MAFEIP User Guide

Version 2.0

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Introduction

This MAFEIP User Guide is developed as part of the MAFEIP study (Support Services for the Management and Utilization of Monitoring and Assessment of the EIP - MAFEIP Tool) which is performed for the European Commission by Open Evidence and empirica.

The study aims at facilitating the use of the MAFEIP tool by members of the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA). The study will foster the building of a MAFEIP User Community (MUC) around the tool and provide training and support to utilizing MAFEIP, including data introduction, evidence-based data gathering from secondary sources and results interpretation. Based on user feedback, improvement measures to the tool will be carried out and implications and recommendations regarding its routine utilization and data management will be documented. The results achieved by the MUC will be reported and visualised. Through the study, the Community is expected to grow, contributing to the wider utilization of the MAFEIP tool in Europe.

The MAFEIP User Guide is to be seen as a living document, which will be enriched by various organisations from the MAFEIP User Community. The study is actively seeking for new organisations interested in using MAFEIP and contributing to the further development of the MAFEIP User Guide by providing new case studies to be included in the guide. Please contact us at info@mafeip.eu or visit mafeip.eu for more information.

The MAFEIP User Guide explains step-by-step how the MAFEIP tool is to be used to assess innovative interventions. A running example is provided at each step to illustrate what data is needed and how this data is to be entered.

Chapter 1 of the guide provides background information on MAFEIP.

Chapter 2 describes how to use the Deterministic Analysis Module of the MAFEIP tool by following five steps

Chapter 3 describes how to use the Probabilistic Analysis Module of the MAFEIP tool

Chapter 4 provides strategies for collecting information needed to be input into the tool

A list of references and a glossary are provided as well.

*This version of the User Guide Manual includes Chapters describing the added parameters in the updated version of the MAFEIP tool, namely:

- 4-state and 5-state Markov models
- Time horizon for the analysis
- Initial distribution among states
- Direct input of mortality rates
- One-off and annual recurrent costs for standard care
- Probabilistic Analysis

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1 Background and purpose of the MAFEIP-Tool

1.1 Background

The European Innovation Partnership on Active and Healthy Ageing (EIP on AHA), launched in 2012, is a European Commission led policy initiative to address the challenges of demographic change in Europe. Its overarching target is to increase the average healthy lifespan by two years by 2020 and it will pursue a "Triple Win" for European citizens:

a) Enabling EU citizens to lead healthy, active and independent lives while ageing;
b) Improving the sustainability and efficiency of social and health care systems;
c) Boosting and improving the competitiveness of the markets for innovative products and services, responding to the ageing challenge at both EU and global level, thus creating new opportunities for businesses.

At present, around thousands of entities and stakeholders are committed to EIP on AHA initiatives including monitoring the socio-economic impact of implementing innovative solutions for active and healthy ageing. A need for shared and reliable methodology to monitor impacts across the EIP on AHA domains and interventions has been identified from the start as one of the top (horizontal) goals.

To this end, a first version of a generic and flexible web-based monitoring and assessment tool called MAFEIP (Monitoring and Assessment Framework of the EIP), has been developed by the Joint Research Centre – IPTS - of the EU Commission in close cooperation with the Commission's services and EIP on AHA partners. The MAFEIP aims to establish a link between the monitoring results, the 2 items of the Triple Win mentioned above and the overarching EIP on AHA target of increasing by two additional healthy life years the average healthy life span of European citizens by 2020.

As indicated by its name, it was originally designed to frame and support the assessment of EIP-AHA related initiatives. This tool has been designed both to measure the impact across the three 'wins' as well as to be used for decision-making processes by public and industry stakeholders investing in innovative solutions for active and healthy ageing, far beyond the scope of EIP on AHA participation.

The first version of the MAFEIP tool was validated in Brussels on 21 September 2015, by external experts (for a technical description: see article (free access) published in the "BMC Medical Informatics and Decision Making" in 20152). This tool registered broad support from this wide and multi-stakeholder audience to become a framework of reference for measuring impact of their policies in their respective fields of interventions. The MAFEIP study was commissioned to further promote the tool and provide training and support to the interested stakeholders.

This MAFEIP User Guide is part of the support materials that the study will provide.

1.2 Purpose

The purpose of the MAFEIP-tool is to estimate the health and economic outcomes of a large variety of social and technological innovations in the health and care sector relative to current care. Indeed, MAFEIP provides an early assessment of the likelihood that interventions will achieve the anticipated impact, and also helps to identify what drives interventions' effectiveness or efficiency in order to guide further design, development or evaluation. MAFEIP therefore represents a clear support to the decision-making process.

The Commission does not intend to assess the incremental cost-effectiveness of an intervention carried out by an EIP on AHA commitment, nor intend to compare several interventions on their cost-effectiveness. Rather, the general aim of the MAFEIP project is to

estimate the aggregated impact of the EIP on AHA on its overall health and health system objectives.

1.3 The states used in the model

The MAFEIP tool rests on the principles of Decision Analytic Modelling (DAM), an approach that is commonly used in health economic evaluations to assess the health and economic impact of healthcare innovations.[1,2] More precisely, MAFEIP is based on a generic Markov model, which provides the flexibility required to be adaptable to a large number of commitments within the six thematic Action Groups of the EIP on AHA. These Action Groups focus on a variety of objectives, implement different interventions and target different cohorts of individuals with different demographic or disease characteristics.

The outcomes for the intervention and the control group are calculated by simulating the health status of the target population. This is done by simulating the transition of the target population between different health states defined in the Markov model. The MAFEIP tool has been upgraded to allow the user to choose the number of states of the Markov model, which varies from 3 to 5 *i.e.* there is a 3-state model, a 4-state model, and a 5-state model to choose from depending on which model best reflects the intervention to be assessed.

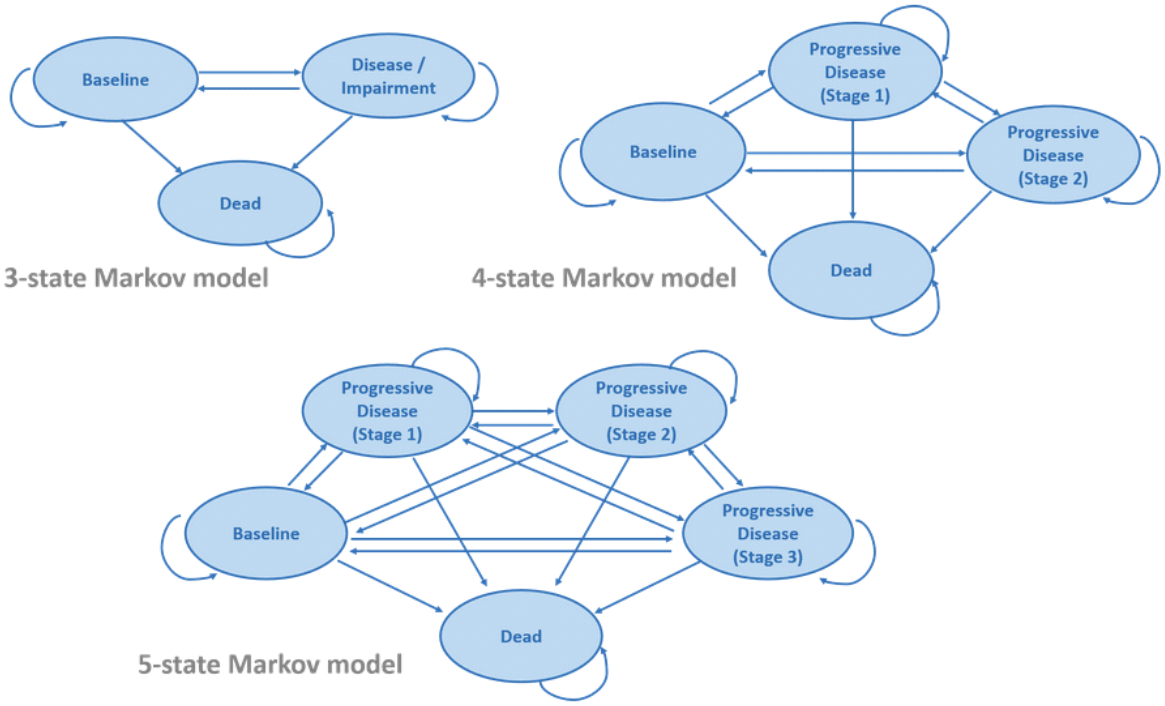


Figure 1. The three types of Markov models used in MAFEIP.

In all these Markov models, the *baseline health* state represents the general health status of the target population. The *disease/impairment health* state(s) reflect(s) the health status of people who experience the condition of interest (the condition that the intervention aims to prevent, relieve or cure). Each health state is defined by an amount of resource use and quality of life (utility). This represents the average resource use and quality of life of a patient in that health state.

[1] Briggs A, Claxton K, Sculpher M: Decision modelling for health economic evaluation Oxford, Oxford University Press; 2006.

[2] Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL: Methods for economic health evaluation of health care programmes. 3 edition. Oxford, Oxford University Press; 2005.

The simulated population will transfer between the Markov states based on the following transition probabilities:

- A transition from the baseline health to the progressive disease or impairment health state represents the worsening of a patient's condition. These are the incidence rates.
- It is also possible for patients to move from the progressive disease or impairment health state back to the baseline health state or back to a previous stage of the progressive disease, when their health condition improves. These are the recovery rates.
- At any time in the simulation patients can die. This is represented by a transition to the dead state from any of the other states.

In order to estimate the incremental health gain from a particular intervention delivered within an EIP on AHA commitment, the defined model needs to be run twice: a) with parameter estimates for the respective intervention under assessment; b) with parameters corresponding to the standard care scenario.

In the model, these two scenarios may differ in terms of the transition probabilities (disease incidence, recovery and mortality), as well as the HRQoL weight, healthcare and societal costs attached to the health states.

When the model simulates a hypothetical cohort of patients moving between these health states over time, the differences in survival, HRQoL and costs will accumulate to an estimate of the incremental costs (ΔC) and health effects (ΔE) that can be expected from the intervention under evaluation.

Therefore, the tool can be used to estimate the Incremental Cost Effectiveness Ratio ($ICER = \frac{\Delta C}{\Delta E}$) or the Incremental Net Monetary Benefit ($INMB = \Delta E * \boldsymbol{\lambda} - \Delta \boldsymbol{C}$) of one intervention compared to another, where $\boldsymbol{\lambda}$ denotes the willingness to pay threshold for an additional unit of health gain.

1.3.1 The 3-state model

The 3-state Markov model comprises two alive states and one dead state. The two alive states include a *baseline state*, which represents the general health status of the target population, and a *disease/impairment state*, which reflects the health status of people who experience the condition of interest (the condition that the intervention aims to prevent, relieve or cure). The Figure below illustrates the 3-state Markov model.

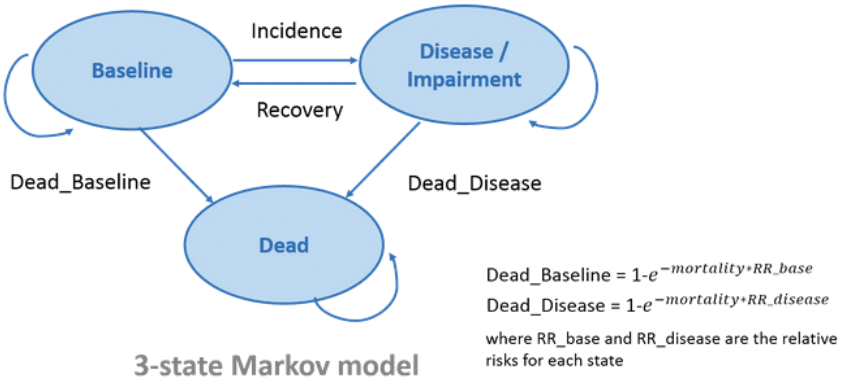


Figure 2. The 3-state Markov model

1.3.2 4-state model

The 4-state Markov model considers three alive states and one dead state. The three alive states include a *baseline state*, which represents the general health status of the target population, and two different *stages of the disease or health condition* (*e.g.* progressive disease from stage 1 to stage 2, as the patient's health condition worsens),. The Figure below illustrates the 4-state Markov model.

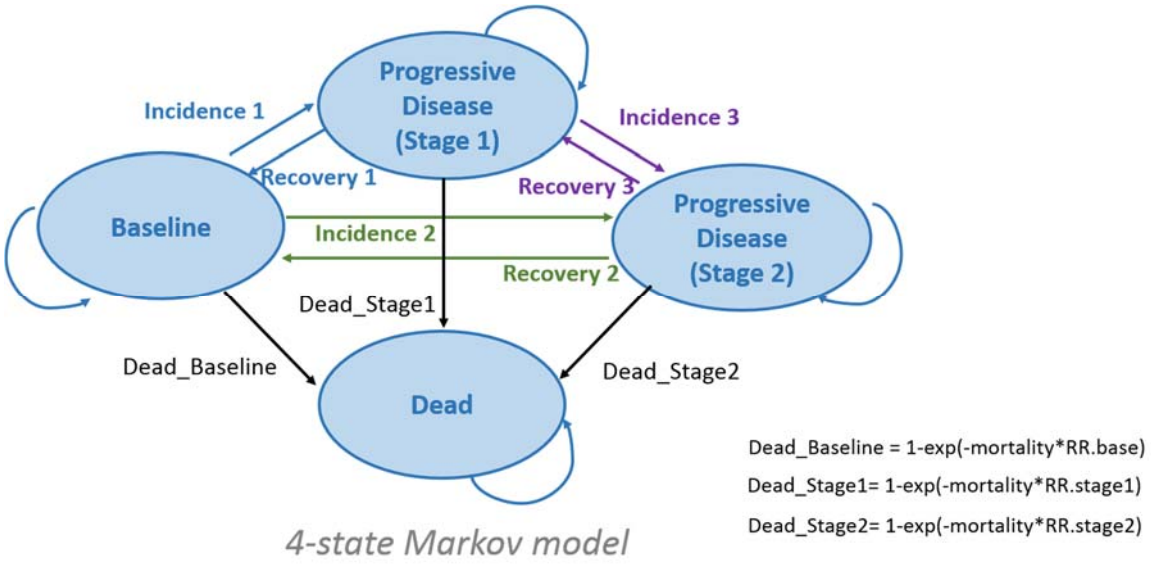


Figure 3. The 4-state Markov model

1.3.3 5-state Model

The 5-state Markov model considers four alive states and one dead state. The three alive states include a *baseline state*, which represents the general health status of the target population, and three different *stages of the disease or health condition* (*e.g.* progressive disease from stage 1 to stage 3, as the patient's health condition worsens),. The Figure below illustrates the 5-state Markov model.

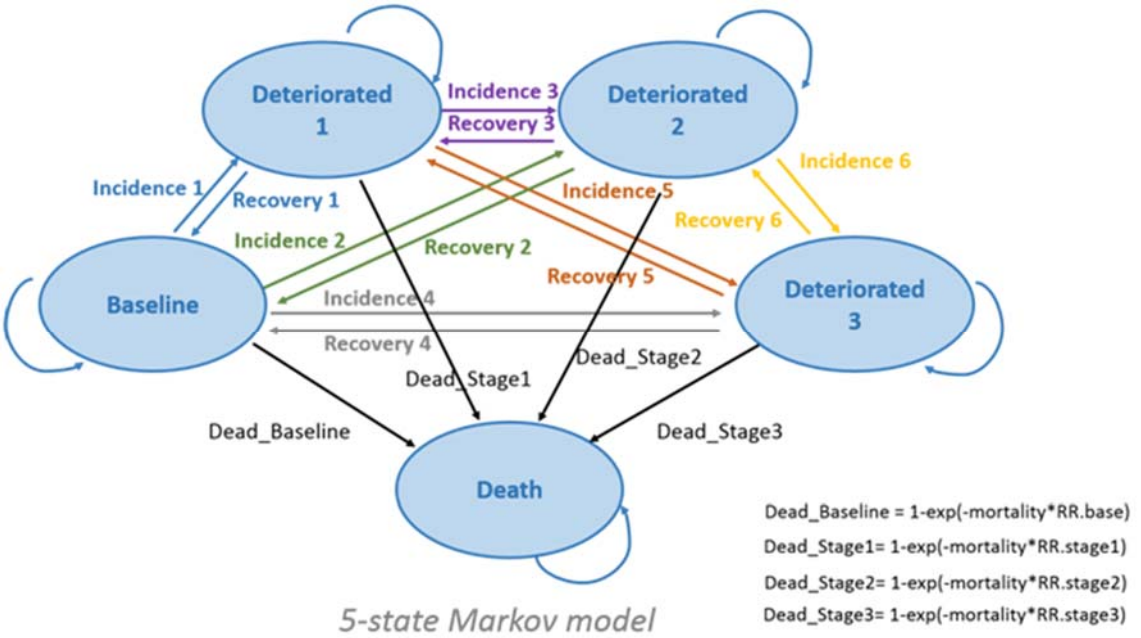


Figure 4. The 5-state Markov model

2 Using the MAFEIP tool: Deterministic Analysis

This is the default analysis for all users and is recommended for first-time users of the MAFEIP tool. Advanced users may opt to request access to the Probabilistic Analysis by contacting info@mafeip.eu. More details on the Probabilistic Analysis is described in Part 3 “Using the MAFEIP tool: Probabilistic Analysis”.

The Deterministic Analysis module of the MAFEIP tool contains 5 steps: (1) Information, (2) Model Input, (3) Model Output, (4) Sensitivity Analysis, and (5) Model Output of the Sensitivity Analysis. This Manual will guide the user through these 5 steps.

2.1 Selecting the Model

As described in Section 1.3, the MAFEIP tool has been expanded to include more than just an analysis based on a 3-state Markov model. Markov models with more than 3 states would be useful in simulating different patient groups that are distinguished by the different progressive stages of their disease or condition.

For example, choosing a 5-state model would lead to more precise results for a study with patient groups that have mild, moderate and severe heart failure in addition to the patients with no heart failure. In such a case, there is a patient group with a baseline health state, and 3 patient groups with 3 progressive disease health states. The 5th state would be the dead state.

Before continuing to use the tool, the user is already able to select on the Markov-state model that would best represent the conditions of the patient group(s) that are targeted by their intervention through the green button as shown in the Figure below:

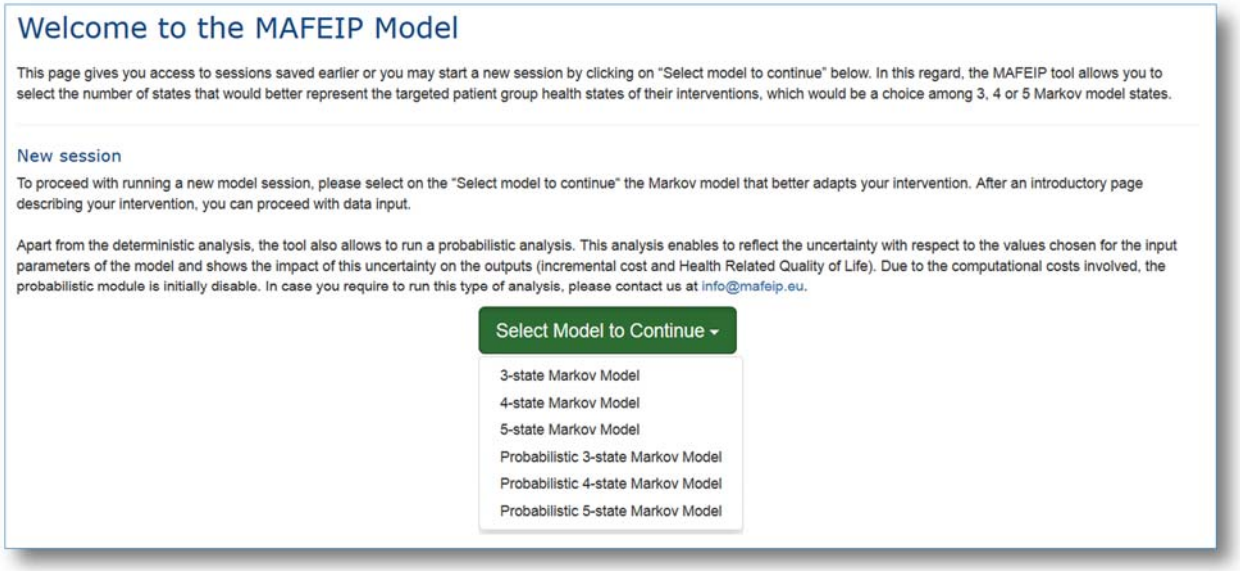


Figure 5. The user is able to select the type of Markov model that would best represent the conditions of the target group of their intervention by clicking on the green button “Select Model to Continue”. Probabilistic analysis (the last 3 options) is initially disabled but the user may request for access.

2.2 Step 1: Information

In these sections, the 3-state model deterministic analysis will first be considered. A few examples for the 5-state model deterministic analysis will also be shown.

This section allows the user to specify the characteristics and aims of the intervention that is to be evaluated.

2.2.1 General information

Tip: To adjust the size of the box (e.g. to make the box bigger), click and drag the lower right edge of the text box.

This is where the user would specify the name or acronym of the intervention.

An appropriate action group for the intervention should also be chosen. The action groups are defined in the Strategic Implementation Plan of the EIP on AHA[3] as follows:

- A1. Prescription and adherence action at regional level;
- A2. Personalised health management, starting with a Falls Prevention Initiative;
- A3. Actions for prevention of functional decline and frailty;
- B3 Replicating and tutoring integrated care for chronic diseases, including remote monitoring at regional level;
- C2. Development of interoperable independent living solutions, including guidelines for business models;
- D4. Innovation for age friendly buildings, cities and environments.

Figure 6. An example of filled-in text fields under “General Information”.

[3] Strategic Implementation Plan for the European Innovation Partnership on Active and Healthy Ageing, Steering Group Working Document. See: http://ec.europa.eu/research/innovation-union/pdf/active-healthy-ageing/steering-group/implementation_plan.pdf#view=fit&pagemode=none.

2.2.2 Setting and target population

This is where the user would specify characteristics about the target group of the intervention as well as the main aim that the intervention plans to achieve.

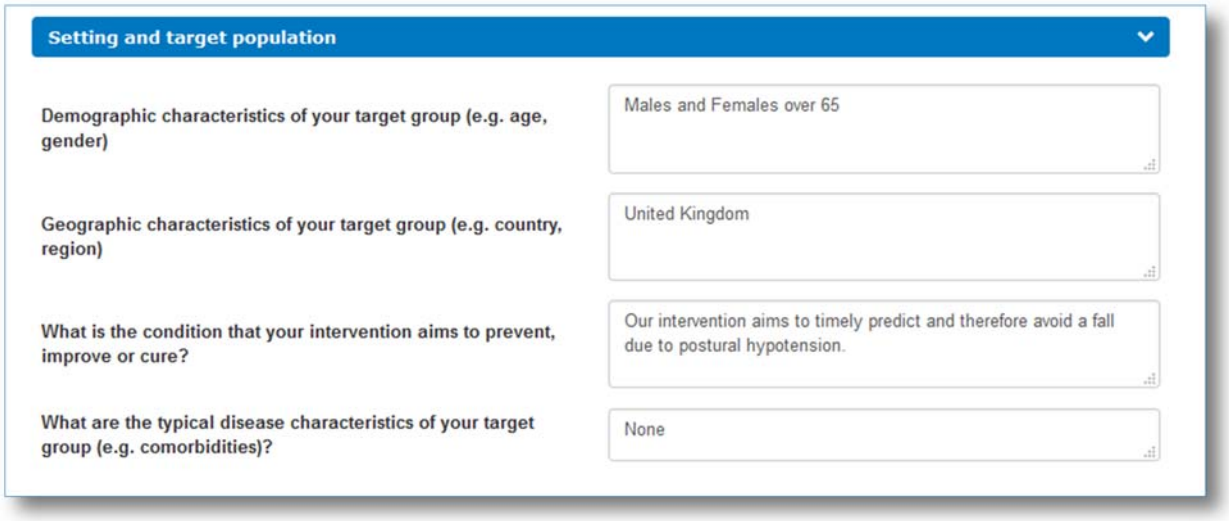


Figure 7. An example of filled-in text fields under "Setting and Target Population".

2.2.3 About your intervention

This is where more details about the intervention are given. Some questions to consider are: What type of intervention is it? Is it a device or a management process? Who will use the intervention and in which scenarios should it be used? Are there already similar interventions being used (locally or in other countries)? How far has this intervention already been implemented? Are there already studies in which the intervention has been tested?

The user would also be asked to specify at which stage of development the intervention is:

- Pre-trial (*e.g.* proof of concept) – at this stage, the intervention is still being explored – related questions to ponder on are:
  - Will the intervention meet the needs of the researchers involved?
  - Will the intervention perform as proposed?
  - Is the proposed solution feasible?
- Clinical trials
- Pilot implementation – this is the stage in which the intervention is already being used as though it has already been fully established, but at a smaller scale (*e.g.* 10% of the set target population)
- Routine use – at this stage, the intervention is already being widely used.

Sample answers related to the running example could be found in the Figure below.

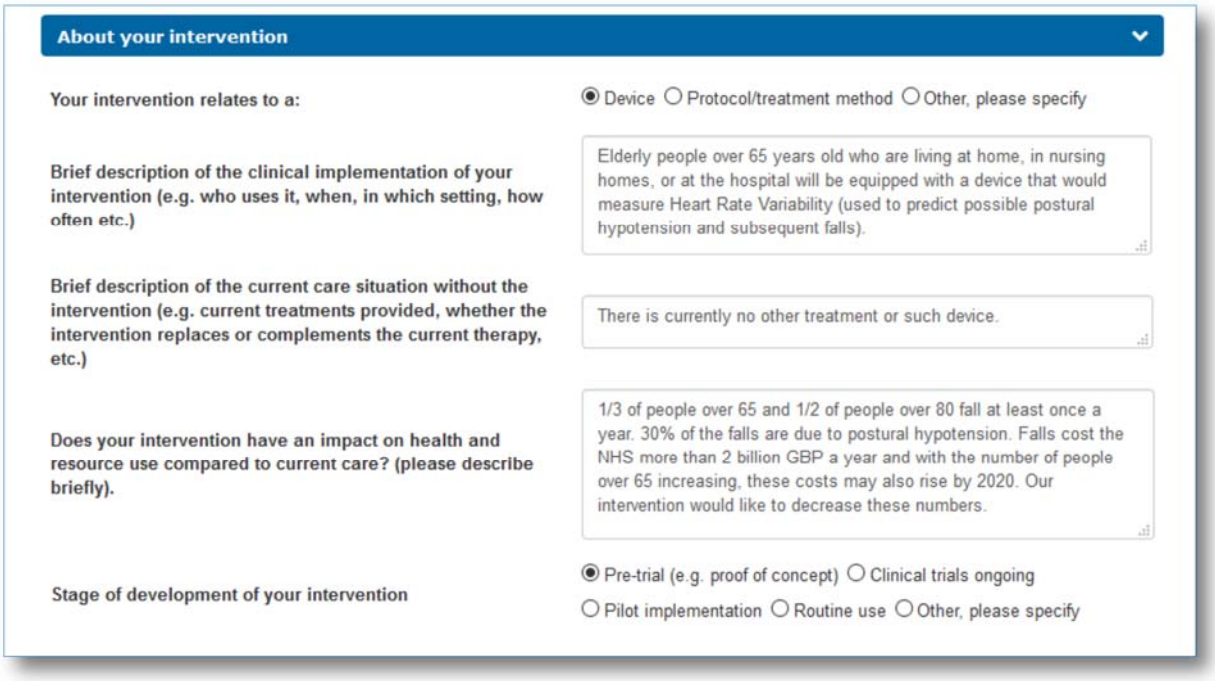


Figure 8. An example of filled-in text fields under “About Your Intervention”.

