation phase to initiate the first line of therapy. For every other patient, the pre-treatment phase ends at the time of relapse from spontaneous response, regardless of whether relapse occurs before or after either the user-specified universal maximum or the patient-specific preliminary estimate of time to initiation of first-line therapy.

[2] Under all scenarios including the base case, for the "no active treatment" pathway (i.e., the pathway devoid of all modeled treatments, specified in the UI by selecting "No active treatment" for the pathway's first line of therapy), simulated patients begin and remain in the "post-treatment" phase for the entirety of the modeled time horizon.

[3] In the base case, the value of the user-modifiable input for likelihood of spontaneous PR is 0%, disallowing transitions to PR via spontaneous response.

Figure 4: Pre-treatment phase simplified flow diagram



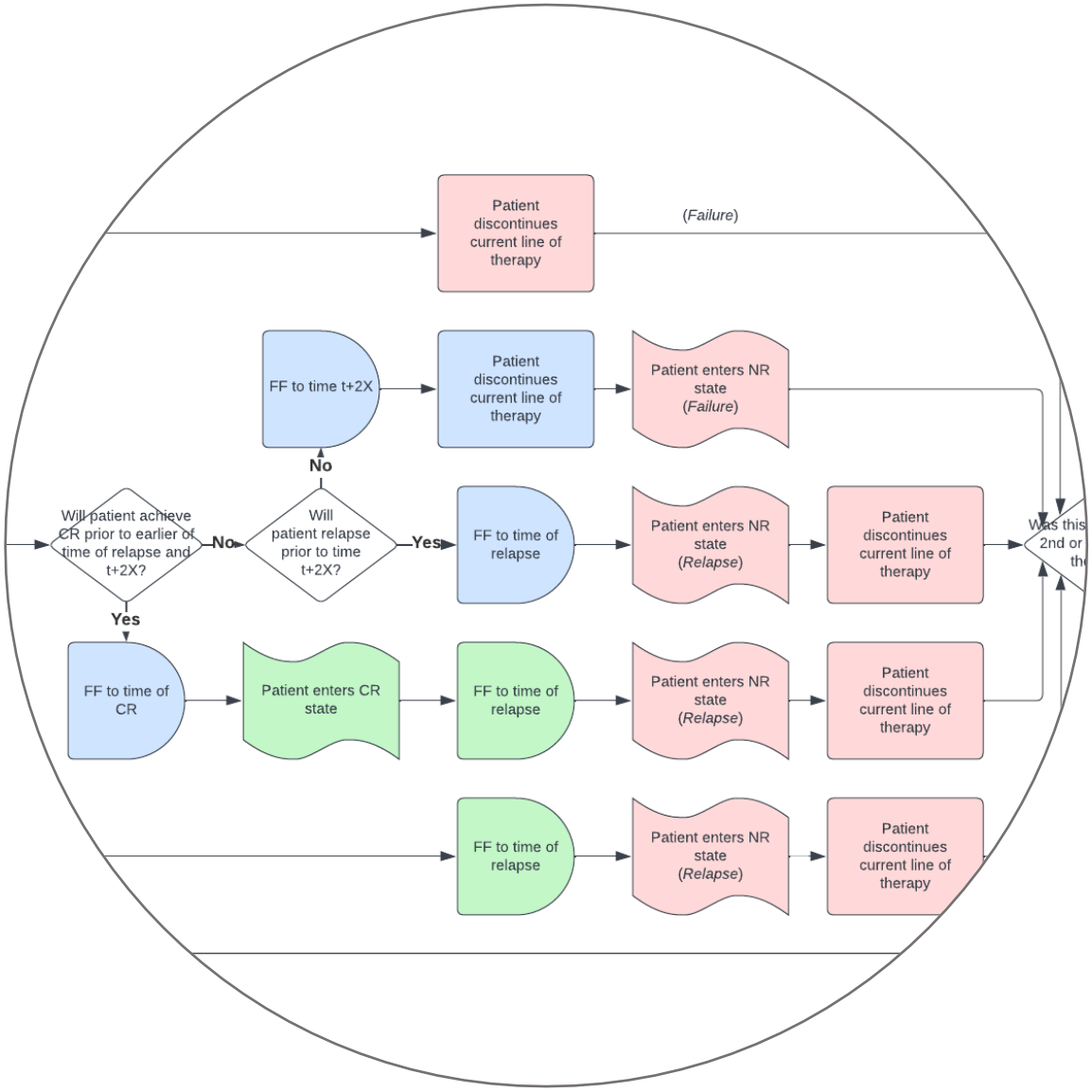
CR, complete response; NR, no response; PR, partial response.

After the initiation phase, patients who have not transitioned to CR or PR are assumed to immediately discontinue the current line of therapy and exit the current initiation phase, heading to either the next initiation phase to begin the next line of therapy, if applicable, or to the terminal post-treatment phase should completion of the most recent line of therapy coincide with completion of all available lines of therapy in the pathway (**Figure 3**). Patients headed to the next initiation phase with additional lines of therapy to explore may do so immediately on the heels of the previous initiation phase or following a stint in an interim gap phase characterized by lack of treatment. Patients in CR at the end of the initiation phase remain on treatment and proceed directly to the maintenance phase. Finally, patients in PR at the end of the initiation phase are given additional time to achieve CR during an initiation extension phase lasting at most eight weeks in the base case and occurring immediately following the initiation phase.

During the initiation extension phase, patients may remain in PR for the duration of the phase, transition to CR, or relapse before or after first achieving CR (**Figure 5** and **Figure 6**). In the base case, patients who remain in PR throughout the full eight-week initiation extension phase without relapsing or achieving CR are assumed to discontinue the current line of therapy and return to NR upon exiting the phase at the end of the eight weeks. However, for positive values of a user-modifiable input parameter for likelihood of procession to maintenance while in PR, a subset of these patients may instead continue treatment with the current line of therapy and proceed directly

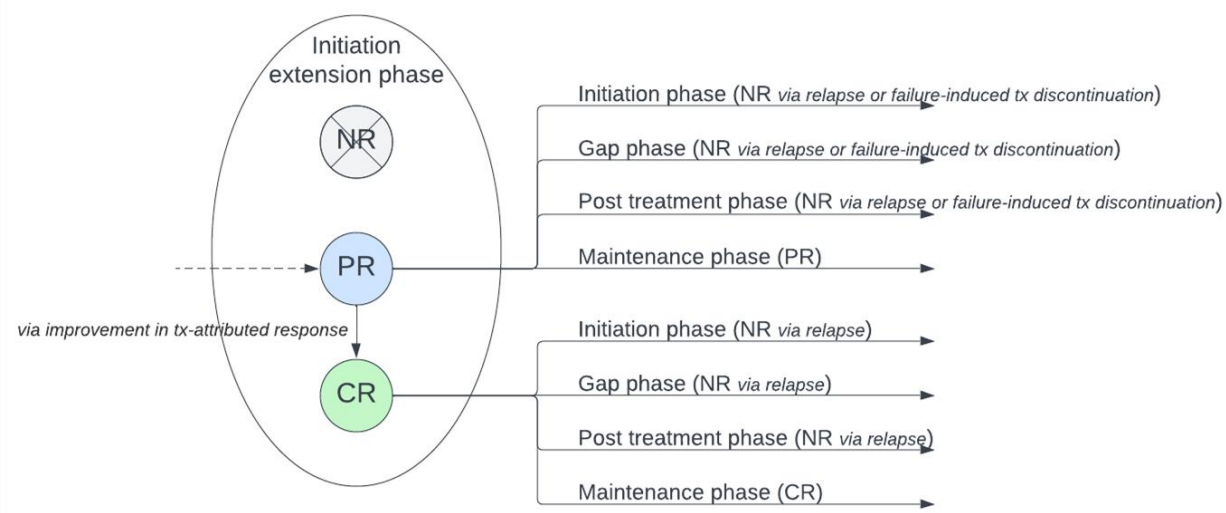
from the initiation extension phase to the maintenance phase despite having never achieved CR (**Figure 6**). Patients who relapse mid-phase, with or without having first achieved CR, are assumed to discontinue the current line of therapy, return to NR, and exit the initiation extension phase at the time of relapse. Finally, similar to patients who fail to respond to treatment during the initiation phase, patients who either fail to achieve adequate response or relapse from either PR or CR during the initiation extension phase may proceed to either the next initiation phase, a gap phase, or the post-treatment phase depending on whether there is at least one more line of therapy available to the patient in the given pathway.

Figure 5: Treatment initiation extension and maintenance phases process map



CR, complete response; FF, fast forward; NR, no response; PR, partial response; X, initiation phase duration and maximum duration of initiation extension phase.

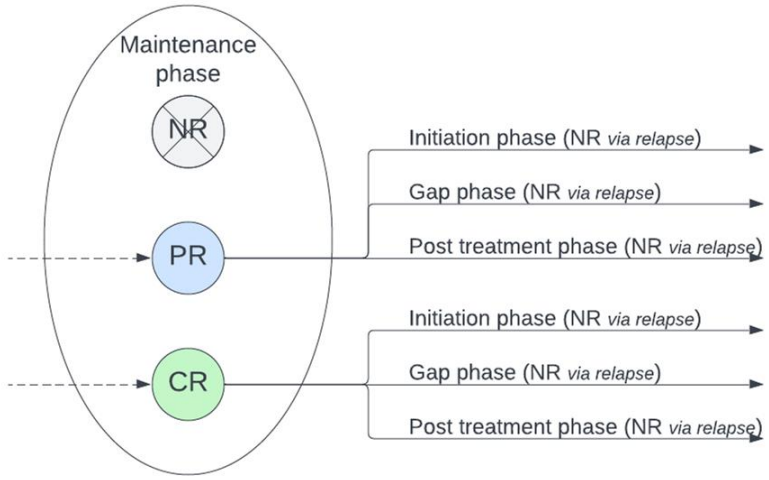
Figure 6: Treatment initiation extension phase simplified flow diagram



CR, complete response; NR, no response; PR, partial response; tx, treatment.

During the maintenance phase, patients remain on treatment and in the same state (CR or PR) they were in upon arrival (**Figure 7**). The maintenance phase ends when the patient eventually relapses, at which time the patient transitions to NR, discontinues the current line of therapy, and exits the phase (**Figure 5**). As with patients who fail to achieve adequate response or relapse during the initiation extension phase, following relapse, patients exiting the maintenance phase may proceed to either the next initiation phase, a gap phase, or the post-treatment phase depending on whether there is at least one more line of therapy available to the patient in the given pathway.

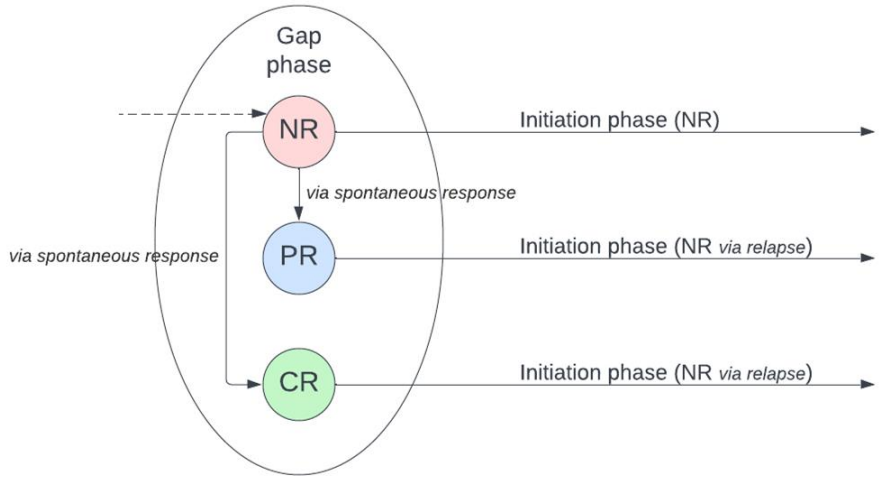
Figure 7: Treatment maintenance phase simplified flow diagram



CR, complete response; NR, no response; PR, partial response.

