

# An early Health Technology Assessment into the expected impacts and potential cost-effectiveness of the LoAD e-Health application to combat knee osteoarthritis

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**Abstract:**

**Background:** Total knee replacement is the final treatment option for knee osteoarthritis patients. However, knee prosthetics have limited life spans and revision total knee replacements often have worse outcomes than primary total knee replacements. Therefore, an e-health application is being developed by the LoAD consortium that could slow down disease progression based on personalised movement advice. To inform its development, an early Health Technology Assessment is performed.

**Methods:** The cost-effectiveness was explored by means of an individual level state transition model. Monte Carlo simulations and scenario analyses were performed to explore the impact of uncertainty of input parameters on the robustness of the ICER. Finally, a headroom analysis was performed to explore the maximum acceptable cost of the e-health application.

**Results:** Across all scenarios, annual costs per patient ranged between €137294 and 135370 on average. Annual QALYs ranged between 14.80 and 14.82. Cost-savings ranged between €570 and €2494 per patient per year on average. Reducing the chance of disease progression and progression to surgery resulted in QALY losses ranging between -0.01 and -0.03. The reason for this was that pre-surgical utilities were lower. The maximum acceptable costs per patient per year ranged between €351 and €1998 at a WTP of €20000 per QALY. The probability that the intervention was cost-saving ranged between 75.8% and 99.8%.

**Conclusion:** The probability that the intervention was cost-effective ranged between 62% and 93% compared to the SOC at a WTP of €20000 per QALY. The application did not provide extra effect for additional costs, instead it provided cost-savings for similar health outcomes.

## 1. Introduction

Approximately 1.6 million Dutch individuals suffer from knee osteoarthritis (KOA) and this number is expected to increase with 36.0% by the year 2040 [1]. The burden of disease in KOA is high, indicated by a utility score of 0.7 [2]. In 2019, the expenditure on KOA patient related care in the Netherlands alone was approximately 500 million euros and it is believed that these medical costs represent approximately 75.0% of the total costs, suggesting that the societal costs would be approximately 667 million euros [3, 4], showcasing the immense societal burden of KOA.

KOA is characterized by progressive joint space narrowing (degrading cartilage), osteophyte formation, subchondral cyst formation and is associated by debilitating pain and loss of function in the knee [5]. In the Netherlands, the diagnosis of KOA is based on clinical criteria. Radiographic images are taken when there is an unexpected progression of symptoms that does not align with typical disease progression [6]. Radiography can capture the natural progression of the disease and allow for classification using the Kellgren-Lawrence (KL) system [7]. This system correlates with clinical observations of symptom severity [8]. However, on an individual level, KOA is a very heterogeneous disease with different rates of progression and varying severity of symptoms [9].

In the Netherlands, standard of care (SOC) for KOA patients is based on the severity of the symptoms. Regimens often start with conservative treatment. This entails lifestyle management, predominantly focussed on weight loss, physiotherapy, analgesics and orthopaedic aids [6]. Total knee arthroplasty (TKA) is a last resort and conservative treatment aims to postpone the need for TKA as long as possible as TKA implants have limited life spans of approximately 10 years on average [10]. Premature TKAs increases the risk of requiring a revision TKA (rTKA) later in life, which has worse outcomes than primary TKAs and leads to a substantial risk of requiring re-rTKA [11].

One of the discussed strategies in literature to slow down progression of KOA is weight loss, as there seems to be a relationship between biomechanical loading on joints and cartilage health through the conversion of mechanical signals into biochemical responses [12-14]. Various studies have shown that there is a “Goldilocks zone”, which is a zone of biomechanical load and frequency of that load where joint preservation is optimized [14]. The principles behind the Goldilocks zone can also be used to develop exercises for KOA patients to ultimately slow down the progression of KOA and avoid cartilage deterioration.

Such exercises can be provided to patients through e-health applications and can be tailored to their preferences and needs through holistic monitoring. Utilizing the Goldilocks zone, could potentially postpone primary TKAs even further, which could result in cost-savings and improved quality of life (QoL) retention. The concept of such an e-health application is currently being developed by the Load consortium in the Netherlands [15]. One of the main aims of the Load consortium is to develop an e-health application that would slow down disease progression. This would be achieved by providing personalised movement advice based on holistic monitoring. Although previously developed applications also focussed on managing the patient’s disease (m-health), these did not provide real-time personalized advice through holistic monitoring [16, 17], provided only general information on osteoarthritis and treatment [18, 19], or provided exercise advice solely for the pre- and/or post-operative stage [20-23]. Therefore, the Load consortium application distinguishes itself from other applications by integrating individually measured patient data in the provided advice to the patients, from the moment of diagnosis.

Since the potential benefit of the Load application will depend on its effectiveness, cost, and acceptability to end-users and care professionals, performing an early Health Technology Assessment (eHTA) during its development is important, because the eHTA will give insight into what aspects of the application may need further development to increase the chance of the application in reaching KOA patients.

Therefore, the aim of this study is to explore the health economic impact of the e-health application in comparison to SOC for diagnosed KOA patients, through an eHTA. The minimum requirements for the e-health application to be cost-effective are explored by means of a headroom analysis of the maximum acceptable costs (MAC). Probabilistic sensitivity analyses (PSA) and scenario analyses will be performed to assess the impact of uncertainty in input parameters and the potential effect of the intervention on the robustness of the incremental cost-effectiveness ratio (ICER), respectively.

## 2. Methods

In this study, an individual level state transition model (il-STM) was developed reflecting disease progression in

KOA. The model was populated with data, representing as closely as possible the Dutch KOA patient population. The model integrated costs from a societal perspective and compared the associated costs and effects of utilising the LoAd intervention with SOC using Monte Carlo simulations.

## 2.1. Model description

The model was developed based on diagnostic and treatment guidelines in the Netherlands [6, 24]. Each model cycle was equivalent to 1 year with a total of 50 cycles. The model consisted of two phases, the conservative and surgical phase, and all patients started in KL2 and ended in Death, see Figure 1. The conservative phase is characterized by the progression of disease as depicted by the KL system [7]. A KL2 knee is used as the diagnostic criterium for KOA, since from this stage on, the patient shows unambiguous KOA symptoms. Therefore, the conservative phase included 3 health states, namely KL2 to KL4, see Figure 1.

During the conservative phase a patient is educated on their disease and is treated with a combination of physical therapy, analgesics, orthopaedic aids and disease self-management. The SOC for KOA is defined by any combination of these components, because treatment regimens can vary per person and is based on symptom severity. If conservative treatment does not alleviate the patients symptoms, the patient would enter the surgical phase. Since the duration that a KOA patient receives conservative treatment can vary, the conservative phase of the model implements the possibility to transition from any of the three KL health states to the surgical phase. This phase starts with total knee arthroplasty (TKA) and ultimately is followed up with either a rTKA or death, see Figure 1. Post-TKA, the patient would either experience a net benefit from the surgery or no net benefit. This is depicted by the health states FB\_pTKA and NB\_pTKA, respectively [25]. The same reasoning was true for post rTKA, so the post rTKA health states were FB\_prTKA and NB\_prTKA, respectively. These health states are characterized by different costs and utility data. It was assumed that each patient could undergo a maximum of 1 rTKA, because no data could be found for re-rTKA health states. Finally, patients could transition to the death state from any other health state in the model.