2.2.4 Evidence

For the purposes of MAFEIP, it is important to note that the innovative character of many technologies/intervention under assessment, and the vast amount of interventions to assess is likely to limit both the availability of high quality evidence to populate the tool and the time available to source and analyse this evidence.

The following questions try to perform a brief assessment of the empirical evidence of the data provided to populate the model in order to know if experimental methods have been used or the data are based on a less robust observational design with or even without a control group. If empirical evidence has already been collected, the user will be prompted to choose one of the following methods of study: Randomized Controlled Trial, Longitudinal observational, Cross-sectional observational, Case-control, or another study.

More information on each study method may be found in the Glossary at the end of this paper.

Selecting “Yes” in any of these choices, will lead to a question asking whether a control group has been used in the selected study method. This means that during the study, patients were divided into two groups: one with patients who were not given the intervention (control group), and one with patients who were given the intervention (intervention group). The exact number of patients that have participated in the study should also be provided.

Selecting a “No” in any of the study method choices would lead to being asked whether other means of collecting evidence (*e.g.* literature, expert advice, or databases) have been used.

A Figure with sample answers is shown below:

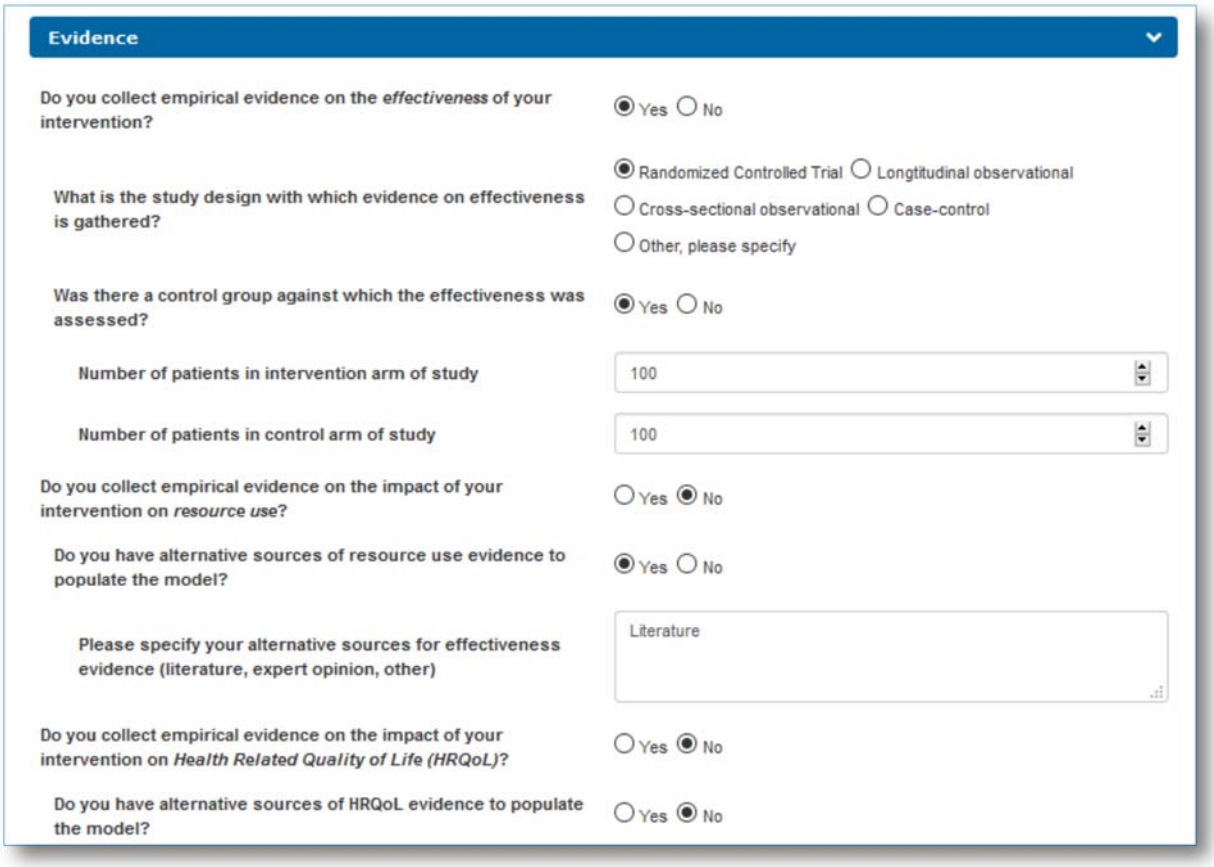


Figure 9. An example of answered and filled-in text fields under “Evidence”.

2.3 Step 2: Model input

This is where the user would input the parameters required to run the model.

2.3.1 Set-up

The parameters in this section control how the analysis will be performed and how the results will be presented. These parameters set the frame for the analysis.

The parameters required are divided into four sections: (1) model analysis, (2) costs associated with health states and intervention costs, (3) transition probabilities for moving between states with and without the intervention, and (4) utilities (also called quality of life weights) that are associated with each state. A value has to be selected for each input parameter in order to run the model

Model assumptions

The discount factors for costs and effects are used to estimate outcomes while taking into account the future costs and health effects. This means adjusting for differences in the timing of costs (expenditure) compared to health benefits (outcomes). Therefore, properly applied discount factors express future costs or benefits at today's equivalent value.

Discount factor rates are usually between 3% and 5%, and are usually the same for both cost and outcomes. The default value in the tool is 3.5%, but the user may opt to change this value.

Tip: Scroll over the information button (i) beside e.g. "Discount Factor for costs" to read more information.

The user may consult the website given (in Figure 10 below, boxed in red) to identify the discount rate of the country chosen. In this external website, the user must select the country of choice, and the user will then be redirected to a new page with a table. The suggested % values can be found under the rows "Discounting costs" and "Discounting outcomes".

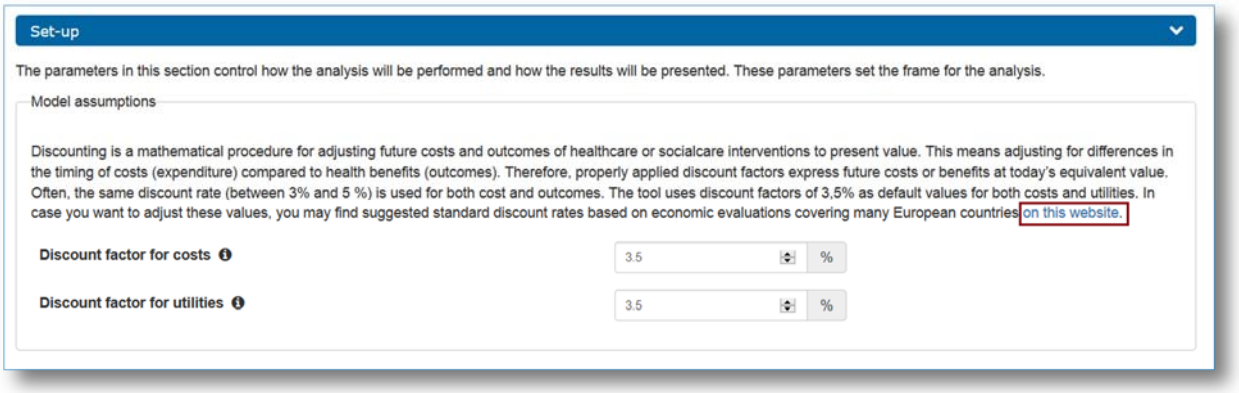


Figure 10. The discount factor rates for costs and utilities for a particular country are listed in the website link given in the tool (boxed in red). The standard given discount factor rates for both costs and utilities is 3.5%.

Time horizon for the analysis

In this section, the user is able to specify the number of cycles that the model will run, which represents the timeframe in which the impact of the intervention will be evaluated. For example, if the user would want to see estimates of the incremental costs (and effects) of the intervention within 10 years, the user must enter "10" in the text field as shown in the Figure below.

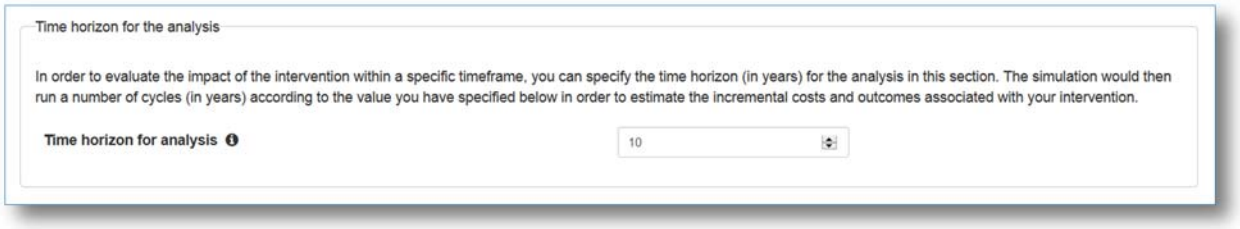


Figure 11. An example of a filled-in text field under "Set-up, Time horizon for analysis".

Target population

In this section the user may indicate the minimum and maximum age and country of the target population. This will be used to select baseline mortalities from the Human Mortality Database. These baseline mortalities are sex- and age-dependent and would be used in the presented results in the next Section (*e.g.* in the later Section 2.4.1 (Incremental costs and effects (age and gender specific))).

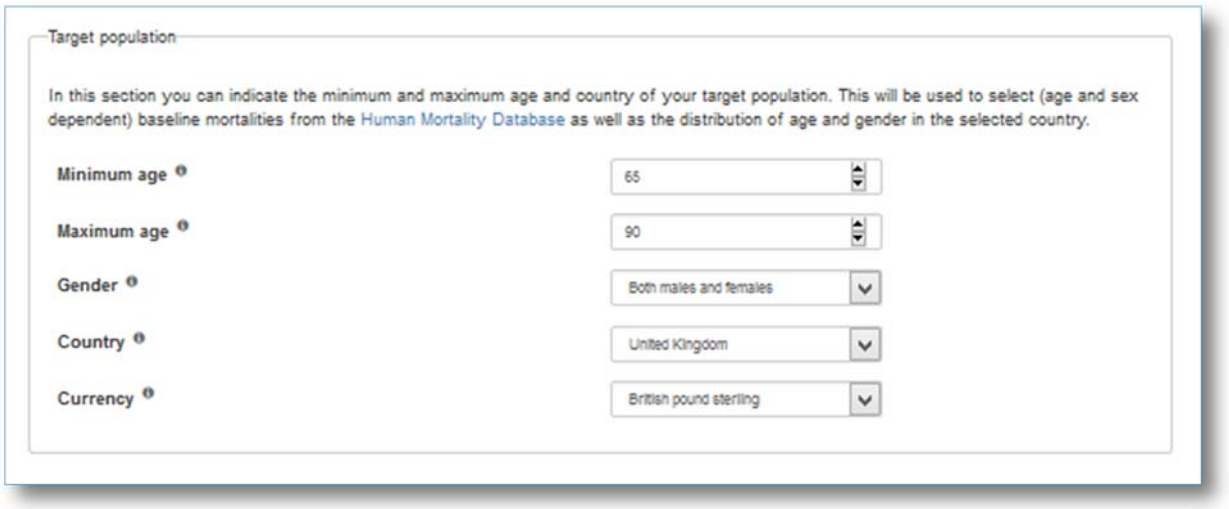


Figure 12. An example of filled-in text fields under "Setup, Target Population".

Patient flow through model states

Here the user is asked to specify the gender and age that would be fed into the Markov model (as explained above). These specifications would be the focus for the results in Section 2.4.4 (Patient flow through model states).

The model would later on show the effect of the intervention on the probability of a person to stay in each state of the model (model flow). This can only be shown for one specific age-gender combination. The user may indicate here for which age-gender combination the outcome would be based on.

The age-gender combination selected here has no impact on the other outcomes (*e.g.* it will have no impact on the results about how cost-effective the intervention is, as those will depend on the age and gender selected in the previous section "Target Population").

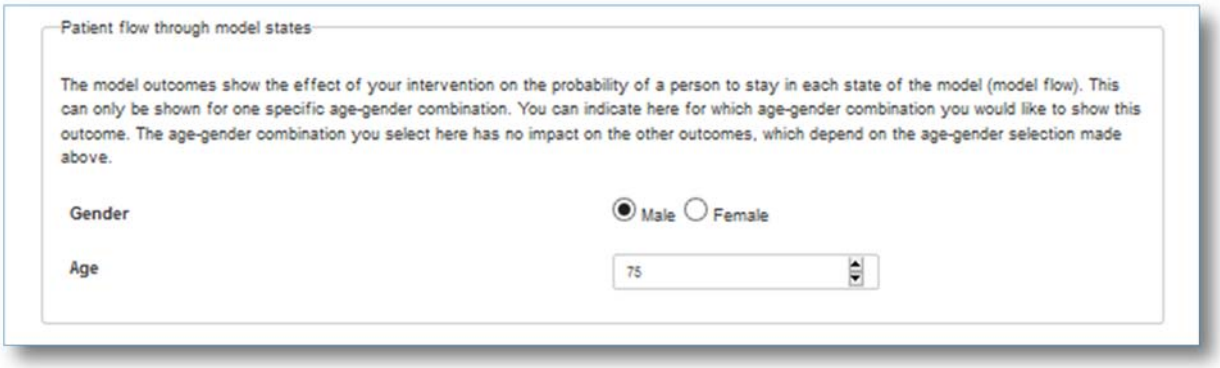


Figure 13. An example of filled-in text fields under "Setup, Patient flow through model states".

2.3.2 Probabilities

The probability parameters depend on the type of model initially chosen by the user (3-state, 4-state, or 5-state). In this section, the 3-state model is primarily considered. An example of text fields associated with the 5-state model is also given under the Section "Transition Probability fields for the 5-state model" below.

Note: The following sections describe patients grouped according to whether they have been treated with the proposed intervention or not. From this point onwards, **"Control Group"** refers to patients who have not been treated with the proposed intervention (standard care) and **"Intervention Group"** refers to patients that have received or have been treated with the proposed intervention.

Initial distribution among states

In this section the user is able to specify the starting distribution of patients over the alive health states (baseline and disease/impairment) in both the control and intervention group. This would allow the tool to take preventive and curative interventions into consideration.

For example, the proposed intervention would like to treat seniors from 65 to 90 who have diabetes or prevent those who are likely to have diabetes, given the scenario as follows:

In a certain healthcare centre, there were 210 patients over 65 to 90 that are considered fit for the study.

- Among the 210 patients in the study, 110 out of the 210 patients were treated with the intervention, and therefore this is the "Intervention Group"
    - Among the 110 patients in the Intervention Group, 60 of the patients have diabetes and 50 do not (but have a family history of diabetes).
    - In this case, the proportion of the patients in the baseline state (those with no diabetes) in the intervention group is 50/110 or 45.5%.
    - Meanwhile the proportion of the patients in the disease/impairment state in the intervention group is 60/110 or 54.5%

The tool parameters are then filled out with these percentages as shown in the Figure below:

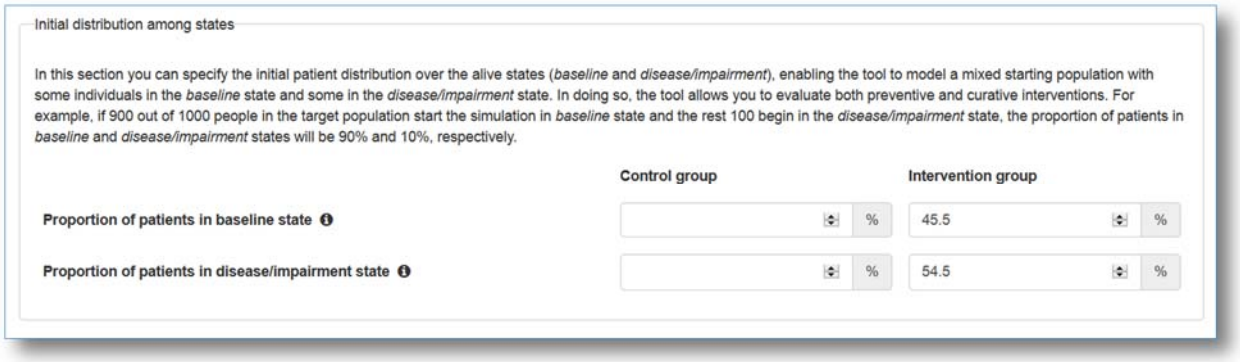


Figure 14. An example of filled-in text fields under "Probabilities, Initial distribution among states; Intervention group".

Going back to the example:

- Among the 210 patients in the study, 100 out of the 210 patients were not treated with the intervention i.e. they continued to be treated with standard care.
    - Among the 100, 60 of the patients have diabetes and 40 do not.
    - In this case, the proportion of the patients in the baseline state (those with no diabetes) in the intervention group is 40/100 or 40%.
    - Meanwhile the proportion of the patients in the disease/impairment state in the intervention group is 60/100 or 60%

The tool parameters are then filled out with these additional percentages as shown in the Figure below:

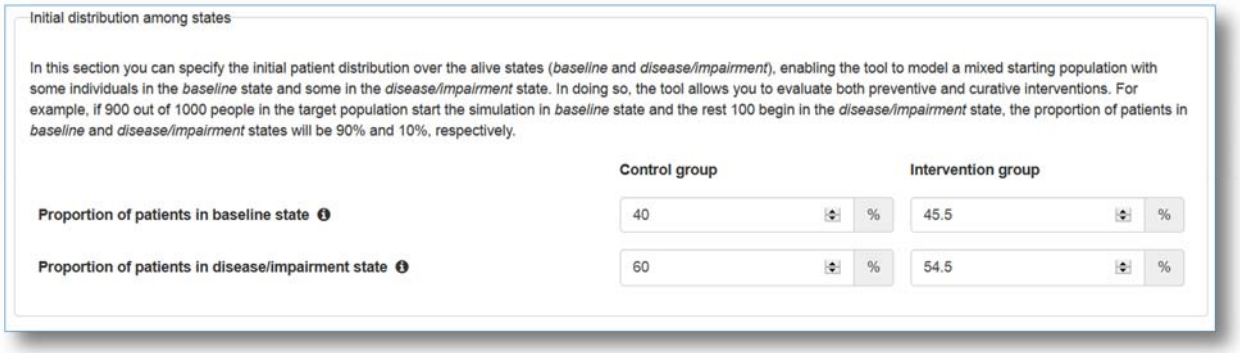


Figure 15. An example of filled-in text fields under "Probabilities, Initial distribution among states".

Transition Probabilities

Here the user is asked to provide data on the probability of an individual to move from one health state to another. These probabilities are called transition probabilities and are entered into the MAFEIP tool as percentages.

The transition probabilities are defined as follows:

(1) Incidence – the probability of an individual to move from baseline state to disease or impairment state (condition has worsened).
(2) Recovery – the probability of an individual to go back from a disease or impairment state to the baseline state (condition has improved).
(3) Mortality – the probability of an individual to go from one of the alive states (either baseline or disease/impairment) to the dead state. (input on mortality rates are done in the next Section under "Relative risks for mortality and mortality rates").

Data on the incidence and recovery rates are input into the tool based on one of plenty data sources *e.g.* data that has been collected from the user's study cohorts or data that has been taken from literature.

For example, if in a given year 300 out of 1000 people in the target population become ill (condition has worsened), the annual incidence would be 30%. This would be input under the incidence rate of the “Control Group” as it describes a general occurrence rather than the patients that have already been treated by the proposed intervention.

On the other hand, if in the given year 100 out of 200 ill target patients have recovered without being treated with the proposed intervention, then the yearly recovery rate for the Control Group is calculated as 100/200 or 50%.

These percentages would then be input as shown in the Figure below.

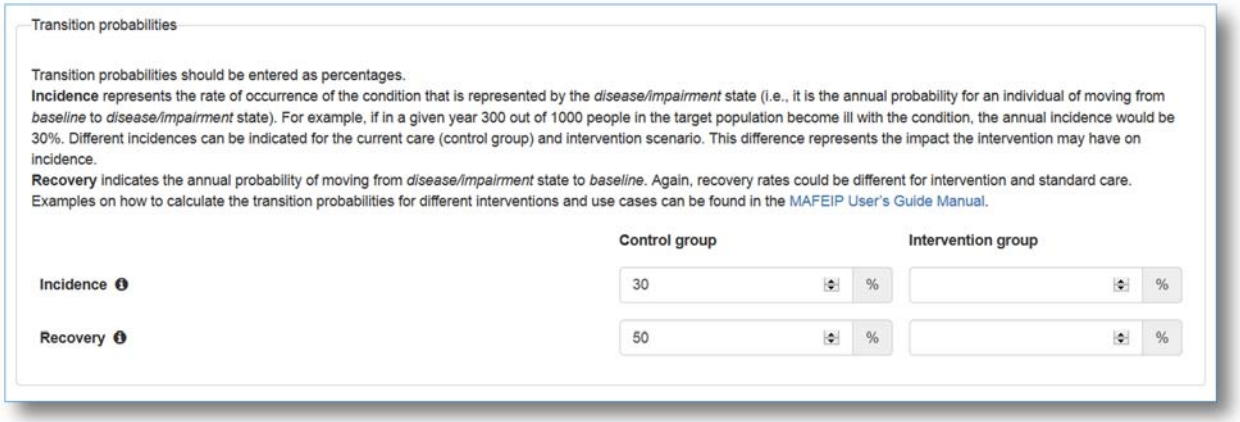


Figure 16. A simplified manner of calculating the incidence rate of the control group is to count the number of patients (not treated with the intervention) that have gone from “healthy state” to “disease or impairment health state” in one year.

The incidence and recovery rates of the intervention group are calculated in a similar manner as described previously. Ideally, the intervention would aim to result to a lower incidence rate and higher recovery rate, examples of which are shown in the Figure below.

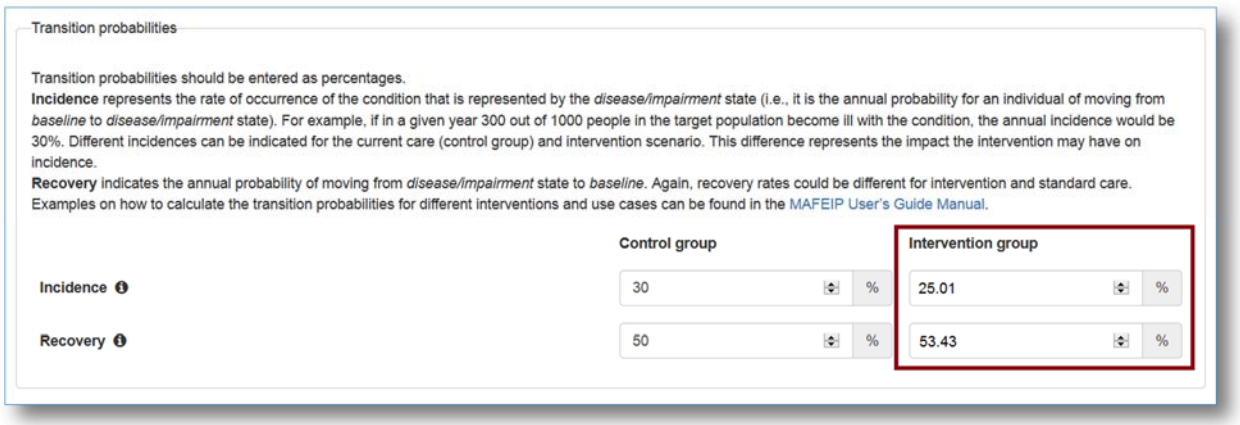


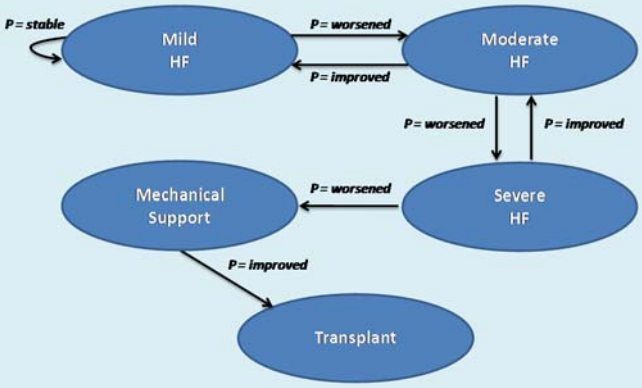
Figure 17. An example of filled-in text fields under “Probabilities, Transition Probabilities”. In an ideal case, the intervention group would have lower incidence rates and higher recovery rates.

Transition Probability fields for the 5-state model

As the 5-state model has more states, there are also more transition probabilities as each transition between each state (until the dead state is reached) is considered. For example, for the baseline state, there are (1) three incidence rates to consider: (1a) the transition from baseline to progressive disease stage 1, (1b) the transition from baseline to progressive disease stage 2, and (1c) the transition from baseline to progressive disease stage 3; as well as (2) three recovery rates: (2a) the transition from progressive disease stage 1 back to baseline, (2b) the transition from progressive disease stage 2 back to baseline, and (2c) the

transition from progressive disease stage 3 back to baseline. The corresponding text fields for Transition Probabilities input are illustrated in the Figure below.

For example, in a study** with patients that have heart failure (HF), 5 cohorts have been defined: (1) those with Mild HF, (2) those with Moderate HF, (3) those with Severe HF, (4) those who need mechanical support, and (5) those who need a transplant.



