COMPREHENSIVE DISCRETE EVENT SIMULATION MODEL FOR THE EVALUATION OF HEALTH CARE TECHNOLOGIES IN DEPRESSION

Version 1.1

29 November 2013

Project team members

Expert board

Prof. Mondher Toumi (University of Lyon, France)
Prof. Fernando Antoñanzas (University of La Rioja, Logrono, Spain)
Prof. John Brazier (University of Sheffield, UK)
Dr. Leona Hakkaart (Erasmus University Rotterdam, The Netherlands)
Dr. Raymond W. Lam (University of British Columbia, Vancouver, Canada)
Prof. Paul McCrone (King's College London, UK)
Prof. Ulf Persson (The Swedish Institute for Health Economics, Lund, Sweden)

Project implementation

Anne-Lise Vataire (Creativ-Ceutical France, University of Lyon)
Samuel Aballéa (Creativ-Ceutical France, University of Lyon)
Olivier Cristeau (Creativ-Ceutical France)
Julie Dorey (Creativ-Ceutical France, Ecole Pratique des Hautes Etudes, Paris)
Xiaoxi Zhao (Ecole Centrale, Beijing)

Table of Contents

List of tables

List of figures

Mains definitions

Addition	Addition of an antipsychotic
Clinical remission	MADRS total score ≤10
Major AE	adverse event requiring to switch to another antidepressant
Minor AE	adverse event not requiring switch of treatment but only treatment adjustment (down-titration and/or adding a medication for an AE)
Normal functioning	defined as a specific score in an instrument assessing the patient's functional capacity
Partial response	a ≥ 25% decrease in severity scale from the beginning of episode
Recovery	clinical remission since at least 6 months.
Recurrence	new depressive episode after recovery
Relapse	new depressive symptoms after clinical remission but before recovery
Switch	Treatment change to a new antidepressant or a combination of antidepressants for either lack of efficacy or major AE
Therapeutic strategy	specific antidepressant or a combination of several antidepressants

List of abbreviations and definitions of terms

AD	Antidepressant
AE	Adverse event
APMS	Adult Psychiatric Morbidity Survey
DES	Discrete-Event Simulation
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
EQ-5D	EUROQOL – 5 Dimensions
FAS	Full-Analysis Set
FDA	Food and Drugs Administration
GP	General Practitioner
GPRD	General Practice Research Database
HAMD	Hamilton Depression Scale
ICER	Incremental Cost-Effectiveness Ratio
LoE	Lack of Efficacy
MADRS	Montgomery Åsberg Depression Rating Scale
MDD	Major Depressive Disorder
MEPS	Medical Expenditure Panel Survey
NHS	National Health Service
NICE	National Institute for Clinical Excellence
PSS	Personal Social Services
QALY	Quality-Adjusted Life-Years
SD	Standard Deviation
SE	Standard Error
SmPC	Summary of Product Characteristics
SSRI	Serotonin-Specific Reuptake Inhibitor
TPP	Third-Party Payer
TTO	Time Trade-Off
UK	United-Kingdom
US	United States

Introduction

1.1 Background

Depression has been widely described and shown to be a disabling disease, characterized by multiple recurrent episodes and involving important functional and social impairment[1] as well as a heavy economic burden [2]. Major depressive disorder (MDD) is generally diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) classification, where five (or more) of a list of symptoms must have been present during the same 2-weeks period. Major depressive disorder (MDD) is among the most important causes of disability worldwide, in both developing and developed countries.

Most economic models used to evaluate the cost-effectiveness of antidepressants were structured as decision trees or Markov models. Such models focused on the acute treatment phase and used relatively short time-horizons, typically 6 months. However the most widely used strategy to prevent relapse and recurrence is to continue treatment beyond acute phase, often for long term. Therefore it would be desirable to assess the cost-effectiveness of antidepressants over longer periods, taking into account the impact of treatment on relapses and recurrences.

Le Lay *et al*.[3] showed that discrete-event simulation (DES) modelling has advantages over Markov models for modelling MDD. DES model is flexible and allows simulating patient pathways in a very realistic manner. Simulated events in a DES model may occur at any time, as opposed to Markov models, in which events may only occur at fixed time points. Furthermore, DES models are better suited than Markov models for integrating treatment switches. DES is fully time-dependent compared to Markov models which lack memory and becomes quickly unmanageable complex by increasing the number of health states to make up for that. In addition, a DES model would allow taking into consideration the evolution of attitudes towards treatment, in particular treatment discontinuation, and adherence which may be affected by treatment effects in the past (whether positive or negative).

1.2 Objective

The objective of this project was to develop a core model for Major Depressive Disorder (MDD). This model can be used to assess the impact of patient characteristics, events or treatment on costs and health outcomes in patients with MDD. Furthermore, this model is able to evaluate the cost-effectiveness of an antidepressant as first-line or second-line therapy for MDD. The primary cost-effectiveness measure is the incremental cost per quality-adjusted life-year (QALY) gained.

---

[1] Hirschfeld RM, Montgomery SA, Keller MB, Kasper S, Schatzberg AF, Möller HJ, Healy D, Baldwin D, Humble M, Versiani M, Montenegro R,Bourgeois M. Social functioning in depression: a review. J Clin Psychiatry. 2000 Apr;61(4):268-75.

[2] Greenberg PE, Kessler RC, Birnbaum HG, Leong SA, Lowe SW, Berglund PA, et al. The economic burden of depression in the United States: how did it change between 1990 and 2000? J Clin Psychiatry. 2003 Dec;64(12):1465-75.

[3] Le Lay A, Despiegel N, François C, Duru G. Can discrete event simulation be of use in modelling major depression? Cost Eff Resour Alloc. 2006 Dec 5;4:19.

2 Core model

A discrete event simulation (DES) model was used to simulate pathways of patient with MDD in order to either assess a treatment strategy for MDD or to compare alternative treatment strategies in terms of costs and health outcomes. In case of treatment strategy comparison, an incremental cost effectiveness ratio by quality-adjusted life year (QALY*)* will be assessed.

2.1 Treatment strategy

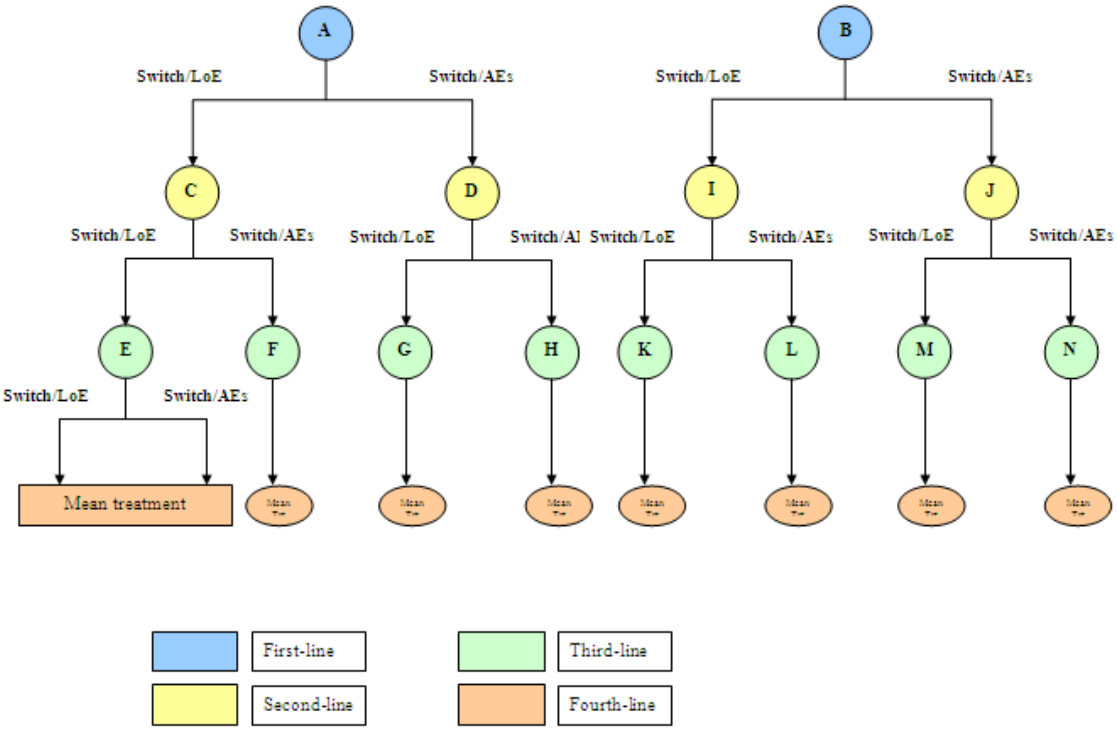
The model allows assessing a treatment strategy or comparing treatment strategies rather than single treatment option(s). A treatment strategy is defined as a sequence of treatments. In this model, the sequence corresponds to four lines of treatment, meaning that a patient can receive up to four treatments.

The first three lines of treatments can be adapted and have to be specified by the user in the input data. In line with clinical practice, the model differentiated switches (treatment changes) due to lack of efficacy and switches due to adverse event. As a consequence, two treatments in the second line and four in the third line have to be specified for each treatment strategy (Figure 1). The model provides the flexibility to specify a treatment as a specific drug or a combination of several antidepressants for adaptations to different countries, by configuring treatment parameters.

Treatment duration is defined as a period when a patient takes his/her treatment until he/she interrupts it. It is not treatment-specific. The treatment duration corresponds to a *time to treatment interruption*, evaluated by an exponential law with the average duration by line of treatment as mean.

The fourth treatment line is an average treatment independent of the previously received treatments. This assumed average treatment is expected to have little impact on results since the proportion of patients reaching the 4^{th} treatment line should be relatively small.

Figure 1: Treatment strategies



2.2 Model structure

A DES model consists in a modelling technique that conceptualizes the course of patients in terms of **events** they experience and the effect these have on current and future health, medical resource use and other components in continuous time, allowing chance to play a role. Patient characteristics, so-called **attributes**, can influence the occurrence of events and can be updated according to the previously occurred ones.

The model structure as well as events and attributes were validated by clinical expert and health economist experts.

2.2.1 Patient attributes

The attributes listed in Table 1 are generated for each patient individually.

Table 1: Attributes of patients

Variable	Type of variable
Age	Continuous
Sex	Binary (Male/female)
Work status	Binary (Worker/ Non worker)
Number of previous episodes	Categorical (1,2, 3 and more)
Residual symptoms	Binary (Residual symptoms: yes/no)
Depression status	Categorical (depression, partial response, clinical remission, full remission, recovery)

Before starting simulations of patient pathways, age, sex, work status and number of previous episode are simulated. Age is updated according to the patient's elapsed time in the model. Number of previous episodes is updated at each new episode (i.e. after each relapse and recurrence).

In the model, workers are all considered as full-time workers (i.e. distinctiveness of part-time not included).

All patients enter the model with a moderate to severe MDD episode. Depression status and residual symptoms are simulated at this time.

The patient's status corresponds to the patient's clinical state in respect of his depressive disorder evaluation matching the clinical event.

- Depression is defined as moderate to severe MDD (MADRS can be used to define this attribute more precisely and input data should correspond to the definition)
- In the Partial response status, the patient has experienced the partial response event
- In the Clinical remission status, the patient has experienced the clinical remission event

- In the Full remission status, the patient has experienced the full remission event
- In Recovery, the patient has experienced a clinical remission for at least 6 months (without any relapse).

Residual symptoms are symptoms delaying return to normal functioning after achieving clinical remission. In the core model, residual symptoms do not refer to a specific type of symptom. In model adaptations, this attribute could be used to represent a specific type of symptoms for which the evaluated treatment is more effective than other treatments. It is a binary variable, i.e. the simulated episode is associated / not associated with residual symptoms.

The patient's status is updated after reaching the corresponding events whereas residual symptoms are updated at each new episode.

2.2.2 Events

Definitions of considered events are given in the Table 2.