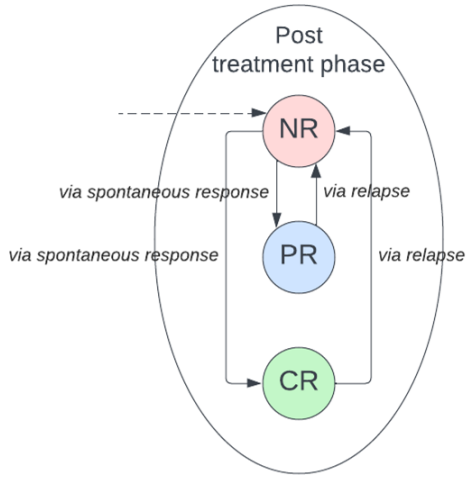
As in the pre-treatment phase, patients may only enter the gap and post-treatment phases while in NR, receive no treatment during the phase, but may transition from NR to PR or CR via spontaneous response (**Figure 4**, **Figure 8**, and **Figure 9**). However, a handful of key differences distinguish the pre-treatment, gap, and post-treatment phases from one another. First, while the amount of time a patient may spend in the pre-treatment phase without achieving spontaneous response may be limited by a user-modifiable maximum value, both the gap phase and the post-treatment phase may last through the end of the modeled time horizon regardless of a patient's state. Second, while patients may enter and exit the gap phase throughout the simulation, the initiation phase is the model's only phase that is accessible exclusively at model time 0. Moreover, the post-treatment phase is the model's only terminal phase for patients who survive through the entire modeled time horizon; every surviving patient who enters the post-treatment phase must remain there until the end of the simulation. Third, while patients who achieve spontaneous response mid-phase must exit both the pre-treatment and gap phases at the time of relapse, patients in the post-treatment phase may experience multiple bouts of spontaneous response and subsequent relapse during the phase.

Figure 8: Treatment gap phase simplified flow diagram



CR, complete response; NR, no response; PR, partial response.

Figure 9: Post-treatment phase simplified flow diagram



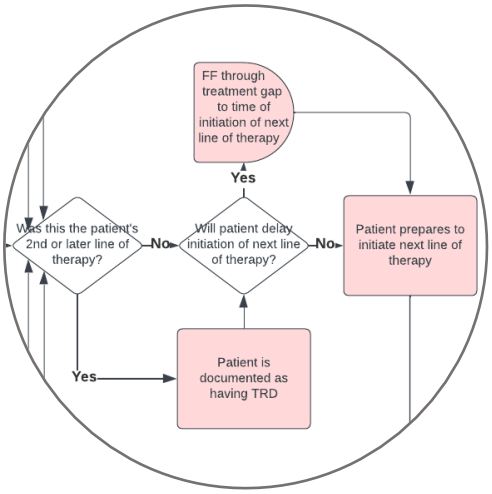
CR, complete response; NR, no response; PR, partial response.

Finally, all three phases are also distinguishable by the proportions of patients to whom utility, cost, and mortality inputs specific to "treatment-resistant" depression (TRD) may apply during these phases. In this model, TRD-specific inputs are applied to individuals who have completed at least two lines of therapy (**Figure 10**) or have no lines of therapy remaining. Because patients may only visit the pre-treatment phase prior to the first line of therapy[4], by definition, it is impossible

[4] When modeling the pathway containing no treatment options, patients proceed directly to the post-treatment phase at model time 0 and remain there for the duration of the modeled time horizon.

for anyone in this phase to have already obtained TRD status. At the other extreme, patients may only enter the post-treatment phase after exhausting all available lines of therapy in a given pathway. Only the gap phase may host both patients who have and patients who have not yet reached TRD status. This is owed to the fact that patients may enter the gap phase following completion of any but the last line of therapy in a given pathway as long as the user-modifiable inputs specifying gap likelihoods are positive and the pathway contains at least three lines of therapy.

Figure 10: Development of TRD with additional treatment options remaining



FF, fast forward; TRD, treatment-resistant depression.

Refer to **Section 4.8.1** for more information regarding the rationale behind the model's definition of TRD.

3.3 Timing of discrete events

The relative time at which a patient's next change of state or phase (i.e., event) occurs may be either pre-determined and fixed or stochastic depending on the event. For example, in general, the duration of each treatment initiation phase (i.e., time from start of the initiation phase to start of the next phase) is a deterministic function of the treatment(s) initiated at the start of the phase. However, time from treatment initiation at the start of the initiation phase to first response (PR or CR) is randomly determined for each patient based on input or calculated initiation-phase likelihoods of PR and CR.

In this model, if time to a given event is stochastic, it is assumed to be exponentially distributed. These distributional assumptions were made based on data availability. Users may specify alternative distributional assumptions by modifying the model R code. The exponential distribution is consistent with use of constant transition probabilities in cycle-based Markov models and is analogous to using single-cycle transition probabilities in a discrete-time model with infinitely short cycles.

3.3.1 The exponential distribution

If time to a given event T is exponentially distributed with rate λ (in units of events per unit of time), then the probability p that T is less than or equal to a given non-negative real number t is given by its cumulative distribution function $F(t|\lambda)$:

$$F(t|\lambda) = \mathbb{P}(T \leq t|\lambda) = 1 - e^{\lambda t} = p$$

In some cases, model inputs used to determine timing of events are given as rates, but more often they are given in terms of probabilities. We can convert a probability to a rate by solving for rate λ in the equation above:

$$\lambda = \frac{\ln(1-p)}{t}$$

3.3.2 Inverse sampling

For an exponentially distributed random variable T with rate λ and cumulative distribution function $F(t|\lambda)$ defined for real-valued $t \geq 0$, the inverse cumulative distribution function $F^{-1}(p|\lambda)$ for $p \in [0,1]$ can be calculated by solving for t in the equation for $F(t|\lambda)$ provided above:

$$F^{-1}(p|\lambda) = \frac{\ln(1-p)}{\lambda} = t$$

Thus, a unique random sample $\hat{T}$ can be taken from T's distribution using the inverse sampling method. In the model, time $\hat{T}$ to a given event for a given patient is randomly determined using the inverse sampling method via the following steps:

1. Generate a random number u between 0 and 1, inclusive.

2. Calculate $\hat{T} = F^{-1}(u|\lambda) = \frac{\ln(1-u)}{\lambda}$.

3.3.3 Events by phase

Treatment initiation phase

As mentioned previously, duration of each initiation phase is fixed. However, patients may transition from NR to either CR or PR during the phase, and time from phase start to this transition is randomly determined for each patient and initiation phase. Given phase duration d, initiation-phase likelihood of CR $p_{CR|NR}$, and initiation-phase likelihood of PR $p_{PR|NR}$, rates of CR, PR, and overall response (CR or PR) are $\lambda_{CR|NR}, \lambda_{PR|NR}$, and $\lambda = \lambda_{CR|NR} + \lambda_{PR|NR}$, respectively, for exponentially-distributed times to CR, PR, and overall response $T_{CR|NR}, T_{PR|NR}$, and $T = \min(T_{CR|NR}, T_{PR|NR})$, respectively, are calculated assuming:

$$\mathbb{P}\left(T_{CR|NR} \leq d \mid \lambda_{CR|NR}\right) = p_{CR|NR}$$

$$\mathbb{P}\left(T_{PR|NR} \leq d \mid \lambda_{PR|NR}\right) = p_{PR|NR}$$

$$\mathbb{P}\left(T = \min\left(T_{CR|NR}, T_{PR|NR}\right) \leq d \mid \lambda = \lambda_{CR|NR} + \lambda_{PR|NR}\right) = p_{CR|NR} + p_{PR|NR}$$

Where $\mathbb{P}(\cdot)$ denotes probability. At the start of each initiation phase, a preliminary estimate $\hat{T}$ of time to response T is randomly generated as described above. If $\hat{T} \leq d$, the patient is assumed to achieve response after $\hat{T}$ days of the initiation phase and a second random real number $u \in [0,1]$ is generated to determine whether the patient transitions to CR or PR. If $u < \frac{\lambda_{PR|NR}}{\lambda}$, the patient

transitions to PR; otherwise, the patient transitions to CR. If, on the other hand, $d < \hat{T}$, the patient remains in NR for the duration of the initiation phase.

Pre-treatment phase

At the start of the simulation, a uniformly distributed real number $u \in [0,1]$ is randomly generated and compared to a given likelihood of delayed initiation of first-line therapy q. If $u \leq q$, the patient delays initiation of first-line treatment and enters the pre-treatment phase. Given a fixed maximum time to treatment initiation assuming no spontaneous response d_{max}, 56-day (eight-week) likelihood of spontaneous CR $p_{CR|NR}$, and 56-day likelihood of spontaneous PR $p_{PR|CR}$, rates of treatment initiation, spontaneous CR, spontaneous PR, and spontaneous response overall are $\gamma, \lambda_{CR|NR}, \lambda_{PR|NR}$, and $\lambda = \lambda_{CR|NR} + \lambda_{PR|NR}$, respectively, for exponentially-distributed times to treatment initiation, spontaneous CR, spontaneous PR, and any spontaneous response $T_{tx}, T_{CR|NR}, T_{PR|NR}$, and $T = \min(T_{CR|NR}, T_{PR|NR})$, respectively, are calculated assuming:

$$\mathbb{P}(T_{tx} \leq d_{max} \mid \gamma) = q$$

$$\mathbb{P}\left(T_{CR|NR} \leq 56 \mid \lambda_{CR|NR}\right) = p_{CR|NR}$$

$$\mathbb{P}\left(T_{PR|NR} \leq 56 \mid \lambda_{PR|NR}\right) = p_{PR|NR}$$

$$\mathbb{P}\left(T = \min\left(T_{CR|NR}, T_{PR|NR}\right) \leq 56 \mid \lambda = \lambda_{CR|NR} + \lambda_{PR|NR}\right) = p_{CR|NR} + p_{PR|NR}$$

At the start of the pre-treatment phase, random samples $\hat{T}_{tx}$ and $\hat{T}$ of time to treatment initiation T_{tx} and time to any spontaneous response T are generated based on calculated rates γ and λ, respectively. If $\hat{T} < \min(d_{max}, \hat{T}_{tx})$, the patient is assumed to achieve spontaneous response after $\hat{T}$ days of the pre-treatment phase and a second random real number $v \in [0,1]$ is generated to determine whether the patient transitions to CR or PR at time $\hat{T}$. If $v < \frac{\lambda_{PR|NR}}{\lambda}$, the patient transitions to PR; otherwise, the patient transitions to CR. If, on the other hand, $\min\left(d_{max}, \hat{T}_{tx}\right) \leq \hat{T}$, the patient remains in NR for the duration of the pre-treatment phase or $\min\left(d_{max}, \hat{T}_{tx}\right)$ days.

For a patient who achieves spontaneous response after $\hat{T}$ days in the pre-treatment phase, relapse rate ρ for exponentially distributed time to relapse T_{NR} is estimated assuming:

$$\mathbb{P}(T_{NR} \leq 365 \mid \rho) = r$$

for a given annual probability of relapse r. At the time of spontaneous response, a random sample $\hat{T}_{NR}$ of time to relapse T_{NR} is generated based on calculated rate ρ and used to determine the time at which the patient will relapse from spontaneous response and exit the pre-treatment phase.

Treatment initiation extension phase

Given a fixed maximum initiation extension phase duration d_{max}, a probability of transitioning from PR to CR during the phase $p_{CR|PR}$, an annual likelihood of relapse from PR $r_{NR|PR}$, and an annual likelihood of relapse from CR $r_{NR|CR}$, rates of CR, relapse from PR, and relapse from CR, $\lambda_{\mathrm{CR}|PR}, \rho_{NR|PR}$, and $\rho_{NR|CR}$, respectively, for exponentially-distributed times to CR, relapse from PR, and relapse from CR $T_{CR|\mathrm{PR}}, T_{NR|\mathrm{PR}}$, and $T_{NR|CR}$, respectively, are calculated assuming:

$$\mathbb{P}\left(T_{CR|PR} \leq d_{max} \mid \lambda_{CR|PR}\right) = p_{CR|PR}$$

$$\mathbb{P}\left(T_{NR|PR} \leq 365 \mid \rho_{NR|PR}\right) = r_{NR|PR}$$

$$\mathbb{P}\left(T_{NR|CR} \leq 365 \mid \rho_{NR|CR}\right) = r_{NR|CR}$$

At the start of each treatment initiation extension phase, random samples $\hat{T}_{CR|PR}$ and $\hat{T}_{NR|PR}$ of times to CR ($T_{CR|PR}$) and relapse from PR ($T_{NR|PR}$) are generated based on rates $\lambda_{CR|PR}$ and $\rho_{NR|PR}$, respectively. If $\hat{T}_{CR|PR} < \min\left(d_{max}, \hat{T}_{NR|PR}\right)$, the patient is assumed to achieve and transition to CR after $\hat{T}_{CR|PR}$ days in the initiation extension phase. If, on the other hand, $\min\left(d_{max}, \hat{T}_{NR|PR}\right) \leq \hat{T}_{CR|PR}$, the patient is assumed to remain in PR for $\min\left(d_{max}, \hat{T}_{NR|PR}\right)$ days, after which the patient exits the phase.