With a given transition probability matrix for standard care as defined below:

Transition Matrix – Standard care					
	Mild HF	Moderate HF	Severe HF	Mechanical Support	Transplant
Mild HF	0.50	0.50			
Moderate HF	0.60		0.40		
Severe HF		0.05		0.25	
Mechanical Support					0.75
Transplant					

**Taken from the MAFEIP Use Case "MD-Paedigree"[4]

The data from the example given above can be mapped into the MAFEIP Markov model health states as follows:

- Mild HF = baseline state
- Moderate HF = progressive disease stage 1
- Severe HF = progressive disease stage 2
- Mechanical Support = progressive disease stage 3

And the data will then be input into the MAFEIP tool as shown in the Figure below:

[4] http://mafeip.eu/assets/files/MAFEIP_UC_MD-Paedigree_20170509.pdfs

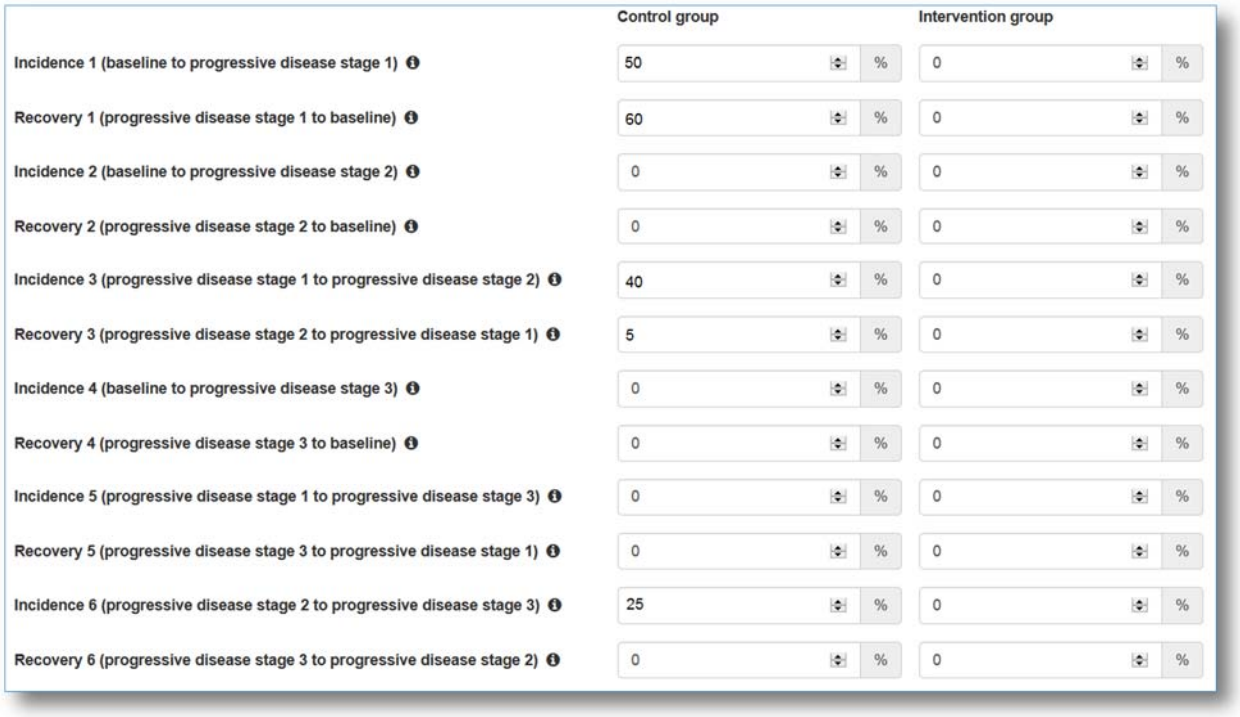


Figure 18. An example of filled-in text fields under “Probabilities, Transition Probabilities” for the control group in a 5-state model scenario.

Relative risks for mortality and mortality rates

Mortality rates can be input in two ways.

If the user already has data on patient mortality rates from their study, then the user is able to input these mortality rates directly into the tool.

On the other hand, the user may also opt to have the rates internally calculated by the tool by using the all-cause mortality rates (age and sex dependent) extracted from the Human Mortality Database. The mortality rates can be adjusted by means of the relative risk (RR) parameter, which is explained under the Section “Relative risks for mortality” below.

In the tool, the user is asked whether they want to specify the mortality rates associated with the cohort or not:

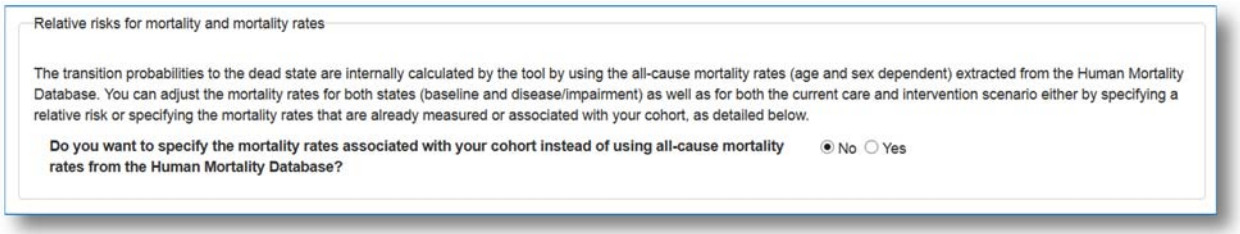


Figure 19. There are two ways to input mortality rates, by using available mortality rates from the user’s cohort or by estimating relative risks of mortality.

Ticking “No” leads the user to input relative risk for mortality as shown in the Figure below:

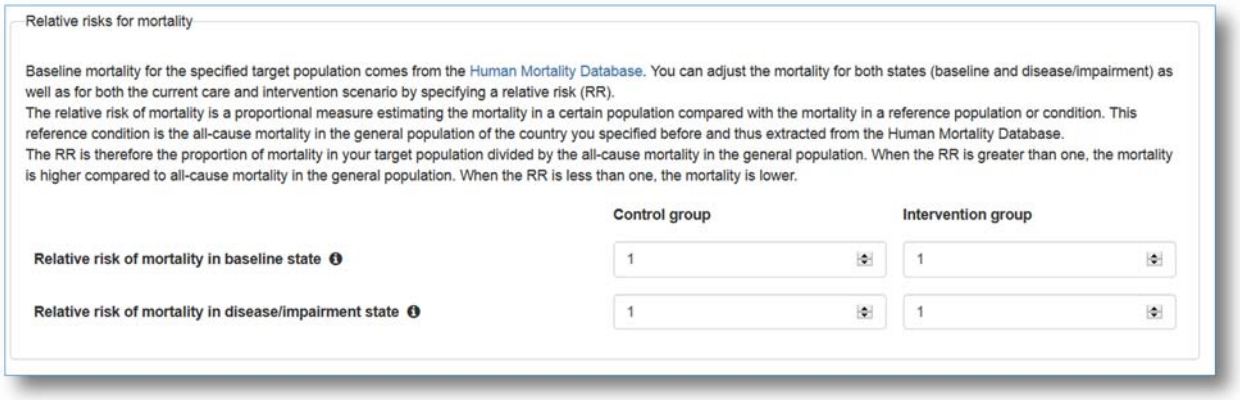


Figure 20. Text fields for estimating mortality through relative risks of mortality

Ticking "Yes" leads the user to input mortality rates directly as shown in the Figure below:

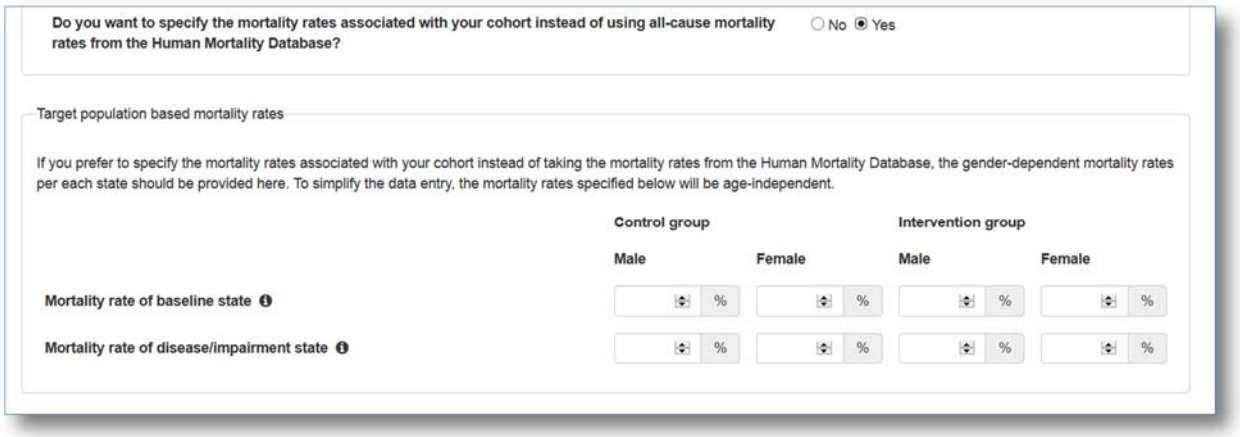


Figure 21. Text fields for direct input of mortality rates associated with the user's cohort

More details on both options are found in the next two Sections below ("Relatives risks for mortality" and "Target population based mortality rates").

Relative risks for mortality

Choosing this option would mean that the baseline mortality for the specified target population would come from the Human Mortality Database.

The relative risk of mortality (RR) is a measure estimating the mortality in a certain population (*e.g.* of the people who participated in you study) compared with (divided by) the mortality in a reference population or condition (in this case, from the Human Mortality Database). The reference condition considers the all-cause mortality in the general population of the country you specified before (in our example, the UK).

If the RR is greater than 1 (RR>1), this means that there is a higher mortality rate in the specified target group (having the given condition) compared to the all-cause mortality given in the Human Mortality Database.

If the RR is less than 1, this means that there are less people dying in the specified target group (that have the given condition) as compared to the general all-cause mortality.

Note: Leaving the input as "1" (RR=1) would prompt the tool to simply use data that is stored in the Human Mortality Database. This is the default option.

Choosing a value that is RR>1 would lead to the tool interpreting this as excess mortality to be added to the existing data from the Human Mortality Database.

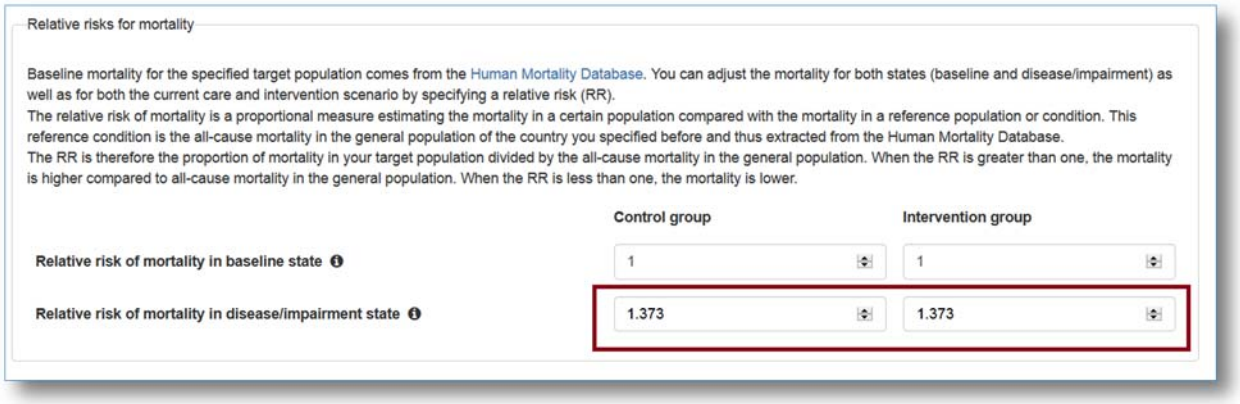


Figure 22 .An example of filled-in text fields under "Probabilities, Relative Risks for Mortality", whereas a value higher than 1 indicates that there is a higher mortality rate in the specified target group (having the given condition) compared to the all-cause mortality given in the Human Mortality Database.

Target population based mortality rates

If the user already has data on mortality rates associated to the relevant study cohort, the user may input these rates in this Section. The mortality rates are dependent on gender but not on age.

For example, based on data from a clinical trial[5], survival rates were higher in dementia patients (disease/impairment state) who were given placebo drugs (intervention group) instead of the standard neuroleptics (control group). At an average, results showed a survival rate of 69% for the intervention group and 49% for the control group. The mortality rates can be derived from these survival rates by subtracting the values from 100%, leading to a mortality rate of 31% for the intervention group and 51% for the control group.** These values may be input as shown in the Figure below. (Note: mortality rates for the baseline state were not input in this example).

***This example was derived from the MAFEIP Use case "Therapeutic Guideline for treatment of Behavioural and Psychological Symptoms of Dementia"[6]*

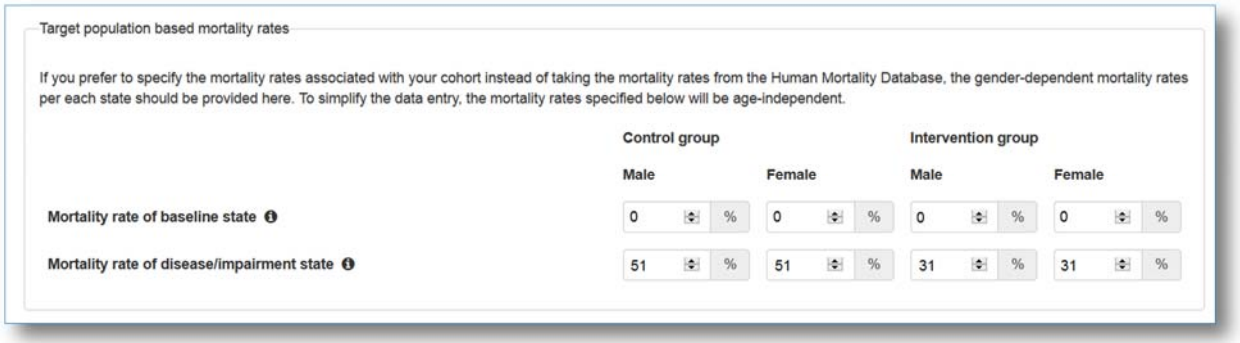


Figure 23. An example of filled-in text fields under "Probabilities, Target population-based mortality rates".

2.3.3 Costs

The costs associated with both the intervention and the standard care scenario should be provided here. Examples of costs would be patient medication, hospital inpatient episodes,

[5] Ballard C, Lana MM, Theodoulou M, Douglas S, McShane R, Jacoby R, et al. (2008) A Randomised, Blinded, Placebo-Controlled Trial in Dementia Patients Continuing or Stopping Neuroleptics (The DART-AD Trial). PLoS Med 5(4): e76. https://doi.org/10.1371/journal.pmed.0050076

[6] http://mafeip.eu/assets/files/MAFEIP_UC_Gencat_Dementia_20170706.pdf

primary care visits, stays in nursing homes, travel to and from the hospital, and caring by family and friends, among others.

One-off and annual recurrent costs

Intervention costs

One-off intervention cost

This is the cost that the patient would have to pay for the intervention at the beginning (*i.e.* upon usage of intervention / service). This may be a one-time necessary surgical procedure or the cost of a telemonitoring device (i.e. the cost of buying the hardware itself).

For example, the price of the predictive wearable device that the patient has to pay to acquire it is 40 GBP. This would be a one-time payment.

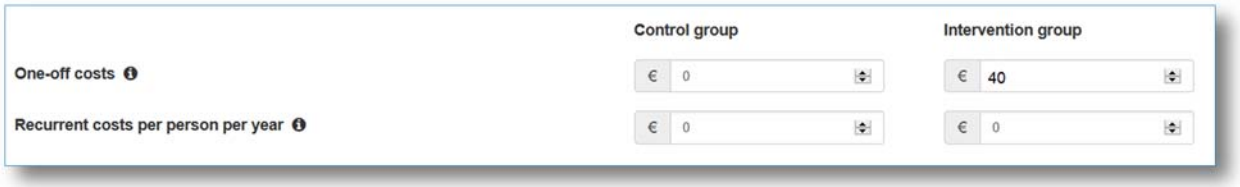


Figure 24. . An example of filled-in text fields under “Costs, on-off intervention costs”

Recurrent costs per person per year

The total intervention cost per person per year represents the annual recurrent cost incurred for delivering the intervention and consists of two components: First, variable costs of the intervention that are incurred for each individual and each year (e.g., software license of the programme used, maintenence of the service, etc.). Second, the share of annual fixed costs per patient currently treated or targeted by the intervention represents, for instance, the annual cost of the infrastructure used for all patients divided by the number of patients currently treated or targeted by the intervention.

Intervention costs comprise two sections. (1) costs of the intervention such as maintenance, delivery, any related assistance services, and the like; and (2) the yearly costs related to all patients of the target group in general *e.g.* any hospital machines used for the target group as a whole divided by the number of patients currently using the intervention (the division ensures a per person per year amount).

Standard care costs

The tool also allows the user to input one-off and annual costs per patient for the standard care. These values will be placed under “Control Group”.

This would enable the simulation to deal with e.g. situations in which the intervention replaces existing care pathways characterized by higher costs. It is not possible to input negative values for costs, but any cost savings provided by the innovation can be computed as an additional cost of the standard care scenario.

For example, recurrent cost savings for the intervention were found to be GBP 100. Instead of indicating “-100” under the intervention group, “100” could be added to the control group.

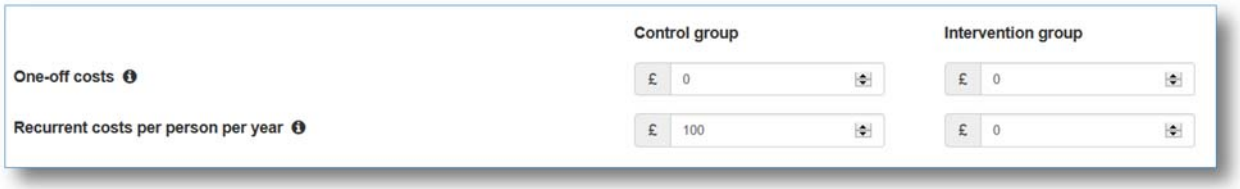


Figure 25. An example of a filled-in text field for recurrent cost savings of the intervention.

Health State Costs

The health state costs represent the costs for both the intervention and control group in baseline and disease/impairment states. These costs are defined per person.

Healthcare costs

Healthcare costs refer to resource use (translated into costs) within the healthcare system, excluding the cost for the intervention itself (which has already been stated in the Section above).

Examples would be any additional patient medication (unrelated to the intervention but needed by the target group), hospital inpatient episodes, primary care visits, and stays in nursing homes, among others.

Societal costs

Societal costs would include healthcare costs as well as other costs outside the healthcare sector. Some examples of such other costs are travel costs for patients (*e.g.* if they live far away and have to drive to another city to be admitted to a hospital and costs of relatives acting as caretakers at home.

A sample cost calculation may be found in the Tables below. The values stated below are for explanatory purposes only and are not representative of any actual cases.

Table 1. Sample Calculation for Healthcare and Societal Costs of Patients in Baseline Health.

Patient in Baseline Health (e.g. patient has not fallen)					
(A) Resource item *(What was given to the patient?)*	Resource use over 12 months for whole target group *(how many times was the resource used in 1 year?)*		Unit cost *(how much is one unit?)*	**(D)** Costs of the intervention per year in GBP (=B1*C)	**(E)** Costs of standard care per year in GBP (=B2*C)
	(B1) With the Intervention (n=100)	**(B2)** With standard care (n=100)	**(C)** GBP per item		
Medication	-	-	-	-	-
Hospital admission	-	1	15	-	15
Outpatient visit	-	-	-	-	-
Travel costs	-	-	-	-	-
Caretaker costs	-	300	10	-	3000
(F) Healthcare costs per year (only adding medication, hospital admission and outpatient visit)				-	15
(G) Societal costs per year (adding up everything)				-	3015

Please note that at the total has been calculated per year only. To get a per year and per patient calculation, divide each total (F and G) with the number of patients in the study group (in the case above, n=100):

Healthcare costs per year per person: 15 / 100 = **0.15**

Societal costs per year per person: 3015 / 100 = **30.15**

Table 2. Sample Calculation for Healthcare and Societal Costs of Patients in Deteriorated Health.

Patient in Deteriorated Health (e.g. patient has already fallen)					
(A) Resource item *(What was given to the patient?)*	Resource use over 12 months for whole target group *(how many times was the resource used in 1 year?)*		Unit cost *(how much is one unit?)*	**(D)** Costs of the intervention per year in GBP (=B1*C)	**(E)** Costs of standard care per year in GBP (=B2*C)
	(B1) With the Intervention (n=2)	**(B2)** With standard care (n=3)	**(C)** GBP per item		
Medication	1,000	1,500	2	2,000	3,000
Hospital admission	2	3	10	20	30
Outpatient visit	10	15	5	50	75
Travel costs	2	3	100	200	300
Caretaker costs	10	15	10	100	150
(F) Healthcare costs per year (only adding medication, hospital admission and outpatient visit)				2,070	3,105
(G) Societal costs per year (adding up everything)				2,370	3,555

To calculate costs per person, divide each total (F and G) with the number of patients in the study group (in the case above, n=2 for the intervention group, and n=3 for the control group)

Intervention group:

Healthcare costs per year per person: 2,070 / 2 = **1,035**

Societal costs per year per person: 2,370 / 2 = **1,185**

Control group:

Healthcare costs per year per person: 3,105 / 3 = **1,035**

Societal costs per year per person: 3,555 / 3 = **1,185**

These values can now be typed into the tool as shown in the Figure below.

Take note that decimal values are not allowed.

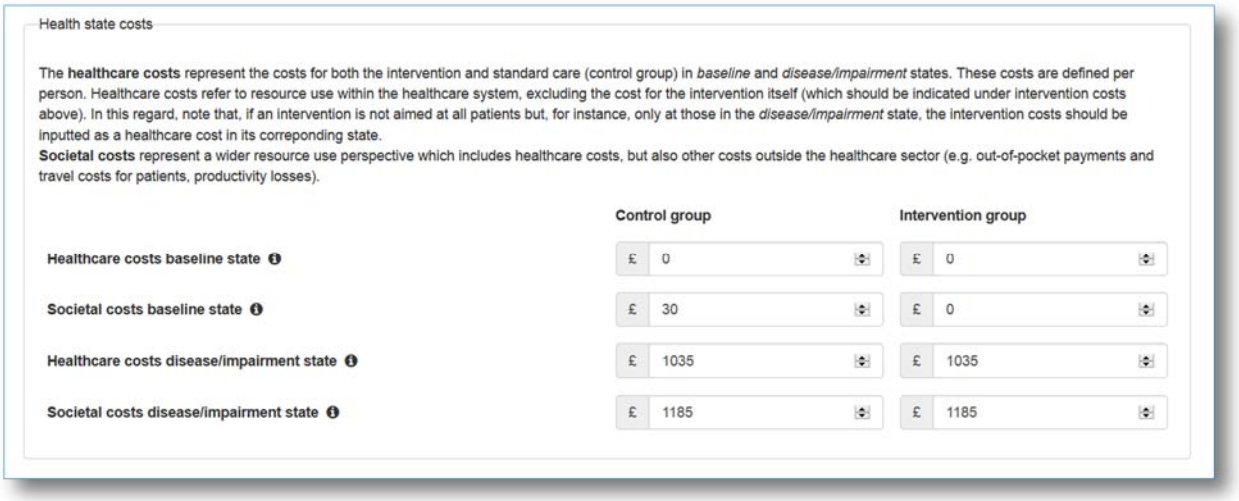


Figure 26. An example of filled-in text fields under "Costs, Health state costs". These values were based on calculations done in the previous Tables.

Health State Costs text fields for the 5-state model

Healthcare and Societal costs are considered per patient health state, and these may be input separately as illustrated in the Figure below.

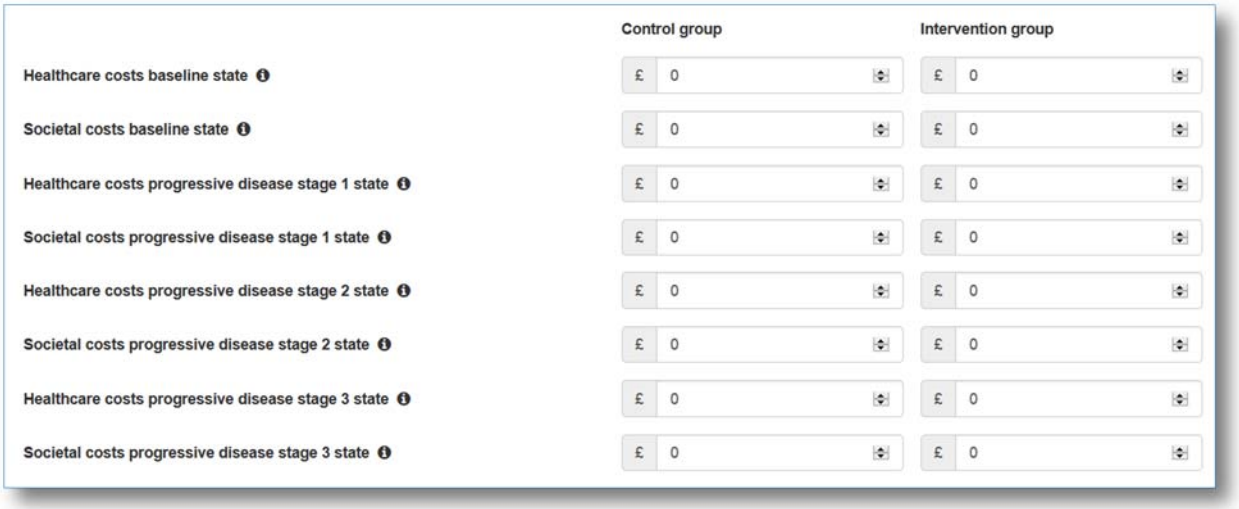


Figure 27. An illustration of the text fields for the Health state costs associated to a 5-state model

2.3.4 Utilities

This is where the user would evaluate the Health-related quality of life (HRQoL) of the selected group with or without the proposed intervention. The HRQoL as expressed through a quality-of-life weight (utility) represents a particular health outcome, whereas a utility of 1 would refer to the quality of life in perfect health and a utility of 0 would refer to no quality or dead. The utility values summarize both positive and negative effects of an intervention into one value that is within this 0 – 1 range.

There are numerous online tools that are helpful for calculating the HRQoL. Common examples are the EQ-5D[7], the Short Form (36) Health Survey (SF-36) or RAND-36[8] and the World Health Organization Quality of Life (WHOQoL)[9].

Among these tools, the EQ-5D is recommended to be used within the MAFEIP context. EQ-5D is conceptually based on a holistic view of health (*i.e.* not only including the medical aspect, but also physical, emotional and social functioning of the patient). Nevertheless, HRQoL scores calculated by other tools (such as those listed above) may also be mapped into EQ-5D scores.

Additionally, if none of these methods have been used to assess health outcomes, other variables may also be used as a proxy for quality of life (*e.g.* patient scores on satisfaction with life), but the scores must be mapped into a range of 0-1.

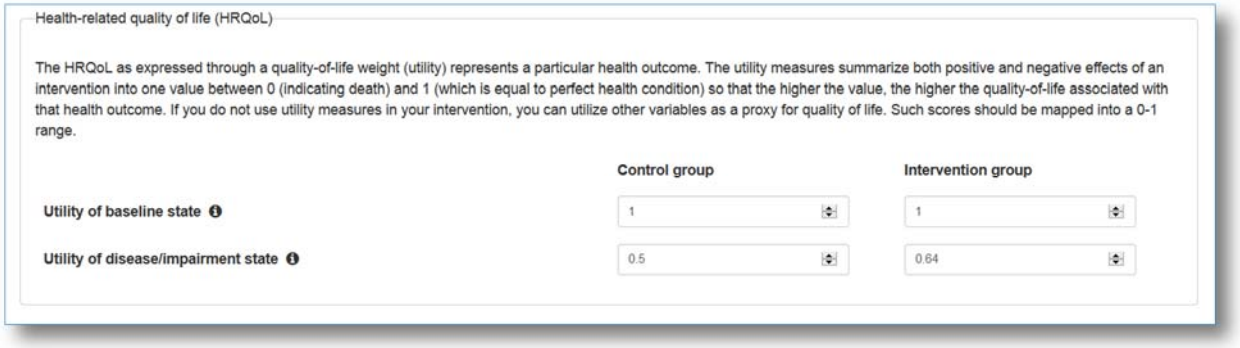


Figure 28. . An example of filled-in text fields under “Utilities”.

