Advanced Simulation for Health Economic Analysis

The assignment will provide you with hands-on experience in developing and analyzing health economic simulation models and using these models for the optimization of clinical guidelines. More specifically, the assignment exists of the following two parts:

Part 1:	Health Economic Modeling (Control Strategy)
Part 2:	Health Economic Modeling (Experimental Strategy and Analysis)

Both parts of this assignment are based on a single case study and will be performed in R Statistical Software. You will be provided with an initial set of documents (e.g. data, results, etc.) at the beginning of Part 1. Depending on the total number of students, you should work in groups of two or three.

This document starts with a general introduction to the case study. Next, the required R packages and provided files, such as a dataset and starting templates for the code, are discussed. Carefully read the introduction and descriptions of the different parts in this assignment, as they all contain information that is essential for successfully completing the assignment.

Good luck!

Introduction: Description of the clinical case study

For this assignment, we consider the case of a metastatic cancer disease, such as metastatic colorectal cancer, which is typically characterized by a short expected survival of the patients suffering from the disease. There are two types of chemotherapy available for treatment, i.e. Tx1 and Tx2. Treatment with each of these chemotherapies consists of maximum 5 cycles. This means that, for example, treatment with Tx1 is started by providing the first treatment cycle. After a certain period, the second cycle of Tx1 can be provided, and so on. After stopping treatment with Tx1, because the maximum number of five treatment cycles have been provided or because of a different reason, treatment with Tx2 can be started.

A clinical study was performed to assess the health and economic impact of first treating patients with Tx1 and subsequently with Tx2. For each patient in the study, the treatments were provided until the maximum amount of treatment cycles was received by that specific patient, or the patient needed to stop treatment due to another reason. The trial showed that both treatments are costly and are burdensome to the patients. More specifically, the treatments are associated with a substantial risk of treatment-related complications, which can be either minor or major complications. Minor complications did not inhibit treatment continuation, nor did it affect the number of treatment cycles received. However, minor complications did cause health and economic burden in terms of disutility (reduction in quality of life) for the patients and additional costs to the healthcare system. Major complications are also associated with health and economic burden, having a more significant impact compared to those of the minor complications, but also force a patient to stop the current treatment (either Tx1 or Tx2). Fortunately, patients in whom Tx1 was stopped due to major complications could still start treatment with Tx2.

Besides being treated, patients could also remain in a so-called follow-up state. All patients that were still alive after treatment with Tx1 spent some time in the first follow up before second-line treatment with Tx2 was started. Unfortunately, some patients died during this follow-up period. After stopping treatment with Tx2, due to any reason, patients end up in another follow-up process, i.e. the second follow up, until death. This second follow-up phase is called palliative care. A graphical representation of the clinical pathway, as investigated by the trial and as described above, is provided in Figure 1.

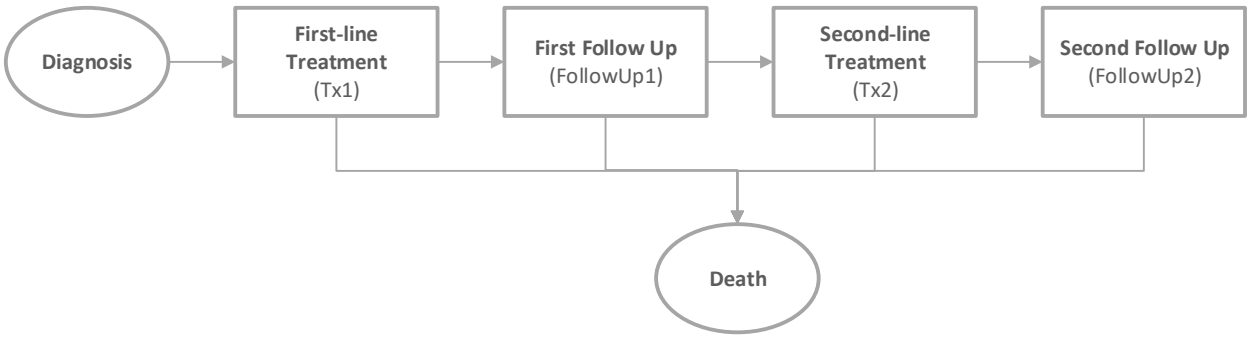

Figure 1. Graphical representation of the clinical pathway

The high health and economic burden of treatments Tx1 and Tx2 induce that avoiding overtreatment is very important for the sake of the patients and the affordability of the healthcare system. Therefore, it is of great interest to investigate whether tests can be used to assess patients' response to treatment before the maximum amount of treatment is provided or complications occur, which is what this assignment is about. Besides the occurrence of events, e.g., complications and death, and health economic outcomes, the trial also captured test results of four tests, i.e., the PET-CT and novel diagnostics Dx1, Dx2, and Dx3. The PET-CT is assumed to perfectly indicate whether a patient is responding to current treatment or not. However, this test is too expensive to use for treatment switching in clinical practice.