A specificity of this model is that two types of remission are considered: a "clinical remission" and a "full remission" event. The former is remission as defined in clinical trials, based on the MADRS score. The latter is a combination of clinical remission and normal functioning. This is to account for the fact that functioning may remain impaired for some period following clinical remission. The model also includes a "partial response" event. The reason for including this event in the model is to allow for a possible change in treatment, in case of a lack of improvement after a month of treatment.

Another particularity of the model is the level of detail relating to adverse events. Rather than combining all adverse events as one single event, different adverse events are considered, in order to account for specific tolerability profiles associated with different antidepressants. Treatment related adverse events are considered as short term adverse events with the exception of sexual dysfunction which is considered as a long term AE. Short-term adverse events can occur during the first month of treatment and do not last beyond treatment discontinuation. The duration of those events are only considered in the model through a QALY decrement associated with each type of AE.

Moreover, a distinction is made between minor and major adverse events according to the impact of the AE on the patient's pathway. A major adverse event requires a switch in contrary to minor adverse event which implies a treatment adjustment only (dose reduction).

For each short-term adverse event, a cost increment and a QALY decrement were applied.

Sexual dysfunction is considered as a long term adverse event because this AE has been found petty and not of interest when the patient is depressed but starts to be valuable for the patient when he is getting better. Sexual dysfunction is evaluated during the regular evaluation of clinical remission. The duration of sexual dysfunction is then simulated and a disutility is applied throughout the duration of the dysfunction.

Table 2: Definitions of considered events in the model

Variable	Definition
Disease-related events	
Partial response	A ≥ 25% MADRS score decrease compared to the beginning of the episode
Clinical remission	MADRS total score ≤10. This cut-off was found clinically relevant based on the CGI-S.[4]
Full remission	Clinical remission and normal functioning (defined as a specific score with an instrument assessing the patient's functional capacity)
Relapse	New depressive symptoms during the 6 months following clinical remission
Recurrence	New depressive symptoms while in the recovery status (after 6 months in clinical remission)
Recovery	clinical remission for at least 6 months
Major and minor treatment related adverse events	Major AEs : adverse events requiring to switch to another antidepressant Minor AEs : adverse events not requiring treatment switch but only treatment adjustment (down-titration and/or adding a medication for an AE)
Sexual dysfunction	Long term adverse event : time with sexual dysfunction is taken into account
Nausea	Short term adverse event
Headache	Short term adverse event
Diarrhoea	Short term adverse event
Insomnia	Short term adverse event
Other adverse events	Short term adverse event
Events related to treatment patterns:	
Switch	Treatment change to a new antidepressant or a combination of antidepressants for either lack of efficacy or major AE
Treatment adjustment	Dose adjustment (increase or decrease)
Addition	Addition of an antipsychotic
Hospitalization	Hospitalization due to depression
Sick-leave	Sick-leave due to depression
Suicide and suicide attempts	
Stop treatment	Treatment discontinuation
Death	By general mortality or because of MDD

2.2.3 DES algorithm

The model simulates the pathways of patients through successive events. The Figure 2 and Figure 3 describe the patients' pathways regarding their clinical evolution and their treatment. Other events (death, suicide attempt, suicide, hospitalization and sick leave) are not presented in the figures to be clearer but, are presented in specific sections.

[4] Hawley et al, Defining remission by cut off score on the MADRS: selecting the optimal value. J Affect Disord. 2002 Nov;72(2):177-84.

Upon each event occurrence, times to occurrence of the following events are simulated (or adjusted if time to these events are already simulated), and the event with the shortest time to occurrence is assumed to occur. This process is iterated until time horizon (see section 2.3) has been reached, or death of the patient. The probability of death is function of age and sex. The time spent in each state is influenced by occurrence of other events, which depends on patient features and previous events in the models. Patient characteristics are updated after each event.

Figure 2: Model Part 1 (Acute phase)

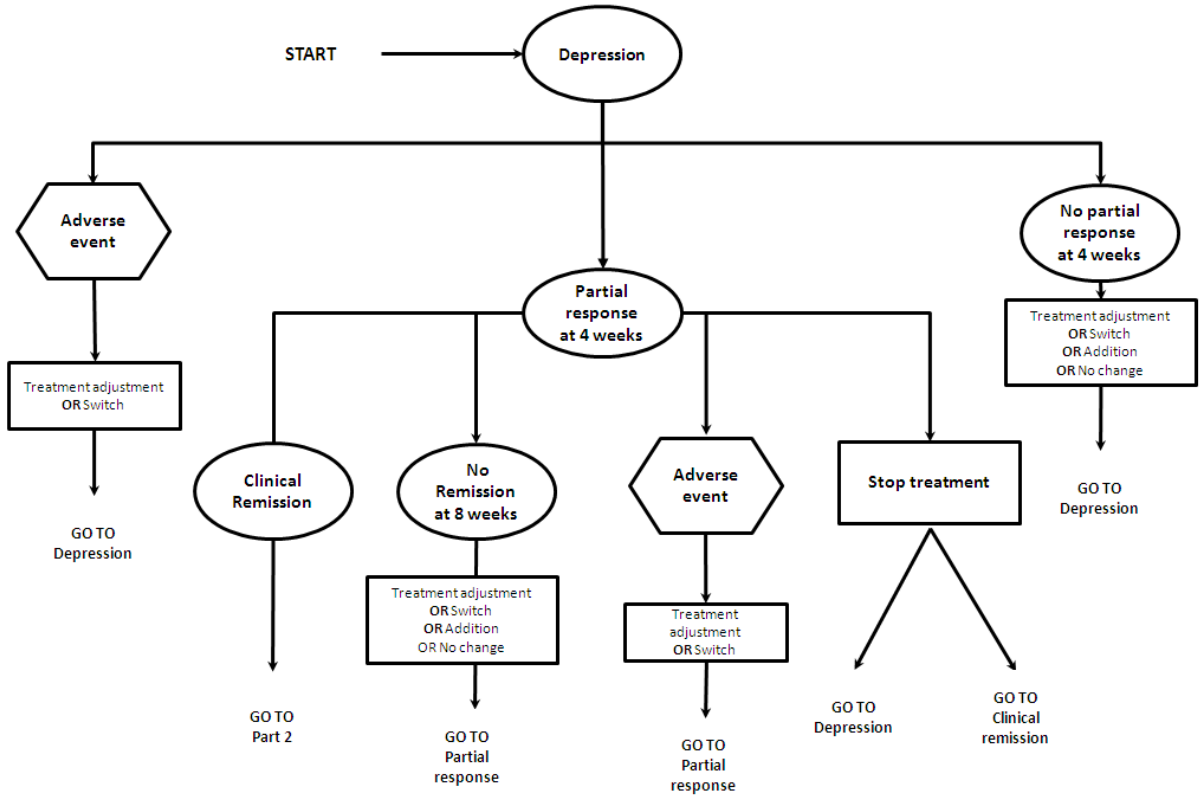
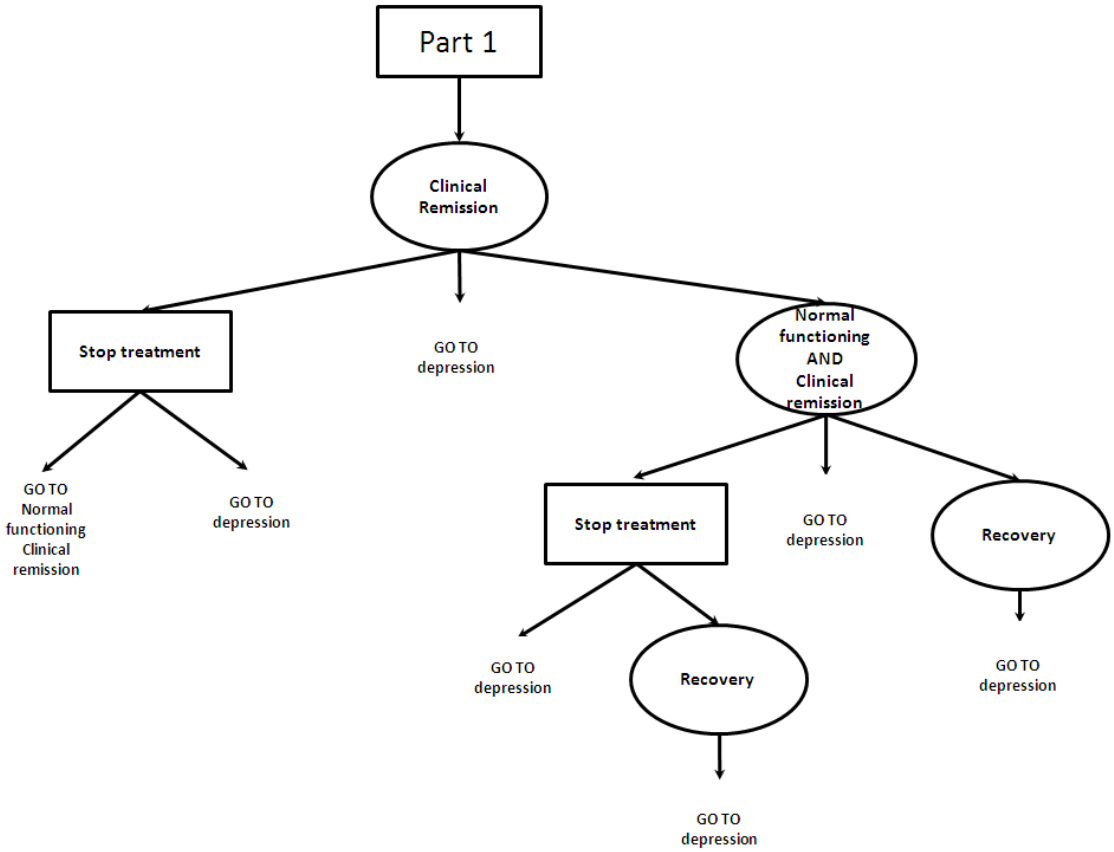


Figure 3: Model Part 2 (Maintenance phase)



2.2.3.1 Mortality

To simplify, the death event is not shown on the figures. The time to death due to all-cause mortality is simulated at the beginning of the simulation process, and is independent of treatments or depression status. The model also accounts death by suicide. The time to suicide attempt is simulated *a posteriori* (i.e. at the end of the model) for each recovery period and non recovery period as well as the risk of death for each suicide attempt. Recovery period is defined as the period when the patient is in recovery status and the non recovery period is the opposite. Therefore, for each defined period a time to suicide attempt is simulated, if the time is lower than the period duration then there is a suicide attempt, otherwise there is no suicide attempt. In case of suicide attempt, the suicide occurrence is evaluated according to a binomial law. If death occurs, costs and health outcomes are calculated until the death by suicide.

2.2.3.2 Patient's pathways

The patient's pathway was conceptualized as a sequence of events. The depression status of the patient was updated according to occurring events.

Start of simulation

The first step of the algorithm is to generate patients. Attributes (Age, Sex, Work status, Number of previous episodes) are assigned to all patients using random functions (2.6).

Residual symptoms and depression status are simulated at the time of MDD episode.

For example, to simulate the gender, we generate a random number between 0 and 1, based on a uniform distribution. If this number is less than the proportion of females, the patient is classified as "female"; otherwise the patient is classified as "male". The same approach is used for all variables. For continuous variables, values are derived from random numbers using the inverse cumulative distribution function.

Start of episode

Once a patient is created, the next step is to create an MDD episode. The number of treatment lines is initialized, patient's status is initialized to depression and residual symptoms are simulated.

Depression

Time to each *short-term adverse event,* time to *partial response* and time to *treatment interruption*are generated randomly, based on time-to-event functions (2.6). Time to *treatment interruption* is generated then but it is not included in the comparison to determinate the shortest time to event before partial response.

The patient pathway in depression depends on simulated times as the closest event or the regular evaluation at 4 weeks occurs.