Mapping other utility scores into EQ-5D values

Utility values that were not measured through the EQ-5D tool may be mapped into EQ-5D values in a variety of ways as suggested by Boehler, et al. [10]

[7] http://www.euroqol.org/about-eq-5d.html

[8] http://www.rand.org/health/surveys_tools/mos/36-item-short-form.html

[9] http://depts.washington.edu/seaqol/WHOQOL-BREF

[10] http://is.jrc.ec.europa.eu/pages/TFS/documents/02COP_2014_dataworkshop_001.pdf

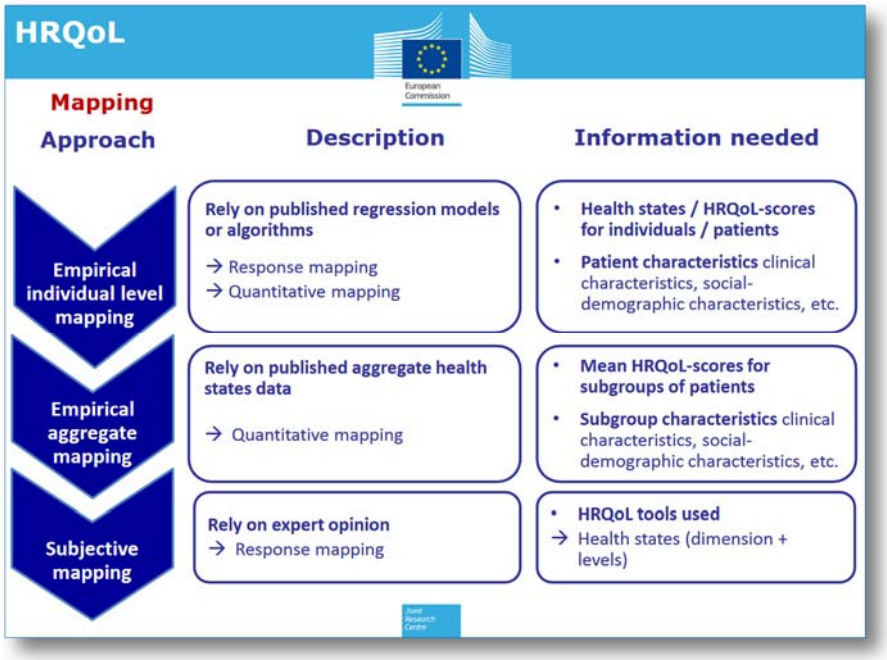


Figure 29. Mapping approaches as suggested by Boehler et al.

In the BeyondSilos study, Barthel Index[11] scores were used to account for utility. This was mapped into EQ5D values by using the formula from Kaambwa, Billingham, & Bryan (2013)[12].

Other variables may also be used as a proxy for quality of life (*e.g.* patient scores on satisfaction with life), but the scores must be mapped into a range of 0-1 (whereas 1 describes perfect health).

For example, in a study where patients were asked to rate how satisfied they are with life and how satisfied they are with their mental health given the following scales (7-point Likert scale):

(1) Strongly disagree, (2) Disagree, (3) More or less disagree, (4) Undecided, (5) More or less agree, (6) Agree, (7) Strongly agree

The answers were mapped into a 0-1 range using the formula $x_{utility} = (x_{answer} - 1) / 6$ **

This meant that an answer of "2" (Disagree) would correspond to a utility of (2-1)/6 or 0.17.

On the other hand, an answer of "6" would correspond to a utility of (6-1)/6 or 0.83.

**Derived from the MAFEIP use case "MasterMind"[13]

[11] http://camapcanada.ca/Barthel.pdf

[12] Kaambwa, Billingham, & Bryan. (2013). Mapping utility scores from the Barthel index. European Journal of Health Economics, 14(2), 231–241.

[13] http://mafeip.eu/assets/files/07_UC7_MastermindcCBT_AR_20170704.pdf

2.4 Step 3: Model Output

This section shows the first results of analysis (sensitivity analysis is not included yet) based on the input parameters that were defined in the model input section (Step 2).

Four types of output are presented: 1) incremental cost and health-related quality of life per age-gender combination in the target population; 2) average per person incremental gains in terms of economic and health outcomes (incremental cost and effects); 3) population level impact; and 4) the impact of the intervention on the probability of the patient specified in the input environment to reside in each of the model states.

There are two perspectives on the outcomes: a healthcare or societal cost perspective. They may each be viewed by using the button as found below (this requires that societal costs have been specified in the Model Input section / Health State Costs).

In the following sections, only the interpretation of healthcare costs would be explained. An interpretation of the societal costs would be similar.

2.4.1 Incremental costs and effects (age and gender specific)

Incremental cost and health-related quality of life are shown here for every age-gender combination in the specified target population.

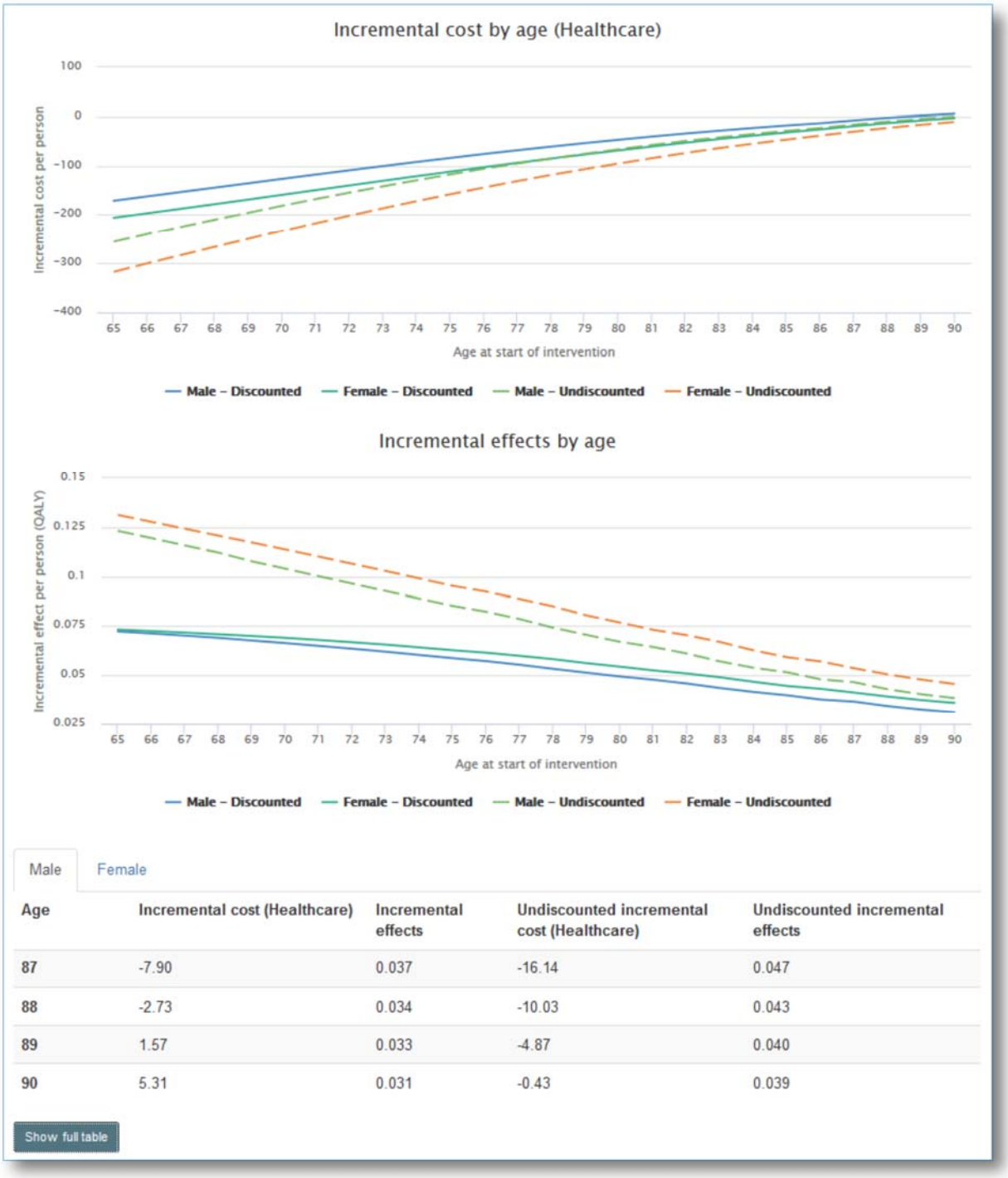
On the one hand, incremental costs refer to the difference between the cost that a person from a specific age and gender would have if he/she received the intervention minus the cost that would have if he/she followed current care.

On the other hand, the incremental effects values show how much quality of life (utility) is gained when the intervention is used instead of the standard care. These are also shown per age-gender group.

Both the discounted and the undiscounted incremental outcomes are presented. Moving the cursor over the curves will display the incremental outcomes for each age-category. This information is also provided in the expandable table below.

The charts below represent incremental costs and incremental effects (as Quality-adjusted Life years or QALYs) accumulated for every age-gender combination in the specified target population (*e.g.* for both males and females and ages 65 to 90, which was chosen in the previous section “Target Population”).

Here the results are displayed in graphs and a table, an example of which can be found below:



Age	Incremental cost (Healthcare)	Incremental effects	Undiscounted incremental cost (Healthcare)	Undiscounted incremental effects
87	-7.90	0.037	-16.14	0.047
88	-2.73	0.034	-10.03	0.043
89	1.57	0.033	-4.87	0.040
90	5.31	0.031	-0.43	0.039

Show full table

Figure 30. An example of how the preliminary results would look like.

Tip: The full table may be displayed by clicking the icon at the bottom left of the table. The result would appear as follows:

Table 3. An expanded view of the table that is shown in Figure 30 above.

Male | Female

Age	Incremental cost (Healthcare)	Incremental effects	Undiscounted incremental cost (Healthcare)	Undiscounted incremental effects
65	-171.36	0.072	-255.71	0.123
66	-162.39	0.071	-240.17	0.120
67	-153.46	0.070	-225.00	0.116
68	-144.57	0.069	-210.22	0.112
69	-135.68	0.068	-195.95	0.108
70	-126.69	0.066	-181.67	0.104
71	-117.89	0.065	-167.94	0.100
72	-109.25	0.064	-154.72	0.096
73	-100.65	0.062	-141.82	0.093
74	-92.25	0.060	-129.44	0.089
75	-84.05	0.059	-117.58	0.085
76	-75.96	0.057	-105.92	0.082
77	-68.31	0.055	-95.18	0.079
78	-60.97	0.053	-85.21	0.074
79	-53.83	0.051	-75.48	0.071
80	-47.04	0.049	-66.38	0.067
81	-40.43	0.048	-57.50	0.064
82	-34.24	0.046	-49.40	0.061
83	-28.51	0.044	-42.14	0.057
84	-23.06	0.042	-35.17	0.054
85	-18.06	0.040	-28.67	0.052
86	-13.51	0.038	-23.09	0.048
87	-7.90	0.037	-16.14	0.047
88	-2.73	0.034	-10.03	0.043
89	1.57	0.033	-4.87	0.040
90	5.31	0.031	-0.43	0.039

Hide full table

Tip: Clicking on a particular legend (e.g. "Male - undiscounted") below the graph would remove it from being displayed in the graph as shown below:

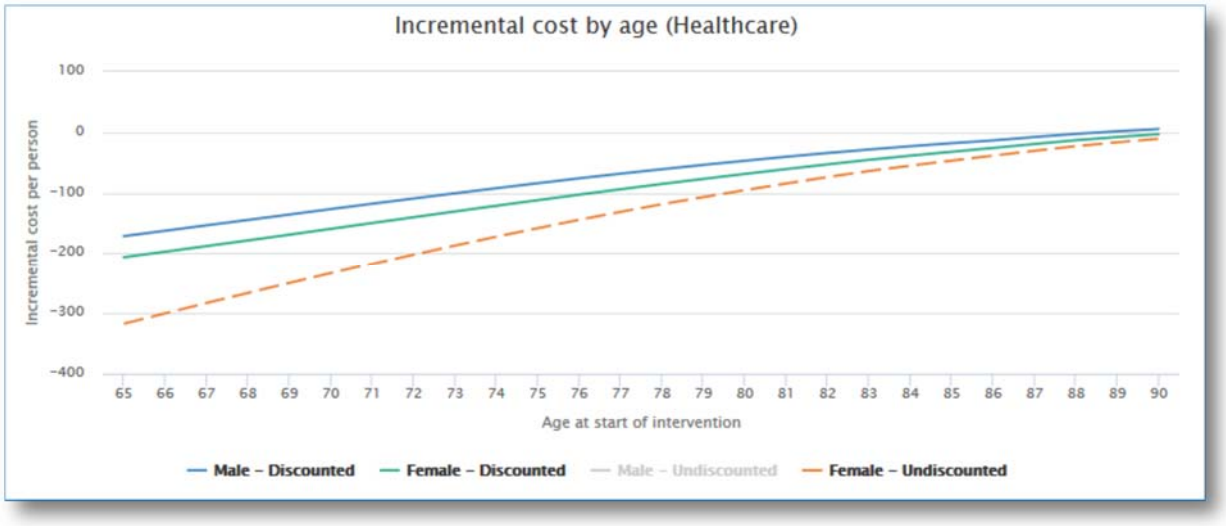


Figure 31. It is possible to click over a particular legend in order to exclude or include it from the resulting graphs.

Interpreting the results

Incremental cost (healthcare)

The incremental costs (ΔC) are calculated roughly by subtracting the costs of standard care from the costs of the proposed intervention.

$\Delta C = C_i - C_c$ where C_i is the cost associated with the intervention, and C_c is the respective cost incurred in the standard care scenario).

Hence, if the proposed intervention is less costly than what is currently available, then this would result to negative values in incremental cost calculations. This is to be interpreted as beneficial. The Figure shows a hypothetical summary of costs for a multimodal intervention to reduce lower back pain. The costs of standard care of the lower back pain are also shown.

Note: The example below is unrelated to the running example case study presented in this paper (usually shown in blue boxes). Furthermore, the values are hypothetical and are used for illustrative purposes only. It is worthy to note that the example below does not distinguish between age groups or genders, contrary to the results given in the tool (e.g. in Figure 31)

Table 4. A summarized table of hypothetical costs of an intervention to reduce lower back pain versus the costs of standard care. The incremental cost of intervention at a certain time point (value shown in the Figure as -244) is calculated by the difference between the total costs of the intervention and the standard care.

Source: adapted from http://is.jrc.ec.europa.eu/pages/TFS/documents/02COP_2014_dataworkshop_001.pdf

Resource Item	Resource use over 12 months		Unit cost		
	Intervention (n=100 patients)	Standard care (n=100 patients)	Euro per item	Intervention	Standard Care
Multimodal treatment cost	100	-	2,000	200,000	-
Medication	20,000	100,000	2	40,000	200,000
Hospital admissions	10	25	3,500	35,000	87,500
Outpatient visits	30	200	70	2,100	14,000
Per patient cost at t=1				**2,771**	**3,015**
Incremental cost of intervention at t=1				**2,771 – 3,015 = -244**	

In the Table above, it can be seen that the cost of the intervention is less than that of the standard care. Hence, the incremental cost of intervention results to a negative value (-244). This may be interpreted as “the savings” made at a given time point. Then, the intervention should be used instead of the standard care.

Going back to Table 3 above, it can be seen that the biggest “savings” (e.g. -171.36) correspond to the earlier years (e.g. 65 years old). The higher the age, the lesser “savings” there are. At the age of 89 and 90, the costs of the intervention are already considered slightly higher than that of standard care. This is also shown in the incremental cost graph:

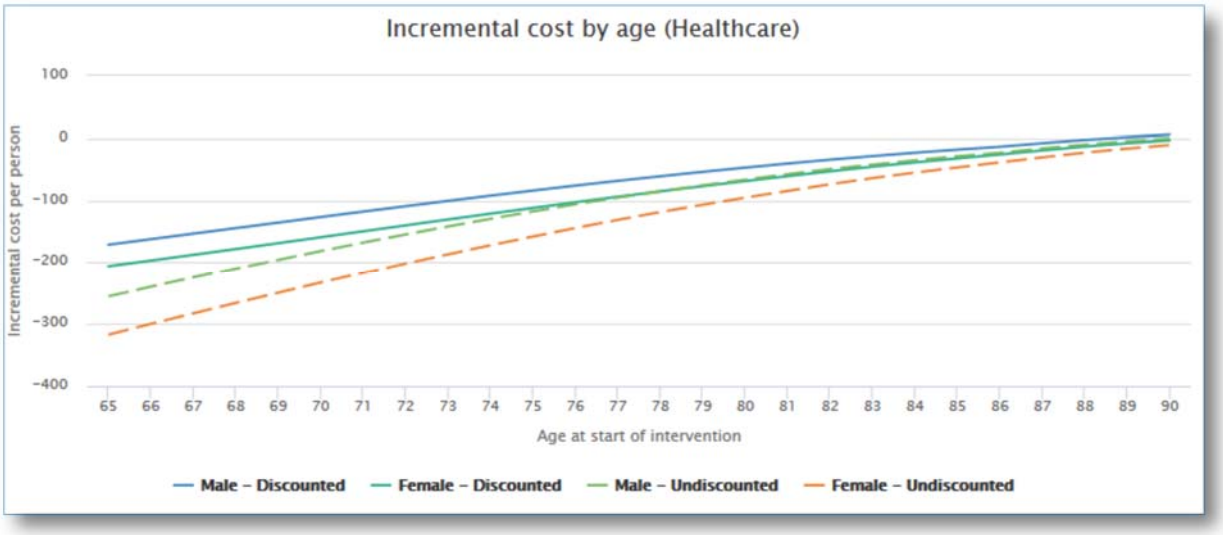


Figure 32. The incremental costs of intervention per person are plotted against the age at which a patient starts to use the intervention. The upward curve shows that the costs of intervention per person increases for both males and females as age increases.

The graph depicts a curve increasing over time, showing that intervention costs increase as age increases.

Incremental Effects

The incremental effects values show how much QALYs are gained when the intervention is used instead of the standard care. These are also shown per age group.

Table 3 above shows that as age increases, the QALY gained decreases. This is also depicted in the corresponding graph:

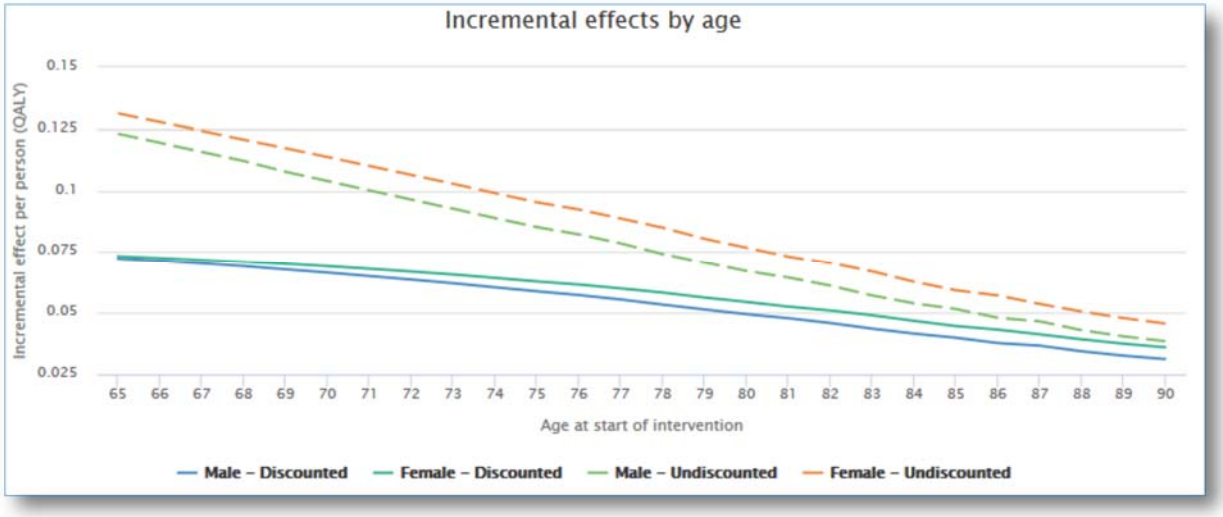


Figure 33. The incremental effects of intervention per person (QALYs) are plotted against the age at which a patient starts to use the intervention. The downward curve shows that the QALYs gained per person decrease for both males and females as age increases.

The incremental effects (ΔE) are calculated similarly:

$\Delta E = E_i - E_c$ where E_i is the health expectancy with intervention, and E_c the respective health expectancy with the standard care).

Discounted or undiscounted

Discounted results take into account the set Discount Factor in the Model Setup (Section 2.3.1, Model assumptions).

2.4.2 Cost-effectiveness

This section presents the overall impact of the intervention on healthcare/societal cost and quality-adjusted life years (QALYs) for the total target population. Results represent the average per-patient outcome across all age-gender combinations (weighted by the age-gender distribution in the specified target country and age range).

The results are summarized in a table (red box in Figure below) and in a cost-effectiveness plane (see the graph in Figure below).

A sample result is found below:

Sample Result #1

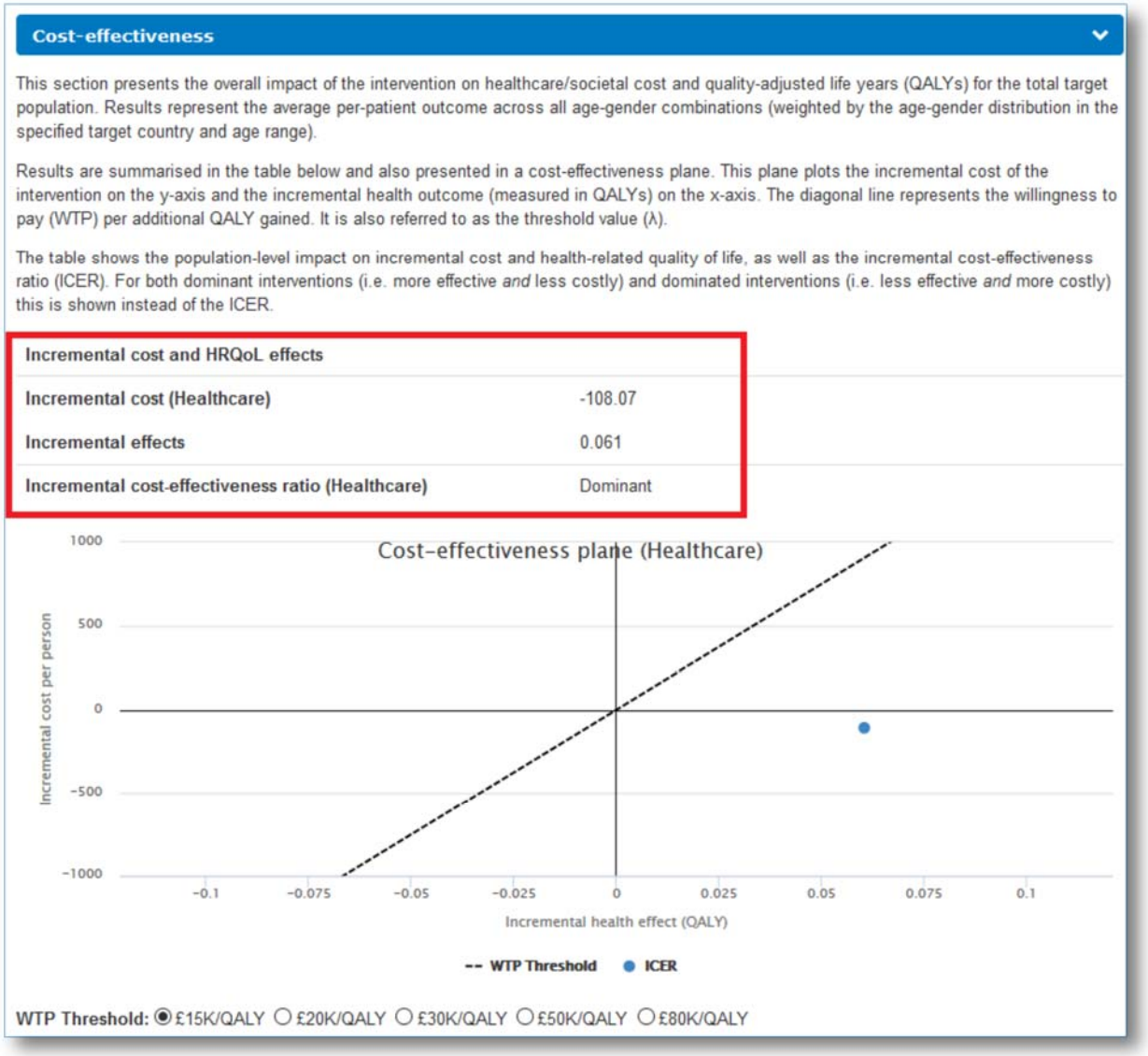


Figure 34. A sample result showing characteristics of an intervention that would be considered acceptable. Such characteristics include a "Dominant" incremental cost-effectiveness ratio as stated in the table (in red box) and depicted by the location of the ICER blue dot (as being within the lower right quadrant).

The Incremental cost and HRQoL effects table

The incremental cost (Healthcare) result is the average of incremental cost values per person shown previously (e.g. in the table under Section 2.4.1).

Likewise, the incremental effects result is the average of incremental effects values per person shown in the table under Section 2.4.1.

The incremental cost-effectiveness ratio (Healthcare) or the ICER is computed using the following formula:

$$ICER = \Delta C/\Delta E$$

whereas ΔC is $Cost_{intervention}$- $Cost_{standardcare}$ and ΔE is $Effect_{intervention}$ – $Effect_{standardcare}$

The incremental cost-effectiveness ratio may either display “Dominant” or “Dominated”. A specific value (obtained from using the equation above) may also be shown as seen in another Sample Result found below:

Sample Result #2

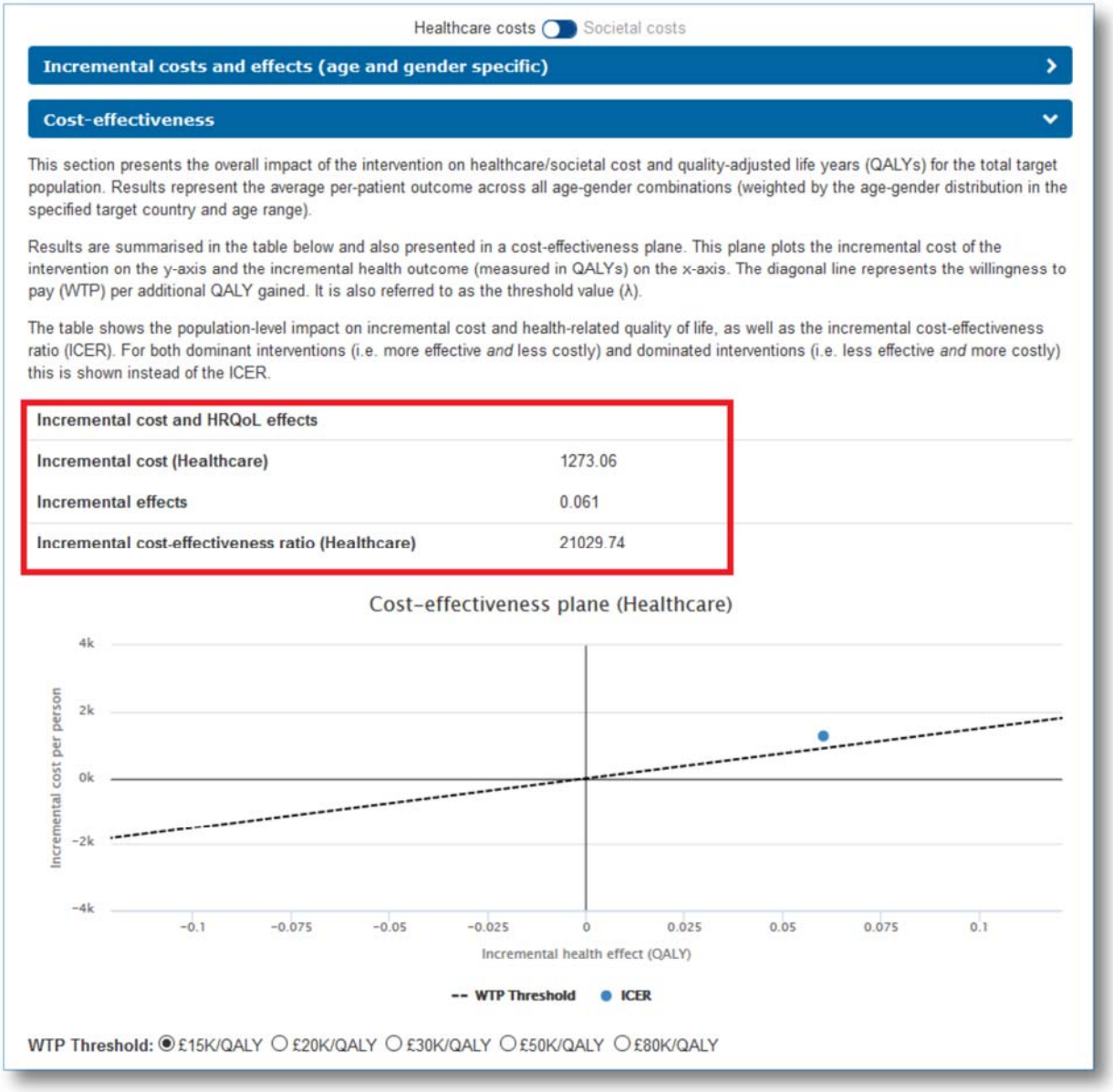


Figure 35. A sample result showing characteristics of an intervention that has to be further evaluated before defining the intervention as accepted (or not). Characteristics include a specific value for the incremental cost-effectiveness ratio (as shown in red box), and the location of the ICER blue dot in either the upper right quadrant or the lower left quadrant.