The scientific community wants to investigate whether it is possible to use the combined test results of Dx1, Dx2, and Dx3 to detect patients' treatment response, rather than using the PET-CT, as these tests are less expensive. Therefore, the use of these tests to guide early treatment discontinuation (switching from Tx1 to Tx2) may be worthwhile and may decrease the health and economic burden associated with overtreatment. Whereas the PET-CT gives a binary outcome (1=positive/response, 0=negative/no response), Dx1, Dx2, and Dx3 all have continuous outcomes, though on different scales. These continuous test outcomes relate to a probability that the patient is responding (or not responding) to current treatment. The objective of this assignment is to investigate whether the combined results of these three novel tests, i.e. Dx1, Dx2, and Dx3, can be used as a decision tool so that clinicians can validly and safely decide to stop current treatment in patients with all three test results above a test-specific threshold (so there are three thresholds).

Part 1: Health Economic Modeling (Control Strategy)

The first part of the assignment is about modeling the current treatment strategy in a health economic model. This model will be implemented as a discrete event simulation model using the *simmer* package in R Statistical Software. First, the model will be structured and populated using assumed parameter values. Next, the individual patient data gathered by the clinical trial, as described in the introduction, will be analyzed to define more accurate parameter values. After completing Part 1, the experimental treatment strategy, including the test results, will be modeled, and probabilistic sensitivity analysis (PSA) will be performed to reflect the uncertainty in the accumulated evidence used for the analysis.

For Part 1 of the assignment, four files are provided:

1) bca_startcode.R — *R code that serves as a starting point the base-case analysis*
2) trial_dataset.RData — *R data object containing the trial data*
3) getSingleAttribute.R — *R code defining a function that will be used*
4) getMultipleAttributes.R — *R code defining a function that will be used*

While developing the model and analyzing the data, some R packages will be used. Make sure these packages, including their dependencies, are successfully installed before you start working on the assignment. The required packages are:

1) simmer — *define and run discrete event simulation models*
2) simmer.plot — *plot simmer models and results*
3) fitdistrplus — *fit parametric distributions to data*

Before rushing into Part 1 of the assignment, it is important to have a careful look at the code in the "bca_startcode.R" file and the structure of the trial data in the "trial_dataset.RData" file.

R script: *bca_startcode.R*

This file contains code that will serve as a starting point for Part 1 of the assignment. Different sections are defined in the code, which will now be briefly discussed.

Section 1: Initialization

Here the workspace is cleared, i.e., all defined variables, functions, etc. are removed, so there is a "blank sheet" to start with. Next, the working directory is set, the required packages are loaded, and functions (i.e. "getSingleAttribute" and "getMultipleAttributes") are loaded that can be used to extract monitored patient attributes from *simmer* simulations.

Section 2: Data analysis

The trial data is loaded in this section. Later on in the assignment, parameters will be defined, and the available dataset will be analyzed in this section.

Section 3: Supportive functions

Supportive functions are functions that, for example, can be called from the simulation model. Some functions are already defined to get you started more easily. Function "Tx1.time" can be used to determine a (random) time for the duration of a treatment cycle of Tx1, which is fixed at 30 days for now. Function "Tx1.event" can be used to determine the event to occur during the cycle, which is now a random selection between the events of completing a cycle and death.

Section 4: Discrete event simulation model

In this section, the actual model structures will be defined. The first part of the model for the current practice, i.e., best standard care, is already defined. It provides each simulated patient with an attribute "alive" and simulates cycles of Tx1 until the patient dies (using the supportive functions defined earlier). This defined trajectory can be visualized using the *plot()* command for validation purposes, as is done after defining the trajectory in the code.

Section 5: Simulation

In this section, the simulation is performed based on the model defined in Section 4. Notice that the required resources are defined, and the hypothetical patients are generated before running the model. This section needs to be run every time a simulation is to be performed.