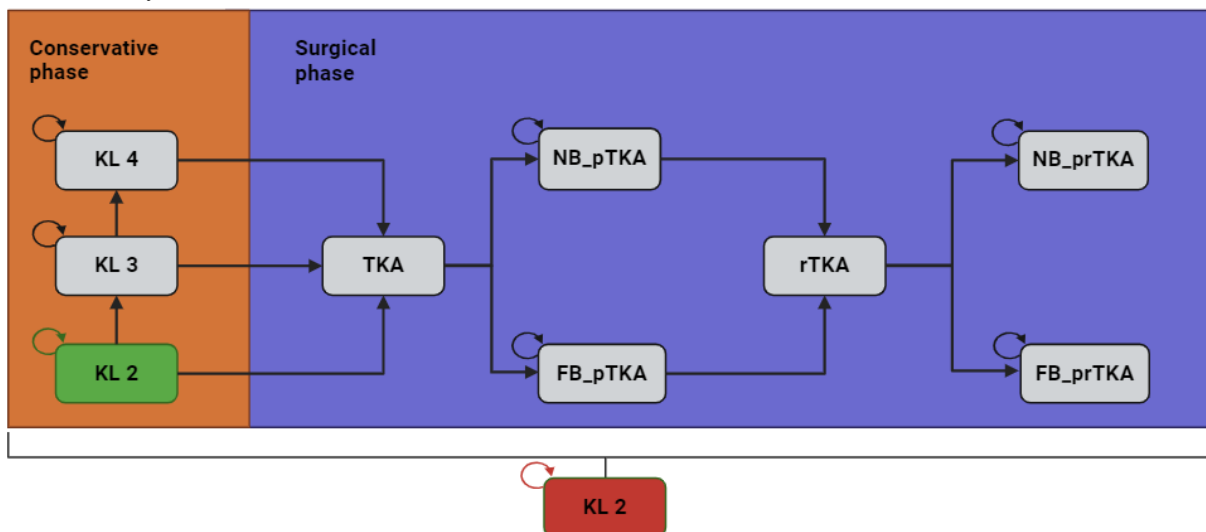


Figure 1. Individual level state transition model showcasing the possible transitions. All patients start in KL2 (green) and end in the “Death” (red) health state. KL2 = Kellgren-Lawrence grade 2, KL3 = Kellgren-Lawrence grade 3, KL4 = Kellgren-Lawrence grade 4, TKA = Total knee arthroplasty, FB\_pTKA = Full benefit post total knee arthroplasty, NB\_pTKA = No benefit post total knee arthroplasty, rTKA = revision total knee arthroplasty, FB\_prTKA = Full benefit post revision total knee arthroplasty, NB\_prTKA = No benefit post revision total knee arthroplasty.

### 2.2.1 Intervention e-health application and scenario analyses

During this eHTA, information on the contents of the application were not yet available. To mimic the main aim of the application, the simulation model was used to explore certain scenarios, where plausible assumptions were made regarding disease progression. This was done using scenario analysis, where KOA patients were exposed to lower transition probabilities in the conservative stages using relative risks (RR). This concerned the transition probabilities of KL2 to KL3, KL3 to KL4, KL2 to TKA, KL3 to TKA and KL4 to TKA. In total there were 6 scenarios. Scenarios 1 to 3 applied RRs of 0.95, 0.90 and 0.85 to the previously mentioned transition probabilities, respectively. Patients were only simulated with the adjusted probabilities, cost and utilities if they were adherent to the intervention.

### 2.2.2 Adherence

Adherence was reflected in the model by generating a beta distribution of predefined probabilities for adherence with an average probability of 0.65 [26]. Each Monte Carlo simulation, a different probability was drawn from the respective distribution. A patient was deemed adherent if the randomly drawn value from a uniform distribution for that patient was lower than the predefined probability for adherence that was set for each Monte Carlo simulation. This process is called stochastic assignment. Therefore, the results of the six scenarios showed a group average of adherent and non-adherent patients. To investigate the maximum potential of the intervention, a secondary analysis was performed assuming all patients were adherent. To allow comparison, the same RRs were used as in Scenario 2 and this new scenario was called Scenario 2A.

### 2.2.3 Comorbidity

Patients with KOA can develop comorbidities, such as diabetes mellitus type II (DMII) [27]. DMII is especially interesting due to the direct relation between KOA and physical inactivity, as the latter may result in increased body weight, which in turn results in excess risk of cardiovascular and metabolic diseases, including DMII. The development of DMII in KOA patients was implemented in the model by means of stochastic assignment, meaning that random values were drawn from a uniform distribution and if these were lower than the probability of developing DMII, the patient would be classified as a DMII case. To explore the impact of the intervention on the development of DMII, 3 scenarios were defined in which a conservative RR of 0.95 was applied to the probability of developing DMII, namely scenarios 4, 5 and 6. Scenarios 4 to 6 were essentially scenarios 1 to 3 in combination with a RRs of 0.95 for developing DMII. In this model, DMII was an individual level attribute, not a health state.

### 2.3. Study population

Two identical cohorts of 1000 patients, representative of the Dutch population, were generated. One cohort received SOC and the other received the e-health application in addition to SOC. The demographics of the cohorts were generated using probabilities and distributions retrieved from literature, see Supplementary file C. The cohort was defined as patients having KL2, being 45 years or older, having no previous history of knee surgery and not having received unicompartmental knee arthroplasty or uncemented knee arthroplasty.

### 2.4. Model Inputs: Costs, utilities and probabilities

The cost-effectiveness was assessed from the Dutch societal perspective. Therefore, the costs per health state include both medical costs and productivity costs. These societal costs for the conservative phase were obtained from Salmon et al. [28]. Costs of the surgical phase were retrieved from Van der Woude et al. [29] and Brunenberg et al. [30]. Productivity costs were based on the friction cost method as described in Dutch guidelines [31]. Annual costs of DMII management were also taken into account [32]. All costs were adjusted to the 2023 index. Future costs were discounted by 3.0% as according to Dutch guidelines [31].

Utilities per health state in the conservative phase were retrieved from Hermans et al. [2]. For the surgical phases they were recovered from Rehman et al. [33] and the British National Health Institute (NHS) dataset [34], which archives patient reported outcome measures for KOA care. Utilities per health state were adjusted for the presence of the DMII [35, 36]. Future utilities were discounted 1.5% as according to Dutch guidelines [31]. Both costs and utilities were personalized by randomly assigning each KOA patient a single percentile score based on a normal distribution. This single percentile score was then used to obtain the respective costs and utilities from the cost and utility distributions of the various health states. Percentile scores were applied to avoid strong fluctuations in utility scores and costs associated with the different health states.

Transition probabilities were all personalized based on age, sex, weight status or a combination thereof based on whether available evidence allowed stratification. Where necessary, transition probabilities from literature were converted into annual transition probabilities using the following formula [37]:

$$F1: \quad p = 1 - (1 - p)^{1/n}$$

Here,  $p$  is the probability from literature that needed to be converted to an annual probability, and  $n$  is the number of years the original probability was estimated for. Transition probabilities in the conservative phase were retrieved from Losina et al. [38] and were stratified for sex and BMI, but were the same for each +1 KL. Transition probabilities to post-TKA stages and post rTKA stages were retrieved from the NHS dataset and were stratified for age category and sex [34]. Transition probabilities to the rTKA stage were based on Gademan et al. and were also stratified by age and sex [39]. Finally, the transition probabilities to the death health state were collected from Nüesch et al. [40], Zhou et al. [41], Inacio et al. [42] and the Statistics Netherlands open access dataset and were also stratified for age and sex [43, 44]. All probabilities and utilities were generated using beta distributions.

Gamma distributions were used for cost data. All cost, utility and probability tables including explanations can be found in Supplementary file A.

## 2.5. Outcome measures

Primary outcome measures included absolute and incremental costs, quality adjusted life years (QALYs), and cost-effectiveness ratios. Cost-effectiveness acceptability curves (CEAC) were generated to analyse the probability of being cost-effective at different willingness-to-pay (WTP) thresholds. For each strategy and each Monte Carlo simulation, the model estimated the total cost and QALYs. Utility scores accrued in each health state were multiplied by the time spent in each respective health state. The sum of this gave the number of QALYs. QALYs and costs were averaged out over the Monte Carlo simulations. The average costs and QALYs were used to calculate the ICER as follows:

$$F2: \quad ICER_{e-health} = \frac{Cost_{e-health} - Cost_{SOC}}{QALY_{e-health} - QALY_{SOC}}$$

The e-health application is deemed cost-effective if the ICER is less than a WTP of €20000 per QALY. The WTP was based on the proportional shortfall score, which most likely will range between 0.16 and 0.37 based on estimations that were made for osteoporosis and rheumatoid arthritis [44, 45].