The difference between these (Dominant vs. Dominated vs. A specific value) will be explained in the next Sections.

The cost-effectiveness plane

The cost-effectiveness plane can be interpreted by first taking note of where the ICER point is (this is the blue dot) and in which quadrant of the plane this blue dot is located. Each quadrant has a different interpretation as shown in the Figure below.

Interpreting the quadrants

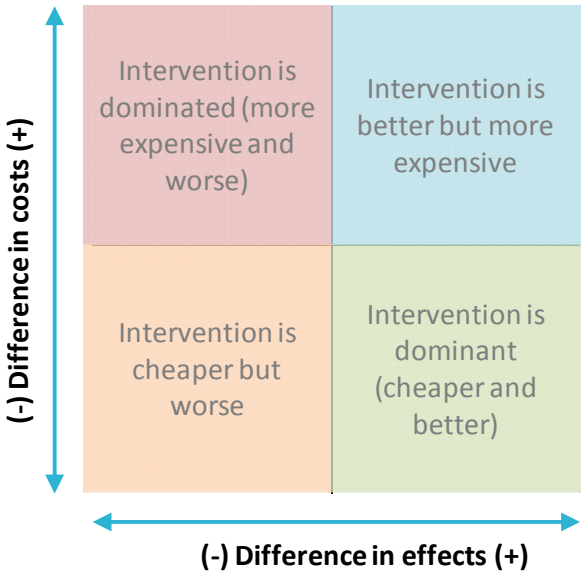


Figure 36. A summary on how to interpret the quadrants of the cost-effectiveness plane. Lower right (green) means intervention would always be accepted while upper left (red) means intervention would not be accepted. If the ICER lies in the other two quadrants, then the intervention may or may not be accepted depending on the ICER and WTP threshold values.

If the blue dot is at the upper left quadrant (coloured red in Figure 36 above), this means that the proposed intervention is both more expensive as well as worse (less effective) than the current care. In this case, the intervention would not be considered acceptable in any case (dominated).

On the other hand, if the blue dot is at the lower right quadrant (green in Figure 36 above), then it means that the proposed intervention is cheaper and better than what current care is able to provide, and in this case the intervention would always be considered acceptable (dominant).

In Sample Result #1, the blue dot is located in the lower right quadrant. This means that the proposed intervention is cheaper and better (Dominant) and would definitely be considered “acceptable” (more on what is acceptable in the later sections).

In Sample Result #2, we see that the blue dot is located at the upper right quadrant. This means that our intervention is better (more effective) than the current (standard) care, but it is also more expensive. In this case, in order to know whether the intervention is acceptable or not, there would be a need to compare the ICER (the value of the blue dot or the fourth value in our table “Incremental cost-effective ratio”) to the Willingness to Pay (WTP) threshold. Sample WTP thresholds can be found under the cost-effectiveness plane (red box in Figure below):

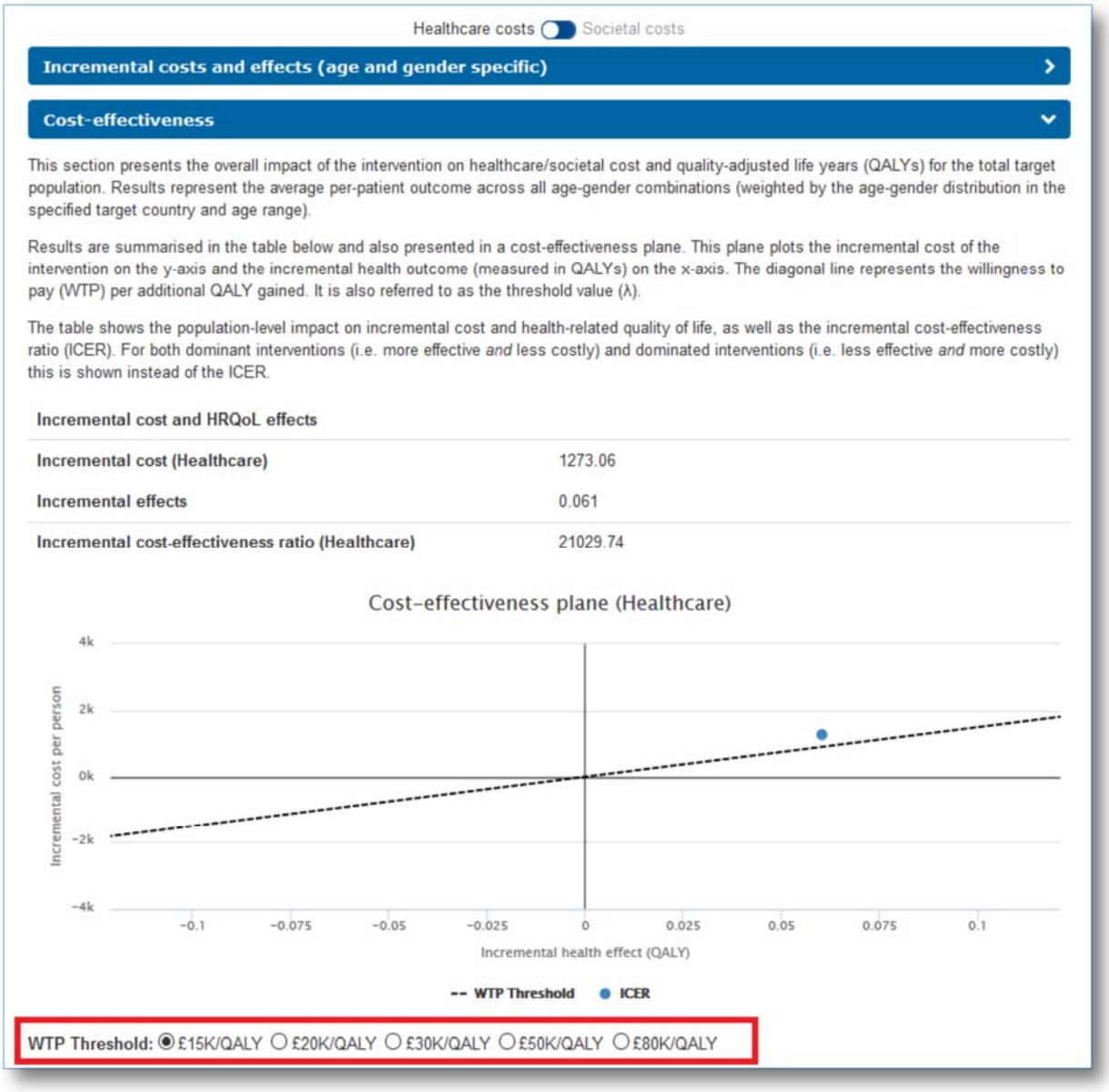


Figure 37. The tool offers 5 different given WTP thresholds as bases of comparison. The user may select the value that is most appropriate.

What is the WTP threshold?

The Willingness to Pay (WTP) threshold is the maximum amount that a patient is willing to give in exchange for a better quality of life. This is shown as a linear plot in the cost effectiveness plane. Different thresholds (choices located inside red box in Figure 37 above) may also be selected. The user does not need to know a specific WTP value at this moment. These values are just given for comparative reasons (explained below).

Suggestions on how to obtain specific WTP threshold values related to the specified target group may be found under the Section “Strategies for collecting relevant data to feed into MAFEIP)”.

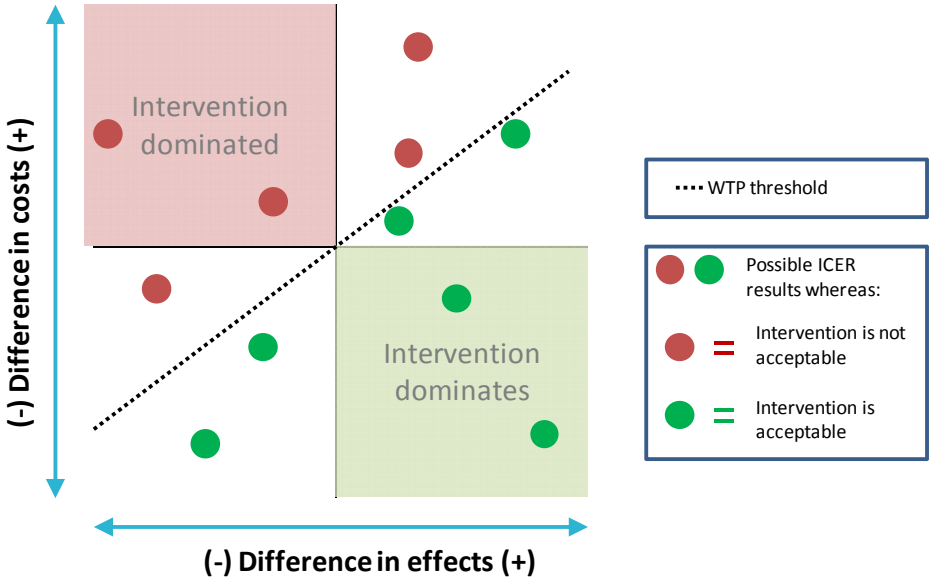


Figure 38. A quick overview relating the location of the ICER blue dot and whether the intervention is acceptable or not. In this Figure, green dots (and their corresponding locations) point to the intervention being accepted.

Interpreting the ICER in comparison to the WTP Threshold

Figure 38 above shows the possible placements of the ICER (represented by a blue dot in previous Figures – take note that the result would only have 1 blue dot). A closer look at the Figure above shows that if the blue dot is located "under" the WTP threshold plot, then the intervention is considered acceptable.

In mathematical terms, if the ICER (blue dot) value < WTP (linear plot) value, then the proposed intervention is deemed acceptable. This would ultimately mean that the costs of the intervention are less than the maximum price people are will to pay for a better quality of life. Hence, the patients would then theoretically be willing to pay for the intervention, despite it being more costly than the standard care.

What does *"intervention is accepted or acceptable"* mean?

The MAFEIP tool may be applied to assess technologies even as they are at an early stage of development. It may be used to assess the potential of a new technology, allowing the users to take on an "investor's perspective". [14]

Whether an intervention is deemed "acceptable" or not may be of valuable information for:

- The developer of a technology to decide upon further investment and
- The EIP on AHA to provide the right support for the innovation to progress faster to the next stage of development[15]

The Incremental cost-effectiveness ratio

Going back to our Sample Result #2, the Incremental cost-effectiveness ratio or ICER value (see top red box in Figure below) is at 21,029.74 GBP. On the other hand, the WTP threshold chosen was 15,000 GBP. This means that a patient would not pay more than 15,000 GBP per QALY and since 21,000 is above 15,000 (ICER > WTP) then the proposed intervention would not be considered accepted.

[14] http://is.jrc.ec.europa.eu/pages/TFS/documents/06COP2015Toolpresentation.pdf

[15] http://is.jrc.ec.europa.eu/pages/TFS/documents/06COP2015Toolpresentation.pdf

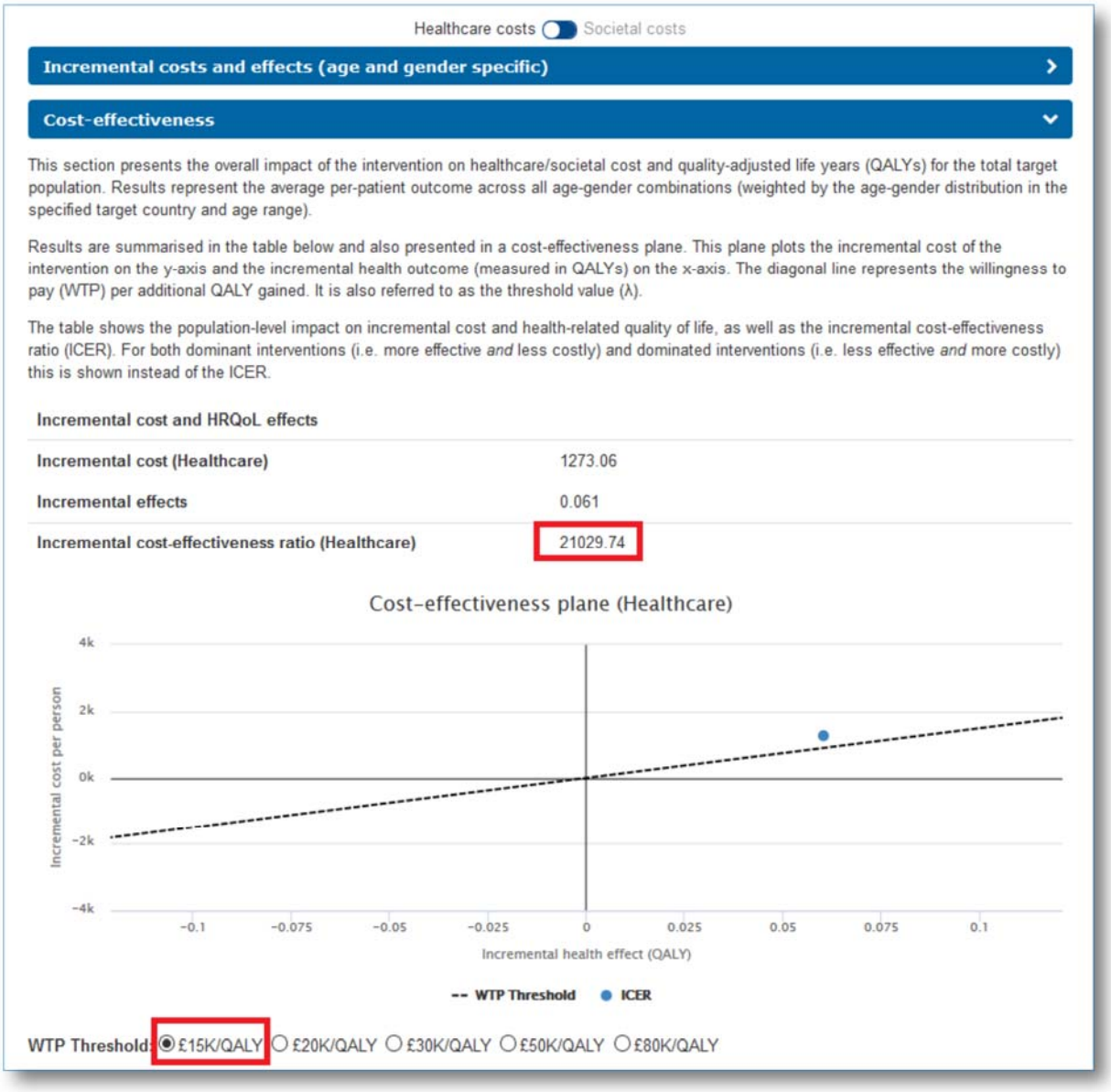


Figure 39. Comparing the Incremental cost-effectiveness ratio value and the WTP threshold value would also show whether the intervention would be considered accepted or not. If the values of ICER < WTP (ICER value less than WTP threshold), then the intervention is accepted.

Dominant or Dominated

As mentioned previously, this parameter may also state “Dominant” (as in Sample Result #1) or “Dominated”). Dominant would mean that the intervention would always be considered accepted as it is cheaper and better than standard care, and Dominated would mean that the intervention would not be considered accepted as it is more expensive and “worse” than the current standard care.

Changing the WTP Threshold Parameter

Changing the WTP threshold to a higher value may lead to more desirable results when the ICER (the blue dot) lies in the upper right quadrant or the lower left quadrant. In the Figure below, 30,000 GBP is selected as a threshold value (in red box) instead of 15,000 GBP.

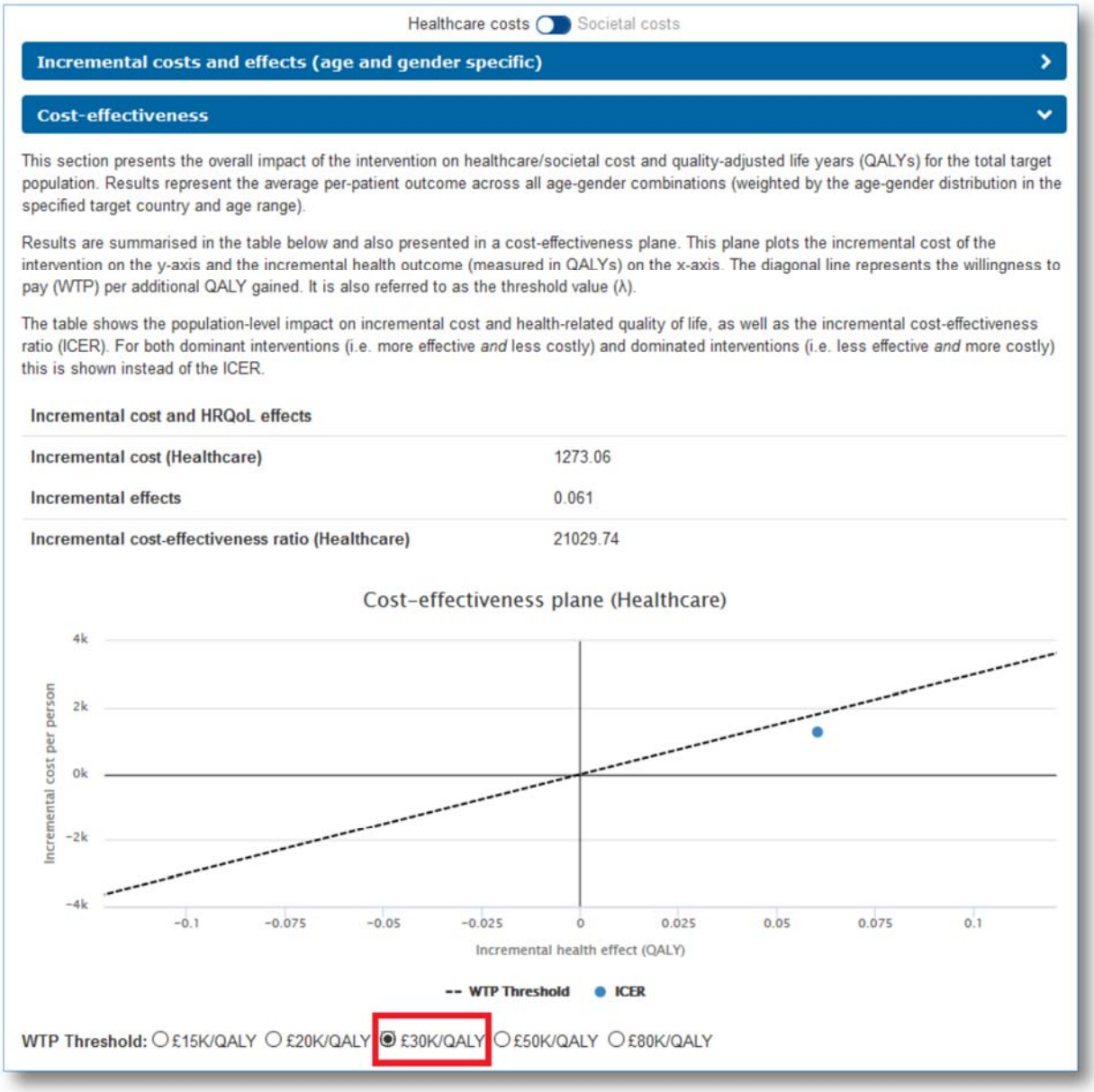


Figure 40. The plot shows that when the WTP threshold is higher *i.e.* patients are willing to pay more for a better quality of life, then the intervention has a chance of being accepted.

Now the blue dot (ICER) is below the WTP Threshold plot, indicating (as shown previously in Figure 38) that the proposed intervention would (now) be accepted. In this scenario patients would be willing to pay up to 30,000 GBP, and hence, costs of 21,030 GBP would still be considered acceptable.

2.4.3 Population impact

The charts below represent incremental costs and incremental effects (QALYs) accumulated over the model time horizon for the whole population.

The default population size value given here is taken from the overall population size value of the country that was selected in previous sections (*e.g.* total population of the UK). This population size can be adjusted based on the target population of the innovation as shown in the Figure below (changed to 100):

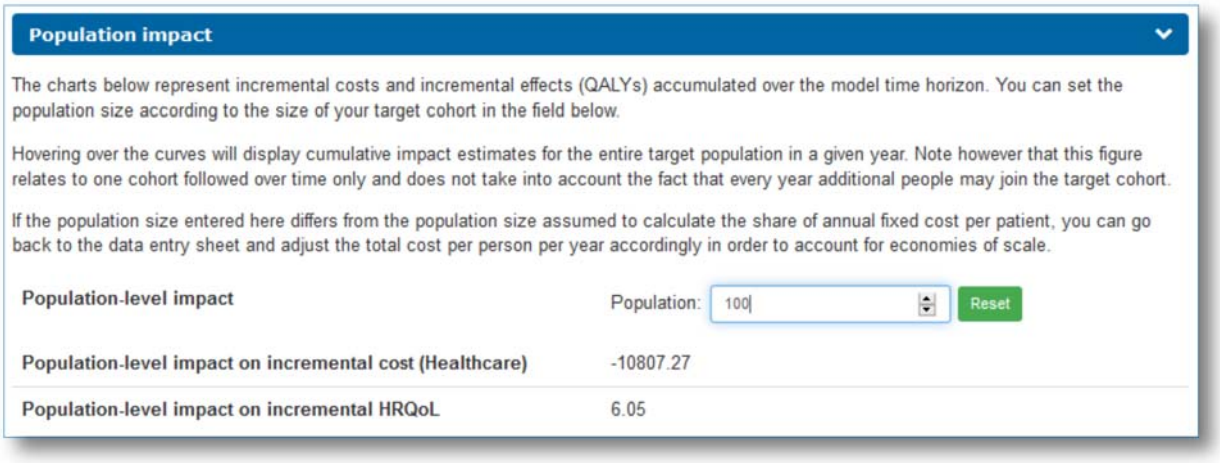


Figure 41. It is possible to change the population number into one that matches the target group population. This would lead to corresponding values under "Population-level impact on incremental cost" and "Population-level impact on incremental HRQoL". This Figure shows the population level impact for the Sample Result #1

Hovering over the curves will display cumulative impact estimates for the entire target population in a given year. Note however that this figure relates to one cohort followed over time only and does not take into account the fact that every year additional people may join the target cohort.

If the population size entered here differs from the population size assumed to calculate the share of annual fixed cost per patient, the user can go back to the data entry sheet and adjust the total cost per person per year accordingly in order to account for economies of scale.

Population-level impact on incremental cost (Healthcare):

This is simply the incremental cost value found in the Cost-effectiveness table (red box in Figure 34 above) multiplied by the population number. This is then the average amount of costs of the whole population either saved (if the value is negative) or additionally paid for (if the value is positive) by using the intervention instead of the standard care.

Population level impact on incremental HRQoL:

Similarly, this is the incremental effects value found in the Cost-effectiveness table (red box in Figure 34) multiplied by the population number. It is the averaged, accumulated quality of life gained or lost by the total population of patients when the intervention is used instead of standard care.

Interpreting the graphs

The graph on Cumulative Incremental costs over Model Horizon (shown in Figure 42 below) shows the cumulative incremental costs of intervention use per patient per year along a certain time span.

The Figure below shows a sample result. The graph depicts an initial downward curve, indicating that the costs decrease during approximately the first 20 years of intervention usage. After this, the costs remain stable, but still lower than the value at the beginning.

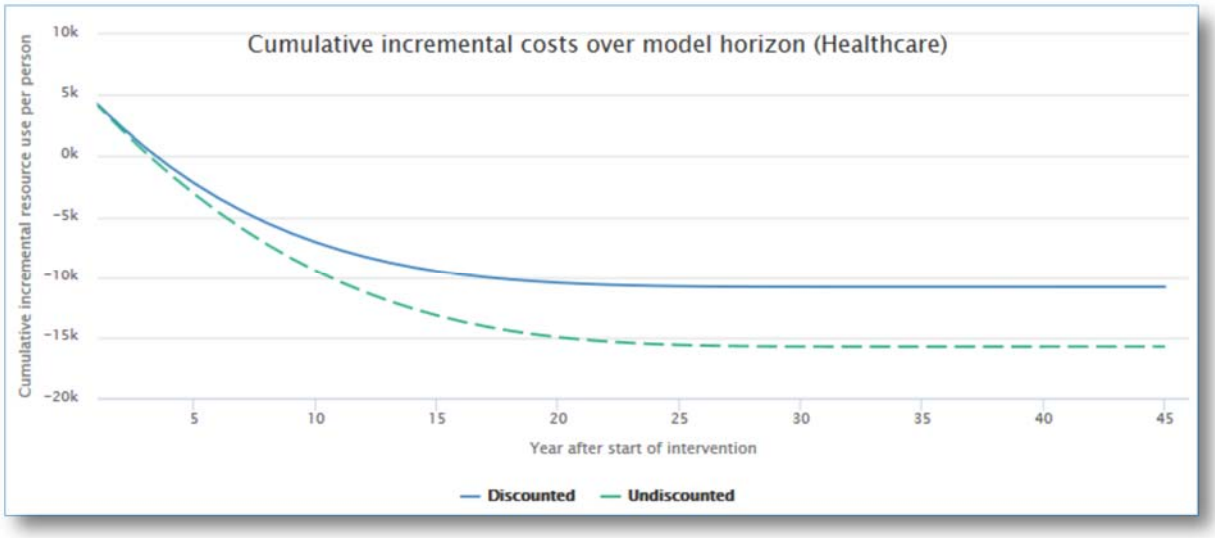


Figure 42. This Figure shows the cumulative incremental costs using the data from Sample Result #1.