For each patient who achieves CR after $\hat{T}_{CR|PR}$ days in the treatment initiation extension phase, at the time of transition to CR, a random sample $\hat{T}_{NR|CR}$ of time to relapse from CR, $T_{NR|CR,}$, is generated based on calculated rate $\rho_{NR|CR}$ and used to determine a tentative time at which the patient will relapse from CR. The patient is then assumed to exit the initiation extension phase after a total time in phase of min $(d_{max}, \hat{T}_{CR|PR} + \hat{T}_{NR|CR})$ days.

Treatment maintenance phase

Given an annual probability of relapse from treatment-attributed response r, the relapse rate ρ for exponentially distributed time to relapse T_{NR} is calculated assuming:

$$\mathbb{P}(T_{NR} \leq 365 \mid \rho) = r$$

At the start of each maintenance phase, a random sample $\hat{T}_{NR}$ of time to relapse T_{NR} is generated and used to determine time from phase start to three simultaneous events precipitated by relapse from treatment-attributed response: phase exit, return to NR, and treatment discontinuation.

Treatment gap phase

Each time a patient relapses or experiences treatment failure after initiation of the first line of therapy but prior to initiation of the last line of therapy in a given modeled pathway, a uniformly distributed real number $u \in [0,1]$ is randomly generated and compared to a given likelihood of delayed treatment re-initiation (i.e., likelihood of experiencing a treatment gap between lines of therapy) q. If $u \leq q$, the patient delays initiation of the next line of therapy and enters a new treatment gap phase. For a patient entering a gap phase, given 56-day likelihoods of spontaneous CR and spontaneous PR, $p_{CR|NR}$ and $p_{PR|CR}$, respectively, and rates of spontaneous CR, spontaneous PR, and any spontaneous response (CR or PR), $\lambda_{CR|NR}, \lambda_{PR|NR}$, and $\lambda = \lambda_{CR|NR} + \lambda_{PR|NR}$, respectively, for exponentially distributed times to spontaneous CR, spontaneous PR, and any spontaneous response, $T_{CR|NR}, T_{PR|NR}$, and $T = \min(T_{CR|NR}, T_{PR|NR})$, respectively, are calculated assuming:

$$\mathbb{P}\left(T_{CR|NR} \leq 56 \mid \lambda_{CR|NR}\right) = p_{CR|NR}$$

$$\mathbb{P}\left(T_{PR|NR} \leq 56 \mid \lambda_{PR|NR}\right) = p_{PR|NR}$$

$$\mathbb{P}\left(T = \min\left(T_{CR|NR}, T_{PR|NR}\right) \leq 56 \mid \lambda = \lambda_{CR|NR} + \lambda_{PR|NR}\right) = p_{CR|NR} + p_{PR|NR}$$

At the start of each gap phase, random samples $\hat{T}_{tx}$ and $\hat{T}$ of exponentially distributed time to treatment re-initiation, T_{tx}, and time to any spontaneous response, T, are generated based on a given rate of treatment re-initiation γ and calculated spontaneous-response rate λ. If $\hat{T} < \hat{T}_{tx}$, the patient is assumed to achieve spontaneous response after $\hat{T}$ days of the gap phase and a second random real number $v \in [0,1]$ is generated to determine whether the patient transitions to CR or PR after $\hat{T}$ days in the current gap phase. If $v < \frac{\lambda_{PR|NR}}{\lambda}$, the patient transitions to PR; otherwise, the patient transitions to CR. If, on the other hand, $\hat{T}_{tx} \leq \hat{T}$, the patient remains in NR for $\hat{T}_{tx}$ days before exiting the phase to re-initiate treatment with a new line of therapy in the next initiation phase.

For a patient who achieves spontaneous response after $\hat{T}$ days in the gap phase, relapse rate ρ for exponentially distributed time to relapse T_{NR} is estimated assuming:

$$\mathbb{P}(T_{NR} \leq 365 \mid \rho) = r$$

for a given annual probability of relapse r. At the time of spontaneous response, a random sample $\hat{T}_{NR}$ of time to relapse T_{NR} is generated based on calculated rate ρ and used to determine the time at which the patient will relapse from spontaneous response and exit the gap phase en route to the next treatment initiation phase.

Post-treatment phase

As in the gap phase, at the start of each post-treatment phase, time to spontaneous response is randomly sampled based on a calculated response rate. Each time a patient achieves spontaneous response, time to relapse is randomly sampled based on a calculated relapse rate and used to

determine the time at which a patient returns to NR following a period of spontaneous response. This cycle of spontaneous response followed by subsequent relapse is repeated until the earlier of death and end of the modeled time horizon, each time using a new pair of randomly sampled values for time to response and time to relapse to determine the times at which a patient transitions from one state to the next.

3.3.4 Death

As depicted in **Figure 1**, patients may die at any point in time during the modeled time horizon. Given an annual probability of death k, mortality rate δ for exponentially distributed time to death D is calculated assuming:

$$\mathbb{P}(D \leq 365 \mid \delta) = k$$

Each time a patient's mortality rate changes, whether due to aging or to a change in either health state or TRD status, a new value for time to death is randomly sampled. If, based on the patient's most recently sampled time to death, the patient will die before experiencing the next change of state, phase, or mortality rate, the patient is assumed to die at the time given by the sampled value. Otherwise, the patient remains alive at least until experiencing the next change of state, phase, or mortality rate, at which time a new value of time to death is randomly sampled and compared to one or more other relevant relative event times to determine the next event experienced by the patient and the time at which this event will occur.

3.4 Key features of the economic analysis

The model was developed following good modelling practices (1, 2). **Table 1Error! Reference source not found.** describes the key features of the model, justification, and sources, where relevant.

Table 1: Features of the economic analysis

Feature	Chosen value(s)	Justification & source
Time horizon	Ranging from 1 year to lifetime, as selected by the user.	To cater to different decision needs, the model is designed to run for a range of different time periods, from 1 year to 100 years (lifetime).

Feature	Chosen value(s)	Justification & source
		However, note that because the model is limited to at most four lines of therapy, the average patient (not all those simulated) will likely complete treatment within 3 to 4 years.
Model structure	Continuous-time individual-level simulation model.	Improved model efficiency and flexibility relative to Markov cohort model.
Cycle length	NA.	Continuous-time simulation model; no cycle length.
Half-cycle correction	NA (not required).	Continuous-time simulation model; no cycle length.
Treatment waning effect	Indirectly via relapse.	Continuous-time simulation model with relapse programmed as a function of treatment status; line of therapy, if applicable; and degree and timing of response.
Health state utilities	Health state utility values (HSUVs) from the literature.	The model relies on two sources of state-specific utility values in the base case, one to inform state-specific utility for patients with non-TRD MDD (3), and a second to inform state-specific utility for patients with TRD (4). See **Section 4.8** for further detail.
Disutility for serious adverse events (SAEs).	Disutility for SAE, along with incidence proportions by treatment type, taken from literature.	Sullivan (2004)(5)
Health-state-related healthcare costs	State-specific healthcare costs (excluding cost of modelled MDD treatments) taken from the literature.	Simon (2000)(6), Olfson (2018)(7)
Clinical outcome measures	Months to first CR given any CR, months to first response (CR or PR) given any response, months to first relapse given ≥ 1 relapse, months in remission given any remission, months in response (CR or PR) given any response, months on treatment, months in CR, months in PR, months in NR, months in any response (CR or PR), months in remission, number of relapses given ≥ 1 relapse, number of lines of therapy with SAEs, number of lines of therapy initiated, number of CRs experienced, number of PRs experienced, number of relapses, number of treatment failures, life years, quality-adjusted life years (QALYs)	See **Section 5.1** for further detail.
Economic outcome measures	Costs of treatment, costs of health-state-related (non-treatment) healthcare, productivity loss, average clinical effectiveness ratio (ACER), incremental	Standard measures; see **Section 5.2** for further detail.

Feature	Chosen value(s)	Justification & source
	cost effectiveness ratio (ICER), net monetary benefit (NMB)	
Discount rate for benefits and costs	3% annually.	Standard choice
Perspective	Multiple perspectives are possible: patient, healthcare provider (physician), payer, or society.	Caregiver burden, indirect costs (e.g., productivity losses) are estimated based on inputs from the literature.
Mortality	General all-cause population mortality with multipliers based on health state, treatment status, and line of treatment.	Sources for background mortality are US life-tables; sources for mortality multipliers are from Oude Voshaar (2021)(8) and Reutfors (2018)(9)

ACER, average cost-effectiveness ratio; CR, complete response; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; NA, not applicable; NMB, net monetary benefit; NR, no response; PR, partial response; QALY, quality-adjusted life year; SAE, serious adverse event; TR, treatment resistant; TRD, treatment-resistant depression.

3.5 Interventions

Treatment options considered in the model include:

- No active treatment
- Pharmacotherapy, categorized by drug class (SSRI, SNRI, atypical antidepressant, antipsychotic)
- Psychotherapy (e.g., behavioral therapy, CPT, MBCT, IPT, psychodynamic therapy, supportive therapy)
- Add-on brain stimulation therapy (e.g., ECT, rTMS, VNS, DBS)
- Combination therapies (e.g., SSRI + psychotherapy)

More specific details of each class are shown in **Table 2** below. Individuals can receive up to four lines of therapy during the simulation. Treatment options may be limited to reflect practice.

Table 2: Specific examples of each treatment class and availability by line in model

Treatment group/class	Examples of specific therapies	Availability by line
No active treatment	Standard health care with no specific treatment for MDD	Any line (assumed that if selected, for any given line, a patient does not resume therapy)
SSRI	Citalopram, escitalopram, fluoxetine, paroxetine, sertraline	Any line
SNRI	Venlafaxine, desvenlafaxine, duloxetine	Any line
Atypical antidepressants	Bupropion, esketamine, ketamine, mirtazapine	Any line
Antipsychotics	Aripiprazole, quetiapine, olanzapine	Second line and beyond, in combination with an antidepressant
Psychotherapy	Cognitive behavioral therapy, interpersonal therapy, problem-solving therapy, psychodynamic therapy, supportive therapy	Any line
Combination therapy of antidepressant and psychotherapy	SSRI + psychotherapy, SNRI + psychotherapy, atypical antidepressant and psychotherapy	Any line
Combination therapy of antidepressant and antipsychotics	SSRI + antipsychotic, SNRI + antipsychotic, atypical antidepressant + antipsychotic	Second line and beyond
Brain stimulation therapy (usually in combination with antidepressants and/or psychotherapy)	Deep brain stimulation (DBS), electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), vagus nerve stimulation (VNS)	Fourth line (add-on therapy)

DBS, deep brain stimulation; ECT, electroconvulsive therapy; MDD, major depressive disorder; rTMS, repetitive transcranial magnetic stimulation; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; tDCS, transcranial direct current stimulation; VNS, vagus nerve stimulation.

4 Model inputs

The model inputs were selected from two targeted literature reviews and inputs from our multi-stakeholder advisory group. Incremental searches were also conducted to fill in data gaps. In cases where multiple inputs were available, we prioritized inputs that were most compatible with the target patient population and treatment journey (e.g., line of therapy), and from systematic literature reviews and network-meta-analyses. In the absence of data, assumptions were made based on literature and/or inputs from our clinical expert advisors. These considerations are described in detail below.

4.1 Baseline patient characteristics

Baseline patient characteristics as input into the model to generate a patient cohort are presented in **Table 3** below.

Table 3: Base case background characteristics for population cohort

Patient characteristic	Value (% of model population)	Source
Age at time 0 (years)		
Age 18 to 24	26.6%	Carelon analysis of treatment patterns
Age 25 to 34	24.2%	Carelon analysis of treatment patterns
Age 35 to 44	22.0%	Carelon analysis of treatment patterns
Age 45 to 54	16.9%	Carelon analysis of treatment patterns
Age 55 to 64	10.2%	Carelon analysis of treatment patterns
Percent female	60.1%	Carelon analysis of treatment patterns
Quartile of socioeconomic status (SES)		
SES Q1 (low SES), percent	16.0%	Pizzicato (2023)(10), Table 1, PMID: 37276037
SES Q2, percent	24.3%	Pizzicato (2023), Table 1, PMID: 37276037
SES Q3, percent	28.5%	Pizzicato (2023), Table 1, PMID: 37276037
SES Q4 (high SES), percent	31.2%	Pizzicato (2023), Table 1, PMID: 37276037

SES, socioeconomic status.

4.2 Efficacy inputs for achieving complete or partial response

Efficacy inputs for treatments considered in the model are informed by targeted review of published literature. In the model, first-line efficacy of each individual treatment or combination of treatments apart from add-on brain stimulation therapy is given by a probability of achieving CR within the treatment initiation phase, a relative likelihood of achieving PR vs CR within the treatment initiation phase, and a conditional probability of achieving CR during the initiation extension phase given PR during the initiation phase. The efficacy of add-on brain stimulation therapy is captured via risk ratios (RRs) for CR and PR during the initiation phase relative to the likelihoods of CR and PR for the treatment(s) to which brain stimulation therapy is added.