Trial data: *trial_dataset.RData*

The trial data are already transformed into an R Data object, which can be loaded directly in the R Workspace and used for analysis (Section 2). After loading the trial data, you will see the object "data" in the workspace. A description of the evidence that is provided in the trial data is presented below (an "i" refers to different cycle numbers):

Column name	Data type	Information
ID	Integer number	Patient's unique identifier
Male	Binary (1=male, 0=female)	Patient's sex
Poor	Binary (1=poor, 0=good)	Patient's clinical condition
Age	Number of years	Patient's age
Tx1.Ci.Event	Integer (0=no, 1=death, 2=major, 3=minor)	Observed event in cycle
Tx1.Ci.Time	Number of days	Duration of cycle
Tx1.Ci.QoL	Utility (0-1 scale)	QoL during cycle
Tx1.Ci.Dx.Pet	Binary (1=response, 0=no response)	PET-CT result in cycle
Tx1.Ci.Dx.Test1	Real number	Test1 result in cycle
Tx1.Ci.Dx.Test2	Real number	Test2 result in cycle
Tx1.Ci.Dx.Test3	Real number	Test2 result in cycle
FU1.Event	Integer (0=progression, 1=death)	Observed event in Follow Up 1
FU1.Time	Number of days	Duration of Follow Up 1
Tx2.Ci.Event	Integer (0=no, 1=death, 2=major, 3=minor)	Observed event in cycle
Tx2.Ci.Time	Number of days	Duration of cycle
Tx2.Ci.QoL	Utility (0-1 scale)	QoL during cycle
Tx2.Ci.Dx.Pet	Binary (1=response, 0=no response)	PET-CT result in cycle
Tx2.Ci.Dx.Test1	Real number	Test1 result in cycle
Tx2.Ci.Dx.Test2	Real number	Test2 result in cycle
Tx2.Ci.Dx.Test3	Real number	Test2 result in cycle
FU2.Time	Number of days	Duration of Follow Up 2

After becoming familiar with the case study and the code that will be used as a starting point, the first step is to model the clinical pathway as studied in the clinical trial. This pathway is referred to as the best standard care (BSC). The BSC model will first be defined by using fixed values for the parameters. Next, the patient data obtained from the clinical trial will be used to describe patient-level variation in the parameter values where possible. After the BSC has been modelled, the experimental strategy, i.e. using the tests for treatment switching, will be modeled in Part 2.

Notice that the best standard care (BSC) is something different than the base-case analysis (BCA). Different from a PSA (i.e., probabilistic sensitivity analysis), a BCA does not consider uncertainty in the model parameters, though it may reflect patient-level variation in models (i.e. stochastic uncertainty).

Step 1.1) Patient Characteristics

The first step in the model is to appoint patients with their characteristics, which will be used to tailor the modeled clinical pathway at a later stage. For Step 1.1, the patient-level data is not yet used and the fixed values presented below will be used to populate the model. As illustrated for the attribute "Alive" in Section 4 of the code, define the following attributes for the patients:

Attribute name	Evidence	Information
Male	33% of patients are male	Sex (male/female)
Poor	21% of patients are in poor condition	Clinical condition (good/poor)
Age	The mean age is 60 years	Age (mean value)
Tx1.Response	Assume that all patients are responders	Treatment response (yes/no)
Tx2.Response	Assume that all patients are responders	Treatment response (yes/no)

Hint: always use parameters in functions etc. rather than entering numbers/values directly, as these values will be changed at a later stage. Parameters can be defined in Section 2 of the code, for example.

Hint: recall that attributes are defined by numbers in the simmer package.

Hint: apply descriptive coding, i.e. use binary coding (1 or 0) whenever possible.

Hint: to improve legibility for yourself and others, make use of comments (#) in your script.

Step 1.2) Modeling Best Standard Care

Complete the "bsc.model" trajectory according to the clinical pathway, as defined in Figure 1. Focus on modeling the time-to-events only, as costs and effects will be implemented at a later stage. Make sure to include all competing risks and types of events in each state, e.g., progression and death in Follow Up 1. For Step 1.2, the patient-level data is not yet used and the fixed values presented below will be used to populate the model.