Secondary outcome measures included the number of TKAs, rTKAs and incident DMII cases for SOC and the intervention group.

## 2.6 Analyses

PSAs were performed to assess the impact of uncertainty in input parameters on the robustness of the ICER. This was done by means of 500 Monte Carlo simulations. PSAs were performed for the six previously mentioned scenarios.

Headroom was calculated using the MAC as described by Behr et al. [46]. The MAC for the e-health application was calculated using the following formula:

$$F3: \quad MAC = (EffectivenessGap * WTP) - IncrementalCost$$

The effectiveness gap was defined as the difference between the QALYs obtained with the intervention and SOC. The WTP was always set to €20000. The costs included in this equation were health state related costs from a societal perspective. The development costs of the e-health application were not taken into account as these were unknown.

Annual population and per person Expected Value of Perfect Information (EVPI) and Expected Value of Partial Perfect Information (EVPPPI) analyses were performed to quantify the value of eliminating uncertainty in certain input parameters of the simulation model. For the population EVPIs and EVPPPIs an annual prevalence of 762700 patients were assumed [1]. The input parameters that were included mainly consisted of transition probabilities. The cost and utility data were not included, because simulated patients were assigned costs and utilities based on their assigned percentile scores since individual patient level data was not available.

All simulations and statistical analyses were performed using R Statistical Software (R v4.3.1) and Rstudio (Rstudio v2024.04.0+735) [47]. The scripts containing all the code and all external libraries are available in Supplementary file C.

## 3. Results

In the following sections the results for the scenario, sensitivity and value of information (VOI) analyses will be discussed. Finally, the number of TKAs and DMII cases will be discussed.

### 3.1 Scenario analysis

In all of the scenario analyses, the e-health application was cost-saving and cost-effective for a WTP of €20000, see Table 1. Cost savings in Scenarios 1 to 6 were €-570, €-1359, €-2204, €-674, €-1520 and €-2494 per patient per year. In Scenario 2A, where adherence was 100%, cost-savings were €736 higher compared to Scenario 2, totalling to €-2095, see Supplementary file B.

At the same time, slowing down disease progression and progression to TKA through the e-health application, on average resulted in slightly lower health effects. Scenarios with lower RRs resulted in slightly greater health effect losses, see Table 1. Similar effect losses were observed when there was a chance of preventing comorbid DMII, see Table 1. In Scenario 2A, effect losses were even 0.01 greater than in Scenario 2, totalling a loss of -0.04, see Supplementary file B. These QALY losses can be explained by the fact that pre-surgical utilities are slightly lower than post surgical utilities. This combination of negative incremental costs and QALYs resulted in high positive ICERs for the intervention. Therefore, these ICERs represent the cost-savings per lost QALY rather than the

incremental costs per gained QALY, see Table 1.

Despite the QALY losses, the intervention was very cost-saving in all of the scenario analyses. Therefore, the MACs per patient per year in these scenarios were also relatively high and followed the same pattern as the cost-savings. Scenarios where the application was slowing down the progression of KOA more or had a chance of preventing DMII, had a higher MAC. Therefore, the highest MAC of €1998 per patient per year was observed in Scenario 6 and the lowest MAC of €351 was observed in Scenario 1. Similar to the cost-savings, the MAC had also increased in Scenario 2A compared to Scenario 2 at €1386 per patient per year, see Supplementary B.

Table 1. Individual level state transition model Monte Carlo simulation results.

	Scenario	Cost ehealth (€)	Cost SOC (€)	QALY ehealth	QALY SOC	ΔCost (€)	ΔQALY	ICER (€)	MAC (€)
Without DMII Impact	1	137294	137864	14.82	14.83	-570; 95% CI [-2028 : 734]	-0.01; 95% CI [-0.07 : 0.04]	52178	351
	2	136505	137864	14.81	14.83	-1359; 95% CI [-3284 : 133]	-0.03; 95% CI [-0.10 : 0.04]	51700	833
	3	135660	137864	14.80	14.83	-2204; 95% CI [-4618 : -710]	-0.03; 95% CI [-0.12 : 0.04]	68774	1563
With DMII impact	4	137189	137864	14.82	14.83	-674; 95% CI [-2573 : 967]	-0.01; 95% CI [-0.07 : 0.05]	77981	501
	5	136344	137864	14.81	14.83	-1520; 95% CI [-3535 : 187]	-0.02; 95% CI [-0.10 : 0.04]	66295	1061
	6	135370	137864	14.81	14.83	-2494; 95% CI [-4749 : -634]	-0.03; 95% CI [-0.11 : 0.05]	100496	1998

Note Table 1.  $RR_a$  represents the relative risk that was applied to the transition probabilities of KL2 to KL3, KL3 to KL4, KL4 to TKA, KL3 to TKA and KL2 to TKA to mimic the slowing down of disease progression that the e-health application could potentially have.  $RR_b$  represents the relative risk that was applied to the probability of developing DMII, to showcase what the cost-effectiveness could be if the e-health application would reduce the development of comorbid conditions by slowing KOA progression. ICER = Incremental cost-effectiveness ratio; MAC = Maximum acceptable cost of e-health application.

### 3.1.1 Sensitivity analyses

In general, the majority of the Monte Carlo simulations yielded results that were in accordance with the different scenario averages, see Figures 2A and 2B. For Scenarios 1, 2 and 3, 78.8%, 96.2% and 99.8% of simulations were cost-saving, respectively. In total, 27.4%, 24.6%, and 23.4% of simulations were dominant in scenarios 1, 2 and 3, respectively. There was a 32.4%, 24.6% and a 23.4% chance for the simulations being effective in scenarios 1, 2 and 3. In total, there was a 62.0%, 78.0% and 89.0% chance of the simulations being cost-effective in scenarios 1, 2 and 3. In general, increasing the WTP threshold made the scenarios less cost-effective, see Figures 2C, 2D and 2E.

For scenarios 4, 5 and 6, similar results were observed, see Figure 2F, 2G and 2H. The main difference was that the percentage of dominant simulations had increased to 32.6%, 28.0% and 27.0%, respectively. In total 75.8%, 95.6% and 99.8% of simulation were cost-saving in scenarios 4, 5 and 6, respectively. Concerning the probability of being effective, simulations in scenarios 4, 5 and 6 showed probabilities of 37.6%, 28.4% and 27.0%, respectively. In general, the simulations in scenarios 4, 5 and 6 were more cost-effective with chances of cost-effectiveness being 65.0%, 77.0% and 93.0%, respectively. In Scenario 2A, where adherence was 100%, effective and dominant simulations were 6.6 percentpoints (pp) lower than in Scenario 2, totalling 18%, and 99.6% of simulation were cost-saving, which was 3.4pp higher than in Scenario 2, see Supplementary file B.