Base-case first-line probabilities of CR in the initiation phase for non-brain stimulation therapies are contained in **Table 4**. Values used for efficacy inputs in the base case are based on published literature. In cases where multiple input values were available, inputs from systematic literature review were prioritized. Input values were also reviewed by the Clinical Expert Panel to ensure they generally align with their understandings of real-world patient experiences.

Table 4: First-line probability of CR during the initiation phase by treatment

Treatment class	Likelihood of CR	Source
SSRI	41.6%	Average of values in Khoo (2015)(11), Weinmann (2008)(12), Annemans (2014)(13), Nordström (2012)(14), Montgomery & Andersen (2006)(15), PMID: 16877901
SNRI	46.4%	Average of values in Khoo (2015), Table 1, PMID: 26293743; Annemans (2014); Nordström (2012), Table 1, PMID: 22433753, itself sourcing to Montgomery & Andersen (2006), PMID: 16877901
Atypical antidepressant	43.1%	Average of values in Khoo (2015), Table 1, PMID: 26293743
Psychotherapy	41.5%	Average of values in Koeser (2015)(16), Figure 2, PMID: 26040631; Ross (2019)(17), Table 1, PMID: 31658472, itself sourcing to Gartlehner (2016)(18), PMID: 26857743
SSRI + psychotherapy	52.0%	Multiplication of SSRI 1st-line probability of CR with NMA-derived risk ratio value combined vs. pharmacotherapy (1.25) in Cuijpers (2020)(19), Table 3, PMID: 31922679
SNRI + psychotherapy	58.0%	Multiplication of SNRI 1st-line probability of CR with NMA-derived risk ratio value combined vs. pharmacotherapy (1.25) in Cuijpers (2020), Table 3, PMID: 31922679
Atypical antidepressant + psychotherapy	53.9%	Multiplication of atypical antidepressant 1st-line probability of CR with NMA-derived risk ratio value combined vs. pharmacotherapy (1.25) in Cuijpers (2020), Table 3, PMID: 31922679
SSRI + atypical antidepressant	50.2%	Multiplication of SSRI 1st-line probability of CR with risk ratio of bupropion augmentation based on data from Mohamed (2017)(20), Table 2, PMID: 28697253
SNRI + atypical antidepressant	56.0%	Multiplication of SNRI 1st-line probability of CR with risk ratio of bupropion augmentation based on data from Mohamed (2017), Table 2, PMID: 28697253
SSRI + antipsychotic	53.9%	Multiplication of SSRI 1st-line probability of CR with risk ratio of aripiprazole augmentation based on data from Mohamed (2017), Table 2, PMID: 28697253
SNRI + antipsychotic	60.1%	Multiplication of SNRI 1st-line probability of CR with risk ratio of aripiprazole augmentation based on data from Mohamed (2017), Table 2, PMID: 28697253
Atypical antidepressant + antipsychotic	55.8%	Assumption, based on multiplication of atypical antidepressant 1st-line probability of CR with risk ratio of aripiprazole augmentation based on data from Mohamed (2017), Table 2, PMID: 28697253

CR, complete response; NMA, network meta analysis; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

For each non-brain stimulation therapy, first-line likelihood of PR during the initiation phase is calculated as the product of therapy-specific first-line likelihood of CR during the initiation phase (**Table 4**) and a common ratio of first-line likelihood of PR to first-line likelihood of CR shared

by all non-brain stimulation therapies. The value used in the base case for this ratio is given in **Table 5** below.

Table 5: Relative likelihood of PR vs CR during the initiation phase

Treatment class	Relative likelihood of PR vs CR	Source
Non-brain stimulation therapy	0.487	Average of values in Koeser (2015)(16), Figure 2, PMID: 26040631; Ross (2019)(17), Table 1, PMID: 31658472, referencing Gartlehner (2016)(18), PMID: 26857743

CR, complete response; RR, risk ratio.

Base-case efficacy input values specific to add-on brain stimulation therapy are provided in **Table 6**. For each of CR and PR, likelihood of response during the initiation phase is calculated as the product of the relevant likelihood of response for the treatment(s) to which brain stimulation therapy is added and the appropriate risk ratio specific to add-on brain stimulation therapy.

Table 6: Relative risk (RR) of response with add-on brain stimulation therapy during the initiation phase

Outcome	RR vs no add-on brain stimulation therapy	Source
CR of add-on brain stimulation therapy	2.35	Health Quality Ontario (2016)(21), Figure A4, PMID: 27110317
PR of add-on brain stimulation therapy	2.58	Health Quality Ontario (2016), Figure A3, PMID: 27110317

CR, complete response; PR, partial response; RR, relative risk.

Based on recommendations from clinical guidelines and real-world clinical practice, patients who achieve PR in the initiation phase are allowed to remain on treatment for an additional period of time (defaulted to eight weeks) before either discontinuing treatment or proceeding to maintenance. In the base case, during this initiation extension phase, a first-line probability of achieving CR given PR of 38.0% is applied to all treatments (22).

As patients move through lines of therapy, treatment-specific efficacy is assumed to decrease in the base case based on patterns observed in the STAR*D trial (23). The CR efficacy decrements applied in the base case to lines two and later in both the initiation and initiation extension phases are presented in **Table 7** in the form of risk ratios relative to first-line probabilities of CR.

Table 7: Relative risk (RR) of CR by treatment line

Treatment line	RR of CR vs 1st-line	Source
2nd line	0.83	Estimated from Rush (2006)(23), Table 4, PMID: 17074942
3rd line	0.37	Estimated from Rush (2006), Table 4, PMID: 17074942
4th line	0.35	Estimated from Rush (2006), Table 4, PMID: 17074942

CR, complete response; RR, risk ratio.

Similar efficacy reductions are not applied in the base case to treatment-specific likelihoods of PR in the initiation phase due to inconsistent evidence. However, the model includes a similar set of three risk-ratio inputs specific to PR (each set to 1.00 in the base case) that users may modify to change the likelihoods of PR in later lines of therapy, if desired.

4.3 Spontaneous response

The model allows for the possibility of spontaneously achieved response during phases in which patients do not actively receive treatment (i.e., the pre-treatment, gap, and post-treatment phases). Spontaneous CR is considered by default in the model, with an eight-week likelihood of 12.5% taken directly from a meta-analysis by Mekonen (2022)(24). With a base-case likelihood of 0%, spontaneous PR is not considered by default.

4.4 Relapse as a function of degree and time to response

To better reflect real-world treatment experience, contrary to most models that are "memoryless", time to relapse is specified as a function of specific drivers identified in the literature. Age, line of therapy, treatment type, and adherence were all put forward in the literature as potential drivers of eventual time to relapse for patients with MDD, but the consistent driver in terms of number of studies and weight of evidence was the scale and speed of treatment response. Multiple studies have highlighted that, for various types of pharmacotherapy, the speed and scale of response to treatment is strongly associated with duration of response or remission over the longer term (25-29). Based on these findings, we constructed the model to permit different relapse rates based on response status (PR vs CR) and time from treatment initiation to best response (early vs late), as well as treatment status and line of therapy.

In the model, among treated patients, a hazard ratio (HR) is applied to the relapse rates of patients who achieve "early" response to produce the relapse rates of patients who achieve "late" response, with "early" response defined as response achieved during a response period beginning on the first day of treatment for a given line of therapy. In the base case, this early response period is set to four weeks, per analyses by Chitnis (2023)(30), though the time within which patients must achieve CR or PR to constitute early response is user modifiable. As shown in **Table 8**, in the base case, patients who achieve early CR are assumed to relapse at two-thirds the rate at which patients who achieve late CR relapse (30). Absent published data on the relationship between relapse rates for early vs. late PR, a hazard ratio of 1.0 is assumed, indicating no difference in relapse rates for early vs. late PR.

Table 8: Hazard ratio (HR) of relapse rate for early responders versus late responses by response state

Response state	Relapse HR, early vs late response	Source
CR	0.67	Chitnis (2023)(30), Abstract, DOI: 10.1016/j.jval.2023.03.2335
PR	1.0	Assumption

CR, complete response; HR, hazard ratio; PR, partial response.

Annual probabilities of relapse when treated and in CR (i.e., annual probability of moving from treatment-attributed CR to NR), by line of therapy and applicable to late responders, are contained below in **Table 9**.

Table 9: Annual probability of relapse (CR to NR) by treatment line for patients who achieved CR outside of the early response period

Treatment line	Annual probability of NR given CR	Source
1st line	35.0%	Chitnis (2023)(30), Abstract, DOI: 10.1016/j.jval.2023.03.2335
2nd line	52.0%	Chitnis (2023), Abstract, DOI: 10.1016/j.jval.2023.03.2335
3rd line	45.5%	Chitnis (2023), Abstract, DOI: 10.1016/j.jval.2023.03.2335
4th line	58.3%	Chitnis (2023), Abstract, DOI: 10.1016/j.jval.2023.03.2335

CR, complete response; NR, no response.

Annual probabilities of relapse when treated and in PR (i.e., annual probability of moving from treatment-attributed PR to NR), by line of therapy and specific to late responders, are contained below in **Table 10**.

Table 10: Annual probability of relapse (PR to NR) by treatment line for patients who achieved PR outside of the early response period

Treatment line	Annual probability of NR given PR	Source
1st line	58.6%	Rush (2006)(23), Table 5, PMID: 17074942
2nd line	67.7%	Rush (2006), Table 5, PMID: 17074942
3rd line	76.0%	Rush (2006), Table 5, PMID: 17074942
4th line	83.3%	Rush (2006), Table 5, PMID: 17074942

CR, complete response; NR, no response; PR, partial response.

Finally, patients who are not on treatment but who have achieved response spontaneously are assigned a relapse HR of 2.06 in the base case relative to the maximum relapse rate estimated for patients on treatment, thus increasing the likelihood of relapse for patients not on treatment relative to patients on treatment (31).

Note that HRs must be applied to rates rather than to probabilities. As discussed in **Section 3.3.3**, to convert an annual probability of relapse r to a rate of relapse ρ, the model assumes time to relapse T_{NR} is exponentially distributed with $\mathbb{P}(T_{NR} \leq 365\ days \mid \rho) = r$.

4.5 Treatment gaps

Following relapse (i.e., patient returns to NR from PR or CR *during* the initiation extension or maintenance phase) or treatment failure (i.e., patient fails to achieve PR or CR during the initiation phase or remains in PR through the end of the full initiation extension phase without next proceeding to maintenance) and subsequent treatment discontinuation, a patient may experience a gap in treatment (i.e., gap phase) before beginning a new line of therapy. Base-case probabilities of treatment gaps by line of therapy and cause of treatment discontinuation (i.e., relapse or treatment failure) are contained below in **Table 11**. IVI is currently conducting a claims-based treatment gap analysis with Carelon to derive more updated and granular estimates to populate the base case in the next version of the model.

Table 11: Probability of treatment gap between consecutive lines of therapy

Gap type	Probability	Source
Gap following relapse in line 1	34.7%	Estimated from Rush (2006)([23]), Figure 1, PMID: 17074942
Gap following failure in line 1	34.7%	Estimated from Rush (2006), Figure 1, PMID: 17074942
Gap following relapse in line 2	52.3%	Estimated from Rush (2006), Figure 1, PMID: 17074942
Gap following failure in line 2	52.3%	Estimated from Rush (2006), Figure 1, PMID: 17074942
Gap following relapse in line 3	57.3%	Estimated from Rush (2006), Figure 1, PMID: 17074942
Gap following failure in line 3	57.3%	Estimated from Rush (2006), Figure 1, PMID: 17074942

Barring spontaneous response, gap duration is determined via treatment re-initiation rates in units of patients per day. Base-case rates of re-initiation by line of therapy and cause of treatment discontinuation are contained below in **Table 12**. Similarly, these values will be updated with final results from the treatment gap analysis of Carelon data.

Table 12: Rate of treatment re-initiation between lines of therapy

Gap type	Rate (patients per day)	Implied mean time to treatment re-initiation (days)	Source
Gap following relapse in line 1	0.0167	60	Assumption
Gap following failure in line 1	0.0111	90	Assumption
Gap following relapse in line 2	0.0167	60	Assumption
Gap following failure in line 2	0.0083	120	Assumption
Gap following relapse in line 3	0.0167	60	Assumption
Gap following failure in line 3	0.0067	150	Assumption

By default, delayed initiation of the first line of therapy is not permitted; for pathways with at least one therapeutic option available, patients are assumed to immediately enter the first initiation phase to initiate treatment at model time 0. However, this is customizable via two additional input parameters: probability of delayed initiation prior to line one (equal to 0% in the base case) and maximum time to initiation of line one assuming no spontaneous response.