Use the following information to define the corresponding parameters:

- the duration of a treatment cycle for Tx1 and Tx2 is assumed to be 30 days
- minor complications occur with a probability of 10% and do not affect normal cycle duration
- major complications during both treatments tend to occur on day 6, with a probability of 4%
- death during treatment with Tx1 or Tx2 is expected to occur on day 15, with a probability of 3%
- the duration of Follow Up 1 is assumed to be 63 days before starting treatment with Tx2
- if a patient dies in Follow Up 1, this is expected to happen on day 42, with a probability of 5%
- the duration of Follow Up 2, i.e., palliative care, is assumed to be 100 days

Hint: use the "plot(bsc.model)" command to check whether your code matches your thoughts and test whether the model still runs successfully after adding a line of code. Inspecting the plot may seem pointless, though it will prevent struggling with multiple errors at the same time at a later stage.

Hint: define all required supportive functions in Sections 3 and all required resources in Section 5.

Step 1.3) Health Economic Impact

Define attributes to track a patient's costs (in Euros) and effects (in Quality Adjusted Life-Years), and accordingly track these throughout the modeled pathway. For Step 1.3, the patient-level data is not yet used, and the fixed values presented below will be used to populate the model.

Use the following information:

- Initial costs of Tx1 are €504 per cycle and, furthermore, treatment with Tx1 costs €8 per day
- Initial costs of Tx2 are €4450 per cycle and, furthermore, treatment with Tx2 costs €14 per day
- The costs of experiencing minor or major complications are €381 and €11,032, respectively
- Patients in follow up are assumed to have a 10% higher utility compared to the previous treatment
- The utility (expressed as QoL over one year) during treatment is 0.55 for Tx1 and 0.5 for Tx2
- The disutility of experiencing a minor or major complication is 0.05 and 0.1 respectively, which affect the QoL every day within the treatment cycle the complication occurs, not applicable for successive cycles.

Hint: make sure all additionally required parameters and supportive functions are defined.

Note: due to the time horizon and a generalized disutility disregarding the duration a patient is affected by a complication, patient level utility scores can become negative.

Step 1.4) Patient-level Variation

Fixed parameters were previously assumed to apply to all types of patients. However, it is very unlikely that all (types of) patients, for example, experience events with the same probability and at the same time in practice. Therefore, it is important to reflect patient-level variation (i.e., stochastic uncertainty) and to account for patient characteristics if those impact the patient's clinical pathway, which will be done in this step based on the patient-level data.

Stratify simulation patients and reflect patient-level variation based on the trial data and according to the following instructions:

- Define two distribution to describe variation in the patient's age. One for men, and one for women
- Estimate the effectiveness of Tx1 (i.e., the probability that a patient responds to Tx1), while accounting for the patient's clinical condition, and implement this into the model (previously we have assumed a 100% effectiveness)
- Estimate the effectiveness of Tx2 (i.e., the probability that a patient responds to Tx2), while accounting for the patient's response to Tx1, and implement this into the model (previously we have assumed a 100% effectiveness)
- Stratify the probability of experiencing minor or major complications according to the patient's response to current treatment and clinical condition, based on Cycle 1 (C1) and Cycle 2 (C2) of Tx1 (i.e., Tx1.C1… and Tx1.C2…)
- Fit a logistic regression model to predict the probability of death in a treatment cycle based on the patient's sex and age, based on data from C1 and C2 of Tx1

- Define separate distributions to reflect the variation in time-to-events for all corresponding parameters, e.g. events such as death and major complications (for the cycle lengths of Tx1 and Tx2, fit distributions based on cycles C1 and C2 of Tx1 only)
- Stratify the patients' utility during Tx1 treatment according to their treatment response, based on C1 of Tx1
- Stratify the patients' utility during Tx2 treatment according to their treatment response, based on C1 of Tx2 (do not stratify the disutility)

Hint: if you need to fit and implement a parametric distribution, first think about which distribution would match the parameter in theory, before trying to fit all different types of distributions. For example, a Normal distribution may generate negative values, which might not be appropriate for some parameters.

Hint: if necessary, find out what a logistic regression model is, how it is structured, how the output should be interpreted, and how such a regression model can be estimated in R and used to make predictions for new data, i.e. (simulated) patients.

Handing in the results

Congratulations! You made it through the first (and probably hardest) part of the assignment. Make sure you hand in the following files on Canvas before the deadline:

- Your R code file for the base-case analysis (Step 1.1 - Step 1.4)

Part 2: Health Economic Modeling (Experimental Strategy and Analysis)

Part 2.1 Modeling the Experimental Treatment Strategy

After developing the model representing BSC, it is now time to develop the experimental (EXP) model in which three novel diagnostics will be used to switch treatment based on patients' response to treatment. Using the previously defined model of the BSC as a starting point, clinical decisions to stop or continue treatment with Tx1 based on test results will be implemented. Finally, a probabilistic sensitivity analysis (PSA) will be implemented and performed to reflect parameter (i.e., second-order) uncertainty.