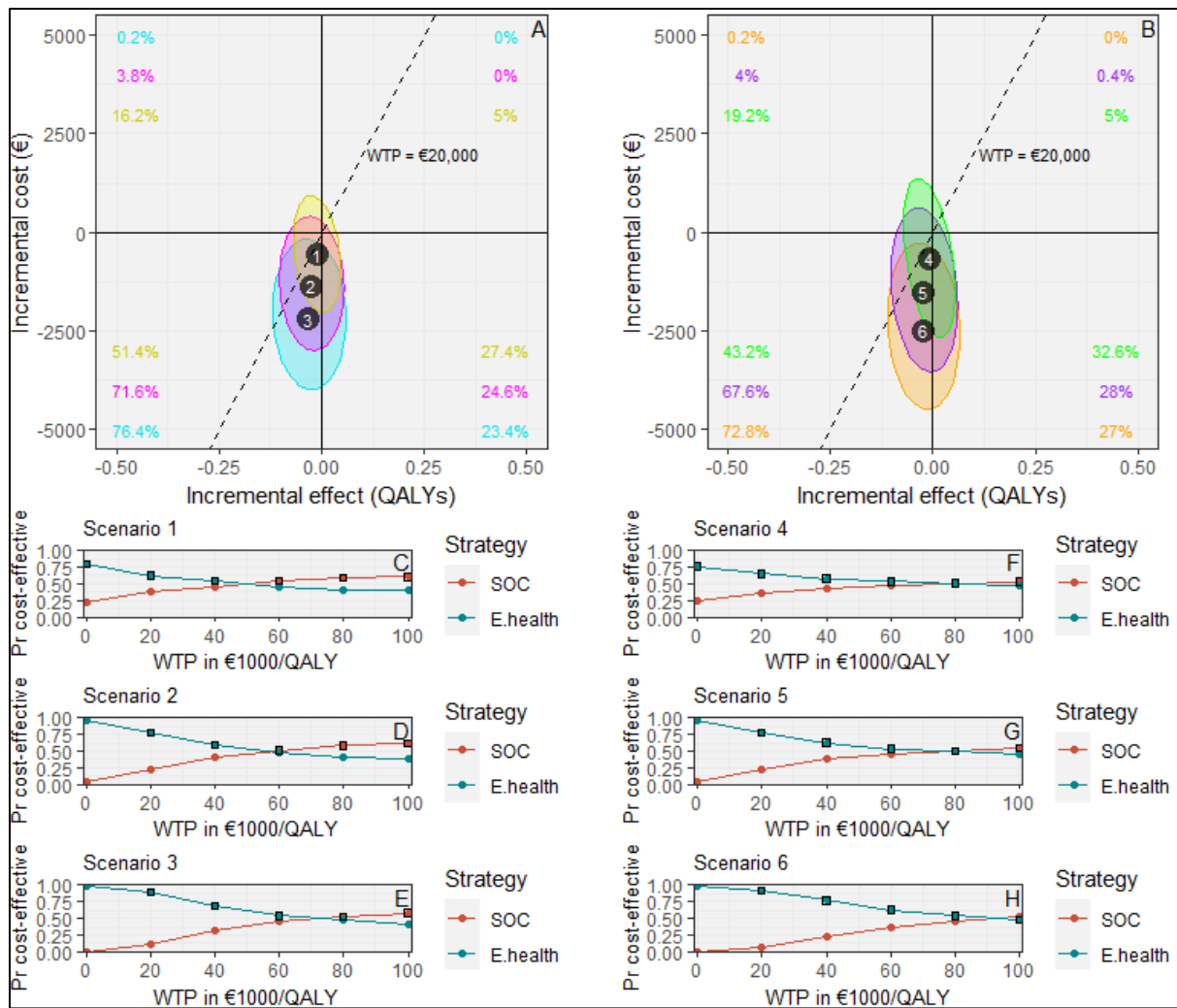


Figure 2. (A) Cost-effectiveness (CE) planes showing 95%CI ellipse of the PSA for Scenarios 1 in yellow, 2 in magenta and 3 in light blue, including percentage of simulations per CE-plane. (B) CE-planes showing 95%CI ellipse of the PSA For scenarios 4 in green, 5 in purple and 6 in orange, including percentage of simulations per CE-plane. (C-H) Cost-effectiveness acceptability curve (CEAC) for Scenarios 1 to 6 with in blue the e-health intervention and in Red the SOC.

### 3.1.2 VOI analyses

With a WTP threshold of €20000 per QALY, Scenarios 1 to 6 had annual population EVPIs of approximately 182, 119, 52, 228, 120, and 33 million euros, respectively, see Figures 3A-F. This is equivalent to a per patient EVPI of €239, €156, €69, €299, €157, and €44 per year.

The annual per patient EVPPI for the probability to transition to the full benefit health state after a rTKA for 60 to 80 year old women was the highest at €4.83, resulting in an annual population EVPPI of approximately 3.68 million euros in Scenario 4, see Figure 3G. Scenario 4 was also the only scenario that consistently showed high EVPPIs, see Figure 3G. The only parameter that showed most consistency across all scenarios concerning the annual population EVPPI was the probability to transition a KL state as a non-obese man. Annual population EVPPIs for this parameter ranged between 0.4 and 1.9 million euros.

In scenario 3, none of the parameters had an annual EVPPI higher than €0, suggesting that the current level of uncertainty in the decision-making process is accounted for, which is interesting since the annual population EVPI is not €0, see Figure 3C.

### 3.2.1 Number of TKA, rTKA and comorbid DMII

It was observed that when a RR risk was applied to slow down the progression of KOA and progression to surgery, this impacted the number of patients that underwent both TKA and rTKA. In all scenarios the SOC group had the



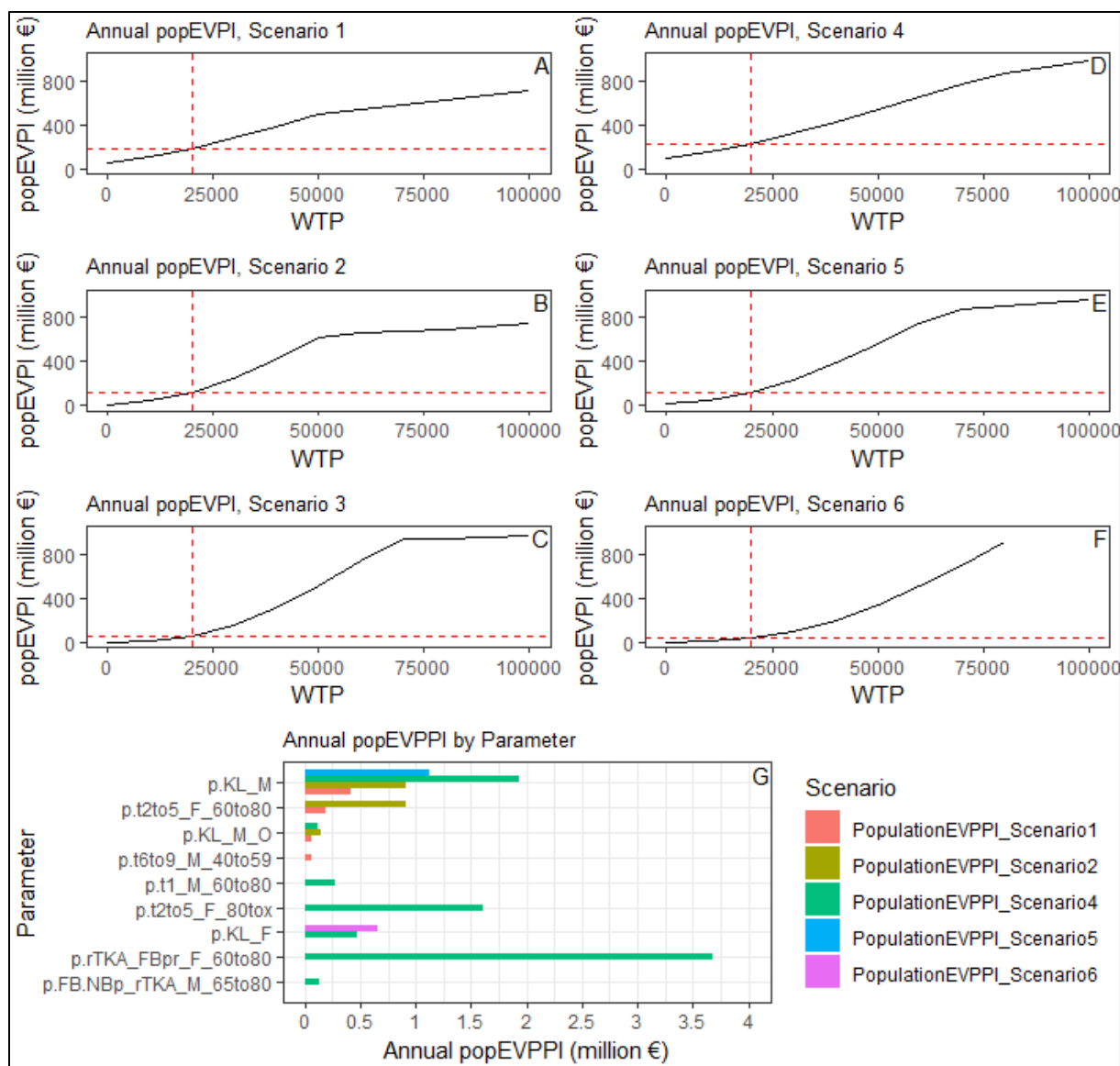


Figure 3. (A-F) Graphs of annual population EVPI (popEVPI) in millions of euros as function of the WTP threshold per QALY in Scenarios 1 to 6 respectively. The red dashed lines represent the intersect with the WTP of €20000. (G) Horizontal bar chart showing annual population EVPPI (popEVPPi) in millions of euros as function of the WTP threshold per QALY.