4.6 Adverse event inputs

The literature on AEs in treatment of depression lacks consensus on a common set of AEs across the different treatment options in our model, and further discussion with the Clinical Expert Panel confirmed this. Studies looking at the rates of AEs across different treatments, including in controlled trials, find they vary widely and are in part driven by the severity of disease in the patient group in question. Another area of contention related to questions as to what extent certain AEs of

treatment are really sequelae of disease. Again, discussions with our Clinical Expert Panel confirmed the lack of consensus in this area. For example, suicide ideation is a recognized sequelae of MDD, but may also be a side effect of treatment initiation. Once on (an effective) treatment, suicide ideation falls compared to untreated populations.

Another facet of the challenges in modeling AEs was determining the severity of the more commonly observed AEs such as dry mouth and nausea, and the extent to which they will impact treatment strategies and patient outcomes. Such events are often less severe for those with active MDD treatments, and do not always trigger removal of treatment or discontinuation because they tend to be less severe. The benefits of receiving treatments often outweigh the risks/impacts of these side effects.

Due to the above considerations, in our base case, we consider only severe adverse events (SAEs) in the model and apply them based on a general rate from the literature, as SAEs are more robustly reported in the literature and more likely to have a notable impact on a patient's health and quality of life. Two incidence proportions for SAEs are considered in the model: one for pharmacotherapy and one for add-on brain stimulation therapy. For lines of therapy containing both add-on brain stimulation therapy and at least one pharmaceutical treatment, likelihood of SAEs is estimated as the maximum of these proportions. It is assumed that psychotherapy will not lead to SAEs.

SAEs do not impact discontinuation rates in our model, as our model uses general discontinuation rates that have likely accounted for discontinuation rates due to SAEs. There is also evidence to suggest AEs are not the primary driver of discontinuation for MDD treatment. Similarly, we do not directly model the impacts of SAEs on healthcare resource utilization, as they are likely accounted for in our inputs for healthcare costs.

Likelihoods of experiencing one or more SAE during a single initiation phase during which patients receive an applicable treatment are contained in **Table 13**. Health utility impacts of SAEs are discussed in **Section 4.8**. The model is constructed such that up to five additional AEs of interest, with user input proportions and associated utility decrements, may be considered by the end user.

Table 13: Probability of experiencing ≥1 SAE by treatment class

Treatment class	Probability	Source
Pharmacotherapy	0.9%	Jakobsen (2017)(32)
Brain stimulation therapy	1.5%	Overvliet (2021)(33)

SAE, serious adverse event.

4.7 Mortality

Mortality rates used in the model are based on all-cause mortality from the 2020 National Life Tables for the US (34), stratifying by age and sex, adjusted with mortality multipliers based on the health state and treatment status (i.e., whether treated, and the line of therapy).

Many MDD models have historically ignored mortality as an outcome, as randomized controlled trials (RCTs) of antidepressants are neither powered to assess mortality outcomes nor conducted for a sufficient period to accrue mortality-comprehensive data for its samples. However, this lack of historical modeling and robust assessment in RCTs does not necessarily indicate that successful treatment of MDD does not lead to mortality benefits. Multiple studies have shown strong empirical evidence that among patients with MDD, those with more severe disease (8), those who have failed more lines of therapy (9), and those who have not received recent care (35) have higher rates of all-cause mortality relative to other patients with MDD. This suggests that provision of mortality benefits from RCTs is non-existent due to limitations in study design, not to a lack of empirical association between disease states and mortality risk. As such, in the context of this model, we believe it is important to include mortality effects, not by treatment, but by health state and TRD status, to properly capture the impacts of access and response to treatment on downstream effects that accrue from treatment failure and relapse from treatment-attributed response. To that end, mortality multipliers in the form of HRs are applied based on both health state and TRD status. Base-case values for these HRs are shown below in **Table 14**, and additional information on the rationale behind the criteria governing application of TRD-specific inputs in the model can be found in **Section 4.8.1**.

Table 14: Mortality HRs applied based on patient state and condition

State / condition	Mortality HR	Source
CR vs no MDD	1.00	Oude Voshaar (2021)(8)

State / condition	Mortality HR	Source
PR vs no MDD	1.41	Oude Voshaar (2021)
NR vs no MDD	2.13	Oude Voshaar (2021)
TRD vs non-TRD, age 18-29	2.03	Reutfors (2018)(9)
TRD vs non-TRD, age 30-49	1.49	Reutfors (2018)
TRD vs non-TRD, age 50-69	1.19	Reutfors (2018)
TRD vs non-TRD, age 70+	1.19	Assumption

CR, complete response; HR, hazard ratio; MDD, major depressive disorder; NR, no response; PR, partial response; TR, treatment resistant; TRD, treatment-resistant depression.

4.8 Health utilities

4.8.1 Derivation of utility data for use in the model

The model incorporates utilities taken from the literature and applies them to simulated patients based on current health state (CR, PR, and NR) and treatment status (i.e., number of completed lines of therapy and number of available lines of therapy remaining). The justification for this level of gradation is found in the literature. In **Table 15** below. We summarize the health state utility values (HSUVs) applied to patients who have not yet completed two lines of therapy and have at least one available line of therapy remaining, and the HSUVs applied to those patients who have either completed two or more lines of therapy or have no lines of therapy remaining, by health state.

Numerous studies have highlighted that TRD populations are regularly shown to be associated with lower quality of life and HSUVs (4), as can be seen in **Table 15**. Various arguments have been put forward for this consistent finding. It is believed that the longer a patient is suffering from MDD, especially after multiple treatment failures, the worse the patient's quality of life, in essence due to the compounding nature of the disease. It is also often believed that those patents for whom multiple treatments are ineffective may in fact be a subgroup of patients whose conditions are inherently more severe than are the conditions of those who successfully find sustainably effective treatment solutions. For this reason, such patients are likely to have lower quality-of-life scores. In the context of this model, these ideas are reflected in the application of TRD-specific utilities and other input values to patients who have completed at least two lines of therapy.

Finally, the application of TRD-specific utilities and other inputs to patients who have exhausted all available lines of therapy in a given pathway is likely justifiable when the impacts of prolonged periods of non-treatment on a patient's health are taken into account. Evidence suggests that off-treatment patients tend to have higher overall relative mortality (35) and possibly higher healthcare costs (36). Furthermore, some research indicates that patients who are non-adherent to therapy have notably lower HSUVs than do those who are adherent to therapy (37). This information is encapsulated in the model via application of TRD-specific utilities and other inputs to patients who are no longer able to receive treatment within a modeled pathway (i.e., who have exhausted all available user-designated treatment options within a given pathway[5]).

Table 15: Utility values by condition and health state

Condition – State	HSUV	Source
Non-TRD – CR	0.82	Sapin (2004)(3)
Non-TRD – PR	0.74	Sapin (2004)
Non-TRD – NR	0.58	Sapin (2004)
TRD – CR	0.82	Yrondi (2020)(4)
TRD – PR	0.54	Yrondi (2020)
TRD – NR	0.39	Yrondi (2020)

CR, complete response; HSUV, health state utility value; MDD, major depressive disorder; NR, no response; PR, partial response; TR, treatment resistant; TRD, treatment-resistant depression.

The model also incorporates disutility associated with SAEs via HSUV decrements. These decrements are applied in the model by adding negative utility values to the total accrued utility among patients experiencing SAEs. The disutility value used for SAEs in the base case model is shown below in **Table 16**.

Table 16: AE-associated HSUV decrement values

Adverse event	HSUV decrement	Source
SAE	-0.129	Sullivan (2004)(38), maximum reported AE disutility

AE, adverse event; HSUV, health state utility value; SAE, serious adverse event.

[5] For the "no active treatment" pathway (i.e., the pathway devoid of all modeled treatments, specified in the UI by selecting "No active treatment" for the pathway's first line of therapy), all simulated patients are considered to have inputs specific to patients with TRD for the duration of the modeled time horizon, as if they had already exhausted all available lines of therapy at model time 0, the time of disease onset.

4.9 Cost and healthcare resource use

4.9.1 Treatment-specific costs

Costs associated with each class of treatment, and the sources from which these cost inputs are derived, are contained below in **Table 17**. For combination therapies, costs are derived from the summation of applicable individual therapies. All costs are presented in 2021 United States dollars (USD). All costs are annual except those for brain stimulation therapy which are a one-time cost incurred at the start of each initiation phase during which brain stimulation therapy is received.

Table 17: Treatment-specific cost inputs

Treatment class	Cost (2021 USD)	Source
SSRI	414.16	Lowest WAC price from Practice Management Information Corporation. Medical Fees 2021. Los Angeles, CA.
SNRI	1,869.32	Sullivan (2004) (38)
Atypical antidepressant	7,042.44	Lowest WAC price for bupropion from Practice Management Information Corporation. Medical Fees 2021. Los Angeles, CA.
Psychotherapy	20,072.00	Lowest price for cognitive behavioral therapy from Practice Management Information Corporation. Medical Fees 2021. Los Angeles, CA.
Antipsychotic	54.80	Lowest WAC price from Practice Management Information Corporation. Medical Fees 2021. Los Angeles, CA.
Brain stimulation therapy	17,532.00	Lowest rTMS price from Practice Management Information Corporation. Medical Fees 2021. Los Angeles, CA.

AE, adverse event; CA, California; rTMS, repetitive transcranial magnetic stimulation; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; USD, United States dollar; WAC, wholesale acquisition cost.

4.9.2 Direct medical costs

Direct medical costs by health state are detailed below in **Table 18**. As with both health utilities and mortality risk, costs are a function of treatment status (i.e., whether patients have gone through two lines of therapy, and whether they have exhausted all available lines of therapy/treatments) and health state (NR, PR and CR). As with health state utilities, TRD-specific inputs were applied to patients who have either completed two or more lines of therapy or have no lines of therapy remaining. In the model, direct disease-related costs unrelated to treatment are calculated for each patient as the sum of the products of days spent in each state and treatment status, and the cost per day associated with the relevant state and treatment status. For example, using the base-case unit costs shown below, if a one-year run of the model finds a patient spending 200 days in CR without

TRD ("non-TRD – CR"), 100 days in NR without TRD ("non-TRD – NR"), and 65 days in NR with TRD ("TRD – NR"), direct medical costs for this patient will be calculated as:

$$\left(200\ days\ \times \frac{\$5{,}673\ /\ year}{365\ days\ /\ year}\right) + \left(100\ days \times \frac{\$8{,}223\ /\ year}{365\ days\ /\ year}\right) + \left(65\ days\ \times \frac{\$14{,}171\ /\ year}{365\ days\ /\ year}\right)$$

Discussion of the rationale behind the model's definition of TRD is provided in **Section 4.8.1**.

All costs are presented as annual 2021 USD.

Table 18: Annual direct medical cost by patient condition and state

Condition - State	Cost (2021 USD)	Source
Non-TRD – CR	5,673.00	Simon (2000)(39)
Non-TRD – PR	6,968.00	Simon (2000)
Non-TRD – NR	8,223.00	Simon (2000)
TRD – CR	9,776.00	Simon (2000), Amos (2018)(40), Olfson (2018)(7)
TRD – PR	12,008.00	Simon (2000), Amos (2018), Olfson (2018)
TRD – NR	14,171.00	Simon (2000), Amos (2018), Olfson (2018)

CR, complete response; MDD, major depressive disorder; NR, no response; PR, partial response; TR, treatment resistant; TRD, treatment-resistant depression; USD, United States dollar.

4.9.3 Adverse event costs

Potential costs associated with adverse events are not explicitly included in this model, as the cost of treatment and subsequent impacts are captured by the background medical costs applied to each health state. As such, adding explicitly AE-related costs would risk double counting.

4.9.4 Indirect costs

Indirect costs as utilized in this model can be broken down into two primary categories: transportation costs in seeking treatments incurred by patients or their family members, and productivity-loss costs (i.e., absenteeism/presenteeism).

Transportation costs by treatment class are presented below in **Table 19**. For combination therapies, costs are assumed to be the maximum of the applicable treatment class categories except for brain stimulation therapy, which is considered an additional one-time add-on cost. All costs are presented as 2021 USD. All costs are annual except brain stimulation therapy, which incurs a one-time cost at use.

Table 19: Transportation indirect costs by treatment class

Treatment Class	Cost (2021 USD)	Source
Pharmacotherapy	404.21	Estimated from Lave (1998)(41), Table 3, PMID: 9672056
Psychotherapy	152.99	Estimated from Lave (1998), Table 3, PMID: 9672056
Brain stimulation therapy	101.05	Estimated from Lave (1998), Table 3, PMID: 9672056

USD, United States dollar.