- If the shortest time within 4 weeks corresponds to a short-term AE (i.e. if the randomly generated time for one adverse event is less than 4 weeks and is lower than the simulated time to *partial response*) , there are two possibilities according to the type of *short-term adverse event* determined according to the probabilities given as input data:
    - *Major adverse event occurrence*: Patient has a physician visit, switches treatment and the number of treatment line is incremented. New times to *short-term adverse events*, to *partial response* and to *treatment interruption* are simulated for the new treatment. The model accounts for the fact that time to *treatment interruption* may depend on the line of treatment. However, time-to-event functions for other *adverse events* and *partial response* do not dependof th treatment line. The next scheduled visit will take place four weeks later.

- *Minor adverse event occurrence*: Patient does not change treatment but has a dose adjustment. Times to other *short-term adverse events*, to *partial response* and to *treatment interruption* are updated by subtracting the time elapsed since the beginning of the depression episode. As the dose is reduced, times to other short-term *adverse events* are then increased and time to *partial response* is decreased by applying a hazard ratio. A new time to occurrence of the same type of *adverse event* that occurred is generated.

- If the shortest time within 4 weeks corresponds to a *partial response,* the patient's status is updated to partial response and patient can experience the potential events relative to this state.

Regular evaluation 4 weeks after the beginning of episode

- If the patient has not experienced a *partial response event*, several events can occur according to the probabilities given as input data:

  - He/she can *switch* due to lack of efficacy. The number of treatment line is incremented. New times to *short-term adverse events*, to *partial response* and to *stopping treatment* are simulated for the new treatment. Multiplicative factors (hazard ratios) are applied to new times to *treatment interruption* and partial response to account for the treatment failure.

  - He/she can have a treatment adjustment (dose increase). Times to other short-term *adverse events*, *partial response* and *stopping treatment* are updated by subtracting the time already elapsed since beginning of treatment. Times to other short-term *adverse events* are decreased by applying a multiplicative factor (hazard ratio). Time to partial response is increased by applying a multiplicative factor (hazard ratio).

  - He/she can receive an additional drug (an antipsychotic drug). Times to each short-term *adverse event*, to *partial response* and to treatment *interruption* are updated according to the time already elapsed and adjusted by applying a multiplicative factor (hazard ratio).

  - He/she can stay on the same antidepressant, without change in dose. Times to each short-term *adverse event*, to *partial response* and to treatment *interruption* are updated according to the time already elapsed.

- As long as *no partial response* occurs, the patient stays in *depression* and is re-evaluated every 4 weeks.

Partial response status

Time to *clinical remission* is simulated. Time to all short-term *adverse events* and to *treatment interruption* are updated by subtracting time previously elapsed. The patient's pathway in *partial response* status depends on simulated times as the closest event or the regular evaluation at 4 weeks occurs.

- The patient may stop treatment within 4 weeks from *partial response*, before *clinical remission*. The patient is at risk of regressing to *depression* status, which implies that patient will start a new treatment. However, the patient may also reach *clinical remission* without treatment. Thus, time to *relapse* and time to *clinical remission* without treatment are simulated and the closest event will occur.

- If an *adverse event* occurs (shortest time within the first 4 weeks in partial response status*)*, there are two possibilities according to the type of adverse event :

    - *Major adverse event*: Patient switches treatment and the number of line of treatment is incremented. Patient remains in partial response status. New times to short-term *adverse events*, to *clinical remission* and *treatment interruption* are simulated for the new treatment. The model accounts for the fact that time to *treatment interruption* may depend on the line of treatment. The line of treatment after *switch* for *adverse event* has no impact on time-to-event functions for other *adverse events* and *clinical remission*.

    - *Minor adverse event*: The patient stays on the same antidepressant treatmentwith a dose adjustment. Times to short-term *adverse events*, to *clinical remission* and *treatment interruption* are updated by subtracting the time elapsed since the beginning of depression episode. As the dose is reduced, time to short-term *adverse events* and time to *clinical remission* are increased by applying a multiplicative factor (hazard ratio). A new time to occurrence of the same type of *adverse event* that occurred is generated.

- If the shortest time within 4 weeks corresponds to a *clinical remission,* patient's status is updated and patient can then experience the potential events relative to the clinical remission status.

Regular evaluation 4 weeks after the beginning of Partial response status

- If the patient is considered as non clinical remitter (no clinical remission occurred):
    - He/she can switch due to lack of efficacy; the number of line of treatment is incremented. New times to short-term *adverse events*, to *clinical remission* and to *treatment interruption* are simulated for the new treatment. Multiplicative factors (hazard ratios) are applied to account for the fact that times to *stopping treatment* and to *clinical remission* are treatment line-dependent.
    - He/she can have a dose adjustment (dose increase). Times to short-term *adverse events*, to *treatment interruption* and to *clinical remission* are updated by subtracting the time previously elapsed and adjusted by applying a multiplicative factor (hazard ratio).
    - He/she can receive an antipsychotic drug in addition. Times to short-term *adverse events*, to *clinical remission* and to *treatment interruption* are updated by subtracting them the time previously elapsed and adjusted by applying a multiplicative factor (hazard ratio).
    - He/she can stay on the same antidepressant treatment. Times to short-term *adverse events*, to *clinical remission* and to *treatment interruption* are updated by subtracting them the time previously elapsed.
    - As long as clinical remission does not occur, patients stay in *partial response status* and are re-evaluated every 4 weeks.

Clinical remission status

When a patient enters in *clinical remission*, a time to *normal functioning* is simulated, and depends on whether the patient has residual symptoms or not. Times to *relapse* and *stopping treatment* are also generated randomly. In addition, the model takes into account that some patients may have *sexual dysfunction*, and for these patients the duration and severity of *sexual dysfunction* are simulated at the regular visit for clinical remission evaluation.

As previously, the event with the shortest time occurs:

- In case of major sexual dysfunction, the patient switches to another treatment and new times to *normal functioning*, *relapse* and *treatment interruption* are simulated.

- In case of minor sexual dysfunction, the patient stays on the same treatment but can have a reduced dose. The time to normal functioning is increased by applying a multiplicative factor (hazard ratio), to account for the reduced effectiveness associated with reduced dose.

- If normal functioning is attained before new episode or treatment *interruption*, the patient enters in full remission status.

- If the patient relapses before full remission, he/she switches treatment and returns to depression status. Time to *short-term adverse events*, time to *partial response* and to *stopping treatment* are generated.

- In case of treatment *interruption* before relapse or full remission (clinical remission and normal functioning), the patient had a reduced probability of achieving *full remission*, and increased risk of *relapse*. New times to relapse and to normal functioning are thus generated. If the patient relapses (i.e. time to relapse is shorter than time to *normal functioning*), he/she switches treatment. Times to short-term *adverse events*, time to *partial response* and to *treatment interruption* are generated. Otherwise, he goes to the full remission status and depression attributes is updated.

Full remission (Clinical remission and normal functioning) status

Time to *relapse* is updated upon entry in *full remission*. The patient is under treatment until the time to treatment *interruption* is elapsed.

- If time to relapse is higher than 6 months, the patient spends 6 months in *full remission* status and goes in *recovery*.

- If the patient stops his/her treatment before *recovery*, the patient may remain in *remission* until *recovery*, but time to relapse is decreased by a multiplicative factor.

- If the patient relapses before *recovery*, he/she switches treatment and returns to the depression status. Times to short-term *adverse events*, time to p*artial response* and to *treatment interruption* are generated.

Recovery status

The patient is under treatment until the treatment *interruption* event occurs.

Time to *recurrence* is simulated to determine when the patient will have a new episode before the end of the model (time horizon). In the case of a new episode, the number of previous episodes is updated and the patient goes back to the depression status.

2.2.3.3 Relative effectiveness and Relative side effect rate

The effects of titration, addition on times to clinical events and adverse events are adjusted by applying multiplicative factors to the baseline time-to-event functions.

$$T_{clinical\_event}(t) = \frac{T_{o\_clinical\_event}(t)}{HR_{Line\_of\_treatment}.HR_{Adjustement\_for\_AE}HR_{Adjustement\_for\_LoE}HR_{AE\_Addition}}$$

$$T_{adverse\_events}(t) = \frac{T_{o\_adverse\_events}(t)}{HR_{Adjustement\_for\_AE}HR_{Adjustement\_for\_LoE}HR_{AE\_Addition}}$$

Explanation about why the multiplicative factor is applied to time and not to the probability is given in the appendix A1.

2.2.3.4 Residual symptoms

A multiplicative factor is applied to time to normal functioning for patients with residual symptoms. If T is the time between clinical remission and normal functioning for a patient without residual symptoms, then the time to normal functioning for a patient with residual symptoms is α.T.

A treatment-specific multiplicative factor is applied to the time to normal functioning for patients with residual symptoms. Thus, the time to normal functioning for patients with residual symptoms receiving a specific treatment is α.β.T.

As a consequence, the treatment will not change the residual symptoms status but has an impact directly on the time to normal functioning (i.e. residual symptoms are resolved when patient is in normal functioning). Therefore the residual symptoms status is not updated during the episode but at each new episode.

2.2.4 General assumptions

The table below summarises the assumptions of the model. These assumptions were validated by clinical and health economics experts.

Table 3: General assumptions of the model

Assumption	Comment
Dose adjustment is always considered possible in the current model	This assumption was made to simplify the model. However, according to the SmPC it is not possible for some treatments as they are not enough available doses. A model adaptation should be done to consider these cases.
Patients developing a new episode after recovery will be treated with the same treatment to which they responded before	This assumption corresponds to clinical practice. It was approved during the expert meeting
It is assumed that adverse events could occur only in "Depression" and "Partial Response" status with the exception of sexual dysfunction	It was approved during the expert meeting
Return to normal functioning occurs after clinical remission	While not entirely supported by the data, it was considered as a reasonable simplification during the expert meeting. This assumption needs further analyses on observational studies.
Patient is either compliant or non-compliant; partial compliance is not considered	To consider compliance as a continuous function needs a lot a data and does not provide a significant improvement. Considering compliance as a binary function was considered acceptable during the expert meeting
Patients do not stop the treatment before reaching partial response	This assumption needs validation on observational studies.
In term of clinical event, residual symptoms have an impact only on time to normal functioning **Residual symptoms improve upon reaching normal functioning**	It was considered reasonable during the expert meeting
Time to recurrence is independent of previous treatment but depends on Number of past episodes	These assumptions is made according to literature (Mueller 1999[5], Burcusa 2007[6])
Disutilities for adverse events are independent of the treatment	It is a simplification due to lack of data. This assumption should be discussed with clinical experts.

[5] Mueller TI, Leon AC, Keller MB, Solomon DA, Endicott J, Coryell W, Warshaw M, Maser JD. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. Am J Psychiatry. 1999 Jul;156(7):1000-6.

[6] Burcusa SL, Iacono WG. Risk for recurrence in depression. Clin Psychol Rev. 2007 Dec;27(8):959-85. Epub 2007 Mar 3.

Previous occurrence of an AE has no impact on adverse events with the next treatments	No data was found on this assumption. A validation with observational studies should be needed.

2.3 Population

It should be noted that we simulate only one cohort of patients having a MDD episode, which runs through all treatment strategies (i.e. we do not generate different cohorts for different strategies). Firstly, this allows to respond to the question which is to determinate the best treatment strategy for a given patient. Indeed, treatments effects are compared, all other things being equal as patients' characteristics and pathway features are the same for each arm. Secondly, this minimises the variability around incremental costs and outcomes between strategies.

2.4 Time horizon

The time horizon should be long enough so that the model captures the whole incremental benefits and costs of alternative treatments. The time horizon is flexible in the model but the following recommendations are given.

Based on preliminary analyses, we found that costs and outcomes were similar between strategies after 3 years, when comparing two strategies with different first-line therapies but similar subsequent therapies. Therefore a time-horizon of 3 years is recommended when only first-line strategies differ between strategies, and a time-horizon of 4 years for comparing strategies with different second-line and third-line therapies. In order to assess only a treatment strategy, time-horizon of 3 years is recommended.