The graph above is to be interpreted in a positive manner as the intervention is shown to accumulate savings (indicated by the negative value) rather than excess spendings.

In contrast, an intervention that would lead to more costs along a big period of time is would result to a graph similar to the one in the Figure below.

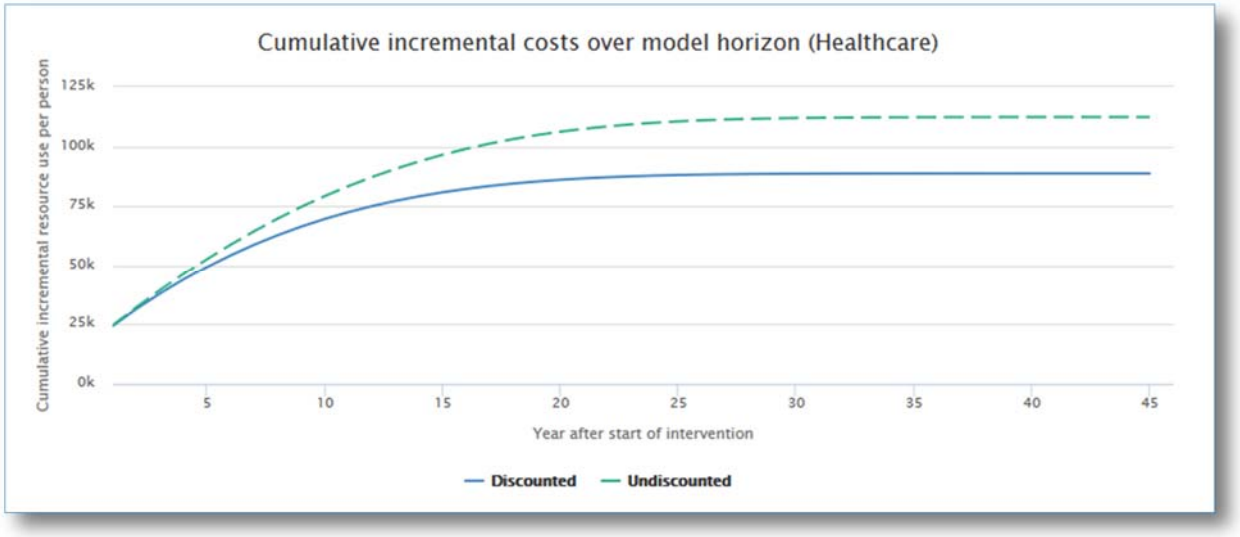


Figure 43. This Figure shows the cumulative incremental costs using the data from Sample Result #2.

Similarly, the second graph shows the cumulative incremental effects of intervention use per patient per year along a certain time span. The Figure below shows an example of a graph depicting an increase in cumulative QALYs gained per patient throughout 45 years of intervention usage. This is to be interpreted positively.

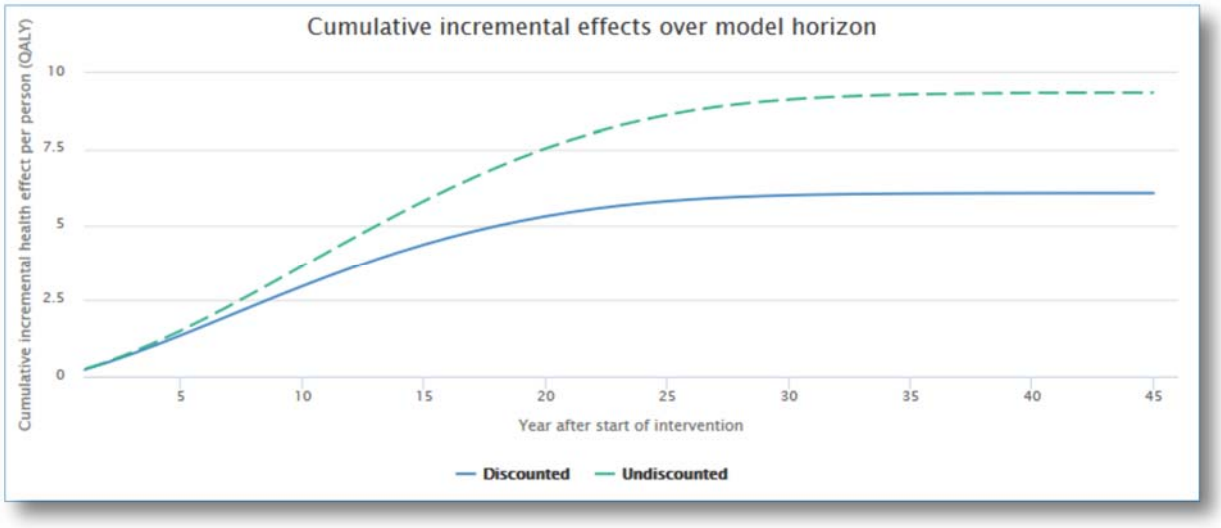


Figure 44. The Figure shows the incremental effects cumulated through use of the intervention using data from the Sample Result #1.

2.4.4 Patient flow through model states

During the previous data input step (under Section 2.3.1 Set-up/ Patient flow through model states), the user was asked to choose only one gender and to input a specific age for the Markov model flow data analysis (Figure 13). The results shown under this section apply to the selected gender. The selected age is chosen as a starting point of the graph.

Both graphs illustrate the probability that a patient would stay in a particular health state when using the intervention or standard care.

Alive states

The first graph depicts the probability of each given age group to stay in either the baseline health state (*e.g.* not yet experiencing a fall) or the disease / impairment state (*e.g.* already experienced a fall) when using the intervention or standard care. An example of how the graph would look like is shown in the Figure below.

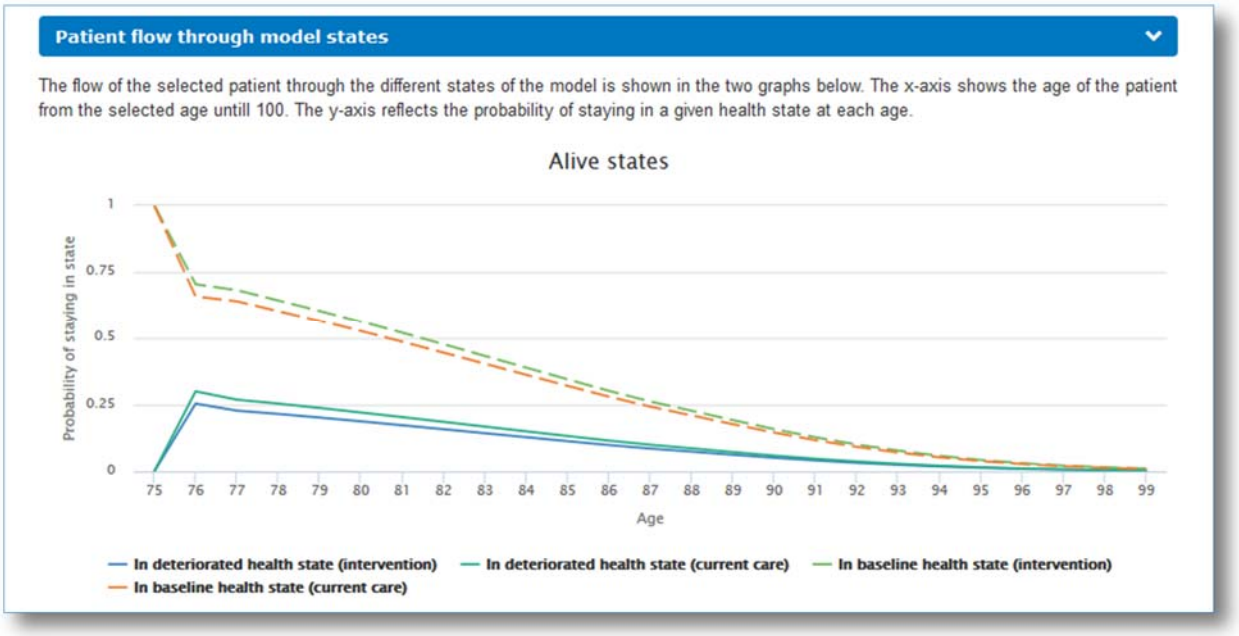


Figure 45. A plot showing the likeliness of a patient to remain in a particular alive state (either baseline health state or deteriorated health state) according to different age groups. The plots include both patients from the control group (current care) and the intervention group (intervention).

It can be seen from the graph in the Figure above that for patients at the baseline health state, there is a higher probability of staying in that health state when the intervention is being used (See dashed lines in the Figure above, compare green against red). This corresponds to the data given in the running example case study whereas the proposed intervention aimed to prevent patients from falling (*i.e.* from going into the deteriorated health state) its usage has shown better / lower incidence rates. Therefore, these patients should have a higher chance of staying in the health state while using the intervention.

Meanwhile, the dotted plots also show a decrease in probability of staying in the particular alive state as age increases, indicating a larger likelihood to move to a different state (*e.g.* baseline→ deteriorated) at an older age.

Similarly, those who are in a baseline health state have more likelihood to remain alive compared to those in the deteriorated health state. This is also seen in the graph when comparing the location of the plot of the dashed lines compared to the plot of the solid lines.

Dead state

The second graph shows the probability of a patient to die while using the intervention or using standard care, according to given age groups. An example is shown in the Figure below.

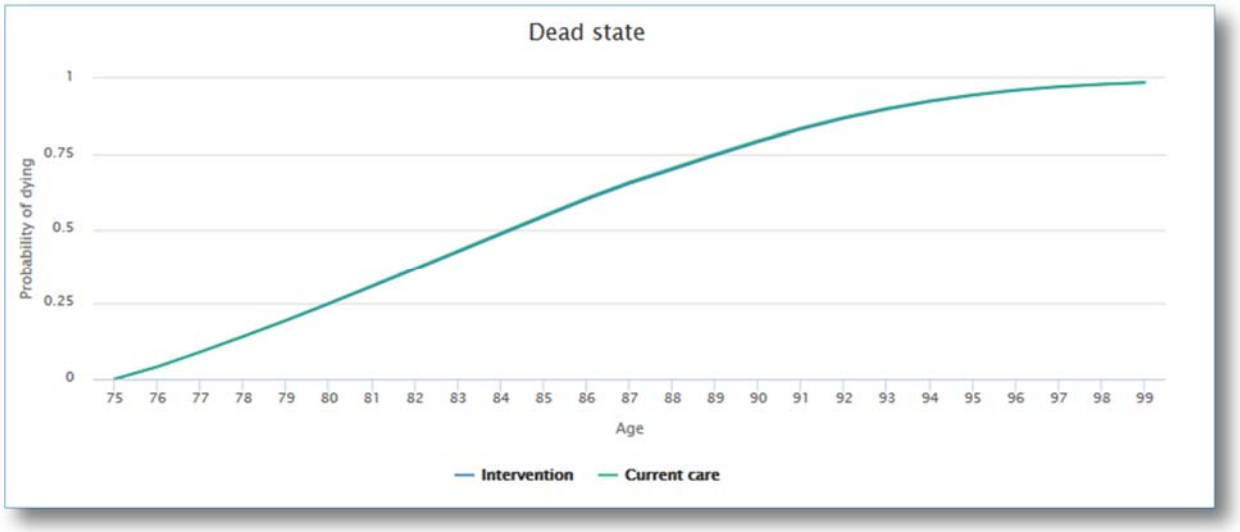


Figure 46. A plot showing the likeliness of a patient to die according to different age groups. The plots include both patients from the control group (current care) and the intervention group (intervention).

It can be seen from the graph above that the higher the age of the patient, the higher the probability to die. It can also be seen that the two plots run along the same path. This means that whether the patient is using the intervention or not, there is the same probability of dying (pointing to the probability of dying being more age-dependent than intervention dependent). This is expected as similar values were put in the relative risks of mortality for the control group and intervention group in Section 2.3.2 Relative risks for mortality.

2.5 Step 4: Sensitivity analysis (additional data input)

This is done via a univariate deterministic sensitivity analysis. This means that all parameters are varied one-by-one over a specified range of input values.

Sensitivity analysis allows the user *to assess the impact of different inputs for selected parameters on the outcome of the evaluation*. In other words, it allows the user to see whether the evaluation of the intervention is "better" or "worse" when certain parameter values (*e.g.* incidence rate, intervention cost, etc.) are changed.

In this Section, the user will be able to choose which of the data (from the Data Input in Section 2.3.1) would be included in the sensitivity analysis. The data parameters are grouped into 4 sections:

- Analysis – includes the Discount Factor values
- Probabilities – includes transition probability and relative risks of mortality values
- Costs – includes intervention costs and health state costs
- Utilities – includes HRQoL values

The user may select which values to include in the sensitivity analysis by ticking the appropriate boxes as shown in the Figure below (tick boxes are boxed in red).

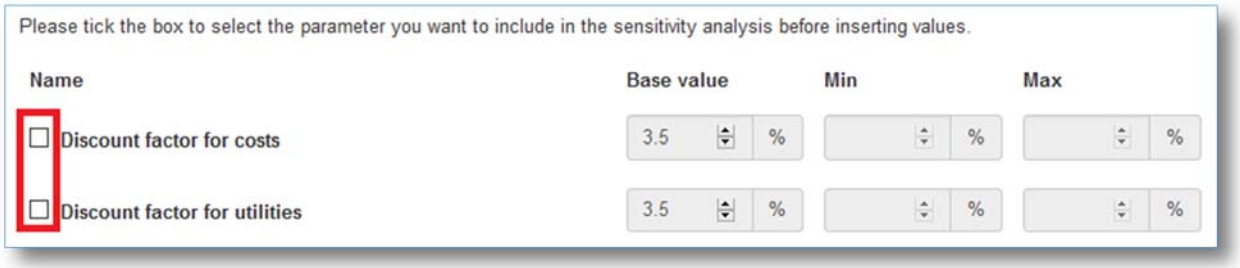


Figure 47. Ticking the box of a certain parameter allows that parameter to be included in the sensitivity analysis.

The user will then also need to specify lower and upper estimates or range of each selected data parameter, under "Min" and "Max" as shown in the Figure below:

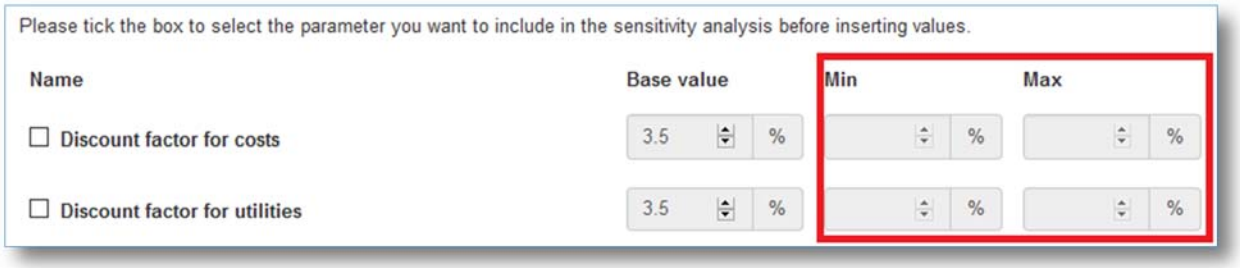


Figure 48. The lower and upper range estimates of each selected parameter may be specified by the user in the corresponding boxes (in red). The Base Value must always be in between the lower estimate (Min) and the upper estimate (Max).

Note: The user will need to first tick the boxes before specifying lower and higher estimates.

The lower estimate may not be higher than the value specified in the base case analysis, and the higher estimate may not be lower than the value specified in the base case analysis.

An example of selected parameters and corresponding given lower and higher estimates can be seen in the Figure below.

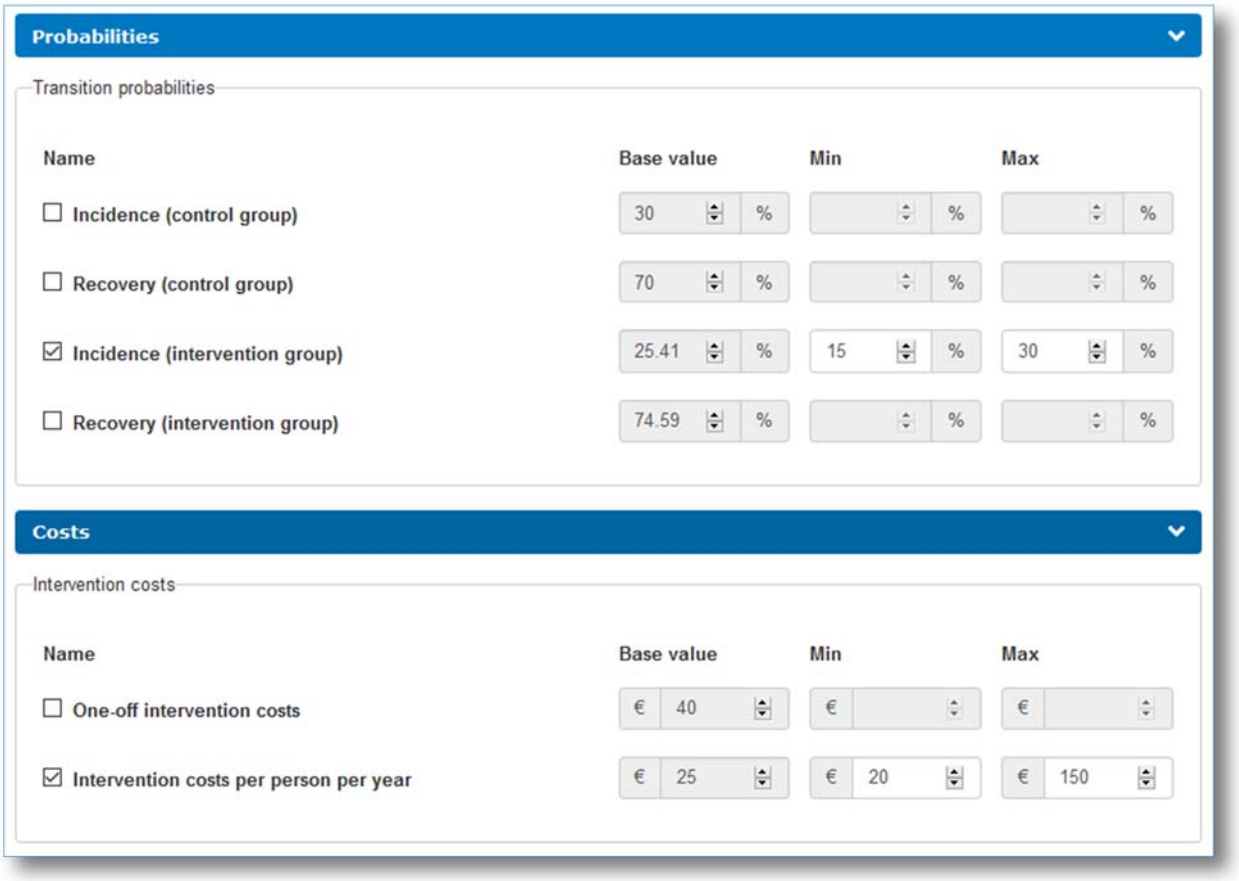


Figure 49. An example of filled-in text fields under “Sensitivity Analysis”. Chosen parameters have their corresponding boxes ticked, and a lower and upper estimate is specified.

2.6 Step 5: Model Output Sensitivity Analysis

The results of the sensitivity analysis with the previously chosen parameters are shown here.

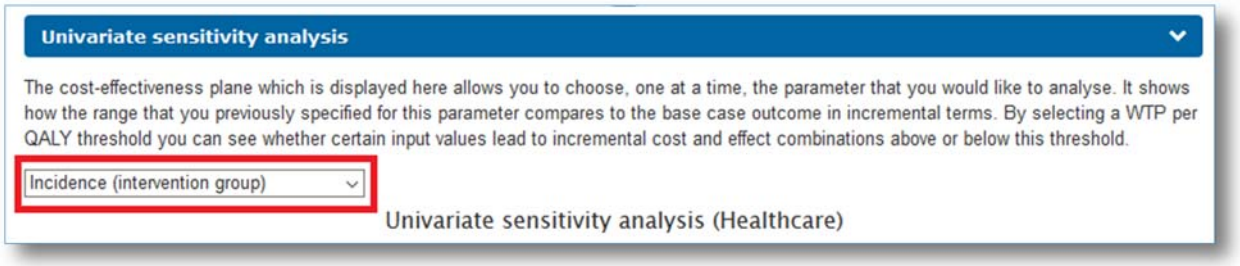
Similar to the previous Model Output, the user may choose between a healthcare or societal cost perspective through the button shown below:

Outcomes are displayed both in a cost-effectiveness plane and Tornado diagrams separately for incremental cost and effects of the intervention.

2.6.1 Univariate Sensitivity Analysis

In this section, a cost-effectiveness plane is displayed showing one selected parameter and its effect on the cost-effectiveness results as compared with the base case (that which was shown under Section 2.4.2)

The results of each parameter may be viewed by selecting the corresponding parameter in the drop-down box as seen below:



Interpreting the cost-effectiveness plane: Example 1

In this example, the parameter to be analyzed in a cost-effectiveness plane is the incidence rate of the intervention group (this is one of the parameters selected as shown in Figure 49 above). The corresponding results are shown in the Figure below:

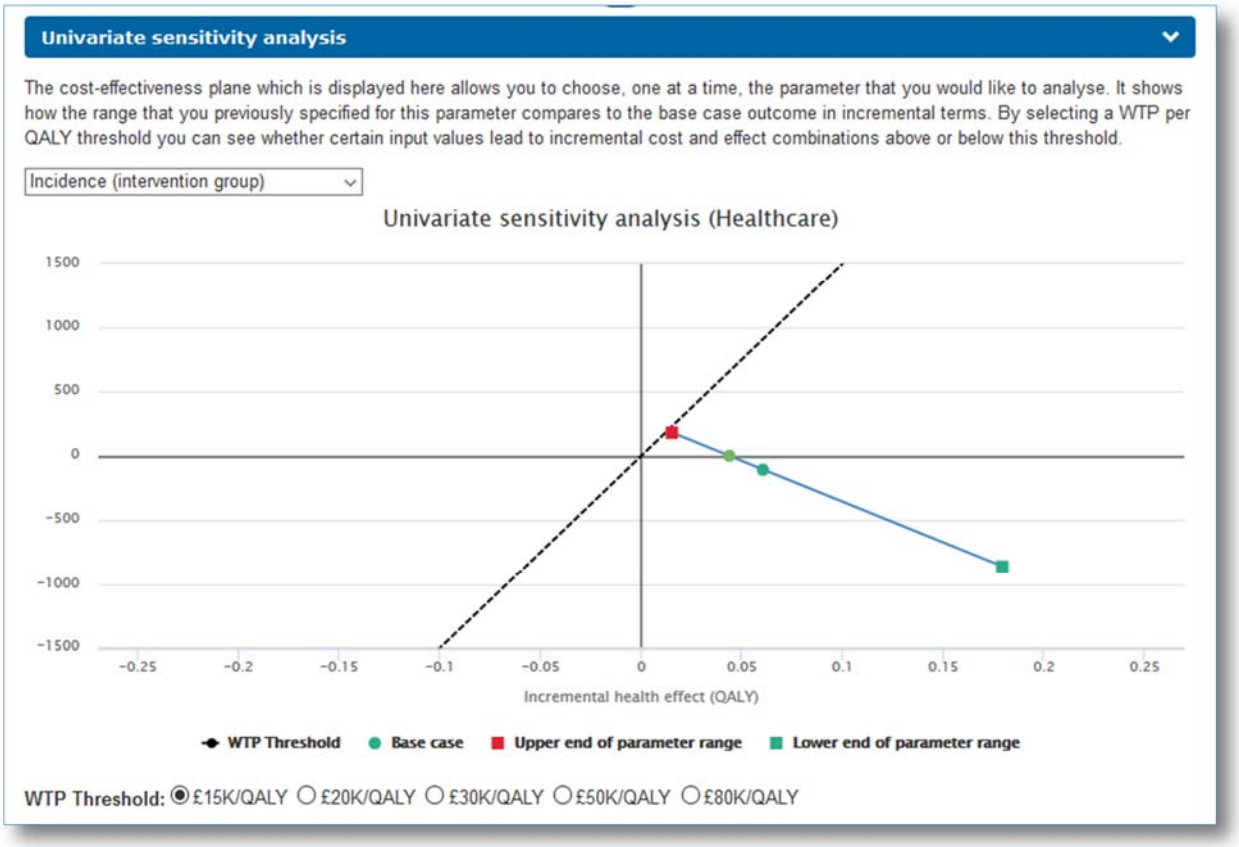


Figure 50. A sample univariate sensitivity analysis result analyzing the incidence rate parameter.

The cost-effectiveness plane shown above is similar to those found in Figure 34 and Figure 35 with additional points marking the effects of the upper and lower estimates that were input previously (Figure 49). This may allow the user to see which change in values under the incidence rates of the intervention group can change the outcome of the intervention being accepted or not.

In the Figure above, it can be seen that all values (upper estimate, base case, and lower estimate) correspond to an ICER located below the WTP threshold plot (Refer to Figure 38), which means that with an incidence rate of 30 (this is the upper estimate that was used in Figure 49), the intervention would still be considered accepted.

Another example is found below.

Interpreting the cost-effectiveness plane: Example 2

In this example, the other parameter, intervention cost per person per year, is considered. The Figure below shows the corresponding results.

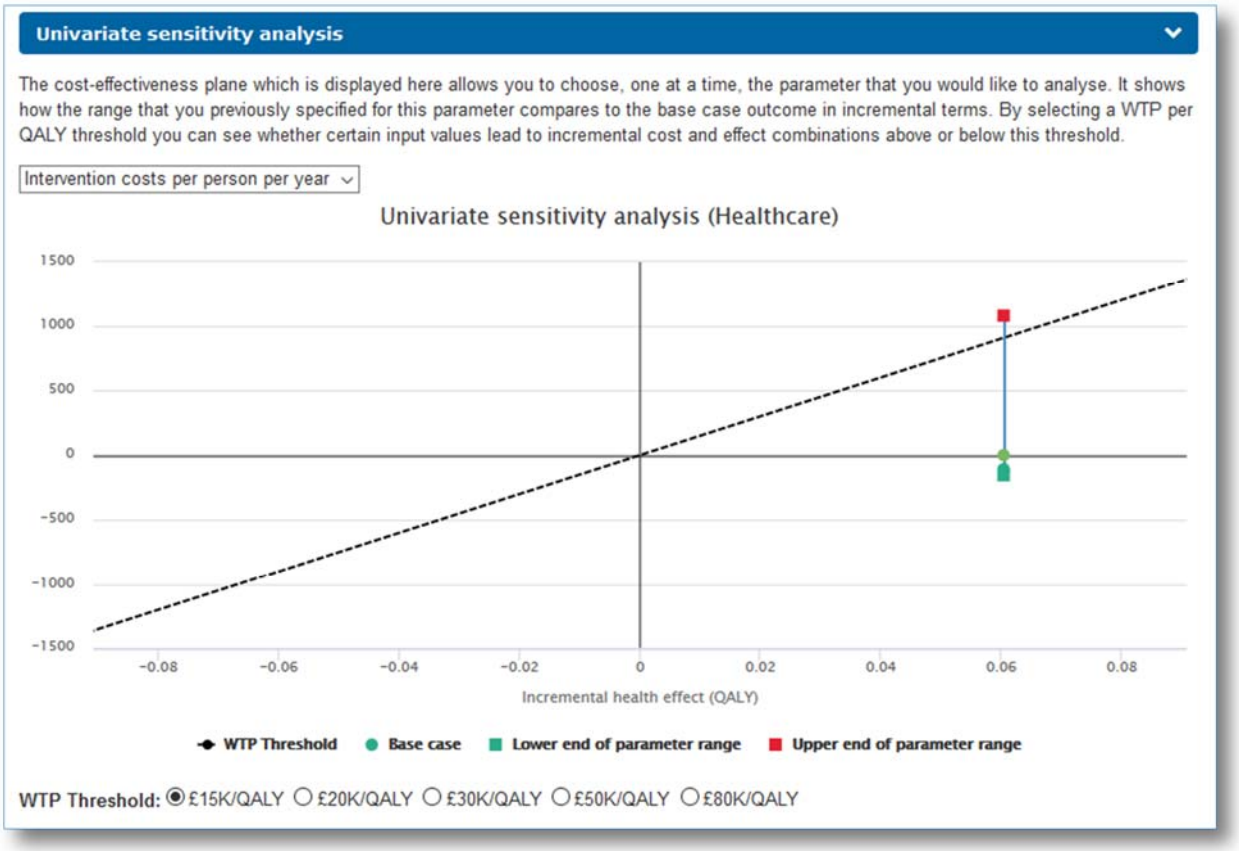


Figure 51. A sample univariate sensitivity analysis result analyzing the intervention costs per person per year parameter.