Indirect costs are derived as the product of the health-state specific percentage of patients experiencing absenteeism and presenteeism and annual income by sex and age. These percentages are displayed below in **Table 20** and earnings in **Table 21**. Annual incomes are presented as 2023 USD. Productivity loss costs are calculated as the sum of the product of average annual income for the patient's current age category, absenteeism and presentism rates for the patient's current health state, and years spent in the relevant age category and health state.

Table 20: Absenteeism and presenteeism percentages by state utilized in productivity-loss indirect cost calculations

Health State	Percentage	Source
Absenteeism		
CR	3.6%	Estimated from Jain (2022)(42), Figure 3b, PMID: 35953786
PR	7.1%	Estimated from Jain (2022), Figure 3b, PMID: 35953786
NR	11.7%	Estimated from Jain (2022), Figure 3b, PMID: 35953786
Presenteeism		
CR	12.5%	Estimated from Jain (2022), Figure 3b, PMID: 35953786
PR	23.4%	Estimated from Jain (2022), Figure 3b, PMID: 35953786
NR	31.2%	Estimated from Jain (2022), Figure 3b, PMID: 35953786

CR, complete response; NR, no response; PR, partial response.

Table 21: Annual income by sex and age utilized in productivity-loss indirect cost calculations.

Demographic (sex, age)	Income (2023 USD)	Source
Female		
Age 18 to 24	16,190.89	Estimated based on BLS data on employment (https://www.bls.gov/cps/demographics.htm) and earnings (https://www.bls.gov/news.release/wkyeng.t03.htm#)
Age 25 to 34	33,713.51	Estimated based on BLS data on employment (https://www.bls.gov/cps/demographics.htm) and earnings (https://www.bls.gov/news.release/wkyeng.t03.htm#)
Age 35 to 44	38,294.09	Estimated based on BLS data on employment (https://www.bls.gov/cps/demographics.htm) and earnings (https://www.bls.gov/news.release/wkyeng.t03.htm#)
Age 45 to 54	37,503.38	Estimated based on BLS data on employment (https://www.bls.gov/cps/demographics.htm) and earnings (https://www.bls.gov/news.release/wkyeng.t03.htm#)
Age 55 to 64	28,226.52	Estimated based on BLS data on employment (https://www.bls.gov/cps/demographics.htm) and earnings (https://www.bls.gov/news.release/wkyeng.t03.htm#)
Age 65+	6,475.573	Estimated based on BLS data on employment (https://www.bls.gov/cps/demographics.htm) and earnings (https://www.bls.gov/news.release/wkyeng.t03.htm#)
Male		
Age 18 to 24	21,170.17	Estimated based on BLS data on employment (https://www.bls.gov/cps/demographics.htm) and earnings (https://www.bls.gov/news.release/wkyeng.t03.htm#)
Age 25 to 34	45,804.54	Estimated based on BLS data on employment (https://www.bls.gov/cps/demographics.htm) and earnings (https://www.bls.gov/news.release/wkyeng.t03.htm#)
Age 35 to 44	57,357.35	Estimated based on BLS data on employment (https://www.bls.gov/cps/demographics.htm) and earnings (https://www.bls.gov/news.release/wkyeng.t03.htm#)
Age 45 to 54	58,506.40	Estimated based on BLS data on employment (https://www.bls.gov/cps/demographics.htm) and earnings (https://www.bls.gov/news.release/wkyeng.t03.htm#)
Age 55 to 64	47,722.85	Estimated based on BLS data on employment (https://www.bls.gov/cps/demographics.htm) and earnings (https://www.bls.gov/news.release/wkyeng.t03.htm#)
Age 65+	13,654.04	Estimated based on BLS data on employment (https://www.bls.gov/cps/demographics.htm) and earnings (https://www.bls.gov/news.release/wkyeng.t03.htm#)

BLS, Bureau of Labor Statistics; USD, United States dollar.

5 Model outcomes

5.1 Clinical outcomes

The model outputs a series of clinical outcomes that are used to construct the composite outcomes for the economic analyses such as time spent in specific states, proportion of patients who have moved beyond the second line of therapy at any specific time, and the time a patient may spend on vs. off treatment. The clinical outcomes can be categorized into three essential types: time-to event/duration outcomes; event rate outcomes, and proportion outcomes. These are listed in the following sections.

5.1.1 Time-to-event/duration outcomes

Conditional outcomes (averaged across the subset of patients meeting a given condition):

- *Months to first CR given any CR* – the mean number of months before a patient achieves their first CR excluding those patients who never achieve CR.
- *Months to first response (CR or PR) given any response* – the mean number of months before a patient achieves their first CR or PR excluding those patients who never achieve a response.
- *Months to first relapse given ≥1 relapse* – the mean number of months before a patient experiences their first relapse excluding those patients who never experience a relapse. (Note: relapse is not limited to patients who have achieved CR; a patient in PR or CR in any phase other than initiation is eligible for relapse.)
- *Months in remission given any remission* – the mean number of months a patient spends in remission excluding those patients who never achieve remission. (Note: a patient is considered to have achieved remission after three months in CR.)
- *Months in response (CR or PR) given any response* – the mean number of months a patient spends in CR or PR excluding those patients who never achieve a response.

Non-conditional outcomes (averaged across all patients):

- *Months on treatment* – the mean number of months a patient receives active treatment.
- *Months in CR* – the mean number of months a patient is in the CR state.
- *Months in PR* – the mean number of months a patient is in the PR state.
- *Months in NR* – the mean number of months a patient is in the NR state.

- *Months in response (CR or PR)* – the mean number of months a patient is in CR or PR state.
- *Months in remission* – the mean number of months a patient is in remission.

5.1.2 Event rate outcomes

Conditional outcomes (averaged across the subset of patients meeting a given condition):

- *Number of relapses given ≥1 relapse* – the mean number of relapses experienced across patients, excluding those patients who never experience a relapse.

Non-conditional outcome (averaged across all patients):

- *Number of SAEs* – the mean number of lines of therapy during which a patient experienced an SAE across patients.
- *Number of lines of therapy initiated* – the mean number of lines of therapy initiated across patients.
- *Number of CRs experienced* – the mean number of CRs experienced across patients.
- *Number of PRs experienced* – the mean number of PRs experienced across patients.
- *Number of responses (CR or PR) experienced* – the mean number of any response state experienced across patients.
- *Number of remissions experienced* – the mean number of remissions experienced across patients.
- *Number of relapses* – the mean number of relapses experienced across patients.
- *Number of treatment failures* – the mean number of treatment failures experienced across patients. (Note: a patient is considered to have failed treatment if in the NR state at the end of the initiation phase or the PR state at the end of the full initiation extension phase.)

5.1.3 Proportion outcomes

All proportion outcomes are represented as the percent of patients (out of the total number of patients in any given model run) who experience the outcome as noted.

- *Percent of patients completing two or more lines of therapy (or exhausting all lines of therapy if pathway set to include fewer than two therapies).*

- *Percent of patients experiencing at least 1 SAE.*
- *Percent of patients ever achieving CR.*
- *Percent of patients ever achieving PR.*
- *Percent of patients ever achieving response (CR or PR).*
- *Percent of patients ever achieving remission.*
- *Percent of patients deceased by the end of the modeled time horizon.*

5.2 Economic outcomes

5.2.1 Life-years (LYs) and quality-adjusted life-years (QALYs) gained

All model runs estimate both patient-specific and average overall numbers of LYs and QALYs accrued throughout the modeled time horizon. At the patient level, total QALYs are estimated by multiplying the time a patient spent in each potential health states and TRD status by the utility weight associated with the state and status and summing across all unique combinations of state and status. The default rate at which QALYs are discounted is currently 3%, but can be modified by the user.

5.2.2 Costs incurred

The following cost measures are also evaluated across all modeled patients, each discounted at 3% annually in the base case:

- *Total costs* – sum of indirect and direct healthcare costs.
- *Total direct healthcare costs* – sum of direct MDD treatment costs and other disease-related costs.
- *Direct MDD treatment costs* – direct costs associated with treatments included in the modeled pathway.
- *Other disease-related (i.e., state-based) healthcare costs*.
- *Total indirect costs* – sum of treatment-related transportation costs and productivity-loss costs.
- *Indirect productivity-loss costs* – sum of costs related to work absenteeism and presenteeism.

5.3 Clinical Cost-Effectiveness Outcomes

5.3.1 Cost per [clinical outcome]

All model runs estimate the overall cost per selected clinical outcome (from those above) for each treatment pathway selected. These are constructed by dividing average per patient costs accrued over the modeled time horizon by average clinical outcome per patient accrued over the same period.

5.3.2 Average cost-effectiveness ratio (ACER)

All model runs estimate the overall ACER for each treatment pathway selected. These are constructed by dividing average per patient costs accrued over the modeled time horizon by average per patient QALYs accrued over the same period. There are three ACERs calculated for each model run: a direct cost ACER (direct healthcare costs only), a total cost ACER (both direct and indirect costs combined), and a treatment cost ACER (MDD treatment costs only). The model discounts both costs and QALYs at a default rate of 3%.

5.3.3 Net monetary benefit (NMB)

All model runs estimate the average net monetary benefit (NMB) for each treatment pathway selected. These are constructed by subtracting average total healthcare costs per patient from the product of average total QALYs accrued per patient and an input value (USD) per QALY. For the default setting, we use $150,000 per QALY. As with the ACERs, three average NMBs are calculated for each model run: a direct cost NMB (direct healthcare costs only), a total cost NMB (both direct and indirect costs combined), and a treatment cost NMB (MDD treatment costs only). Again, the model discounts both costs and QALYs at a default rate of 3%.

5.3.4 Incremental cost-effectiveness ratio (ICER)

All model runs estimate the incremental cost-effectiveness ratio (ICER) for each defined treatment pathway along the cost-effectiveness frontier. Treatment pathways which are more costly but provide fewer QALYs relative to other pathways are considered dominated; treatment pathways which are more costly per additional QALY relative to other pathways are considered extended

dominated. ICERs for dominated and extended dominated pathways are not presented, in keeping with common practice for presenting cost-effectiveness frontier results.

ICERs are constructed by taking mean total healthcare costs accrued over the modeled time horizon for treatment pathway x minus the same for a given reference pathway. This is then divided by the difference between mean total QALYs accrued for treatment pathway x and mean total QALYs accrued for the reference pathway. In other words:

$$\frac{C_x - C_r}{Q_x - Q_r}$$

where C_x represents average costs accrued in treatment pathway x, C_r represents average costs accrued in the reference treatment pathway, Q_x represents average QALYs accrued in treatments pathway x, and Q_r represents average QALYs accrued in the reference treatment pathway. Results include an ICER based on average discounted total healthcare costs measured in USD and average discounted QALYs for each non-dominated pathway, excluding the pathway with the lowest average total healthcare costs, relative to the next most costly pathway on the efficiency frontier (i.e., the next most costly non-dominated pathway).The model output also include labels identifying each pathway as either non-dominated, dominated, or extended dominated. Again, the model discounts both costs and QALYs at a default rate of 3%.

6 Model validation

The model was prepared according to International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Society for Medical Decision Making (SMDM) best practices (1, 2).

To verify the results of the cost-effectiveness model, internal quality control procedures were undertaken by the developers to ensure that mathematical calculations were performed correctly and were consistent with the model's specifications. As part of this process, the model was reviewed for coding errors, inconsistencies, and use of implausible or inapplicable input data. More specifically, the review included the following:

- Extreme-value testing to ensure errorless execution and logical results;

- Logical relationship testing (e.g., if drug acquisition costs increase for a treatment included in a given pathway, do total treatment costs for the pathway increase accordingly?);
- Internal consistency checks (e.g., are drug acquisition costs for a given treatment applied consistently whether the treatment is used first line or fourth line?);
- Input-output consistency checks comparing model output to relevant model input values;
- Review of input data sources to ensure appropriate application of data within the model;
- Checks of code calculations and use of external functions for implementation errors; and
- General review of model structure and input parameters for compatibility with stated goals and intended model design.

In all cases, validation using different routine tests yielded results within expected bounds.