2.5 Cost

2.5.1 Included costs

The following types of costs are included in the model:

- Antidepressant medication
- Management of adverse event
- Addition of an antipsychotic
- General practitioner visits including regular visits and additional visits
- Psychiatrist visits including regular visits and additional visits
- Hospitalizations
- Cost of productivity lost including presenteeism cost
- Costs of suicide and suicide attempt

Quantity of resources uses (general practitioner visits, psychiatrist visits, hospitalizations), number of suicide attempts and suicides are input data and have to be given in average according to specific periods (see Table 7).

Costs are then obtained by multiplying unit costs by quantity of resources used in each depression status and by adding the cost of additional physician visits due to specific events (e.g. switches or titrations), the cost of AE management, antidepressant medication cost, the cost of presenteeism and the cost of productivity lost.

2.5.2 Estimation of productivity loss costs

Only productivity lost due to depression is considered. Other sick leaves are assumed to be the same for all treatments leading to underestimate costs per strategy but having no impact on incremental cost.

The model allowed estimation of productivity costs due to depression using either the human capital approach or friction costs approach. Under the human capital approach, productivity costs are calculated as the product of lost work time by wages. This calculation uses an average number of days of absence per month, dependent on depression status. Under the friction cost approach, productivity costs are values based on the cost for society to replace lost work input. To make this calculation possible, two events were added in the model: *start of work absence* and *end of work absence*. The probabilities of occurrence of those events are dependent on functional status: the risk of *start of work absence* is strictly positive until the patient reaches the status of normal functioning, and then becomes zero. Those two events have no impact on other events, such as clinical events. This approach allows for repeated absences. The cost imputed to an absence is calculated as following:

- For short-term absences: the productivity cost is the product of wages, duration of absence and elasticity of production,

- For long-term absences: the productivity cost is equal to the time before employee replacement multiplied by the wages and elasticity of production, plus the cost of training a new employee.

The choice of approach for the valuation of productivity costs for adaptations to other countries will be dependent on local HTA guidelines.

The cost of presenteeism is implemented in the model as the product between the number of working days and a coefficient of presenteeism.

2.6 Model Inputs

The following tables (Table 4 to Table 9) summarize the input parameters of the model and the way the model takes them into account.

Table 4: inputs for attributes

Attributes	data input	Model function
Age	Percentages by age category (18-34;35-44;45-54;55-64;65-74) and by sex	Multinomial law for age category distribution Uniform law by age category and sex
Sex	Percentage of women in the MDD population	Bernoulli
Work status	Percentage of workers in the MDD population	Bernoulli
Number of previous episodes	Percentages by category (1;2;3 or more previous episodes)	Multinomial
Residual symptoms	Percentage of patients having residual symptoms	Bernoulli

Table 5: inputs for treatment-relative parameters

Parameters linked to treatment effectiveness event and to treatment duration	data input	Model function
Time to end of Sexual dysfunction	-duration	-exponential law
Time to Nausea	-Proportion of patients having experienced nausea at timepoint - timepoint	exponential law
Time to headache	-Proportion of patients having experienced headache at timepoint - timepoint	exponential law
Time to diarrhoea	-Proportion of patients having experienced diarrhoea at timepoint - timepoint	exponential law
Time to insomnia	-Proportion of patients having experienced insomnia at timepoint - timepoint	exponential law
Time to Other AE	-Proportion of patients having experienced Other AE at timepoint - timepoint	exponential law
Time to partial response	-Proportion of patients having a partial response at timepoint - timepoint	exponential law
Time to clinical remission after partial response	-Proportion of patients having a clinical remission after partial response at timepoint - timepoint	exponential law
Time to full remission = Time to normal functioning given that the patient have reached the clinical remission	-Proportion of patients having a full remission at timepoint - timepoint	exponential law
Interaction between treatment and prominent symptoms on time to full remission	Hazard ratio	applied to the time to full remission

The method for simulating an exponential law with the given input data is described in Appendix A3

Table 6: inputs for parameters not linked to treatment

Other	data input	Model function
Time to death (General mortality)	alpha and beta of the Gompertz law	Gompertz law
Time to Treatment discontinuation	Mean time in days by line of treatment	exponential law
Relative effectiveness to normal functioning for people having prominent symptoms	Hazard ratio	applied to the time to full remission
Proportion of major Sexual dysfunction	Proportion of major Sexual dysfunction	Bernoulli
Proportion of major Nausea	Proportion of major Nausea	Bernoulli
Proportion of major Headache	Proportion of major Headache	Bernoulli
Proportion of major Diarrhoea	Proportion of major Diarrhoea	Bernoulli
Proportion of major Insomnia	Proportion of major Insomnia	Bernoulli
Proportion of major Other adverse events	Proportion of major Other adverse events	Bernoulli
Time to relapse	-Proportion of patients having a relapse at timepoint - timepoint	exponential law
Time to recurrence	shape and scale parameters of Weilbull law	Weibull law
Time to suicide attempt	-Proportion of patients having experienced a suicide attempt at timepoint - timepoint	exponential law
Suicide	probability of death given a suicide attempt	Bernoulli
Relative effectiveness (partial response) after addition for LoE	Hazard ratio	applied to the time to partial response following an addition
Relative effectiveness (clinical remission) after addition for LoE	Hazard ratio	applied to the time to clinical remission following an addition
Relative safety after addition for LoE	Hazard ratio	applied to the time to AE following an addition
Relative effectiveness (partial response)after treatment adjustment for AE	Hazard ratio	applied to the time to partial response following a treatment adjustment for AE
Relative effectiveness (clinical remission) after treatment adjustment for AE	Hazard ratio	applied to the time to clinical remission following a treatment adjustment for AE
Relative safety after treatment adjustment for AE	Hazard ratio	applied to the time to AE following a treatment adjustment for AE
Relative effectiveness (partial response) after treatment adjustment for LoE	Hazard ratio	applied to the time to partial response following a treatment adjustment for LoE
Relative effectiveness (clinical remission) after treatment adjustment for LoE	Hazard ratio	applied to the time to clinical remission following a treatment adjustment for LoE
Relative safety after treatment adjustment for LoE	Hazard ratio	applied to the time to AE following a treatment adjustment for LoE
Relative effectiveness 1st line vs. second line	Hazard ratio	applied to the time to clinical events during the second line treatment

Other	data input	Model function
Treatment pathway after no partial response at 4 weeks	-Probability of switch -Probability of treatment adjustment -Probability of addition -Probability of no change	Bernoulli
Treatment pathway after no clinical remission at 4 weeks after partial-response evaluation	-Probability of switch -Probability of treatment adjustment -Probability of addition -Probability of no change	Bernoulli

Table 7: Inputs for resource utilisation and unit costs

Resource	details
General practitioner visits / Psychiatrist visits	Rate of visit of GP/specialist visits during the acute period (Depression and partial response status) Rate of visit of GP/specialist visits during the maintenance period (remission status). This phase doesn't include neither full remission status or recovery status Mean number of visits for a switch Mean number of visits for addition of an antipsychotic Mean number of visits for dose adjustment Mean number of visits for an AE
Hospitalization	Mean number of hospitalization days during the non recovery period Mean number of hospitalization days during the recovery period
Sick-leave	Mean number of sick-leave days during the non recovery phase
Presenteeism coefficient	Rate of reduction in production among patients with MDD
Elasticity	Elasticity of production to change in labour time, e.g. an elasticity of 80% implies that a 1% reduction in labour time would results in a reduction of production by 0.8%.
GP visit (unit cost)	by visit
Psychiatrist visit (unit cost)	by visit
Inpatient day for depression (unit cost)	by day
Suicide attempt (unit cost)	by event
Completed suicide (unit cost)	by event
Sick leave day (unit cost)	By day
Antidepressant Medication (unit cost)	daily price
Management of AE (unit cost)	by type of adverse event
Addition (addition cost)	by addition

Table 8: inputs for utilities

Utility values and unit costs	details
Utility by health status	Depression status
	Partial response status
	Clinical Remission status
	Full remission status
	Recovery status
QALY decrement for adverse event	Nausea
	Insomnia
	Headache
	Diarrhoea
	Other adverse event
Disutility for sexual dysfunction	

Table 9: Discount rates

Outcome	Details
QALYs	Discount rate applied to QALYs
Health outcomes	Discount rate applied to other health outcomes
Costs	Discount rate applied to costs

2.7 Model Outputs

The model provides the following measures of health benefits and costs by strategy and by year as well as by full time horizon period:

- *Quality-adjusted life years* (*QALYs*)
- Time in depression (days), time in partial response (days), time in clinical remission (days), time in full remission (days), time in recovery (days)
- Costs (physician visit costs, antidepressant costs, addition costs, adverse events costs, hospitalization costs, suicide and suicide attempt costs, lost productivity). Direct total costs include all the costs with the exception of productivity lost. Societal total costs include all the costs. These total costs should be adjusted according to the HTA guidelines.
- ICER (incremental cost-effectiveness ratio) per QALY per perspective (TPP and societal)

The incremental cost-effectiveness ratio (ICER) is defined as the additional cost incurred for each health benefit unit gained. The primary cost-effectiveness measure was the incremental cost per QALY in a TPP perspective.

Costs, health outcomes and QALYS are aggregated for each year and discounted using the following formula:

$$\text{Net present value} = \sum_{y=0}^{n-1} \frac{\text{outcome(y)}}{(1 + \text{discount rate})^{(n-1)}}$$

Where n represents the number of years (time horizon), and the 'outcome' is an outcome measure, by year y.

3 Model implementation

The model was implemented using Scilab.

The Figure 4 shows the Model programming structure. Each box represents a Scilab file. The “Patient generator” module generates randomly a cohort of patient. This cohort will be used in both strategies to ensure relevant results. The “Init” module initializes the variables needed by the script. For both strategies patient pathways are simulated (Figure 5). The simulation of “disease pathway” is processed patient by patients with a recursive algorithm. The time before occurrence of all possible events are simulated and compared. The event with the lowest simulated time will happen. Then the costs and QALYs are calculated by the following modules: ”Suicide simulation”, “sick-leave simulation”, “TRT_Costs” and “Events_counts”. An outcome file is generated for each strategy. Then the differential results, such as ICER, are computed.