same lifetime risk for TKA and rTKA, namely 0.90 and 0.10, respectively. In scenarios 1 to 3, patients in the intervention group had lifetime risks of 0.90, 0.89, and 0.88 for TKA. Scenario 2A also had a lifetime risk of 0.89. Lifetime risks for rTKA were 0.10, 0.10, and 0.09, respectively for scenarios 1 to 3. In Scenario 2A, this lifetime risk was 0.09. In scenarios 1 to 3, the intervention was able to reduce the number of TKAs by 0.6%, 1.3%, and 1.9%, respectively. The number of rTKAs were reduced by 1.7%, 4.2%, and 6.1%, respectively. The number of TKAs and rTKAs were reduced by 1.6% and 6.2%, respectively in Scenario 2A.

The lifetime risk of developing DMII were the same in the SOC and intervention groups in all scenarios, namely 0.49. There were however significant differences in the number of cycles spend with comorbid DMII. On average, the percentual reduction of time spent living with DMII in the intervention group compared to SOC were 0.3%, 0.7% and 1.0%, which is equivalent to 25 days, 56 days, and 80 days, respectively in scenarios 4, 5 and 6.

#### 4. Discussion

In the following sections the main study findings, strengths, weaknesses and future research suggestions are discussed.

##### 4.1. Main findings

Some of the main findings were that the e-health application was highly cost-saving and that if the application could prevent comorbid DMII or reduce the number of years lived with DMII, this could help the e-health application become more cost-saving.

Another finding was that the e-health application resulted in small QALY losses, negatively affecting the MAC. However, its high cost-savings compensated for these losses. Therefore, the MAC reflected the cost-savings, ranging from €351 to €1998 per patient per year for a WTP of €20000. Notably, the simulations did not include the cost of the e-health application itself. Whether it remains cost-saving depends on the total operational, research and development costs. Since current simulations indicate a small health loss, ranging from -0.01 to -0.03 on average, decision makers should keep the price as low as possible, even though the intervention could save societal costs.

The model showed small effect losses because pre-surgical utility values were lower than the post-surgical utility values. Therefore, improving adherence only amplified the cost-saving and effect losing effect that were already observed. One of the reasons for this is that in these analyses, the very stringent assumption was made that utility values obtained in the SOC and intervention group are the same. In reality, the developers could implement lifestyle management components to the application to improve utility scores. Literature on e-health interventions in KOA, such as the study by Kloek et al. [4], show that patients that used the intervention can have higher utility values. In Kloek et al., patients receiving the E-exercise intervention had on average 0.1 higher utility compared to patients that received SOC physiotherapy, respectively 0.7 and 0.8. Therefore, any increment in utility score could make this e-health application a dominating intervention, since it is already cost-saving. Therefore, it would be advisable to re-explore the KL specific utilities for patients using the application through small pilot studies, but first the expected value of sample information (EVSI) should be explored.

Kloek et al. conducted an HTA on a blended e-health physiotherapy intervention in a Dutch hip and knee osteoarthritic population aged 40-80. Similarly, our study focussed on 45+ years old KOA patients. Furthermore, their intervention was essentially online physiotherapy, whereas our intervention focussed on personalised movement advice based on holistic monitoring. Finally, Kloek et al. compared the intervention to SOC physiotherapy, but they did include all other healthcare costs, such as secondary care visits and productivity costs. Therefore, the patient population, the intervention and comparison in the study of Kloek et al. were partially comparable to our study. Similarly, Kloek et al. reported QALYs ranging from -0.1 to 0.1. Our study, however, showed higher probability of cost-savings compared to Kloek et al., respectively between 75.8% to 99.8% and 65.0%, possibly because Kloek et al. did not include surgical phase costs and effects nor did they consider the cost of comorbidities. The fact that our study implemented a lifelong timeframe is a strength compared to other studies such as Kloek et al., which often only use a limited timeframe of 1 to 2 years.

Another HTA on a KOA intervention by Coupé et al. [48] compared SOC physiotherapy with behavioural graded activity, which is similar to the lifestyle management component of our e-health application. Coupé et al. reported a small but uncertain QALY loss of approximately -0.1 and incremental costs ranging between €-4000 and €2000. However, their model timehorizon consisted of 65 weeks, meaning that they also did not take into account the surgical phase into their model.

Hollinghurst et al. looked into telehealth for KOA care [49], involving a telephone advice service. While similar in essence to our intervention, it lacked the holistic monitoring component. Their British population was similar in age, but they did not include productivity and secondary care costs and reported a timehorizon less than a year. The authors reported very small positive incremental costs, because the intervention costs were higher than the SOC, and incremental effects with a lot of uncertainty in both outcomes. This is contradictory to our results, but the study is not completely comparable to our study with regards to time horizon and costs included, which could explain the differences.

In summary, most studies reported in literature do not use an intervention that is completely comparable to ours, but similar outcomes have been observed. Not in absolute numbers, but in incremental effects and the uncertainty surrounding those effects.

The simulations in our model mainly showed uncertainty regarding the probability to transition to the full benefit health state after a rTKA for 60 to 80 year old women, resulting in an annual population EVPPI of approximately 3.68 million euros. In general, the EVPPIs measured were relatively low. However, the total annual EVPI was 228 million euros meaning there is still much unexplained uncertainty. Most likely, a big portion of the uncertainty is caused by the distributions of the cost and utility input parameters since these are essentially fixed. The same reason in combination with the fact that the number of patients and simulations are low is most likely the cause for Scenario 3 not showing any EVPPIs. Since all EVPPI are relatively low, it might be worth collecting extra information on these parameters as long as the cost of the research itself is not higher than the EVPPIs. Therefore, as mentioned before, it would also be wise to explore the EVSI and explore the net benefit of research.

#### **4.2 Strengths, weaknesses and research suggestions**

One of the strengths of this research was that it implemented a lifelong societal perspective for the eHTA. Most papers focus on a limited timeframe for the model simulations, and therefore may ignore potential future impact on costs and effects. Especially since KOA is a condition that patients grow old with, it is important to measure all potential future consequences. Another strength of this study was the implementation of the il-STM. This allowed for more specific simulations as probabilities, costs and utilities were personalised. Also, the fact that the e-health

application was compared to the SOC as a whole, instead of just sole components of the SOC was a strength, as most studies compare an intervention with only physiotherapy or only patient education.

One of the weaknesses of this study is that some of the components in this model rely on assumptions due to lack of evidence in literature, such as the cost data in post-rTKA stages or the cost data for KOA patients that did not experience net benefit post-TKA and post-rTKA. More accurate cost data is needed to get more accurate model output. For future eHTAs, it would be advisable to request cost and utility data from the national registry for orthopaedic interventions (LROI). This organisation archives data on TKAs and rTKAs in the Netherlands and is mentioned frequently in literature.