Ideally, external validation is also performed by comparing a model's clinical predictions to those from previous cost-effectiveness models described in published literature. Unfortunately, to our knowledge, no studies describing other multiple treatment sequence models in MDD have yet been published, therefore precluding comparison to an existing peer-reviewed model. In lieu of such comparisons, the model's structure, design, input parameters, assumptions, base-case input values and results for a handful of treatment pathways were presented to a technical expert advisory panel and a clinical advisory panel, who found all components plausible and acceptable. Additionally, the model's results were compared to those from a five-year naturalistic study conducted among Finnish patients with MDD (43). Base-case results for treatment pathway two (SSRI → SSRI → SSRI → SSRI) were found to be within 10% of those reported in the Finnish study for key outcome measures common to the model and the Finnish study:

- Proportion of patients ever achieving response (CR or PR): 95% (model) vs 90% (Finnish study).
- Mean number of relapses among patients with at least one relapse: 1.57 (model) vs an estimated 1.75 (Finnish study).
- Mean months in CR: 24.7 (model) vs 26.5 (Finnish study).

While some differences in results were also noted, discrepancies can likely be explained by differences in measure definitions and patient populations between the model and the Finnish study

(e.g., the Finnish study includes patients with histories of MDD, a subset of whom were in partial remission at study entry).

7 Variability and uncertainty

The impact of relevant model parameters (as contained below in **Table 22**) is assessed on base-case model results (namely, total life years, QALYs, total costs incurred, and NMB), via univariate sensitivity analysis (SA). In this sensitivity analysis method, each relevant model parameter is varied from the applicable low to high value individually such that the impact of a single parameter on the model can be determined.

Low and high parameter values are produced by adding or subtracting 20% to the base value of the parameter value within the confines of the possible parameter range (e.g., utilities must be within 0 and 1). Parameters to vary in the univariate SA were limited to a subset of all user-modifiable input parameters based on anticipated impact on results, uncertainty in base-case values, and suspected synergistic or dampening relationships with other input parameters (i.e., a parameter anticipated to cascade impacts throughout model, such as relapse rates, rather than anticipated to have impact to limited number of model outcomes, such as transportation costs). A limited subset of parameters was considered in the sensitivity analysis to avoid excessive model run times.

Table 22: Parameters varied in univariate SA with accompanying low and high values

Model Input	Low Value	High Value
Health utilities		
Non-TRD annual utility, CR	0.68	1
Non-TRD annual utility, PR	0.58	0.86
Non-TRD annual utility, NR	0.46	0.70
TRD annual utility, CR	0.66	0.98
TRD annual utility, PR	0.43	0.65
TRD annual utility, NR	0.31	0.47
Efficacy		
8-week probability of CR, no active treatment	0.1	0.15
Annual probability of relapse, patients who achieved CR late in 1st-line initiation phase	0.28	0.42
Annual probability of relapse, patients who achieved CR late in 2nd-line initiation phase	0.42	0.62
Annual probability of relapse, patients who achieved CR late in 3rd-line initiation phase	0.36	0.55
Annual probability of relapse, patients who achieved CR late in 4th-line initiation phase	0.47	0.7
CR probability ratio, 2nd line vs. 1st line	0.66	1
CR probability ratio, 3rd line vs. 1st line	0.3	0.44
CR probability ratio, 4th line vs. 1st line	0.28	0.42

Model Input	Low Value	High Value
Initiation-phase 1st-line probability of CR, atypical antidepressant	0.34	0.52
Initiation-phase 1st-line probability of CR, atypical antidepressant + antipsychotic	0.45	0.67
Initiation-phase 1st-line probability of CR, atypical antidepressant + psychotherapy	0.43	0.65
Initiation-phase 1st-line probability of CR, psychotherapy	0.33	0.5
Initiation-phase 1st-line probability of CR, SNRI	0.37	0.56
Initiation-phase 1st-line probability of CR, SNRI + antipsychotic	0.48	0.72
Initiation-phase 1st-line probability of CR, SNRI + atypical antidepressant	0.45	0.67
Initiation-phase 1st-line probability of CR, SNRI + psychotherapy	0.46	0.7
Initiation-phase 1st-line probability of CR, SSRI	0.33	0.5
Initiation-phase 1st-line probability of CR, SSRI + antipsychotic	0.43	0.65
Initiation-phase 1st-line probability of CR, SSRI + atypical antidepressant	0.4	0.6
Initiation-phase 1st-line probability of CR, SSRI + psychotherapy	0.42	0.62
Initiation-phase 1st-line probability of PR vs CR, non-brain stimulation therapies	0.39	0.58
Treatment gaps		
Probability of treatment gap following failure in line 1	0.28	0.42
Probability of treatment gap following relapse in line 1	0.28	0.42
Probability of treatment gap following failure in line 2	0.42	0.63
Probability of treatment gap following failure in line 3	0.46	0.69
Probability of treatment gap following relapse in line 2	0.42	0.63
Probability of treatment gap following relapse in line 3	0.46	0.69
Costs		
Annual direct cost of treatment, atypical antidepressant	5,633.95	8,450.93
Annual direct cost of treatment, psychotherapy	16,057.60	24,086.40
Annual direct cost of treatment, SNRI	1,495.46	2,243.18
Annual direct cost of treatment, SSRI	331.33	496.99
One-time direct cost of treatment, add-on brain stimulation therapy	14,025.60	21,038.40

CR, complete response; MDD, major depressive disorder; NR, no response; PR, partial response; SA, sensitivity analysis; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TR, treatment resistant; TRD, treatment-resistant depression.

8 Results for Base Case Analysis

Results produced by the model are presented in two distinct categories: main results, which presents key economic outcomes (namely, QALYs gained, ACER, NMB, and ICERs) for five example treatment pathways (referred to within this report as Treatment Pathway One through Five), and sensitivity analyses, which presents results of the univariate SA in Treatment Pathway Five. In the base case, the treatment pathways are simulated for a five-year time horizon with all model inputs set to default values. Note that treatment pathways are user-modifiable (up to five pathways per model run in the user interface), as are many other key model inputs. As such, an end-user may create their own pathways and scenarios for which the results presented in this report are not applicable.

8.1 Main results

8.1.1 Pathways

Example treatment pathways for which results are presented are described below in **Table 23**. All economic outcome results contained in this technical report are discounted at 3% per year.

Table 23: Treatment pathways for which results are presented in this report

Treatment pathway and line	Treatment class
Treatment Pathway One	
First-line therapy	No active treatment
Second-line therapy	No active treatment
Third-line therapy	No active treatment
Fourth-line therapy	No active treatment
Treatment Pathway Two	
First-line therapy	SSRI
Second-line therapy	SSRI
Third-line therapy	SSRI
Fourth-line therapy	SSRI
Treatment Pathway Three	
First-line therapy	SSRI
Second-line therapy	SSRI + psychotherapy
Third-line therapy	SSRI + psychotherapy
Fourth-line therapy	SSRI + psychotherapy
Treatment Pathway Four	
First-line therapy	SSRI
Second-line therapy	SSRI
Third-line therapy	SSRI + psychotherapy
Fourth-line therapy	SSRI + psychotherapy (with brain stimulation add-on)
Treatment Pathway Five	
First-line therapy	SSRI
Second-line therapy	SNRI
Third-line therapy	SNRI + atypical antidepressant
Fourth-line therapy	SNRI + antipsychotic

SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

8.1.2 QALYs gained

The discounted QALYs gained by treatment pathway are reported below in **Table 24**.

Table 24: Discounted QALYs calculated for example treatment pathways

Treatment pathway	QALYs gained
Treatment Pathway One	1.93
Treatment Pathway Two	2.78
Treatment Pathway Three	2.91

Treatment pathway	QALYs gained
Treatment Pathway Four	2.89
Treatment Pathway Five	2.91

QALY, quality-adjusted life years.

8.1.3 ACER

Total cost ACERs, direct cost ACERs, and treatment cost ACERs, all discounted, by treatment pathway are reported below in **Table 25**.

Table 25: Discounted ACERs calculated for example treatment pathways

Treatment pathway	Total cost ACER	Direct cost ACER	Treatment cost ACER
Treatment Pathway One	$69,363	$33,165	$0
Treatment Pathway Two	$37,371	$17,959	$351
Treatment Pathway Three	$44,691	$26,887	$10,711
Treatment Pathway Four	$56,476	$38,406	$21,821
Treatment Pathway Five	$36,154	$18,407	$2,119

ACER, average cost-effectiveness ratio.

8.1.4 NMB

Total cost NMBs, direct cost NMBs, and treatment cost NMBs, all discounted, by treatment pathway are reported below in **Table 26**.

Table 26: Discounted NMBs calculated for example treatment pathways

Treatment pathway	Total cost NMB	Direct cost NMB	Treatment cost NMB
Treatment Pathway One	$155,776	$225,703	$289,771
Treatment Pathway Two	$312,851	$366,772	$415,680
Treatment Pathway Three	$306,091	$357,841	$404,857
Treatment Pathway Four	$270,157	$322,356	$370,265
Treatment Pathway Five	$330,801	$382,368	$429,696

NMB, net monetary benefit.

8.1.5 ICER

ICERs for all treatment pathways, including applicable components of the ICER calculation and dominated status, are contained below in **Table 27**. As noted previously, ICERs are not presented for dominated or extended-dominated pathways.

Table 27: ICERs calculated for example treatment pathways

Treatment pathway	Dir. cost	QALYs	Inc. dir. cost	Inc. QALY	ICER	Status
Treatment Pathway Two	$49,884	2.78				ND
Treatment Pathway Five	$53,486	2.91	3,601	0.13	$28,139	ND
Treatment Pathway Three	$78,149	2.91	24,663	0.00	$27,148,654	ND
Treatment Pathway One	$64,068	1.93				D
Treatment Pathway Four	$110,941	2.89				D

D, dominated; dir., direct; ICER, incremental cost-effectiveness ratio; inc., incremental; ND, non-dominated; QALYs, quality-adjusted life years.

8.2 Sensitivity analyses

Univariate SA results are often visually summarized using a "tornado chart", in which bar graphs representing the impact of each sensitivity parameter on a given model result are stacked one on top of another. These stacked graphs are ordered with the parameter resulting in the greatest impact to model results at the top of the stack and less impactful parameters subsequently beneath it. Parameters which have no impact on a given outcome are removed from the chart. Such charts are presented for applicable model results from Treatment Pathway Five per **Table 23** in **Figure 11**, **Figure 12**, and **Figure 13** below.

Based on these charts, parameters governing treatment efficacy, gaps, and relapses, as well as utility values, have the largest impact on model results in the context of the example Treatment Pathway Five.

Figure 11: Tornado plot of impact by parameter varied on total QALYs, discounted

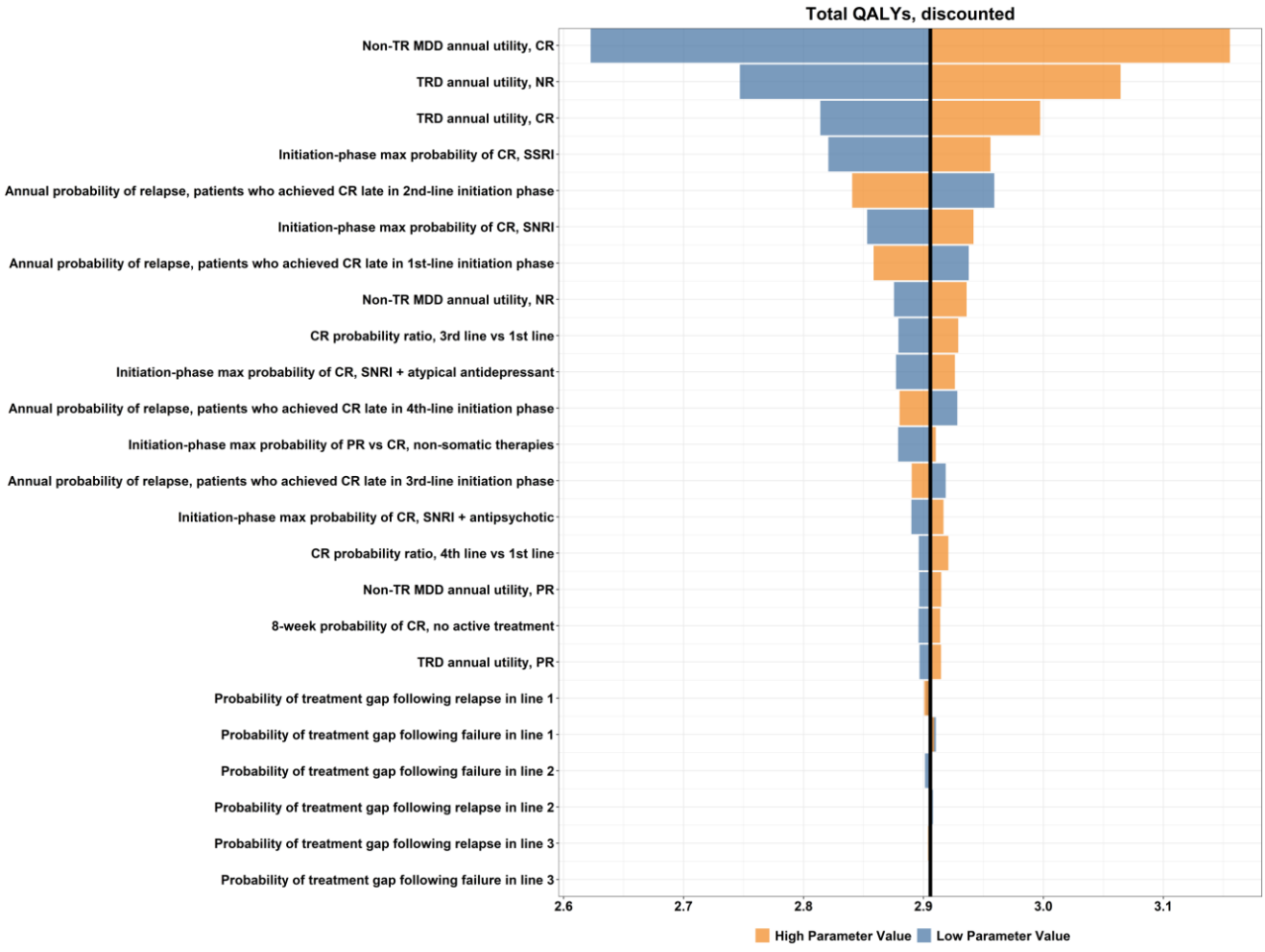


Figure 12: Tornado plot of impact by parameter varied on total costs incurred, discounted