Figure 4 : Model programming structure

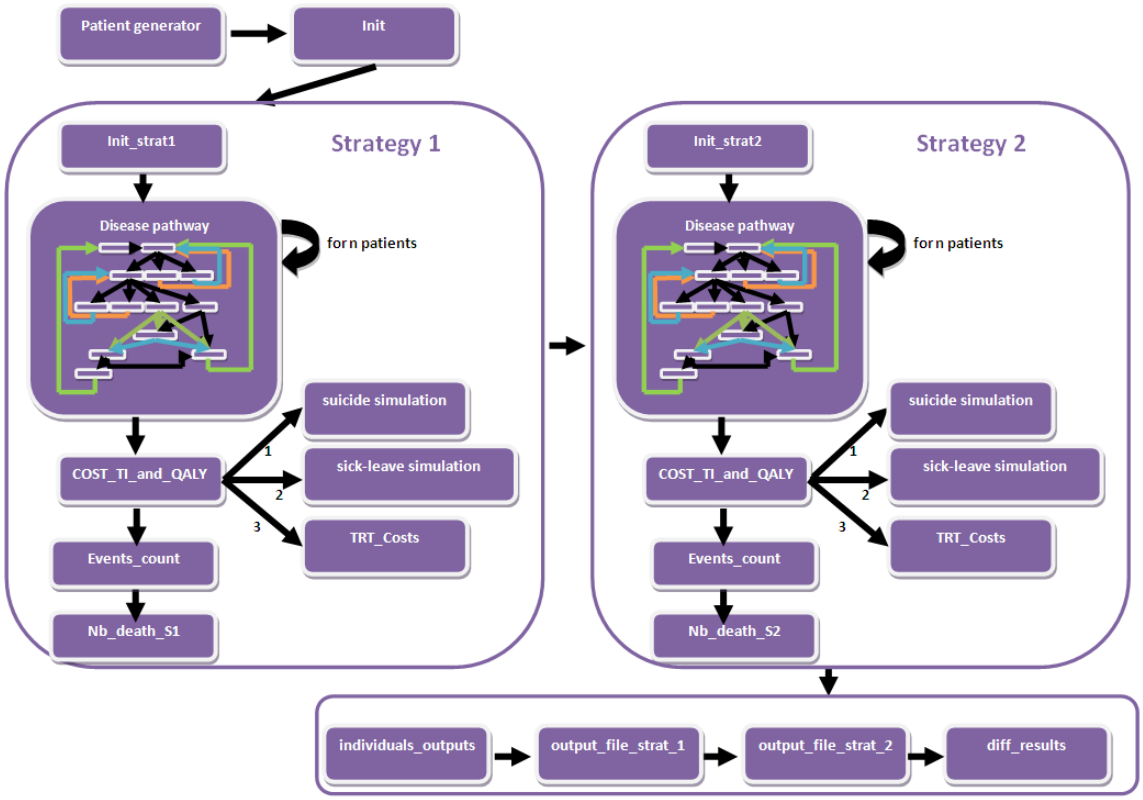
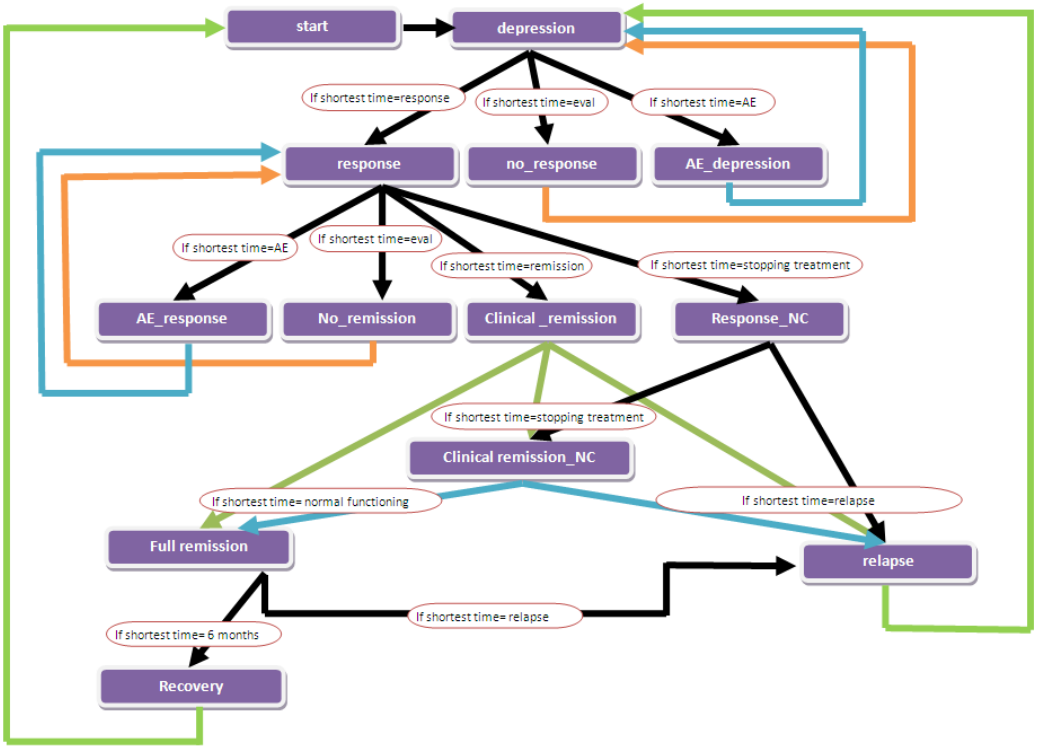


Figure 5 : Disease pathway algorithm



4 Proposed Inputs data

Proposed input data are given in this section. These input data have been obtained from several sources, including scientific literature and grey literature (e.g. national statistics). For some inputs for which no information was found in the literature, expert opinion or assumptions were used.

It was assumed that clinical data from international studies were transferable to United Kingdom.

4.1.1 Initial attributes

Socio-demographic attributes are country-specific. Values for the United Kingdom were used for the preliminary analyses.

Demographic characteristic of UK depressive patients were obtained from The Adult Psychiatric Morbidity Survey (APMS)[7]. This was a survey of psychiatric morbidity among adults living in private households, performed in 2007. It was carried out by the National Centre for Social Research in collaboration with the University of Leicester, and was commissioned by The NHS Information Centre for health and social care. The aim was to collect data on mental health among adults aged 16 and over living in private households in England. The distribution of the population with depression by age group and gender found in this survey was applied in the model (c.f. Table 10). Overall, 63% of depressive patients in England were female.

[7] Bebbington A , Brugha T, Coid J,Crawford M, Adult psychiatric morbidity in England, 2007 Results of a household survey, The NHS Information Centre for health and social care 2007

The work status was not available in the Adult Psychiatric Morbidity Survey. The percentage of working patients was obtained from the study of Borghi and Guest (2000)[8]. This study combined resource use data derived from a panel of general practitioners and psychiatrists and clinical trial outcomes to model the expected direct NHS costs and the indirect societal costs, due to lost productivity, of managing moderate and severe depression with mirtazapine, amitriptyline and fluoxetine in the UK, as well as the NHS costs related to discontinuation of antidepressant treatment. The percentage of working patients was established by interviewing panel of ten general practitioners and three psychiatrists with semi-structured discussions. They estimated that 47.8% of patients of working age are not in work before they commence a depressive episode. In this paper, there is no distinction of partial and full workers. As a consequence, a rate of full worker was assumed to be 52.2%. The work status is independent of age and gender.

The number of previous episodes was extracted from Mueller 1999[9]. The aim of this study was to explore predictors of recurrence of depressive disorder after recovery from a naturalistic follow-up study including 380 patients major depressive disorder in US. The distribution is available in the Table 10.

No supportive data were found on residual symptoms. We assumed that 20% of patients presenting with MDD has residual symptoms.

The table below summarises input data for initial attributes.

Table 10: Input data for initial attributes

Variable	Source	Value for the UK						Distribution
Age	Adult psychiatric morbidity in England, 2007		**18-34**	**35-44**	**45-54**	**55-64**	**65-74**	Multinomial for age category
		Male	23%	22%	24%	20%	11%	
		Female	24%	18%	26%	16%	16%	Uniform for age within each age category
Sex	Adult psychiatric morbidity in England, 2007	63 % of Female						Bernoulli
Work status	Borghi 2000	52.2% of worker						Bernoulli
Number of previous episodes	Mueller 1999	0 : 37% / 1 : 23% / 2 : 13% / 3 and + : 27%						Multinomial
Residual symptoms	Assumption	20 %						Bernoulli

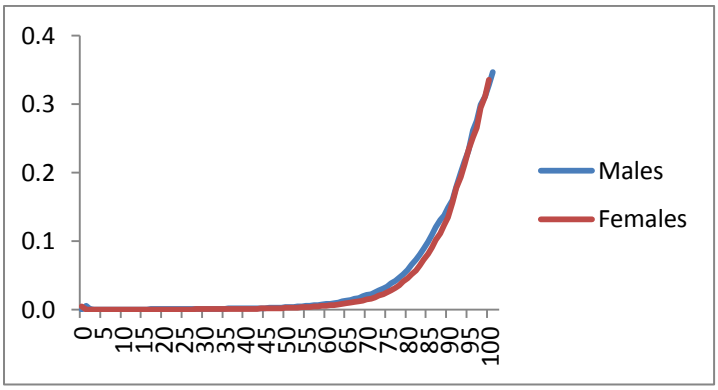
[8] Borghi J, Guest JF.Economic impact of using mirtazapine compared to amitriptyline and fluoxetine in the treatment of moderate and severe depression in the UK. Eur Psychiatry. 2000 Sep;15(6):378-87.

[9] Mueller TI, Leon AC, Keller MB, Solomon DA, Endicott J, Coryell W, Warshaw M, Maser JD. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. Am J Psychiatry. 1999 Jul;156(7):1000-6.

4.1.2 General mortality

The UK lifetable for 2007-2009 was downloaded from the UK Office for National Statistics website[10]. Different mortality rates were used for men and women.

Figure 6: Mortality rate (risk of death) by age in the United Kingdom in 2007-2009



The Gompertz–Makeham function was fitted to the UK lifetable in order to model mortality, for men and women separately. The Gompertz law can be written as following:

$$S(x) = \exp\left[\frac{\alpha}{\beta}(1 - \exp^{\beta x})\right]$$

The criterion used for fitting the function was the least means square error. The following parameters were obtained: alpha =0.0000370 and beta =0.0925091 for men and alpha=0.0000144, and beta=0.0999890 for women.

4.1.3 Clinical inputs

4.1.3.1 Time to each adverse event

Probabilities of adverse events were extracted from the Cochrane review performed by Cipriani in 2009[11].

The objective of this review was to assess the evidence for the efficacy, acceptability and tolerability of escitalopram in comparison with tricyclics, other SSRIs, hetero-cyclics and newer agents in the acute-phase treatment of major depression. All randomised controlled trials comparing escitalopram against any other antidepressant for patients with major depressive disorder up to July 2008 were included. Fourteen trials comparing escitalopram with another SSRI and eight comparing escitalopram with a newer antidepressive agent (venlafaxine, bupropion and duloxetine) were found.

As no specific treatment was used for this core-model, the higher and the lower rate of adverse events of all treatments reviewed in the Cipriani 2009 were selected for each adverse event nausea,

[10] http://www.statistics.gov.uk/

[11] Cipriani A, Santilli C, Furukawa TA, Signoretti A, Nakagawa A, McGuire H, Churchill R, Barbui C. Escitalopram versus other antidepressive agents for depression.Cochrane Database Syst Rev. 2009 Apr 15;(2):CD006532. Review.

headache, diarrhoea, insomnia and sexual dysfunction (table 5). Sexual dysfunction was reported in the Cipriani's review as "decreased libido". The follow-up period for most studies was 8 weeks, one study was a 6-week trial (Yevtushenko 2007) and three studies had a follow-up up to 24 weeks (Boulenger 2006[12]; Colonna 2005[13]; Wade 2007[14]). A sensitivity analysis with exclusion of studies with follow-up period not equal to 8 weeks was performed. Only two rates changed: the maximum rate of nausea became 25% (vs. 26% in the main analysis) still for duloxetine; and the maximum rate of headache was 18%, for sertraline (instead of 20% for paroxetine in the main analysis). This sensitivity analysis supports the assumption that it is not needed that AEs be considered on long-term. Figures at 8 weeks were selected in the model.

For the category of "other adverse events", for each treatment in the review, the probability of occurrence was calculated as the probability of having at least one adverse event given in the review minus the probability of having at least one AE of these "specific" types of short AE: nausea headache, diarrhoea, insomnia.

Probability to have no "specific" AE is given by

$$P(no\_specific\_AE) = (1 - P(nausea)) * (1 - P(Diarrhoea)) * (1 - P(Headache)) * (1 - P(Insomnia))$$

Therefore, the probability of other adverse event is given by

$$P(other\_AE) = P(All\_AE) - (1 - P(no\_specific\_AE))$$

The minimum probability was 21%, for paroxetine, and the maximum value was 37%, for sertraline.

Table 11: Adverse event rates extracted from Cipriani 2009

	Treatment with min rate	Minimum rate	Treatment with max rate	Maximum rate
Nausea	citalopram or fluoxetine	12%	duloxetine	26%
Headache	fluoxetine	11%	paroxetine	20%
Diarrhoea	bupropion	6%	sertraline	18%
Insomnia	citalopram	7%	bupropion	14%
Sexual dysfunction	fluoxetine	4%	venlafaxine	9%
Other	citalopram	21%	sertraline	37%

[12] Boulenger JP, Huusom AK, Florea I, Baekdal T, Sarchiapone M. A comparative study of the efficacy of long-term treatment with escitalopram and paroxetine in severely depressed patients.Curr Med Res Opin. 2006 Jul;22(7):1331-41.