Figure 51 above shows that although the ICER corresponding to the base case and lower estimate are below the WTP threshold (green dots), the ICER corresponding to the upper estimate value is already located above the WTP threshold plot. This means that with intervention costs at 150 GBP (see Figure 49) per person per year, the intervention would still be considered better than standard care, but also more expensive (as explained in Figure 36) and the intervention (with such costs) would then not be considered accepted (Figure 38).

2.6.2 Parameter impact on incremental costs

The parameter leading to the highest change in incremental costs is displayed at the top of the diagram, followed by the parameter leading to the second highest change in incremental cost of the intervention, and so on and so forth. Ordering parameters from the one having most impact to the one with least impact on incremental costs leads to the characteristic tornado-shape of the diagram.

In this Section, the user will see a graph (called a Tornado diagram) showing the impact of each selected parameter on the incremental cost of the intervention as compared to the base case (*i.e.* the values the user input in Section 0.)

Tornado diagram

The Tornado diagram displayed here summarises the impact of a change in each parameter on incremental effects of the intervention relative to the base case.

The parameter leading to the highest change in incremental effects is displayed at the top of the diagram, followed by the parameter leading to the second highest change in incremental effects of the intervention, and so on and so forth. Ordering parameters from the one having

most impact to the one with least impact on incremental effects leads to the characteristic tornado-shape of the diagram.

The Tornado diagram plots all chosen parameters according to decreasing impact on another parameter (here: the incremental costs). This means that the parameter leading to the highest change in incremental costs of the intervention is displayed at the top of the diagram, followed by the parameter leading to the second highest change, and so on and so forth. In the example below, the parameter “Intervention costs per person per year” is that which affects the incremental costs of the intervention the most and is therefore displayed on top of the other parameter (incidence of intervention group).

Interpreting the graph

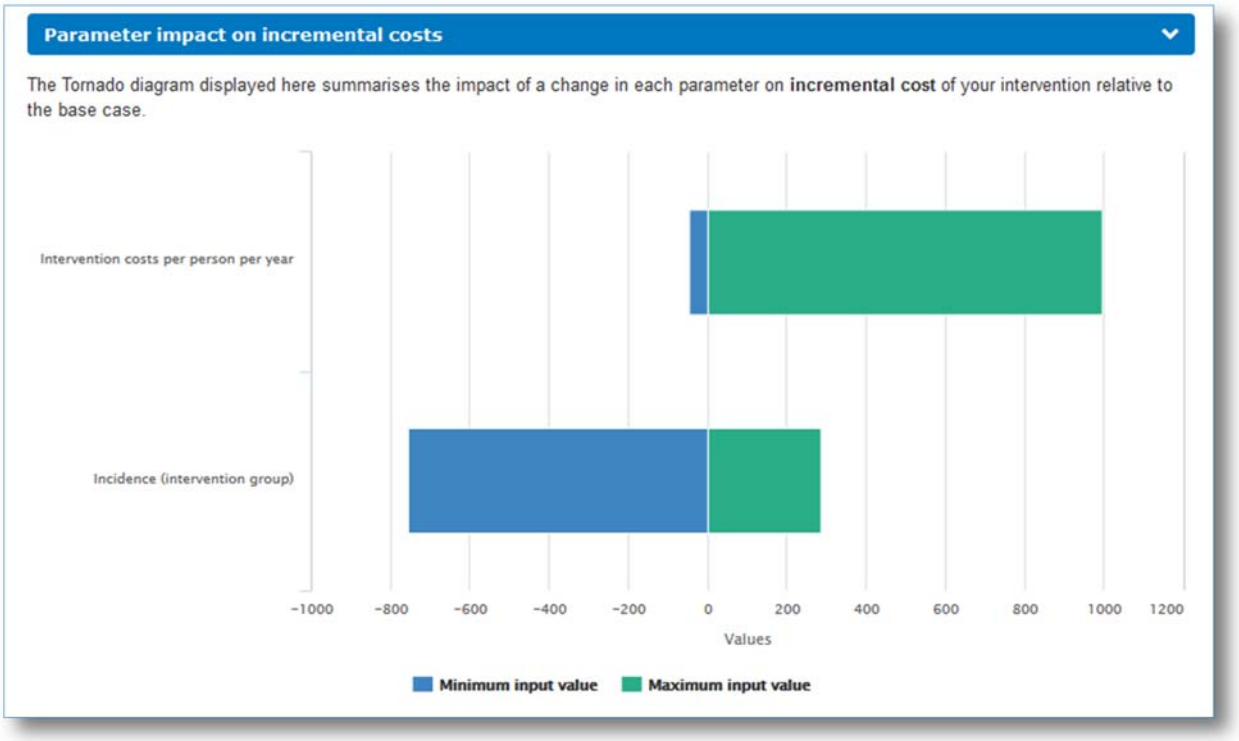


Figure 52. An example of a Tornado diagram that plots the impact of the 2 previously chosen parameters (Intervention costs per person per year, incidence of intervention group) against incremental costs of the intervention, whereas 0 is base case and the top-most parameter is that which has the greatest impact against incremental costs of the intervention.

Figure 52 shows that the intervention costs per person per year has a higher impact towards incremental costs of the intervention when compared to the incidence rate of the intervention group. The longer bar of the top most parameter (intervention costs per person per year) also indicates a greater sensitivity (impact) towards the incremental costs of the intervention.

The Figure above displays the two parameters chosen in the previous example (Figure 49). Naturally, if the user previously selected more parameters, then these would also be displayed in the Tornado diagram (as illustrated in the Figure below).

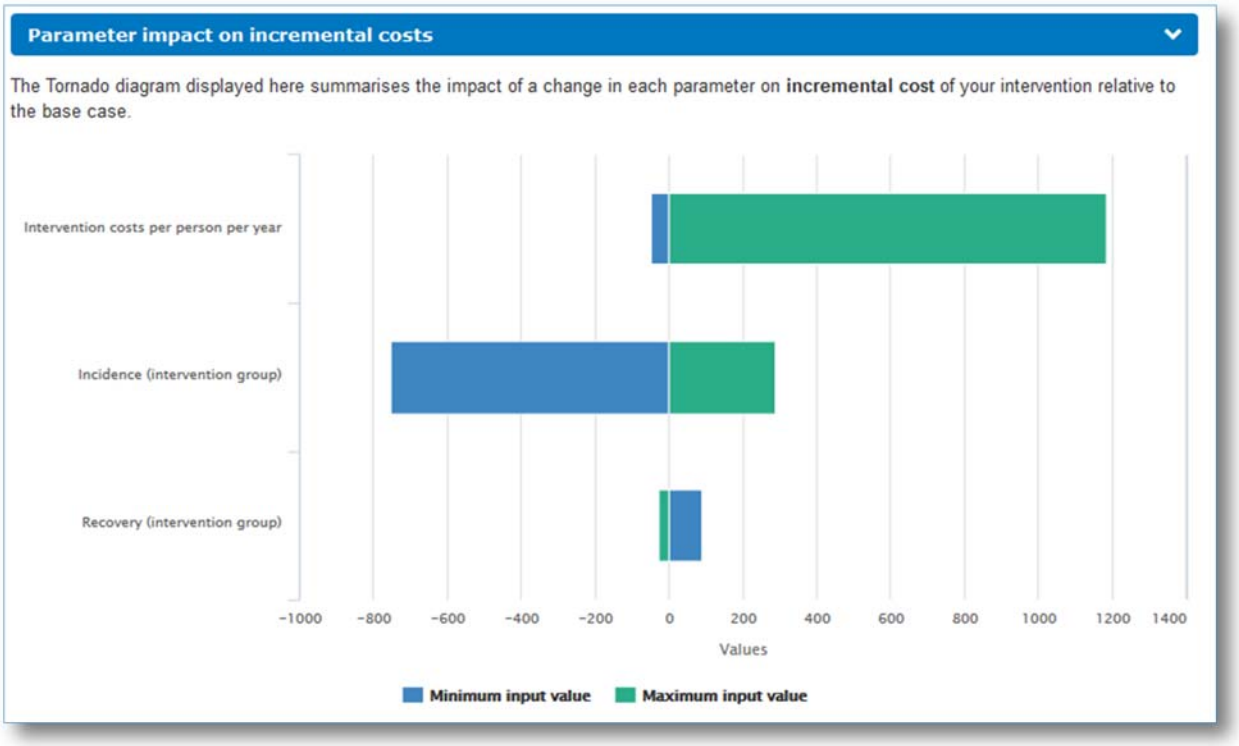


Figure 53. An example of a Tornado diagram that plots the impact of 3 parameters (Intervention costs per person per year, incidence of intervention group, and recovery of intervention group) against incremental costs of the intervention.

A view on the top most parameters as those that lead to the biggest changes in the incremental costs allows the user to re-examine those particular parameters or to realize that those parameters are important to consider regarding the incremental costs of the intervention.

2.6.3 Parameter impact on incremental effects

Similar to the previous Section, the Tornado diagram displayed in this Section shows the impact of each selected parameter on a given parameter, this time the incremental cost of the intervention as compared to the base case. Once more, the parameter that leads to the highest change in incremental costs of the intervention is displayed at the top. An example is shown in the Figure below.

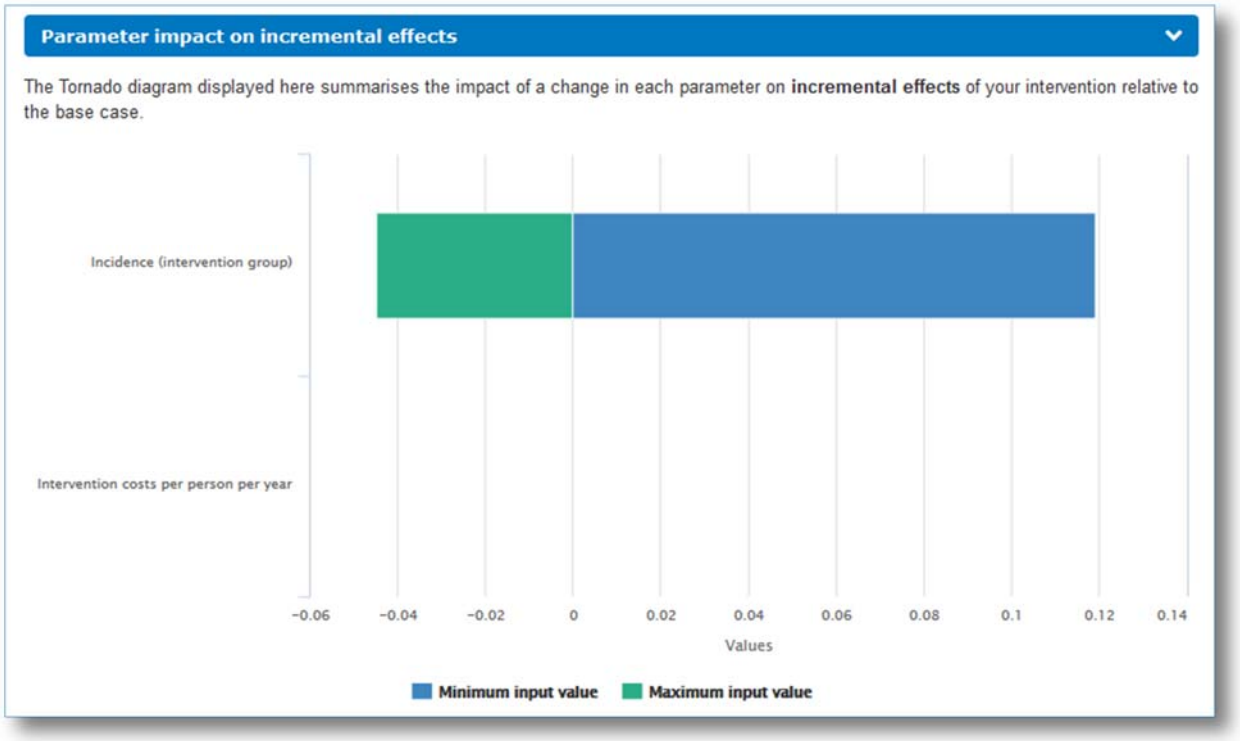


Figure 54. An example of a Tornado diagram that plots the impact of the 2 previously chosen parameters (Intervention costs per person per year, incidence of intervention group) against incremental effects of the intervention, whereas 0 is base case and the top-most parameter is that which has the greatest impact against the incremental effects of the intervention.

The Figure above shows that the incidence rate of the intervention group has a higher impact on the incremental effects of the intervention. Moreover, it can be seen that the intervention costs per person per year do not have an impact on the incremental effects at all.

3 Using the MAFEIP tool: Probabilistic Analysis

This probabilistic model enables the tool to account for the uncertainty with respect to the input model parameters and show the impact of this uncertainty on the outputs (incremental cost and Health Related Quality of Life). The uncertainty related to the input parameter values is represented by a probability distribution for each parameter. On the other hand, the uncertainty related to model outputs is calculated by running the model multiple times. Each time the probabilistic model is run (one run is called one iteration), a value is drawn from the probability distribution for each parameter. The model results are then calculated with these randomly selected values.

The Probabilistic Analysis Module of the MAFEIP tool is designed for advanced users that have already gained prior experience in this field, are familiar with this type of analysis, or have already used the MAFEIP Deterministic Analysis Module and would like an additional, more precise analysis of their innovation. In these cases, the user must request for access by contacting the team at info@mafeip.eu.

Similar to the Deterministic Analysis Module, the user is able to choose among a 3-state, 4-state or 5-state Markov model, depending on which model best represents their patient cohorts. The following sections describe the Probabilistic Analysis Module for a 3-state model.

3.1 Step 1: Probabilistic Model Input

This is the section in which the user would provide the input data required to run the probabilistic analysis of the 3-state Markov model.

The parameters are divided into four sections: (1) model analysis, (2) transition probabilities for moving between health states with and without the intervention, (3) costs associated with health states and intervention costs, and (4) utilities (also called quality of life-weights) that are associated with each health state.

For each set of parameters (transition probabilities, costs and utilities) a specific distribution is used to represent uncertainty in the parameter values. More details on each section are provided below.

3.1.1 Analysis

The parameters in this section control how the analysis is performed and how the results are presented. As there is no uncertainty involved in the values for these parameters, they are not defined as probability distributions. Rather, the values for these parameters will most likely be equal to the values used in the main analysis (deterministic model).

Model analysis

In this section, the user is requested to provide input on Iterations, Time horizon for analysis, and Discount factors.

Iterations

The number of iterations given would be the number of random draws that would be taken from the probability distribution for each parameter in the “Probabilities, Costs and Utilities” sections below.

Time horizon for analysis

The time horizon for analysis would be the time frame for the analysis of the impact of the intervention. This is specified in years. For example, the user must input “10” in the given text field if they would like to visualise the impact of the intervention within 10 years.

Discounting factor for costs and for utilities

The discount factors for costs and utilities are used to estimate outcomes while taking into account the future costs and health effects. This means adjusting for differences in the timing of costs (expenditure) compared to health benefits (outcomes). Therefore, properly applied discount factors express future costs or benefits at today's equivalent value.

Discount factor rates are usually between 3% and 5%, and are usually the same for both cost and outcomes. The default value in the tool is 3.5%, but the user may opt to change this value after consulting the website given (underlined in red, in the Figure below).

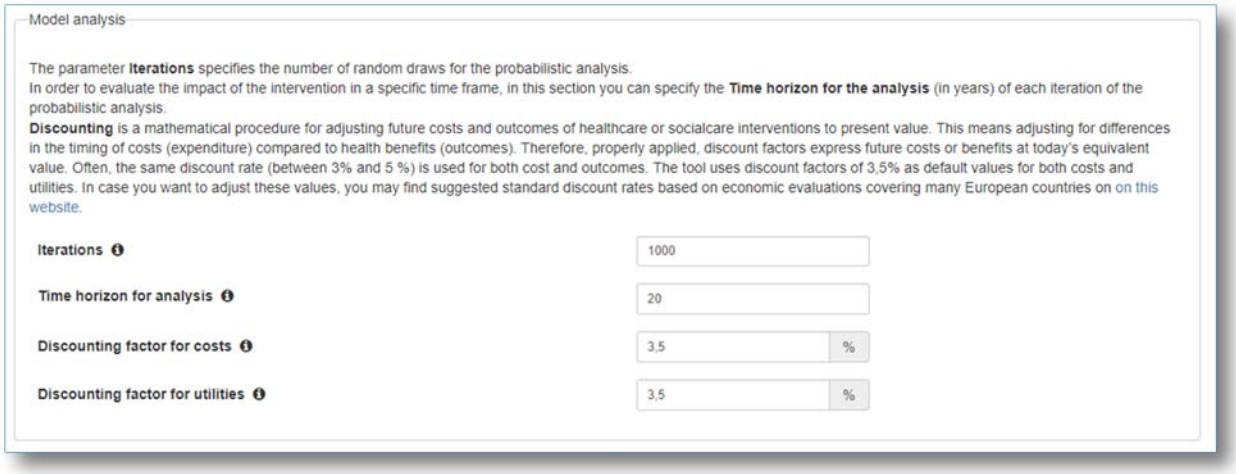


Figure 55. An example of filled-in text fields under "Analysis, Model analysis".

Target population

In this section the user would be able to indicate the minimum age, maximum age, and the country of the target population. These will be used to select the age- and sex-dependent baseline mortalities from the Human Mortality Database, as well as the distribution of age and gender in the selected country.

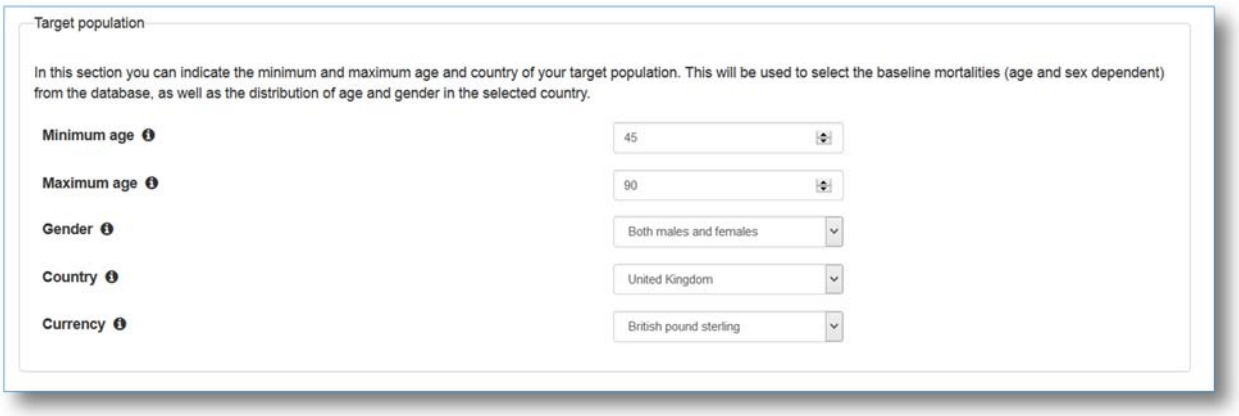


Figure 56. An example of filled-in text fields under "Analysis, Target Population".

Initial distribution among states

In this section the user is able to specify the starting distribution of patients over the alive health states (baseline and disease/impairment) in both the control and intervention group. This would allow the tool to take preventive and curative interventions into consideration.

For example, the proposed intervention would like to treat seniors from 65 to 90 who have diabetes or prevent those who are likely to have diabetes, given the scenario as follows:

In a certain healthcare centre, there were 210 patients over 65 to 90 that are considered fit for the study.

- Among the 210 patients in the study, 110 out of the 210 patients were treated with the intervention, and therefore this is the “Intervention Group”
    - Among the 110 patients in the Intervention Group, 60 of the patients have diabetes and 50 do not (but have a family history of diabetes).
    - In this case, the proportion of the patients in the baseline state (those with no diabetes) in the intervention group is 50/110 or 45.5%.
    - Meanwhile the proportion of the patients in the disease/impairment state in the intervention group is 60/110 or 54.5%

The tool parameters are then filled out with these percentages as shown in the Figure below:

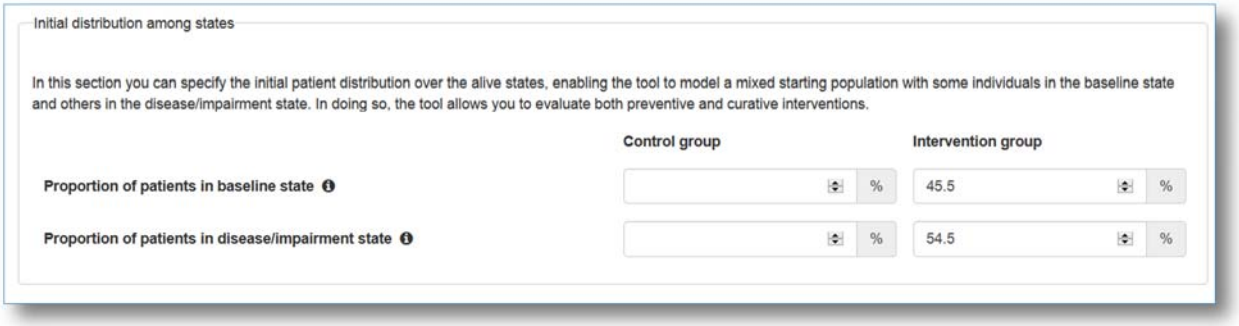


Figure 57. An example of filled-in text fields under “Analysis, Initial patient distribution”.

The values for the Control Group may be calculated in a similar manner.

3.1.2 Probabilities

Here the user is asked to provide data on the probability of an individual to move from one health state to another.

The transition probabilities are defined as follows:

(1) Incidence – the probability of an individual to move from baseline state to disease or impairment state (condition has worsened).
(2) Recovery – the probability of an individual to go back from a disease or impairment state to the baseline state (condition has improved).
(3) Mortality – the probability of an individual to go from one of the alive states (either baseline or disease/impairment) to the dead state. (input on mortality rates are done in the next Section under “Relative risks for mortality and mortality rates”).

Input on the transition probabilities depend on the corresponding Markov model chosen (3-, 4-, or 5-state).

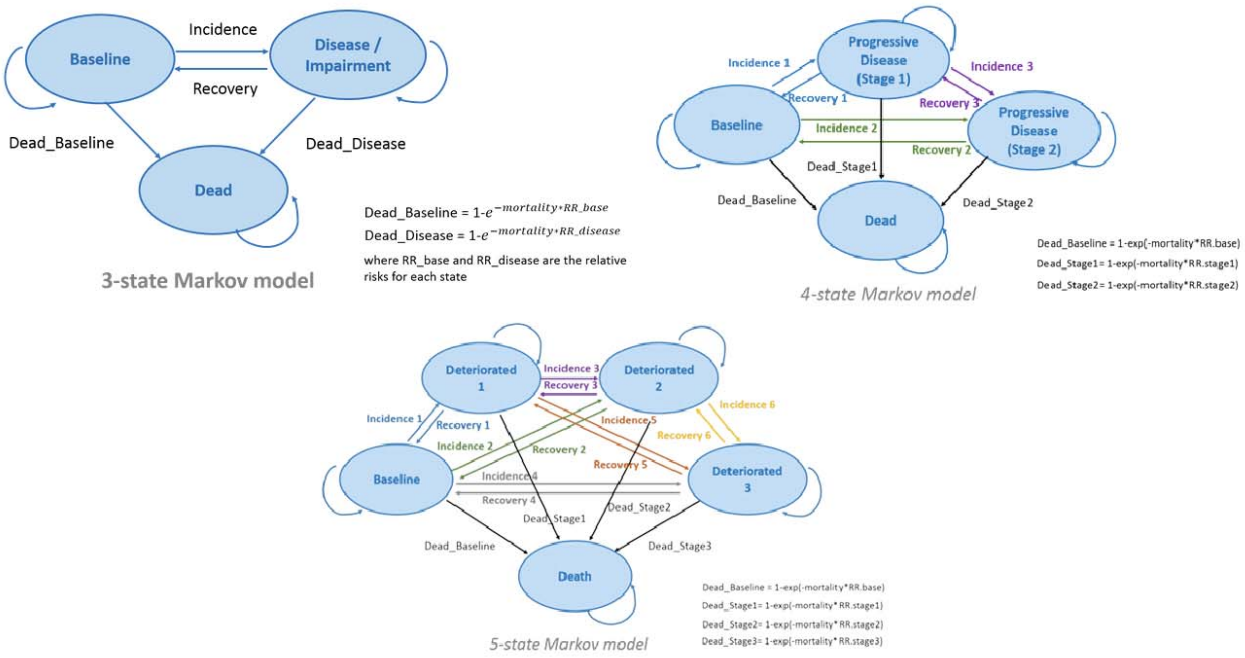


Figure 58. An overview of the different Markov models and the corresponding transition probabilities involved.

Transition Probabilities

In the probabilistic module transition probabilities are described by beta distributions, confined to the interval [0, 1]. The distribution is defined by two parameters, alpha and beta, whereby the probability density function is described in the following formula:

$$\frac{x^{\alpha-1}(1-x)^{\beta-1}}{\mathrm{B}(\alpha,\beta)}$$

The parameters alpha and beta of the beta distribution can be extracted from the mean and variance of the variable x.

Figure 59 shows the parameters to be entered to specify the transition probabilities for the 3-state Markov model.