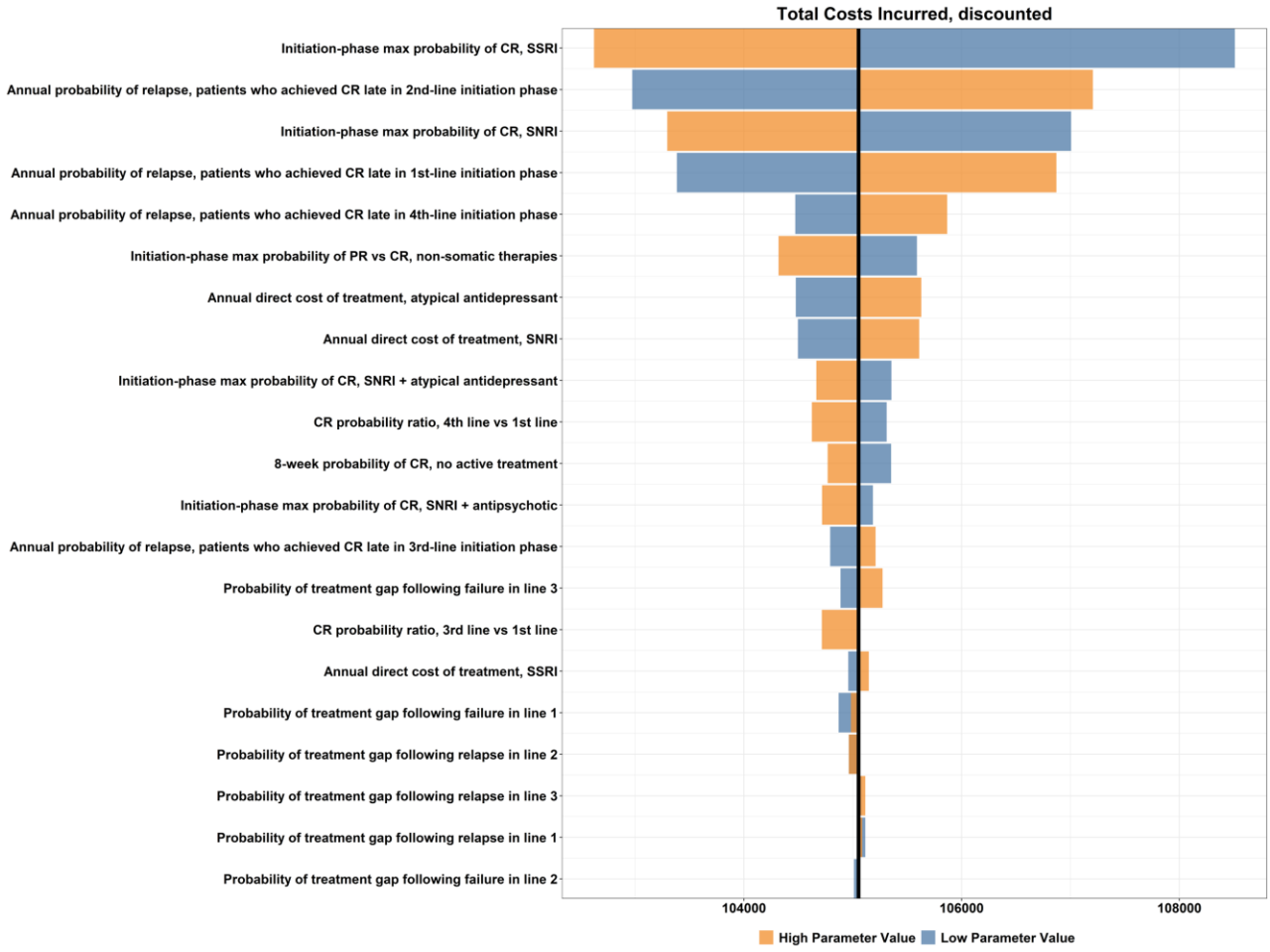
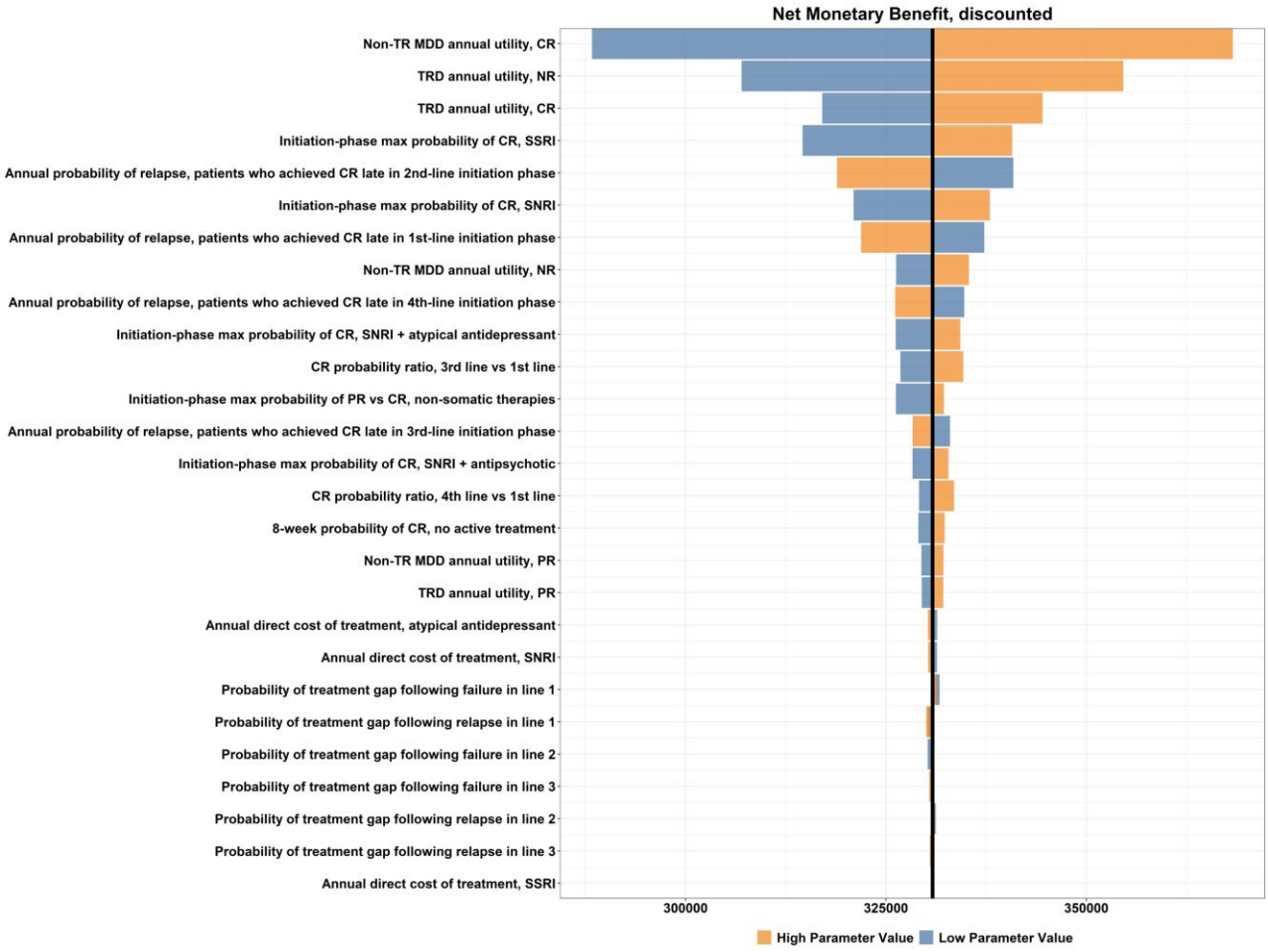


Figure 13: Tornado plot of impact by parameter varied on net monetary benefit, discounted



9 Strengths and limitations

IPS models offer a number of advantages over standard Markov cohort models. For example, the memoryless property of Markov cohort models is a known and well-documented limitation, particularly in disease areas where it is believed prior states or patient characteristics are predictive of future states. IPS models do not rely on this memoryless Markov assumption (44). Utilizing a continuous-time framework offers increased model efficiency as well, as "cycles" in which a patient does not move health states can essentially be "fast-forwarded" (i.e., the model only needs to record timepoints at which an event is predicted).

An additional strength to this model is the programming language in which it is built: R. As an open-source statistical programming language commonly utilized across academic and

commercial institutions, R offers the transparent framework on which this model could be built. Applicable model code is accessible to reviewers and any non-base packages leveraged within the model, such as for data manipulation or standard cost-effectiveness calculations (e.g., ICERs), are themselves open-source, freely available, and robustly documented. Furthermore, R offers notable computational advantages to other software often utilized in modelling (e.g., Microsoft Excel). Model run times for models based directly in programming languages such as R can be notably shorter compared to models built in spreadsheet software (44, 45). R-based models also offer versatile portability, allowing for direct integration into web interfaces, thus further improving the accessibility of the model.

One of the biggest limitations of any model is the availability of comprehensive quality input data. In particular, as is common among mainstream cost-effectiveness models in general, this model is limited by imperfect input data in its ability to: (1) properly address patient heterogeneity questions such as variance in outcomes and disparities, (2) elevate our understanding beyond simple extrapolation of efficacy from RCTs and reflect real-world practices and experiences, and (3) reflect true variance in the weighting of patient preferences around the relative importance of different aspects of disease burden in populations of need.

For (1), there are currently few sets of input data that can be applied separately by patient characteristic or time-point in a treatment pathway. Studies examining relative effectiveness or treatment cost tend to limit themselves to population averages and rarely look at variance by patient subgroup, provider type, or even demographic or contextual factors such as location (e.g., comparing relative effectiveness of psychotherapy in areas with a scarcity of psychiatrists compared to areas with a surplus of psychiatrists).

Heterogeneity of treatment effect is just one part of overall heterogeneity in modeling dynamic variance in economic models. Ideally, we would also have relative data on burden, access to care, time to diagnosis, time to treatment initiation, and time spent untreated, all for different types of patients or providers. For variance in time off treatment, IVI intends to explore this in phase two of this exercise, but there will continue to be gaps unless we build models that in some way encourage organizations to increase the reporting of outcomes to allow for modeling heterogeneity properly.

For (2), current cost-effectiveness modeling in MDD oversimplifies the translation of efficacy from RCTs into real-world settings. This is due in part to the overly simplistic nature of traditional models that rely on population averages and to the lack of heterogeneity in data that we describe above, but it is also partly due to the lack of data on how real world drivers of relative effectiveness (i.e., factors that differentiate efficacy from effectiveness) impact time-variant or dynamic outcomes like time to response, time to relapse, discontinuation, time in remission, and time spent out of treatment. In addition, we often have efficacy for treatment-naïve or treatment-experienced patients, but it is generalized, not specific to the type of previous treatment. As such, we are applying line-of-therapy decrements from generalized (non-specific) data, which again is something of a compromise.

For (3), IVI is working closely with the University of Maryland's PAVE (Patient Driven Values in Healthcare Evaluation) initiative to overcome this limitation and it is hoped that in future model iterations, and the Multi-Criteria Decision Analysis (MCDA) module in particular, this work will be encapsulated and enable us to develop a more patient-oriented set of outcomes.

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