[13] Colonna L, Andersen HF, Reines EH.A randomized, double-blind, 24-week study of escitalopram (10 mg/day) versus citalopram (20 mg/day) in primary care patients with major depressive disorder.Curr Med Res Opin. 2005 Oct;21(10):1659-68.

[14] Wade A, Gembert K, Florea I. A comparative study of the efficacy of acute and continuation treatment with escitalopram versus duloxetine in patients with major depressive disorder.Curr Med Res Opin. 2007 Jul;23(7):1605-14.

The table below describes the rate of each adverse event at 8 weeks used in the model. The medium rate corresponded to the mean of the maximum and the minimum rate.

Table 12: Adverse event rate at 8 weeks

	Low rate	Medium rate	High rate
Nausea	12%	19%	26%
Headache	11%	15.5%	20%
Diarrhoea	6%	12%	18%
Insomnia	7%	10.5%	14%
Sexual dysfunction	4%	6.5%	9%
Other	21%	29%	37%

Times to each adverse event were assumed to be exponentially distributed. This implies that the probability of adverse event was the same for each day on treatment. The advantage of this distribution is that it is fully determined by one data point. In reality, it is likely that the probability of adverse event is greater on first days of treatment. To take this into consideration, it is not sufficient to have one data point (such as the probability of event within 8 weeks), but we would need a survival curve for each event. However, the model is compatible with more complex distributions.

As no data on sexual dysfunction duration was available at this stage, a mean duration between 30 and 60 days was assumed.

4.1.3.2 Percentage of major adverse event

As no data are published on the percentage of adverse events requiring a switch, an expert was asked to provide estimations based on his experience. The following rates were chosen for these analyses:

- Sexual dysfunction : 5%
- Nausea : 1%
- Headache : 2%
- Diarrhea : 1%
- Insomnia : 3%
- All other adverse events : 3%

4.1.3.3 Time to partial response

As no data on partial response (defined by a $\geq$ 25% decrease in severity score over 4 weeks from the beginning of episode) was published in the literature, the following assumptions were made for the rates:

- High rate : 70%
- Medium rate : 55%
- Low rate : 40%

Times to partial response were assumed to be exponentially distributed.

4.1.3.4 Time to remission after partial response

As for partial response, no data on remission 4 weeks after partial response was reported in the literature, the following assumptions were made:

- High rate : 50%
- Medium rate: 40%
- Low rate : 30%

Times to remission were assumed to be exponentially distributed.

4.1.3.5 Normal functioning

No data are available on time from remission to normal functioning. For this model, percentages of normal functioning after clinical remission are needed. It was assumed that the normal function rate after clinical remission is obtained in a population without residual symptoms

For this model, the following rates of normal functioning two weeks after clinical remission were used (assumptions):

- High rate : 80%
- Medium rate: 60%
- Low rate : 40%

The time from clinical remission to normal functioning was assumed to be exponentially distributed.

4.1.3.6 Time to relapse

Gilchrist et al.[15] published a systematic review of observational studies in depression in 2007. Only two studies in the review presented data on relapse rates. Limosin et al. (2004)[16] reported that 11% of patients with major depressive disorder relapsed at 6 months after remission. According to Oldehinkel et al. (2000)[17], the relapse rate among depressed patients was 30%; relapse being described as "transition from an asymptomatic state of at least two months to a state of mental disorder". In addition, a relapse rate of 33.5% at 4.4 months was reported in the STAR*D study.

The following rates of relapse were used for these analyses:

- Treatment with high relapse rate : 33.5% at 4.4 months
- Treatment with medium relapse rate : 20% at 6 months
- Treatment with low relapse rate : 10 % at 6 months

For patient who stops treatment before recovery, the high rate of relapse was applied.

---

[15] Gilchrist G, Gunn J.Observational studies of depression in primary care: what do we know? BMC Fam Pract. 2007 May 11;8:28.

[16] Limosin F, Loze JY, Zylberman-Bouhassira M, Schmidt ME, Perrin E, Rouillon F: The course of depressive illness in general practice. Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie 2004, 49:119-123.

[17] Oldehinkel AJ, Ormel J, Neeleman J: Predictors of time to remission from depression in primary care patients: Do some people benefit more from positive life change than others? Journal of Abnormal Psychology 2000, 109:299-307.

The time from remission to relapse was assumed to be exponentially distributed.

4.1.3.7 Recurrence

Mueller et al. 1999[18] estimated time to recurrence in 380 subjects from a naturalistic follow-up study including 955 patients with psychiatric treatment for a mood disorder in the US. These 380 subjects suffered from major depressive disorder and recovered during the 15 years follow-up of the study. It was found that sex (OR=1.43) and number of previous episodes (OR=1.18) were predictors of recurrence. Probabilities of survival without recurrence were read from a Kaplan-Maier curve for total population using the Grafula software. A Weibull survival function was fitted on this curve. The Weibull distribution is frequently used in DES models. More details are given about this law in the appendix A2.

The time to recurrence was simulated with the following parameters: λ =0.66 (scale parameter) and γ =245 (shape parameter). The median time to recurrence was 134 weeks. Identified predictors (sex and number previous episodes) were not integrated in the function.

4.1.3.8 Risk of suicide

The majority of patients with depression have at least episodic suicidal ideation. Khan 2001[19] found that differences in rates of attempted suicides and completed suicides between antidepressants and placebo were small and non-significant. Therefore it was assumed in this model that suicide and attempted suicide were not treatment-specific.

Time to suicide attempts was based on a Pharmetrics-based study performed in 2009. The objective of this study was to assess the occurrence of attempted suicides using a US real-life prescription database. The sample consisted of 1,337,506 patients with a new antidepressant prescription which occurred between 2002 and 2006. As no specific code exists for suicide in Pharmetrics, other diagnostics were used as proxies. A depressive episode was defined as the 6 months after the start of antidepressant treatment and recovery period as the period between 6 and 1 month before start of treatment. Estimated rates of suicide attempts for depressive patients were to 49.38 per 100,000 at one month, and 10.35 per 100,000 in recovery.

Khan 2001 collected public domain data on FDA-reviewed studies for venlafaxine and citalopram to assessed suicide risk among MDD patients. The risk of dying in such an attempt was estimated at 10%.

4.1.3.9 Treatment duration

---

[18] Mueller TI, Leon AC, Keller MB, Solomon DA, Endicott J, Coryell W, Warshaw M, Maser JD. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. Am J Psychiatry. 1999 Jul;156(7):1000-6.

[19] Khan A, Khan SR, Leventhal RM, Brown WA.Symptom reduction and suicide risk among patients treated with placebo in antipsychotic clinical trials: an analysis of the food and drug administration database.Am J Psychiatry. 2001 Sep;158(9):1449-54.

Treatment duration corresponds to the duration of treatment in general by line of treatment for treated patients and not the total duration under specific treatment.

Data on treatment duration were based on GPRD analysis. The mean duration by line of treatment was estimated at:

- 201 days in first line
- 157 days in second line
- 161 days in third line
- 143 days in fourth line and more

Treatment duration was assumed to be exponentially distributed.

4.1.3.10 Proportions of switch, dose adjustment and addition

Data are scarce about treatment pathways in case of non partial response or non remission at 8 weeks. For first analysis, assumptions were made. In a US study based on a large managed care database (McLaughlin 2004[20]), changes in treatment due to lack of effectiveness were titration for 75% of cases, switch for 15% and addition for 10%. The proportions of patients without change were not estimated. It was assumed in our model that in case of absence of partial response at 4 weeks and in case of non-remission 4 weeks after partial response, the probability of absence of change was 50%. As a consequence, the probability of switch was 7.5 %, the probability of dose adjustment 37.5 %, and the probability of addition 5%.

4.1.3.11 Relative effectiveness and Relative side effect rate

As no data were available at this stage, all relative effectiveness and side effect rate were assumed to be equal to 1:

- Hazard ratio for side effect after treatment adjustment for AE =1
- Hazard ratio for side effect after treatment adjustment for lack of efficacy =1
- Hazard ratio for side effect rate after addition for LoE =1
- Hazard ratio for partial response after treatment adjustment for AE =1
- Hazard ratio for partial response after treatment adjustment for lack of efficacy =1
- Hazard ratio for partial response after addition for LoE =1
- Hazard ratio for remission after treatment adjustment for AE =1
- Hazard ratio for remission after treatment adjustment for lack of efficacy =1

---

[20] McLaughlin TP, Eaddy MT, Grudzinski AN. A claims analysis comparing citalopram with sertraline as initial pharmacotherapy for a new episode of depression: impact on depression-related treatment charges. Clin Ther 2004;26:115-24

- Hazard ratio for remission after addition for LoE =1

4.1.3.12 Residual symptoms

Due to lack of evidence for now, data on residual symptoms are based only on assumptions. It is arbitrarily assumed that at each new episode a patient has a probability of residual symptoms of 20%.

It is difficult to find data on the impact of residual symptoms on normal functioning because rates of normal functioning obtained from clinical trials or observational studies (for example) take into account that part of the population with MDD has residual symptoms. Therefore we need to get time to normal functioning for each treatment both in a population without residual symptoms (different from the population of the clinical trials and observational studies) and in a population with residual symptoms.

All treatments were assumed to have no impact on residual symptoms in the base case analysis.

4.1.3.13 Utilities

Utilities depend on clinical remission status, normal functioning and recovery. In case of adverse event, a QALY decrement was applied to the utility of the current status of the patient.

Utility values associated with depression are available from several studies in the literature, summarised in the table below (Bennett et al. 2000[21]; Pyne et al. 2003[22]; Revicki and Wood 1998[23]; Sapin et al. 2004[24]; Schaffer et al. 2002[25]) :

Table 13: Utility values associated with depression in the literature

Study	Definition of health states	Population	Valuation method	Results
Bennett et al 2000	Three psychiatrist nurses and three social workers assessed depression health. The health state descriptions referred to	105 patients with history of MDD in the previous 2 years.	McSad health state classification system	**Temporary states (6-mo):** mild depression 0.59 (0.55-0.62) moderate depression 0.32 (0.29-0.34) severe depression 0.09 (0.05-0.13) **Clinical States (lifetime):** self reported health state 0.79 (0.74-0.83) severe depression 0.04 (0.01-0.07)

[21] Bennett KJ, Torrance GW, Boyle MH, Guscott R. Cost-utility analysis in depression: the McSad utility measure for depression health states.Psychiatr Serv. 2000 Sep;51(9):1171-6.

[22] Pyne JM, Sieber WJ, David K, Kaplan RM, Hyman Rapaport M, Keith Williams D.Use of the quality of well-being self-administered version (QWB-SA) in assessing health-related quality of life in depressed patients.J Affect Disord. 2003 Sep;76(1-3):237-47

[23] Revicki DA, Wood M. Patient-assigned health state utilities for depression-related outcomes: differences by depression severity and antidepressant medications.J Affect Disord. 1998 Feb;48(1):25-36.

[24] Sapin C, Fantino B, Nowicki ML, Kind P.Usefulness of EQ-5D in assessing health status in primary care patients with major depressive disorder. Health Qual Life Outcomes. 2004 May 5;2:20.