Another weakness was the stringent assumption that utilities in the intervention and SOC group were the same, whereas in reality this will most likely not be the case, as depicted by literature. If not the case, researchers should keep this difference in mind for future simulation models assessing this matter.

Another weakness is that the model assumes that KOA patients without DMII and KOA patients with DMII have the same transition probabilities. Future models should incorporate the KOA DMII relationship and any other comorbid relationships with KOA to better reflect disease progression.

Finally, the low number of patients and simulations are a weakness. More patients and simulations should be generated to get more accurate results.

The biggest limitation of this study lies in its PSA and VOI analyses, because the cost and utility data for the different health states were not taken into account. This introduced a lot of uncertainty in the output of the model. Future HTAs should either include patient level data or should bootstrap available data, which would allow the estimation of uncertainty in the utility and cost distributions themselves. This will strengthen the PSA and VOI analyses.

Furthermore, another limitation is that a positive correlation was assumed between costs and utilities when assigning these values using an identical percentile score. A strong negative correlation would be more likely as it would be expected that individuals with bad QoL also are the patients that incur higher medical and productivity costs.

Finally, it would be advisable to analyse literature to identify what defines a fast progressor. The current eHTA implemented the possibility to progress fast, but the determining factors have not been explored. Exploring this would be a great addition to the model, because if the developers of the application know the determining factors, they could try to build the application in a way that it influences the disease progression even better by providing more personalized movement advice.

Also, performing a secondary analysis looking into the health care perspective could provide meaningful insights, as it could show which party in society incurs the main costs.

## **5.0 Conclusion**

In conclusion, the e-health application is cost-effective at a WTP of €20000 and the probability of the intervention being cost-effective compared to SOC ranged between 0.62 and 0.93 across scenarios. However, not in the sense that it provides extra QALYs for higher costs, but in the sense that it saves costs while incurring a very small QALY loss. The small QALY losses were due to pre-surgical utilities being lower. Therefore, the retention of patients in the conservative treatment phase for longer and preventing TKAs and rTKAs resulted in small QALY losses. Current result did not show it, but any increase in utilities could make the intervention dominant since the loss in QALYs is very low. Therefore, it would be advisable to continue on the development of the application while exploring other variables that affect disease progression and potentially collaborate with LROI to get more accurate cost and utility data for the Dutch setting. Since the model showed high cost-saving potentials, the price of the product can be set quite high with MAC values ranging up to €1998 per person per year.

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## Supplementary file A: Costs, utilities and probabilities

### Cost input parameters KL2, KL3 and KL4

For the conservative phases, cost data about Dutch individuals that met the inclusion and exclusion criteria was reported on by Hermans et al. [2] and Kloek et al. [4]. Hermans et al., reported a mean annual medical cost of €2307.95 and a median cost of €2122.08 in 2012. It was reported that the medical costs made up 17.0% of the total costs. The other 83.0% were productivity costs. Hermans et al. reported the costs as an average over health states KL1, KL2 and KL3 instead of separated over these health states. This meant that the reported costs could not be integrated into the simulation model, as it would mean that the costs would be the same over the three increasing severity levels of KOA, whereas in reality these costs should increase with severity. The more recent paper by Kloek et al., from 2018, reported that the total medical costs would make up approximately 75.0% of the total cost, which is quite a discrepancy in comparison to the paper by Hermans et al. The reason for this could have been the difference in study populations. Hermans et al. focused on a working population aged 18-65 years old with quite the over representation of intermediate and high level educated patients, which earned a higher hourly rate when compared to the study population in Kloek et al. The study population, in the work of Kloek et al., was aged 40-80 years old, therefore including retired patients, that earn a much lower hourly rate and of whom productivity costs were lower.

The next paper that reported on a population that came closest to the Dutch population was a paper by Salmon et al. [28]. Salmon et al. reported on costs per KL state within a French population. The main difference between the paper by Kloek et al. and Salmon et al. were the distributions of the costs. Even though the mean costs in both papers were very similar, the distributions were very different. The cost distribution in the French cohort were more right-skewed. Another main difference was that Salmon et al. reported over a 100 times smaller productivity cost losses. Since the mean costs for direct medical treatments were very similar, it was decided to implement the distributions as reported for the French cohort. To still be representative for the Dutch population, it was decided to use the notion that 25.0% of total costs are productivity costs. Therefore, to calculate the total average costs, the direct medical costs reported by Salmon et al. were divided by 0.75, see supplementary Table 1.

### Cost input parameters TKA, FB\_pTKA and NB\_pTKA

The costs for TKA and rTKA were retrieved from Van der Woude et al. [29]. In their paper, they reported mean TKA costs of €14604, see Supplementary Table 1. They did not report productivity costs. Brunenberg et al. did report on productivity costs. They reported the losses in productivity costs were €1502.03 in the year of the TKA, see supplementary Table 1. Therefore, the costs for the health state TKA are calculated by taking the sum of c.TKA and c.TKA.prod. Brunenberg et al. also reported first year post-discharge costs of €5800.53. This included formal medical care costs, informal costs and productivity costs. They did not report the standard deviations for these numbers or any other statistics that would allow the generation of a gamma distribution. For the total cost they did mention a minimum value and a maximum value. Based on these descriptive statistics, a standard deviation was estimated using the methodology as described by Hozo et al. [50]. The estimated standard deviation for the total mean cost of €12877 was €8427. The assumption was then made that shape of the distribution of the total mean cost would be transferable to any subdomain cost distribution, because it is most likely that the individuals that incur the highest total costs also incur higher medical and productivity costs, suggesting consistency in their behaviour. Since productivity costs are a subdomain of the total costs, the shape of the distribution of the productivity costs was assumed to be similar to that of the total costs. Hence, the ratio between the mean and standard deviation of the total costs ( $12877/8427 = 1.528$ ) was applied to the mean costs of c.TKA.prod, c.FB\_pTKA and c.NB\_pTKA to estimate the standard deviations for these respective costs. For c.FB\_pTKA and c.NB\_pTKA this was €3866.35 and for c.TKA.prod this was €983.04, see supplementary Table 1. It was assumed that KOA patients that experienced no net benefits from the TKA, would have higher costs than patients that experience net benefit. The magnitude by which this was higher, was retrieved from a paper by Marsh et al. [51]. Marsh et al., reported on costs accrued by KOA patients that were satisfied and patients that were dissatisfied. Here the assumption was made that people with net benefit are always satisfied and patients without benefit are always dissatisfied. Since costs were reported for the American population, the ratio between the means of the two groups was calculated. The c. NB\_pTKA was then multiplied by this factor, which was 1.54.

### Cost input parameters rTKA, FB\_prTKA and NB\_prTKA

No relevant cost data could be found for the revision states in literature. Only the direct medical cost of the rTKA was reported by Van der Woude et al. to be €24327.31. Therefore assumptions had to be made about the costs of the rTKA health state and the post revision health states. It was assumed that the FB\_prTKA and the NB\_prTKA

health states would be more expensive compared to the primary TKA and post primary TKA health states. More precisely, it was assumed that c.TKA.prod, c.FB\_prTKA and c.NB\_prTKA would be approximately 1.67 times more expensive. This is the ratio between c.TKA and c.rTKA. Therefore, the costs in FB\_prTKA were calculated by multiplying c.FB\_pTKA by 1.67. The costs in NB\_pTKA was calculated by multiplying by 1.67 and 1.54. Finally, the productivity costs for the year of the rTKA was calculated by multiplying c.TKA.prod by 1.67. Therefore, costs for the revision states do not have separate input parameters, except for the rTKA.

### Cost input parameters DMII

Finally, some conditional cost distributions were created for KOA patients that developed a comorbidity due to the KOA. Whenever a KOA patient developed DMII, the annual cost of managing the DMII would get added to the annual cost of managing their KOA, see supplementary Table 1. Janssen et al. [32] reported 6 monthly costs. These costs were multiplied by two to get the costs in supplementary Table 1 [32].