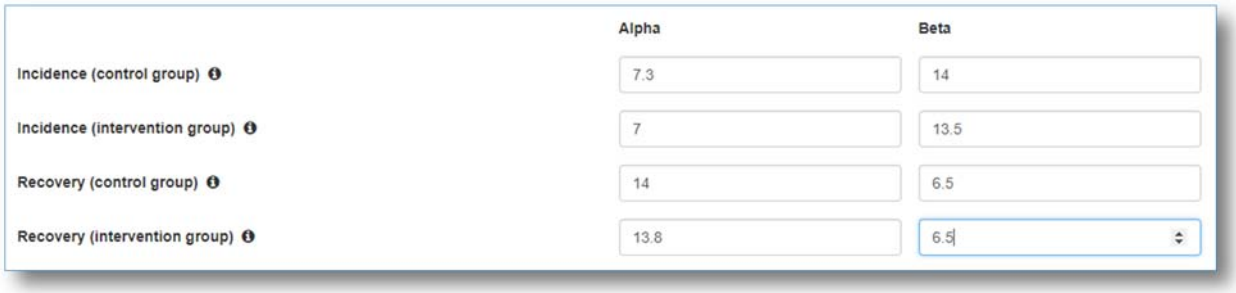


Figure 59. Transition probabilities are described by beta distributions, defined by two parameters (alpha and beta).

Relative Risks for Mortality

The relative risks for mortality show the mortality for a given condition of the target population compared to the all-cause mortality in the general population (reference condition). Relative risks for mortality are described by lognormal distributions. This distribution is characterized by a location parameter and a scale parameter that are, respectively, the mean and standard deviation of the distribution on the log scale. Its probability density function is described in the following formula:

$$\frac{1}{x\sigma\sqrt{2\pi}} e^{-\frac{(\ln x-\mu)^2}{2\sigma^2}}$$

where μ denotes the mean (location) and σ denotes the standard deviation (scale).

The parameters location and scale of the lognormal distribution can be extracted from the mean and variance of the variable x.

Figure 60 shows the parameters to be entered to specify the relative risks for mortality for the 3-state Markov model.

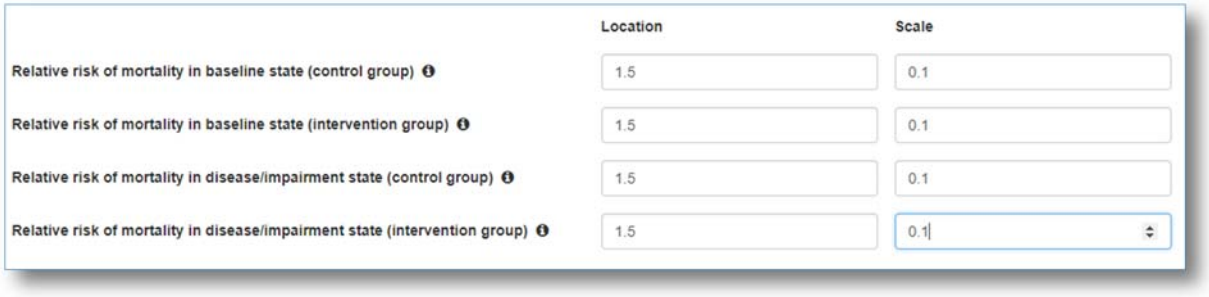


Figure 60. Relative risks are described by lognormal distributions, defined by two parameters (location and scale).

3.1.3 Costs

This section deals with the uncertainty related to the costs of the intervention and the costs under the states defined by the model (i.e., baseline and disease/impairment states). The uncertainty related to costs is represented by a gamma distribution, which allows for positively skewed distributions. The gamma distribution used in the model is defined by a shape and a scale parameter (both must be positive), whereby the probability density function is described as follows:

$$\frac{1}{\Gamma(k)\theta^k} x^{k-1} e^{-\frac{x}{\theta}}$$

where ϰ denotes the shape and θ denotes the scale parameter.

The parameters shape and scale of the gamma distribution can be extracted from the mean and variance of the variable x, as can be derived from here.

Intervention Costs

Cost items to be considered for the intervention include a) one-off intervention cost and b) total intervention cost per person per year.

One-off intervention costs represent the total cost per patient incurred only at the implementation point, thus, total cost incurred only once (e.g. the cost of a surgical procedure that happens only once for each patient in the intervention cohort or the cost of a telemonitoring device).

The total **intervention cost per person per year** represents the annual recurrent cost incurred for delivering the intervention and consists of two components: First, variable costs of the intervention that are incurred for each individual and each year (e.g., software license of the programme used, maintenance of the service, etc.). Second, the share of annual fixed costs per patient currently treated or targeted by the intervention represents, for instance, the annual cost of the infrastructure used for all patients in the target group divided by the number of patients currently treated or targeted by the intervention.

Figure 61 shows the parameters to be entered to specify the intervention costs.

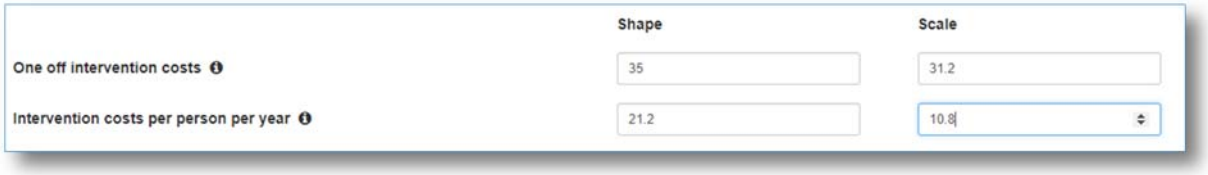


Figure 61. Intervention costs are described by gamma distributions, defined by two parameters (shape and scale).

Health state costs

The health state costs represent the costs for both the intervention and standard care (control group) in baseline and disease/impairment states. These costs are defined per person. Healthcare costs refer to resource use within the healthcare system, excluding the cost for the intervention itself (which should have been indicated under the section on intervention costs above).

Societal costs represent a wider resource use perspective which includes healthcare costs, but also other costs outside the healthcare sector (e.g. out-of-pocket payments and travel costs for patients, productivity losses).

Figure 62 shows the parameters to be entered to specify the health state costs for the 3-state Markov model.

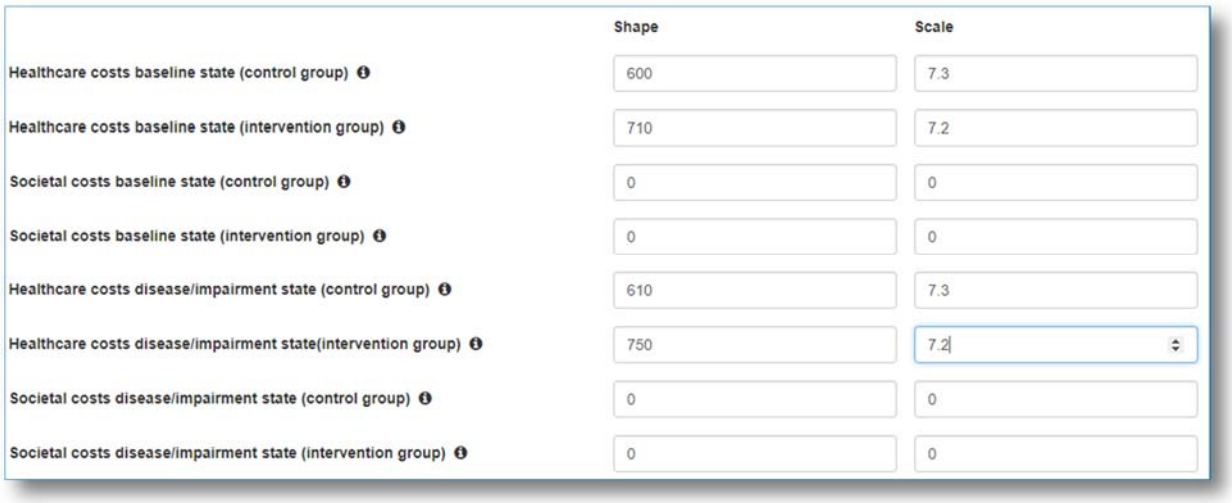


Figure 62. Health state costs are described by gamma distributions, defined by two parameters (shape and scale).

3.1.4 Utilities

To estimate the impact of the intervention in terms of health outcomes, utility weights associated with the states of the models should be provided. In this section the user may further define the uncertainty relating to the health-related quality of life associated with the baseline and disease/impairment states.

Parameters in this section are again described by beta distributions, confined to the interval [0, 1]. The distribution is defined by two parameters, alpha and beta, whereby the probability density function is described as follows:

$$\frac{x^{\alpha-1}(1-x)^{\beta-1}}{\mathrm{B}(\alpha,\beta)}$$

The parameters alpha and beta of the beta distribution can be extracted from the mean and variance of the variable x.

Health-related Quality of Life

The HRQoL as expressed through a quality-of-life weight (utility) represents a particular health outcome. The utility measures summarize both positive and negative effects of an intervention into one value between 0 (indicating death) and 1 (which is equal to a perfect health condition) so that the higher the value, the higher the quality-of-life associated with that health outcome.

If utility measures have not been used in the user's study, other variables may be used as a proxy for quality of life. Such scores should be mapped into a 0-1 range.

Figure 63 shows the parameters to be entered to specify the utilities for the 3-state Markov model.

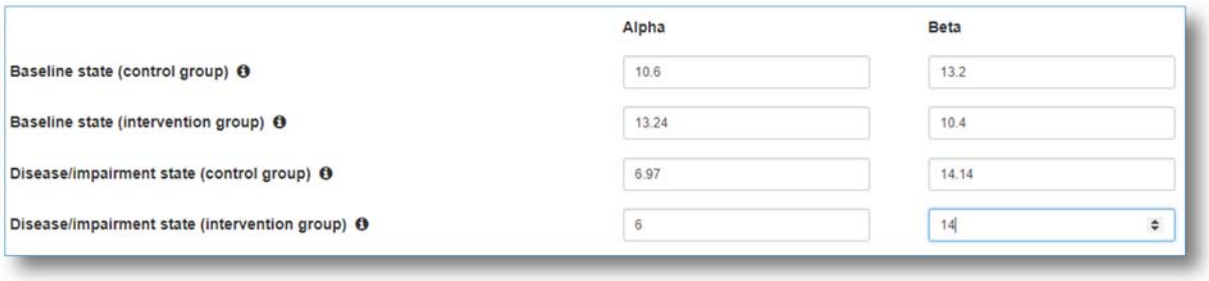


Figure 63. Utilities are described by beta distributions, defined by two parameters (alpha and beta).

3.2 Step 2: Probabilistic Model Output

The results of the probabilistic analysis are presented in this section, based on the uncertainty of input parameters that was defined in the probabilistic model input environment. Two types of output are presented: 1) cost-effectiveness, incremental cost and health-related quality of life, and 2) a cost-effectiveness acceptability curve. Each section provides additional information on the output presented.

The resource use perspective (health care or societal) can be selected below. This will instantly change the presentation of the resource use outcomes for the selected perspective (provided that you have given data for both perspectives in the input section).

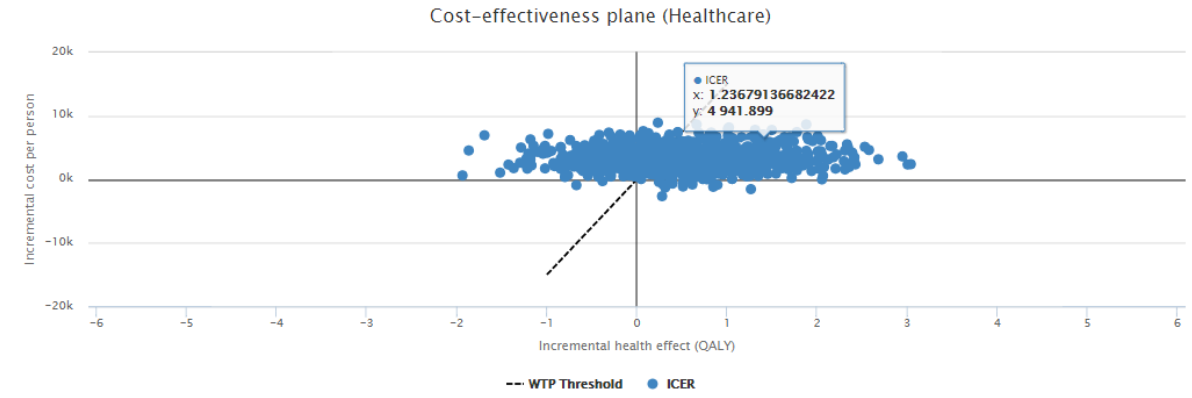
3.2.1 Cost-effectiveness and population impact on resource use and HRQoL effects

These outcomes show the total impact of the intervention on healthcare costs and health-related Quality of Life for the total target population. The outcomes represent the weighted average of the outcomes for each age-gender combination, weighted by the distribution of age-gender in the specified target country and age range.

In this section a cost-effectiveness plane is shown. The y-axis represents the incremental cost per person while the x-axis shows the incremental health effects (QALY). The diagonal line in this graph reflects the willingness-to-pay (WTP) per additional QALY gained, which is the maximum amount that a patient is willing to give in exchange for a better quality of life. Each blue dot represents the model output for one iteration (i.e. one set of input parameters drawn from the probability distributions specified in the previous step).

In addition, the table shows the expected population-level impact on incremental cost and health-related Quality of Life, as well as the incremental cost-effectiveness ratio (ICER). The expected impact on cost and health-related Quality of Life is the average of all iterations. When an intervention is dominant (both more effective and less costly) or dominated (less effective and more costly) in all iterations, this outcome is shown instead of the ICER.

Figure 64 shows an example of the results provided by the tool.



WTP Threshold: €15K/QALY €20K/QALY €30K/QALY €50K/QALY €80K/QALY

Incremental cost and HRQoL effects	
Incremental cost (Healthcare)	3405.91
Incremental HRQoL	0.524
Incremental cost-effectiveness ratio (Healthcare)	6505.85

Figure 64. Cost-effective plane, where each blue dot represents the model output for one iteration.

3.2.2 Cost-effectiveness acceptability curve

The figure below depicts a cost-effectiveness acceptability curve (CEAC). This figure shows the probability of the intervention being cost-effective at a range of WTP levels. This probability at a certain WTP level is the percentage of iterations for which the ICER of the intervention is below that WTP value. As the willingness-to-pay increases, the proportion of iterations falling below this threshold, and thus the probability of the intervention being cost-effective will increase. The probability at WTP = 0 denotes the probability that the intervention is dominant.

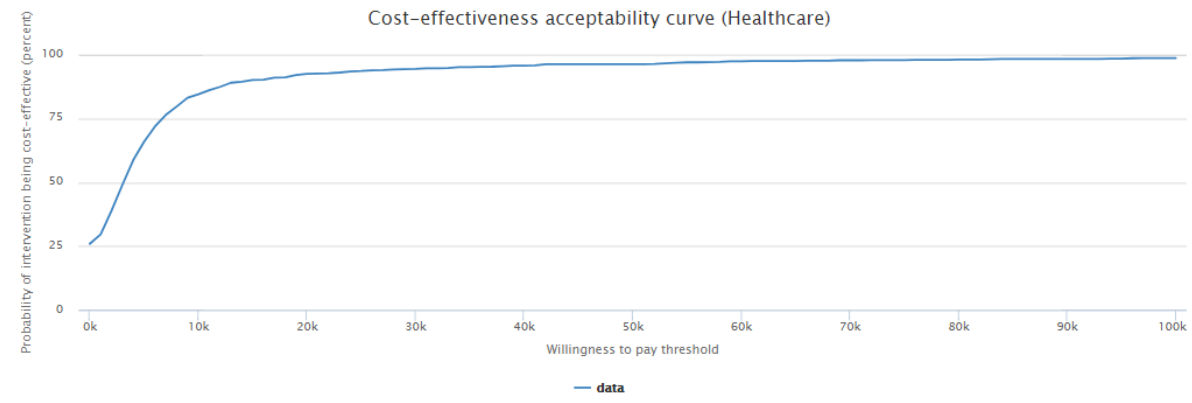


Figure 65. Cost-effectiveness acceptability curve.

4 Strategies for collecting relevant data to feed into MAFEIP (under development)

This section elaborates strategies for collecting relevant data that is needed to perform a meaningful assessment. The strategies are based on existing case studies and documented approaches available in the literature.

Study methods /evidences (Section 2.2.4)

Section 2.1.4 enumerates different study methods that may have been performed by the user in order to acquire data about the intervention and the target group involved. The Glossary also defines the differences among these study methods.

Other methods of acquiring evidences are database or literature searches and analyses (*e.g.* seeing if there are any publications related to studies done with a similar target group as the user's) expert opinions, and

Discount factor values

For the discount factor values, it is recommended to use the website link given in the MAFEIP tool.[16] Upon clicking on this link, a table with a list of countries is shown. Clicking on the particular country would lead to another table, in which the discount factor values are listed (under "discounting costs" and "discounting outcomes").

Incidence rates

The incidence rates may be calculated in the following manners:

(1) By following the calculation given by the running example case study in this paper whereas the only needed information are:
   a. The size of the target group,
   b. The number of observed events (e.g. the number of times a patient experienced a fall / acquired a certain disease), and
   c. The time frame during which these observed events occurred

(2) By checking incidence rates found in databases such as the UK Department of Health, the National Health Service health database, and

(3) By checking other forms of literature data such as

(4) By collecting and analyzing expert opinions using surveys or questionnaires

Recovery rates

The recovery rates may be calculated in the following manners:

(1) By subtracting the incidence rate from 1

(2) By following the running example case study in this paper

(3) By checking databases as listed above and searching for literature related to the proposed intervention or target group

(4) By collecting and analyzing expert opinions using surveys or questionnaires

Relative risks of mortality

- There is a similar explanation found in this website: http://health.mo.gov/training/epi/RelativeRisk-b.html
- Expert opinion / experience
- Using databases

[16] https://www.ispor.org/peguidelines/index.asp

Health-Related Quality of Life (HrQoL) values

- The HrQoL may be calculated using tools readily available online such as those mentioned in Section 2.3.4 (Utilities), namely:
    - EQ-5D[17]
    - the Short Form (36) Health Survey (SF-36) or RAND-36[18] and
    - the World Health Organization Quality of Life (WHOQoL)[19]

Under the context of MAFEIP and in order to maintain uniformity, the EQ-5D tool is recommended.

The EQ-5D is a 2-page questionnaire that would ask the respondent to indicate their health state and to answer questions related to mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The respondents answer by ticking the box against the most appropriate statement among the choices given.[20] More information on the EQ-5D may be found on the website: http://www.euroqol.org/about-eq-5d/how-to-use-eq-5d.html

If the user has already used a different method of obtaining HrQoL, there are also ways in which these values may be "mapped" or "converted" into EQ-5D values. Mapping can rely on expert opinion (subjective mapping), on published aggregate health states data (empirical aggregate mapping), or on published regression models or algorithms (empirical individual level mapping).[21]

- HrQoL values may also be obtained by using patient satisfaction questionnaires developed by the user as proxies (*i.e.* instead of using ready online tools). For an example on how this is done (including how to map answers from the patient satisfaction questionnaire to QoL value) please consult the Socio-economic Impact Assessment Deliverable (D5.4) of the INCA project[22] found on the following website: http://www.in3ca.eu/?wpfb_dl=196&lang=en

Willingness to Pay (WTP) threshold

Willingness to Pay data may be obtained either directly (*e.g.* by asking patients to directly state how much they are willing to pay) or indirectly (*e.g.* by asking patients to select a specific value from an already-given set of WTP values via methods like "multiple choice") through surveys or questionnaires.

A questionnaire with a WTP module has also been developed by empirica under the PEARL project. Users are asked around 6 questions such as "*Was the intervention worth it or not*" or "*Would you pay x, y or z EUR per month to use the intervention?*" The WTP module can be used in two manners: *via* self-completion or interview, and guidelines for each are provided. For more information on this WTP module, please contact empirica at: info@empirica.com.

[17] http://www.euroqol.org/about-eq-5d.html

[18] http://www.rand.org/health/surveys_tools/mos/36-item-short-form.html

[19] http://depts.washington.edu/seaqol/WHOQOL-BREF

[20] http://www.euroqol.org/about-eq-5d/how-to-use-eq-5d.html

[21] http://is.jrc.ec.europa.eu/pages/TFS/documents/02COP_2014_dataworkshop_001.pdf

[22] INCA = Inclusive Introduction of Integrated Care. http://www.in3ca.eu/?lang=en

5 References

Key documents on MAFEIP are listed below:

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http://publications.jrc.ec.europa.eu/repository/bitstream/JRC91162/jrc91162.pdf

Abadie, Fabienne, Christian Boehler, Maria Lluch, Ramon Sabes Figuera, and Maria Bernarda Zamora Talaya. *Monitoring and Assessment Framework for the European Innovation Partnership on Active and Healthy Ageing (MAFEIP). Second update of the process indicators*. 2014.
http://publications.jrc.ec.europa.eu/repository/bitstream/JRC91174/jrc91174.pdf

Abadie, Fabienne, Maria Lluch, Ramon Sabes Figuera, and Maria Bernarda Zamora Talaya. Monitoring and Assessment Framework for the European Innovation Partnership on Active and Healthy Ageing (MAFEIP). Interim report on the defined process indicators. 2013.
http://ftp.jrc.es/EURdoc/JRC85880.pdf

Abadie, Fabienne, Maria Lluch, Ramon Sabes Figuera, and Maria Bernarda Zamora Talaya. *Monitoring and Assessment Framework for the European Innovation Partnership on Active and Healthy Ageing (MAFEIP). First update of the process indicators*. 2014.
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Boehler, Christian and Fabienne Abadie. *Monitoring and Assessment Framework for the European Innovation Partnership on Active and Healthy Ageing (MAFEIP). Conceptual description of the Monitoring and Assessment Framework for the EIP on AHA*. 2015.
http://publications.jrc.ec.europa.eu/repository/bitstream/JRC96205/jrc96205.pdf

Boehler, Christian, Fabienne Abadie, and Wilco Graafmans. Presentation on *MAFEIP data-workshop.* Conference of Partners, December 2014, Brussels.
http://is.jrc.ec.europa.eu/pages/TFS/documents/02COP_2014_dataworkshop_001.pdf

Boehler, Christian, Gimon De Graaf, Lotte Steuten, Fabienne Abadie, and Leandro Pecchia. Presentation on *Using the EIP on AHA monitoring tool for the early technology assessment of a planned device to predict falls in the elderly.* MAFEIP tool workshop, September 2015, Brussels.
http://is.jrc.ec.europa.eu/pages/TFS/documents/04Falls_case_study.pdf

Boehler, Christian, Gimon De Graaf, Lotte Steuten, Yaling Yang, and Fabienne Abadie. Development of a Web-based Tool for the Assessment of Health and Economic Outcomes of the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA). BMC MEDICAL INFORMATICS AND DECISION MAKING p. S4 no. Suppl 3 vol. 15. 2015.
http://www.biomedcentral.com/1472-6947/15/S3/S4

Boehler, Christian, Gimon De Graaf, Lotte Steuten, Yaling Yang, and Fabienne Abadie. Development of a Web-based Tool for the Assessment of Health and Economic Outcomes of the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA). BMC MEDICAL INFORMATICS AND DECISION MAKING p. S4 no. Suppl 3 vol. 15. 2015.
http://www.biomedcentral.com/1472-6947/15/S3/S4

Boehler, Christian. Presentation on *Conceptual framework, analytic approach and implementation of the MAFEIP-tool.* MAFEIP Tool Workshop, September 2015, Brussels.
http://is.jrc.ec.europa.eu/pages/TFS/documents/03MAFEIP_WS_conceptualframework_001.pdf

Boehler, Christian. Presentation on *Results for process indicators, identification of outcome indicators & building a tool to link outcomes to the EIP on AHA objectives.* Conference of Partners, December 2014, Brussels.
http://is.jrc.ec.europa.eu/pages/TFS/documents/01COP_2014_morning_plenary_001.pdf

Boehler, Christian. Presentation on *The MAFEIP Tool.* EU Summit, December 2016.

Boehler, Christian. Presentation on *Wrap-up of the MAFEIP Tool Workshop.* MAFEIP Tool Workshop, September 2015, Brussels.
http://is.jrc.ec.europa.eu/pages/TFS/documents/05MAFEIP_WS_wrap_up_001.pdf

Castaldo, Rossana, Melillo, Paolo, Izzo, Raffaele, De Luca, Nicola and Pecchia, Leandro. (2016) *Fall prediction in hypertensive patients via short-term HRV analysis. IEEE Journal of Biomedical and Health Informatics*. doi:10.1109/JBHI.2016.2543960. http://wrap.warwick.ac.uk/78146/1/WRAP_1273390-es-190316-fall_prediction_castaldo_et_all_final.pdf

Maghiros, Ioannis, Fabienne Abadie, Maria Lluch, Ramon Sabes Figuera, Elena Villalba, and Maria Bernarda Zamora Talaya. *Monitoring and Assessment Framework for the European Innovation Partnership on Active and Healthy Ageing (MAFEIP). Work Package 1, Deliverable 1.1 Inception Report.* 2013. http://publications.jrc.ec.europa.eu/repository/bitstream/JRC85879/jrc85879.pdf

6 Glossary

Case Control Study (also known as retrospective study or case-referent study)[23]

A study that compares attributes of patients who have a particular disease with patients who do not have that disease. The researchers would then looks back retrospectively to compare how frequently each group has been exposed to a risk factor in order to determine the relationship between the risk factor and the disease.

Cross-sectional (Observational) Study[24]

An observational study is one in which the researchers record data about the patients without interfering with or changing the study environment.

A cross-sectional study is an observational study that was conducted only at one specific time point (as opposed to over many years). Any past and future data recorded would not be compared against one another.

Discount Factor

In simple terms, the discount factor (in this paper, also termed discount rate in economics) is an interest rate that takes into account future events (*e.g.* change in monetary value) in a multi-period model.

Health-Related Quality of Life and Well-Being[25]

The HRQoL as expressed through a quality-of-life weight (utility) represents a particular health outcome. It goes beyond direct measures of population health, life expectancy, and causes of death, and focuses on the impact health status has on quality of life. A utility of 0 indicates no quality of life or dead, whereas a utility of 1 indicates quality-of-life in perfect health.

Incidence rate

Incidence represents the rate of new occurrences of moving from the healthy state to the deteriorated health state. It is the probability for an individual of moving from “healthy” to “unhealthy” at a given time point (*e.g.* in 1 year).

Longitudinal (Observational) Study[26]

An observational study is one in which the researchers record data about the patients without interfering with or changing the study environment.

A longitudinal study is an observational study that is conducted over a period of time. This would enable a detection of the changes or developments in the observed patient characteristics.

Recovery rate

The recovery rate, contrary to the incidence rate, represents the number of occurrences that patients from the target group moved from the deteriorated health state to the baseline health state given a certain time point.

[23] https://himmelfarb.gwu.edu/tutorials/studydesign101/casecontrols.html

[24] http://researchguides.ebling.library.wisc.edu/c.php?g=293229&p=1953448

[25] https://www.healthypeople.gov/2020/about/foundation-health-measures/Health-Related-Quality-of-Life-and-Well-Being

[26] http://researchguides.ebling.library.wisc.edu/c.php?g=293229&p=1953448

Relative Risk for Mortality

The relative risk of mortality is a quantitative measurement that allows the comparison of the risks of death between two groups (*e.g.* between patients that use the intervention and those that stay with the standard care).

Randomized Control Trial

A method of study that determines "whether a cause-effect relation exists between treatment and outcome and for assessing the cost effectiveness of a treatment"[27], with its main feature being that patients are randomly allocated into the control or intervention group. All patient groups are also treated identically except for the given proposed intervention.

WTP Threshold (for a QALY)

WTP stands for Willingness to pay and is the maximum amount a patient is willing to pay to have an increase in QALY.

[27] http://www.bmj.com/content/316/7126/201