[25] Schaffer A, Levitt AJ, Hershkop SK, Oh P, MacDonald C, Lanctot K.Utility scores of symptom profiles in major depression. Psychiatry Res. 2002 Jun 1;110(2):189-97.

	untreated depression.			
Pyne et al. 2003	Prospective observational study conducted over 16 weeks. Response defined as 50% reduction in HRSD-17	58 US patients treated for MDD	Quality of well-Being QWB	**Baseline :** 0.41 **Mild** / **Moderate** **4-week** 0.54 / 0.46 **4-month** 0.63 / 0.43
Revicki & Wood 1998	Depression related states, varying depression severity and antidepressant treatment, and the patient's current health status.	70 patients with MDD from primary care practices in US & Canada	SG	**Severe depression, untreated:** 0.30 (0.22) **Moderate depression** between : 0.55 (0.03) and 0.63 (0.19) **Mild depression**: between 0.64 (.20) and 0.73 (0.21) **Depression remission, maintenance treatment** between 0.72 (0.17) and 0.83 (0.13) **Remission, no treatment:** 0.86 (0.16)
Sapin et al.2004	Multicentre, prospective, non-comparative cohort study, 8 weeks follow-up. Clinical response, defined by MADRS scores. 'remitters': MADRS <=12 'responder': at least 50% decrease in baseline score	250 patients with new episode MDD not treated with AD before inclusion, from French primary care	EQ-5D	**Baseline** Mild Depression: 0.45 (0.22) Moderate Depression: 0.33 (0.24) Severe Depression: 0.15 (0.21) **8 weeks** No Depression: 0.86 (0.13) Mild Depression: 0.74 (0.19) Moderate depression: 0.44 (0.27) Severe Depression: 0.30 (0.27) Responder – remitter : 0.85 (0.13) Responder - non-remitter: 0.72 (0.20) Non-responders: 0.58 (0.28)
Schaffer et al. 2002	Utility scores for 10 individual symptoms of depression, and 3 depression severity profiles	75 Canadian subjects (19 current depression, 21 past depression and 35 healthy controls)	SG	**Mild** / **Moderate** / **Severe** **Current** 0.59(0.33) / 0.51(0.34) / 0.31(0.31) **Past** 0.79(0.28) / 0.67(0.36) / 0.47(0.34) **Controls** 0.80(0.21) / 0.69(0.29) / 0.46(0.28)

We chose to use the utility values reported by Sapin et. al (2004), like in the NICE Clinical Guidance[26].

> *"NICE currently recommends the EQ-5D as the preferred measure of HRQoL in adults for use in cost-utility analyses. The institute also suggests that the measurement of changes in HRQoL should be reported directly from people with the condition examined, and the valuation of health states be based on public preferences elicited using a choice-based method such as time trade-off (TTO) or standard gamble (SG), in a representative sample of the UK population.Therefore, based on these recommendations, the EQ-5D utility scores estimated by Sapin and colleagues (2004) were c onsidered to be the most suitable for calculating QALYs in the guideline economic models.*

The study by Sapin *et al*. (2004) was based on a multicentre, prospective cohort of patients with a new episode of MDD recruited in the French primary care setting. EQ-5D utility scores were stratified

[26] National Institute for Clinical Excellence (NICE) (2009) Depression: the treatment and management of depression in adults. London: National Institute for Clinical Excellence.

according to depression severity, defined by CGI scores, and by clinical response, defined by MADRS scores, at follow-up. It should be noted that utilities associated with different levels of severity were lower at baseline than at 8 weeks: this variation over time is not captured in the model.

The following utilities were used for this model:

- Utility in depression=0.33: this corresponds to the utility at baseline for moderate depression, it is an intermediate value between the utility at baseline for severe depression (0.15) and the utility at 8 weeks for moderate depression (0.44)
- Utility in partial response = 0.72
- Utility in clinical Remission=0.79
- Utility in full remission = 0.85
- Utility in recovery=0.86

The utility in full remission (clinical remission + normal functioning) was not estimated in this study, so the utility in clinical remission was used as approximation, taking into consideration the fact that utilities for clinical remission and recovery were very close according to Sapin *et al*.

QALY decrements for adverse events and disutility for sexual dysfunction were derived from a direct analysis of the data in the 2000 Medical Expenditure Panel Survey (MEPS), a nationally representative survey of the US population. This study, published by Sullivan et. al. 2004[27] was based on the EQ-5D questionnaire. Adverse events were assumed to last two weeks for the calculation of the QALY decrements.

- nausea=-0.0025
- insomnia=-0.004962
- headache=-0.004423
- diarrhoea=-0.001692
- Other adverse event = -0.003269
- Sexual dysfunction =-0.049 (disutility)

Table 14: Utility values

	Source	Value	Comment
Utility by health status	Sapin 2007	Depression =0.33 Partial response=0.72 Clinical Remission=0.79 Full remission = 0.85 Recovery=0.86	Utility on full remission could be estimated thanks to clinical trials

[27] Sullivan PW, Valuck R, Saseen J, MacFall HM. A comparison of the direct costs and cost effectiveness of serotonin reuptake inhibitors and associated adverse drug reactions. CNS Drugs. 2004;18(13):911-32.

QALY decrement for adverse event	Sullivan 2004	nausea=-0.0025 insomnia=-0.004962 headache=-0.004423 diarrhoea=-0.001692 Other adverse event = -0.003269
Disutility for sexual dysfunction	Sullivan 2004	Sexual dysfunction =-0.049

The model allows for different utilities in clinical remission and full remission but no study reported utility for full remission at this stage. Utility in clinical remission was used as approximation and sensibility analyses were performed to measure the impact of this value.

4.1.4 Resource use and unit costs

In the economic model presented in the NICE clinical guidance on antidepressant agent (2009)[28], all patients were assumed to be monitored during both the initial treatment period and the maintenance treatment period. It was assumed that 75% of patients would receive standard GP care whilst the remaining 25% would receive psychiatrist care. It was assumed that patient monitoring in both primary and secondary care consists of two fortnightly visits in the first month followed by one visit in the second month, whilst the maintenance therapy period consists of one GP/specialist visit every two months, based on expert opinion. That included scheduled visits (4 weeks and 8 weeks).

Additional GP visits in case of switch, addition and treatment adjustment were derived from previous cost-effectiveness model and corresponded to clinical practice.

Estimates for hospitalization rates due to severe depression were derived from Borghi and Guest 2000[29]. This study provided probabilities of hospitalisation, health care resource utilization, and costs associated with severe depression in the United Kingdom. Borghi and Guest reported that the mean number of inpatient days per months was equal to 0.225.

For the valuation of productivity costs in analyses for the UK, the human capital approach was used. Borghi and Guest 2000 estimated that a working patient in UK is expected to miss a mean of 2.67 days of work per months during the depressive episode. The cost of presenteeism was implemented

[28] National Institute for Clinical Excellence (NICE) (2009) Depression: the treatment and management of depression in adults. London: National Institute for Clinical Excellence.

[29] Borghi J, Guest JF.Economic impact of using mirtazapine compared to amitriptyline and fluoxetine in the treatment of moderate and severe depression in the UK. Eur Psychiatry. 2000 Sep;15(6):378-87.

in the model as the product of days work by a coefficient of presenteeism. This coefficient is unknown at this stage. In the analyses, presenteeism was not considered.

Costs associated with adverse event management were not considered in the analyses because of a lack of data.

Costs associated with suicide attempts and suicides were considered by multiplying the number of events by the unit costs.

Daily doses of antidepressants were those of antidepressants chosen according to their daily cost (agomelatine and sertraline) (see Table 16).

Table 15: Resource use

	Source	Value
General practitioner visits / Psychiatrist visits	NICE model 2009	Acute period : one GP/specialist visit every two weeks Maintenance period : one GP/specialist visit every two months 75% of GP / 25% of specialist
Mean number of sick-leave days	Borghi 2000	2.67 days per month
Mean number of hospitalization days	Borghi 2000	0.225 days per month
Treatment adjustment	Previous models and clinical practice	1 Additional GP visit
Addition	Previous models and clinical practice	1 Additional GP visit
Switch	Previous models and clinical practice	1 Additional GP visit at the evaluation visit
Adverse event	Previous models and clinical practice	1 Additional GP visit

Unit costs were collected from standard sources for the UK, for the reference year 2010:

- National Reference Costs for Emergency Department visits and hospitalisations

- PSSRU Annual Costs of Health and Social Care for physician visits
- British National Formulary for medication
- Annual Survey of Hours and Earnings for cost of sick-leave day. This survey measured 'the average level and distribution of earnings and paid hours for employee jobs' in the UK. It is based on an initial sample size of 175,000 employees obtained through records held by UK public authorities.

No estimation of cost of adverse event management (including medication cost) were found at this stage for the UK. As these costs are expected to be small, they are assumed to be null for the base-case analysis.

Daily costs of antidepressant were based on costs reported in the British National Formulary (March 2011); the minimum and maximum values were used, they corresponded to setraline and agomelatine respectively..

Table 16: Unit costs

	Value	Source
GP visit	£36	PSSRU[30] / General practitioner — unit costs per per surgery consultation lasting 11.7 minutes
Psychiatrist visit	£110	PSSRU/Consultant: psychiatric per contract hour
Inpatient days for depression	£232	PSSRU/ Acute NHS hospital services for people with mental health problems per inpatient day
Suicide attempt	£911	Netten 2001[31] (in £ 2010)*
Completed suicide	£307	Netten 2001 (in £ 2010)*
Sick leave day	£97.52	Annual Survey of Hours and Earnings, Office for National Statistics

[30] Unit Costs of Health and Social Care 2010, compiled by Lesley Curtis, PSSRU 2011

[31] Netten A, Rees T, Harrison G. Unit costs of health and social care 2001. Canterbury: University of Kent; 2001

Antidepressant Medication	Low price : £0,04 Medium price : £0.8 High price : £1.56	British National Formulary (March 2011)[32] Low price : sertraline daily cost Medium price : mean between agomelatine and sertraline daily cost High price : agomelatine daily cost

*calculation made with the United Kingdom inflation rates from 2001 to 2010 found in Eurostat website.

4.1.5 Discount rate

Costs and benefits were discounted to present values, at the nationally recommended rates of discount (3.5% for the NICE UK guideline).

[32] British National Formulary , BMJ Group and the Royal Pharmaceutical Society of Great Britain,61 2011

4.1.6 Summary of input data

All input data for the base case analysis are summarized in the Table 17.

Table 17: Input data – base case analysis

	Source		Value				
			18-34	**35-44**	**45-54**	**55-64**	**65-74**
Age	Adult psychiatric morbidity in England, 2007	**Male**	23%	22%	24%	20%	11%
		Female	24%	18%	26%	16%	16%
Sex	Adult psychiatric morbidity in England, 2007	63 % of Female					
Work status	Borghi 2000	52.2% of worker					
Number of previous episodes	Mueller 1999	0 : 37% / 1 : 23% / 2 : 13% / 3 and + : 27%					
Residual symptoms	Assumption	20 %					
Treatment impact on Residual symptoms	Assumption	OR=1 for all treatments					
General mortality	UK office of national statistics	Gompertz law dependent on age and sex: Men α =0.0000370 and β =0.0925091 Women α =0.0000144, and β =0.0999890					
Probabilities of sexual dysfunction at remission	Cochrane review (Cipriani 2009)	High rate : 9% Medium rate:6.5% Low rate : 4%					
Duration of sexual dysfunction	Assumption	High duration: 60 days Medium duration : 45 days Low duration: 30 days					
Probabilities of AEs over 8 weeks : nausea	Cochrane review (Cipriani 2009)	High rate : 26% Medium rate:19% Low rate : 12%					
Probabilities of AEs over 8 weeks : headache	Cochrane review (Cipriani 2009)	High rate : 20% Medium rate: 15.5% Low rate : 11%					
Probabilities of AEs over 8 weeks : diarrhea	Cochrane review (Cipriani 2009)	High rate : 18% Medium rate:12% Low rate 6%					
Probabilities of AEs over 8 weeks : insomnia	Cochrane review (Cipriani 2009)	High rate : 14% Medium rate: 10.5% Low rate 7%					