*Supplementary Table 1. Cost table including distribution parameters for Monte Carlo simulations. Costs for the health states are indexed to 2023 and given in euros. All costs are annual costs, except for c.TKA and c.rTKA. These were one-off costs. <sup>a</sup>These costs were reported from a health care perspective. To account for productivity costs, the costs were divided by 0.75, based on the notion from Hermans et al [2]. <sup>b</sup>These costs were reported from a health care perspective, excluding productivity costs. <sup>c</sup>These costs were calculated based on assumptions. SD = standard deviation.*

Parameter	Mean ± SD (2023, €)	Distribution	Shape	Scale	Source
c.KL2 <sup>a</sup>	1960 ± 5600	Gamma	0.1225	16000	Salmon et al. [28]
c.KL3 <sup>a</sup>	2230 ± 5425	Gamma	0.168970	13197.59	Salmon et al. [28]
c.KL4 <sup>a</sup>	2360 ± 4095	Gamma	0.332136	7105.519	Salmon et al. [28]
c.TKA.prod <sup>c</sup>	1502.03 ± 983.04	Gamma	2.334613	643.3744	Assumption based on Van der Woude et al. [29] and Brunenberg et al. [30]
c.FB_pTKA <sup>c</sup>	5800.53 ± 3866.35	Gamma	2.25078	2577.12	Assumption based on Van der Woude et al. [29] and Brunenberg et al. [30]
c.NB_pTKA <sup>c</sup>	5800.53 ± 3866.35	Gamma	2.25078	2577.12	Assumption based on Van der Woude et al. [29] and Brunenberg et al. [30]
c.TKA <sup>b</sup>	14604 ± 1586.36	Gamma	84.75009	172.3184	Van der Woude et al. [29]
c.rTKA <sup>b</sup>	24327.31 ± 1588.79	Gamma	234.6973	103.708	Van der Woude et al. [29]
c.DMII	6012 ± 603	Gamma	99.40388	60.48054	Janssen et al. [32]

### Utility input parameters

The utilities u.KL2 and u.KL3 were derived from Hermans et al. [2]. In their paper they report an average for KL 1 to KL3, but since KL1 was less than 10.0% of the population, the reported statistics were more representative for KL2 and KL3. The utilities for KL4 and TKA were the same, based on the assumption that a patient in TKA experiences the same level of functional inability, due to the extensive rehabilitation track and pain that follows the surgery [33]. After the surgery, a KOA patient either responded well or bad to the surgery. If a patient experienced net benefit, their utility score would increase substantially. If they did not experience net benefit, their utility would on average not change, see supplementary Table 2. The same counts for the revision health states. In case a patient developed DMII during the simulation, their utility score would get adjusted for that using the methodology as described by Flanagan et al. [35]. This methodology essentially is based on the multiplication of the utility for KOA with the utility of DMII.

*Supplementary Table 2. Utilities table including distribution parameters for Monte Carlo simulations. SD = standard deviation.*

Parameter	Mean ± SD	Distribution	Alpha	Beta	Source
u.KL2	0.70 ± 0.23	Beta	323.3098	138.5613	Hermans et al. [2]
u.KL3	0.70 ± 0.23	Beta	323.3098	138.5613	Hermans et al. [2]
u.KL4	0.52 ± 0.18	Beta	624.4044	576.3733	Rehman et al. [33]
u.TKA	0.52 ± 0.18	Beta	624.4044	576.3733	Rehman et al. [33]
u.FB_pTKA	0.82 ± 0.15	Beta	56604.54	12425.39	NHS data-set [34]
u.NB_pTKA	0.57 ± 0.27	Beta	4388.031	3310.269	NHS data-set [34]
u.rTKA	0.41 ± 0.30	Beta	564.9103	812.9196	NHS data-set [34]



u.FB_pTKA	0.75 ± 0.18	Beta	1687.618	562.5394	NHS data-set [34]
u.NB_pTKA	0.43 ± 0.34	Beta	112.6213	149.2887	NHS data-set [34]
u.DMII	0.79 ± 0.24	Beta	3425.909	910.6847	Nauck et al. [36]

### Probability input parameters

All transition probabilities were based on beta distributions or mean point estimates. The transition probabilities from KL2 to KL3 and KL3 to KL4 were based on the paper by Losina et al. [38], see supplementary Table 3. In this paper Losina made the distinction between obese and non-obese men and women from the United States of America. These transition probabilities allowed to simulate KOA patients in a personalized fashion. However, the reported probabilities were measured for any +1 KL-grade increment. Therefore, the probabilities of moving from KL2 to KL3 and KL3 to KL4 were the same.

Since KOA patients are very heterogeneous in disease progression, the model was complemented with the probability to transition from any KL health state to the TKA state. These transition probabilities were retrieved from the NHS data-set containing Patient Reported Outcome Measures (PROMs) for KOA care. The data set allowed for the calculation of probability distributions stratified for sex, age, and duration of symptoms until TKA. Therefore, for each age and sex category in combination with duration of knee symptoms, a transition probability was calculated, see supplementary Table 3. The data-set originally reports four duration categories, namely:

1. Less than one year of symptoms before surgery, which was adjusted to exactly one year in the model, because the cycle length in the model was one year.
2. Two to five years of symptoms before surgery. After the probability distribution for this category was generated, the individually drawn values for the PSA were divided by four, based on the assumption that a patient in each of those four years has an equal chance of transitioning to TKA.
3. Six to nine years of symptoms before surgery. The same assumption was made for this distribution as for the two to five years category.
4. Ten or more years of symptoms before surgery. Probabilities sampled from the distribution generated for this category were not adjusted post-sampling.

Finally, there was the probability to die in either of the three KL health states. These probabilities were calculated by multiplying the standardized mortality ratio's (SMR's) of KOA patients with the chance of dying reported for the general Dutch population by the Central Bureau for Statistics (CBS) in the Netherlands [43]. An overall SMR was reported for men and women with KOA, but not per KL stage. The SMR for men with KOA was 1.58 and the SMR for women with KOA was 1.52 [40]. Using the SMR's and the data provided by the CBS, probabilities of dying were calculated for various age and sex groups, see supplementary Table 3.

The probability of staying in either K2, KL3 or KL4 was calculated by subtracting the sum of the previously mentioned probabilities, being the probability of dying, progressing in KL-grade and transitioning to TKA, from one.

Once the KOA patient entered the TKA health state, they moved to either the FB\_pTKA, NB\_pTKA or the death health states. The probabilities for FB\_pTKA and NB\_pTKA originally came from the same source [34]. Therefore the sum of these two probabilities already equalled one. The probability to die in the year of TKA was retrieved from a different source [41]. Therefore, these probabilities had to get readjusted to sum to one. This was done by multiplying both the probabilities of transitioning to FB\_pTKA and NB\_pTKA with the chance of dying and subtracting it from the prior respective probabilities. Therefore, if the chance of dying was 0.1, the chance of transitioning to FB\_pTKA was 0.8 and the chance of transitioning to NB\_pTKA was 0.2, than these probabilities would become 0.1, 0.72 and 0.18. The chance of dying was again calculated by multiplying a SMR, of 1.08, with the probabilities of the general Dutch population.

Once the KOA patient was in FB\_pTKA or NB\_pTKA, they would transition to the rTKA, stay in their respective health state or move to the death health state, see figure 1 in the main paper. The probabilities to transition to rTKA implemented in the model were retrieved from a Dutch study, but did not mention the probability to transition for patients that did not experience net benefit, because often times there is only few patients that experience no net benefit and the group average is analysed [39]. For this reason, the assumption was made that the transition probability from either of the two health states to the rTKA health state were the same. Since the authors of the paper reported 6 yearly probabilities, these were transformed to annual transition probabilities, meaning that the alpha and beta parameters of the beta distribution in supplementary Table 3 were based on the six year probabilities, but all the values drawn from the beta distribution were transformed into annual chances. The probability of dying

was the same as for the TKA health state. This probability could get higher as the patient stays multiple years in the same stage, because all probabilities were updated with age. The probability to stay in either FB\_pTKA or NB\_pTKA was calculated by subtracting the sum of progressing or dying from one.