For Part 2 of the assignment, five files are provided to use in addition to your code from Part 1:

1) trial_dataset.RData — *R data object containing the trial data*
2) getSingleAttribute.R — *R code defining a function that will be used*
3) getMultipleAttributes.R — *R code defining a function that will be used*
4) psa_startcode.R — *R code that serves as a starting point for the PSA*
5) psa_results.RData — *R data object containing results for the PSA*

Step 2.1) Basic Model Structure

Create a starting point for the EXP model by copying the model representing BSC, and naming it "exp.model". Make sure also to copy the BSC simulation and name it "exp.sim". Adapt the "exp.sim" so that the correct objects are called, e.g. "exp.model" instead of "bsc.model".

Step 2.2) Generating Test Results

Adapt the "exp.model" so that the three novel diagnostic tests are performed before each treatment cycle of Tx1. The outcome, i.e., treatment decision, of performing and analyzing the results of the tests needs to be stored in the patients' attributes.

Take a three-step approach in implementing the test results:

1) If you have not implemented this already, at appropriate places in the pathway, set an attribute "Tx1.Event" to record the event that will happen/treatment decision using a supportive function (e.g., "get.Tx1.event").

2) In this supportive function, generate test results for the three novel diagnostics, i.e. Dx1, Dx2, and Dx3, by defining a multivariate Normal distribution based on the trial data.

3) Based on the three generated test results, implement a treatment decision that is returned from the supportive function to the attribute in the model. Return a fixed value independent of the test results, as the real treatment decision will be implemented in subsequent Step 2.3.

Hint: consider that test results are likely to be different between responders and non-responders, and whether the test results are likely to be independent of each other.

Hint: the distributions of the test results are not different over different treatment cycles of Tx1, so estimate the distributions based on C1 of Tx1 for your convenience.

Step 2.3) Treatment Decisions

Based on the trial data, including the patients' true treatment response defined by the PET-CT, determine a threshold for each test above which a patient is expected to respond to current treatment. Determine these three thresholds so that each test classifies 80% of the non-responders correctly, based on the data for C1 and C2 of Tx1. Implement the determined thresholds in the supportive treatment decision function (Step 2.2) and return a treatment decision based on the test results and threshold. Note that the tests taken before the first treatment cycle will not be used for decision making, as these can be considered baseline test results.

Hint: recall from the introduction that all three test results need to be above their threshold before treatment can be stopped.

Step 2.4) Second-line Effectiveness

Ineffective treatment (i.e. overtreatment) needs to be stopped as soon as possible and, vice versa, effective treatment needs to be provided as long as possible to prevent under treatment, as both will substantially impact the disease status of the patient and, thereby, the probability that subsequent treatment will be effective. Consequently, the effectiveness of second-line treatment with Tx2 in the EXP model is not fixed, as it is in BSC model, but depends on the patient's response to first-line treatment with Tx1 and the number of cycles of Tx1 received by the patient (see Table 1). Implement this evidence into the EXP model.

Table 1. Overview of the estimated effectiveness (i.e., response rates) for second-line treatment with Tx2, stratified by patients' response to Tx1 and the amount of treatment received.

Cycles of Tx1	P(Response onTx2) For non-responders on Tx1	P(Response onTx2) For responders on Tx1
1	0.90	0.52
2	0.78	0.54
3	0.66	0.56
4	0.54	0.58
5	0.42	0.60

Step 2.5) Health Economic Impact

Although the three diagnostic tests are less expensive than the PET-CT, they still induce an economic burden to the healthcare system, which should be accounted for in the model. Therefore, include the following estimated costs for performing the tests in the model:

- Dx1: €278
- Dx2: €256
- Dx3: €194

Part 2.2 Probabilistic Sensitivity Analysis

Now that both the BSC and EXP models are defined, a base-case analysis (BCA) of the models can be performed to estimate the impact of using the three novel diagnostic tests to inform treatment decisions. However, although running the BCA will represent the patient-level variation, i.e., stochastic uncertainty or first-order uncertainty, parameter uncertainty (i.e., second-order uncertainty) is not yet accounted for. According to good research practices and modeling guidelines, parameter uncertainty should be accounted for in a probabilistic sensitivity analysis (PSA) to calculate the expected health economic outcomes and express the uncertainty in these estimates.