Probabilities of AEs over 8 weeks : Other AEs	Cochrane review (Cipriani 2009)	High rate : 37% Medium rate: 29% Low rate: 21%
Proportion of major Sexual dysfunction	Expert	5%
Proportion of major Nausea	Expert	1%
Proportion of major Headache	Expert	2%
Proportion of major Diarrhea	Expert	1%
Proportion of major Insomnia	Expert	3%
Proportion of major Other adverse events	Expert	3%
Partial response rate at 4 weeks	clinical trials	High rate : 70% Medium rate: 55% Low rate : 40%
Clinical remission rate 4 weeks after partial response	clinical trials	High rate : 50% Medium rate: 40% Low rate : 30%
Normal functioning after 2 weeks clinical remission	clinical trials	High rate : 80% Medium rate: 60% Low rate : 40%
Relapse rate at 6 months	Gilchrist 2007	High rate: 46% (33.5% at 4.4 months) Medium rate: 20% Low rate : 10%
Time to recurrence	Mueller 1999	Weibull law (λ =0.66 and k =245)
Treatment duration	GPRD analysis	1st line : 201 days 2nd line : 157days 3rd line : 161 days 4th line : 143 days
Time to suicide attempt	GPRD analyses	Rate per 100000 at 1 month : Depression : 49.38 full remission and recovery :10.35
Risk of dying of suicide attempts	Khan 2011	10%
Variation of time to side effect after treatment adjustment for AE	Assumption	No variation
Variation of time to side effect rate after treatment adjustment or addition for lack of efficacy	Assumption	No variation
Relative effectiveness after addition	Assumption	No variation
Relative effectiveness after treatment adjustment for AE	Assumption	No variation
Relative effectiveness after treatment adjustment or addition for lack of efficacy	Assumption	No variation
Relative effectiveness 1st line vs.	Assumption	No variation

second line		
Treatment pathway after no partial response at 4 weeks	Assumption / US studies	Switch: 7.5% Treatment adjustment : 37.5% Addition : 5% No change : 50%
Treatment pathway after no remission at 4 weeks post partial-response	Assumption / US studies	Switch: 7.5% Treatment adjustment : 37.5% Addition : 5% No change : 50%
Utilities	Sapin 2007	Depression = 0.33 Partial response = 0.72 Clinical Remission = 0.79 Recovery = 0.86 Full remission (assumed identical to recovery) = 0.86
General practitioner visits / Psychiatrist visits	NICE model 2009	Acute period : one GP/specialist visit every two weeks Maintenance period : one GP/specialist visit every two months 75% of GP / 25% of specialist
Mean number of sick-leave days	Borghi 2000	2.67 days per month in depression, 0 days per month in recovery
Mean number of hospitalization days	Borghi 2000	0.225 days per month in depression 0 days per month in recovery
Additional GP visit for treatment adjustment, addition or switch	Previous models and clinical practice	1 Additional GP visit
Additional GP visit for treatment adjustment	Previous models and clinical practice	1 Additional GP visit
Additional GP visit for addition	Previous models and clinical practice	1 Additional GP visit
Additional GP visit for switch	Previous models and clinical practice	1 Additional GP visit
Discount rate	NICE guideline	3.5% for cost and outcomes

5 Conclusion

We developed a core disease model for MDD, which may be used to support economic analysis of antidepressant medications. A DES approach was used, which made it possible to reproduce patient pathways in a flexible and very realistic manner. Specific features of this model included the following:

- long time-horizon,
- the model takes into consideration MDD recurrences
- the model takes into account partial response (and potential changes in treatment in absence of partial response) on between clinical remission and full remission (clinical remission with normal functioning)
- the model allows for differences in effectiveness of AD drugs medication according to treatment line and reasons for switch,
- the model allows for adjustment of effectiveness and safety parameters in case of change in dose or addition of AD medication,
- the model takes into account treatment discontinuation (after partial response).

The following limitations can be emphasized.

It was suggested to consider comorbidities, such as insomnia and anxiety. It is important to be transparent on the reasons for the selection of comorbidities that the model takes into account or not. There are a large number of comorbidities associated with MDD and it would not be feasible to consider all of them. Indeed, if too many comorbidities are included, there is a risk that the model be seen as a "black box". It is recommended to consider comorbidities only if the two following conditions are verified:

- Modelled events, such as remission or return to work, are related to comorbidities;
- There is evidence that treatments differ in their effect on comorbitidies; for example some treatments may have a greater anxiolytic effect than others and improve the probability of remission in patients with anxiety.

Thus, type 2 diabetes mellitus or cancer have been reported to be comorbidities of MDD, but we would not recommend including them in the model since AD drugs have no direct effect on those comorbidities.

However, insomnia and anxiety have an impact on full remission and maybe relapse and it seems plausible that antidepressants vary their effect against anxiety and insomnia but this should be verified at the time of model adaptation. Taking into account anxiety or insomnia would not necessarily require any structural change. It would be possible to allow for a greater time to remission in patients with comorbidities, and for different effects between treatment in patients

with comorbidities, without changing the model structure. But, it is not possible with the current structure to consider costs or utilities associated with comorbidities after remission.

Furthermore, deaths in the model were eight attributable to general mortality or suicides. General mortality in reported analyses was based on the life table of the UK population. Thus we did not take into consideration the fact that the mortality of MDD patients may exceed the mortality of general population not only because of suicides, but also because or comorbidities. MDD may be associated with unhealthy lifestyles (for example smoking), leading to higher mortality than general population.

Another possible limit is that no impact of residual symptoms on relapse was integrated whilst several publications reported it[33-34]. Firstly, as previously discussed, there is currently no information about the effect of treatments on residual symptoms. Secondly, even if the model allows for residual symptoms lasting after clinical remission, no specific type of residual symptom has been considered at this stage. In addition, the way residual symptoms are modelled may need to be reviewed when specific symptoms of interest are identified. In the current version of the model, the treatments do not impact the residual symptoms specifically but directly the time to full remission for patients with residual symptoms.

The high rate of other adverse events was assessed to be 37% based on the Cipriani's review suggesting that another important adverse event was omitted such as the dry mouth reporting over 10% in the studies comparing escitalopram versus news ADs.

The model allows for only two categories of work status: worker and non-worker, and does not allow for change in work status over time. We are not aware of evidence showing that individuals may change of work status due to MDD, for example take a part-time job instead of working full time. However, if such evidence was produced, a revision of the model might be required.

Finally, DES models in general require a lot of input data and often unusual data. As a consequence, several assumptions were made for the input data of the analyses and should be revaluated with new potential source or with expert valuation.

[33] Nierenberg et al, Residual symptoms after remission of major depressive disorder with citalopram and risk of relapse: a STAR*D report, Psychological Medicine (2010), 40, 41–50.

[34] Kennedy N, Paykel ES. Residual symptoms at remission from depression: impact on long-term outcome. J Affect Disord. 2004 Jun;80(2-3):135-44.

A1. Appendix: Multiplicative factors

Multiplicative factors are used to adjust the times to an event (decrease or increase of times). In the model, multiplicative factors are only applied to times modelled with an exponential law.

The expected lifetime is estimated as the area under the survival curve.

$$Tmean = \int_{0+\infty} S(t)dt$$

For an exponential law of a probability p, we have:

$$T_{p,mean} = \int_0^{+\infty} (1-p)^t dt \Leftrightarrow T_{p,mean} = \int_0^{+\infty} \exp(t(\ln(1-p))dt$$

$$\Leftrightarrow T_{p,mean} = \frac{1}{\ln(1-p)}$$

For an exponential law of a probability αp, we have: $T_{\alpha p,mean} = \frac{1}{\ln(1-\alpha p)}$

Therefore, $\frac{T_{\alpha p,mean}}{T_{p,mean}} = \frac{\ln(1-p)}{\ln(1-\alpha p)}$

Furthermore, the hazard function corresponding to the survival function S is

$$h(t) = ln(1-p)$$

Thus the hazard ratio of times $\frac{T_{\alpha p,mean}}{T_{p,mean}}$ is equal to the inverse of the hazard ratio.

In addition, according to the Taylor expansion around 0 of ln(1—x), it may be noted that if p is small then:

$$\frac{T_{p,mean}}{T_{\alpha p,mean}} = \frac{\ln(1-\alpha p)}{\ln(1-p)} \sim \frac{\alpha p}{p} = \alpha$$

Thus, if we consider the probability of a rare event, or the occurrence of an event over a small time interval, then the ratio of probabilities is close to the hazard ratio. This approximation is often acceptable with probabilities below 10%. For example, if we consider probabilities of 10% and 5%, the ratio of probabilities is 2, and the hazard ratio is:

ln(1-0.1)/ln(1-0.05)=2.05

A2. Appendix: Weibull distribution

The Weibull distribution is a generalization of the exponential. It is characterized by two parameters, γ> 0 and λ> 0, which are the shape and scale parameters respectively. The density function of such a law is given by

$$f(t;\ \gamma,\lambda)\ =\ \frac{\gamma}{\lambda}(\frac{t}{\lambda})^{\gamma-1}e^{-(\frac{t}{\lambda})^{\gamma}},t\ >\ 0.$$

If γ = 1, this simplifies as an exponential distribution. It is therefore more flexible than the exponential law.

The cumulative distribution function for the Weibull distribution is

$$F(t;\ \gamma,\lambda)\ =\ 1-e^{-(\frac{t}{\lambda})^{\gamma}},t\ >\ 0$$

The survival function is $S(t)\ =\ e^{-(\frac{t}{\lambda})\gamma}$ and the hazard function is $h(t)\ =\ \frac{\gamma}{\lambda}(\frac{t}{\lambda})^{\gamma-1}$, which is the order of $t^{\gamma-1}$.

The hazard function is monotonically increasing if γ> 1 indicating that the failure rate decreases over time, monotonically decreasing if γ <1 indicating that the failure rate increases with time and constant for γ = 1 indicating that the failure rate is constant over time, so this parameter is called the shape parameter.

As λ is a parameter of scale, different values of λ only change the scale on the horizontal axis.

The model is flexible, and it was shown that it is a good description of several types of survival data. The fact that the density functions, survival and risk have a relatively simple form also explains the popularity of the model.

Another way to characterize the Weibull distribution is to define two parameters: the location parameter μ and the scale parameter σ . This distribution is used by the software SAS in the Lifereg procedure and allows calculating odds ratio associated with covariables and therefore to include them in the model.

The survival function G(t) are respectively the following:

$$G(t)=\exp\left(-\exp\left(-\frac{\mu+\beta X}{\sigma}\right)t^{\frac{1}{\sigma}}\right)$$

We can find the previously results with

$$\sigma=\frac{1}{\gamma}\text{ and }\lambda=\frac{1}{\exp\left(-\frac{\mu+\beta X}{\sigma}\right)}$$

A3. Appendix: simulation of an exponential law

The **exponential distribution** describes the time between events in a Poisson process, i.e. a process in which events occur continuously and independently at a constant average rate.

The cumulative distribution function for x positive is given by

$$F(x;\lambda) = 1 - \mathrm{e}^{-\lambda x}$$

The mean or expected time to occurrence of an event is **$1/\lambda$**

The input parameter for treatment duration corresponds to the mean (i.e. 1/λ).

For other "time to" evaluation, with the exception of time to recurrence that is evaluated with a Weibull law, the mean is assessed as following with two parameters: the follow up duration **D_0** and the percentage **p_0** of patients having experienced the event at the end of the follow up period

The mean of the exponential law is defined as follow

$$\boldsymbol{\lambda} = -\frac{\ln(1 - p_0)}{D_0}$$

The simulated time to event TT is given by:

$$TT = -\frac{\ln(1 - r_0)}{\lambda}$$

With r_0 a number between 0 and 1

Note that λ is the hazard ratio, therefore multiplying λ by a hazard ratio α is equivalent to dividing TT by α.

Another important characteristic of the exponential model is that the mean duration from a date d to occurrence of event, conditional upon surviving without event to the date d is independent of d, it is always 1/λ.

For example, let us consider that a time to suicide has been simulated with an exponential model with parameter λ, and that recurrence is associated a hazard ratio α. If we consider 100 patients without recurrence on a given day, the average time to suicide among these patients is 1/λ (ignoring potential future recurrences). If all these patients have a recurrence on this day, we could divide all the times to suicide by α, and the average time to suicide would be 1/αλ. Equivalently, we can generate new times to suicide with an exponential model with parameter αλ, the average time to suicide will also be 1/αλ.