Step 2.6) Simulation Function

Copy all data analysis and both models and simulations for the BSC and EXP strategy into the "runPSA" function in the "psa_startcode.R" file. The "runPSA" function can be easily called to perform model runs using all CPU cores and returns the costs and effects for both models. The "runPSA" function performs the simulations a pre-specified number of times (i.e., "n.runs" times) for a pre-specified number of patients (i.e., "n.patients" patients) and returns the defined outcomes in a matrix. By using a random parameter value in each of these runs, a PSA is performed, as will be implemented in the next step.

Step 2.7) Parameter Uncertainty

Adapt the "runPSA" function, and possibly the models, so that a single random value from a distribution will be used for the parameters throughout one PSA run for both models (i.e., BSC and EXP). The parameters to be included in the PSA and the evidence that needs to be used to do so, e.g. from the trial or literature, are described below. Implement the following in the PSA/models:

1) The standard error for the mean treatment costs of Tx1 is €36 for the initial costs and €1.50 for the additional costs per day
2) The standard error for the mean treatment costs of Tx2 is €465 for the initial costs and €2 for the additional costs per day
3) Estimate distributions for the mean utility of responding and non-responding patients for Tx1 and Tx2, based on the first cycle of the data of the patients who did not experience any (minor or major) complications
4) Consider whether the parameter value for patients' utility during follow up needs to be adjusted according to 3).

5) Estimate a distribution for the probability of experiencing minor complications during treatment based on C1 and C2 of Tx1 in the trial data (note that we assumed these probabilities to be equal for Tx1 and Tx2)
6) Estimate a distribution for the probability of death during the first follow up based on the data
7) Minor complications have mean costs of €381 (with standard error €41)
8) Major complications have right-skewed costs, with mean €11032 (with standard error €472)
9) A newly published cost study showed the following mean estimated costs and uncertainties surrounding these costs for the diagnostic tests:
   - Mean costs of test 1 are €278 (with standard error €4)
   - Mean costs of test 2 are €256 (with standard error €8)
   - Mean costs of test 3 are €194 (with standard error €2)

Step 2.8) Model Analysis

You can now determine the costs, in Euros, and the health effects, in QALYs of the intervention strategy as well as the control strategy, both from the BCA and the PSA. Run the BCA with 10,000 patients for each treatment strategy and run the PSA for 100 runs with 1000 patients for each treatment strategy. Report the cost and effectiveness outcomes for both analyses.

Step 2.9) Interpreting Cost-Effectiveness Outcomes

To perform a proper PSA for these models, at least 5,000 runs with 10,000 patients for each treatment strategy in each run are required. As this will take (probably) several days on your computers, we performed this analysis for you on a fast computer. The results of this PSA are provided to you in the "psa_results.RData" file, which you need to load into R Studio for this final step of Part 1.

Based on the PSA outcomes provided to you in the "psa_results.RData" file, please report on the following issues:

1) Determine the incremental cost-effectiveness ratio (ICER) of the intervention strategy compared with the control strategy
2) Is this ICER acceptable if society would be willing to pay at most €20,000 for one additional QALY? And what if society would be willing to pay €80,000 for one additional QALY?
3) Create an incremental cost-effectiveness plane and visualize the incremental effects (x-axis) and incremental costs (y-axis) of the intervention strategy compared with the control strategy. Provide a correct label for both axes.
4) Add two solid lines to this plane, one representing a willingness-to-pay (WTP) threshold of €20,000 per QALY gained, and one representing a willingness-to-pay threshold of €80,000 per QALY gained.
5) Determine how many of the PSA samples fall below these respective WTP thresholds.
6) Finally, vary the WTP from €0 to €200,000 per QALY, in steps of €1,000, and determine for each WTP value the fraction of samples (points) falling below that specific WTP. This fraction

represents the probability that the intervention strategy has acceptable cost-effectiveness compared with the control strategy, given that specific WTP. Create a cost-effectiveness acceptability curve (CEAC) that visualizes this probability as a function of the WTP over this range. Also, provide correct labels for both axes.

7) What is your conclusion based on this CEAC?

Handing in the results

Congratulations! You made it through the second and final part of the assignment. Make sure you hand in the following files on Canvas before the deadline:

- Your R code file for the base-case analysis (Step 1.1 - Step 1.4 and Step 2.1 – Step 2.5)
- Your R code file for the probabilistic sensitivity analysis (Step 2.6 – Step 2.7)
  A text document that contains your interpretation of the cost-effectiveness analysis (Step 2.9)