In the rTKA stage a KOA patient could again die, transition to FB\_prTKA or transition to NB\_prTKA. Once again, the probabilities to transition to FB\_prTKA or NB\_prTKA came from one source and the chance of dying came from another source. Therefore, the same normalization method mentioned for the TKA transitions were applied in this stage as well.

In FB\_prTKA and NB\_prTKA patients could either remain in that state or die. The chance of dying was the same as for the rTKA stage and the chance of remaining in the respective states was calculated by subtracting the mortality chance from one. No re-revision stage was added to the model because no data could be found on re-rTKA with regards to transition probabilities to full benefit or no benefit health states or the associated costs and utilities.

*Supplementary Table3. Transition probabilities table including distribution parameters for Monte Carlo simulations. <sup>a</sup>These transition probabilities were representative for any increment in the KL grading scale, meaning from KL2 to KL3 and KL3 to KL4. <sup>b</sup>The alpha and beta values were used to generate a distribution. This distribution was divided by 4, because the assumption was made that each year within the 2-5 year and 6-9 year category, there would be an equal chance of transitioning to TKA. This is already depicted in the mean and SD. <sup>c</sup>The alpha and beta values for the distribution of these transition probabilities were based on 6 year measurement period. Therefore, the distribution was transformed to 1 year transition probabilities, which are depicted in the mean and SD. SD = standard deviation.*

Probability + 1 KL	Mean ± SD	Distribution	Alpha	Beta	Source
Obese & male <sup>a</sup>	0.12 ± 0.03	Beta	15.77	112.91	Losina et al. [38]
Non-obese & male <sup>a</sup>	0.06 ± 0.01	Beta	15.16	256.53	Losina et al. [38]
Obese & female <sup>a</sup>	0.09 ± 0.02	Beta	15.54	158.12	Losina et al. [38]
Non-obese & female <sup>a</sup>	0.04 ± 0.01	Beta	15.02	360.42	Losina et al. [38]
Probability KL → TKA	Mean ± SD	Distribution	Alpha	Beta	Source
1 year & male & 45-59	0.0097 ± 0.005	Beta	4	412	NHS data-set [34]
1 year & male & 60-79	0.0160 ± 0.002	Beta	77	4741	NHS data-set [34]
1 year & male & 80+	0.0133 ± 0.005	Beta	7	521	NHS data-set [34]
1 year & female & 45-59	0.0168 ± 0.005	Beta	14	814	NHS data-set [34]
1 year & female & 60-79	0.0187 ± 0.002	Beta	100	5249	NHS data-set [34]
1 year & female & 80+	0.0287 ± 0.006	Beta	22	747	NHS data-set [34]
2-5 years & male & 45-59 <sup>b</sup>	0.0913 ± 0.006	Beta	152	264	NHS data-set [34]
2-5 years & male & 60-79 <sup>b</sup>	0.1222 ± 0.002	Beta	2355	2463	NHS data-set [34]
2-5 years & male & 80+ <sup>b</sup>	0.1571 ± 0.005	Beta	332	169	NHS data-set [34]
2-5 years & female & 45-59 <sup>b</sup>	0.1235 ± 0.004	Beta	409	419	NHS data-set [34]
2-5 years & female & 60-79 <sup>b</sup>	0.1396 ± 0.002	Beta	2987	2362	NHS data-set [34]
2-5 years & female & 80+ <sup>b</sup>	0.1691 ± 0.004	Beta	520	249	NHS data-set [34]
6-9 years & male & 45-59 <sup>b</sup>	0.0548 ± 0.005	Beta	91	325	NHS data-set [34]
6-9 years & male & 60-79 <sup>b</sup>	0.0642 ± 0.002	Beta	1237	3581	NHS data-set [34]
6-9 years & male & 80+ <sup>b</sup>	0.0516 ± 0.004	Beta	109	419	NHS data-set [34]
6-9 years & female & 45-59 <sup>b</sup>	0.0616 ± 0.004	Beta	204	624	NHS data-set [34]
6-9 years & female & 60-79 <sup>b</sup>	0.0597 ± 0.001	Beta	1278	4071	NHS data-set [34]
6-9 years & female & 80+ <sup>b</sup>	0.0430 ± 0.003	Beta	132	637	NHS data-set [34]
10+ years & male & 45-59	0.4063 ± 0.024	Beta	169	247	NHS data-set [34]
10+ years & male & 60-79	0.2384 ± 0.006	Beta	1149	3669	NHS data-set [34]
10+ years & male & 80+	0.1513 ± 0.016	Beta	80	448	NHS data-set [34]
10+ years & female & 45-59	0.2426 ± 0.015	Beta	201	627	NHS data-set [34]
10+ years & female & 60-79	0.1839 ± 0.005	Beta	984	4365	NHS data-set [34]
10+ years & female & 80+	0.1237 ± 0.012	Beta	95	674	NHS data-set [34]
Probability TKA → FB pTKA	Mean ± SD	Distribution	Alpha	Beta	Source
Male & 45-59	0.8210 ± 0.019	Beta	344	75	NHS data-set [34]
Male & 60-79	0.8193 ± 0.006	Beta	3971	876	NHS data-set [34]
Male & 80+	0.8285 ± 0.016	Beta	440	91	NHS data-set [34]
Female & 45-59	0.7907 ± 0.014	Beta	657	174	NHS data-set [34]
Female & 60-79	0.8268 ± 0.005	Beta	4466	935	NHS data-set [34]
Female & 80+	0.8227 ± 0.0138	Beta	645	139	NHS data-set [34]
Probability FB pTKA → rTKA	Mean ± SD	Distribution	Alpha	Beta	Source
Male & 45-59 <sup>c</sup>	0.0173 ± 0.0004	Beta	1274	11553	Gademan et al. [39]

Male & 60-79 <sup>c</sup>	0.0052 ± 0.0001	Beta	1190	37484	Gademan et al. [39]
Male & 80 <sup>c</sup>	0.0032 ± 0.0003	Beta	118	6103	Gademan et al. [39]
Female & 45-59 <sup>c</sup>	0.0089 ± 0.0002	Beta	1937	35293	Gademan et al. [39]
Female & 60-79 <sup>c</sup>	0.0054 ± 0.0001	Beta	2415	72613	Gademan et al. [39]
Female & 80 <sup>c</sup>	0.0031 ± 0.0002	Beta	352	18505	Gademan et al. [39]
<b>Probability rTKA → FB prTKA</b>	<b>Mean ± SD</b>	<b>Distribution</b>	<b>Alpha</b>	<b>Beta</b>	<b>Source</b>
Male & 45-59	0.7320 ± 0.085	Beta	19	7	NHS data-set [34]
Male & 60-79	0.7247 ± 0.033	Beta	134	51	NHS data-set [34]
Male & 80+	0.8210 ± 0.072	Beta	23	5	NHS data-set [34]
Female & 45-59	0.7151 ± 0.075	Beta	25	10	NHS data-set [34]
Female & 60-79	0.7856 ± 0.029	Beta	158	43	NHS data-set [34]
Female & 80+	0.7890 ± 0.066	Beta	30	8	NHS data-set [34]
<b>Probability KL → D</b>	<b>Mean</b>	<b>Distribution</b>	<b>Source</b>		
Male & 45-64	0.0072	-	Nüesch et al. & CBS [40, 43]		
Male & 65-80	0.0399	-	Nüesch et al. & CBS [40, 43]		
Male & 80-85	0.1111	-	Nüesch et al. & CBS [40, 43]		
Male & 85-90	0.2137	-	Nüesch et al. & CBS [40, 43]		
Male & 90-95	0.3959	-	Nüesch et al. & CBS [40, 43]		
Male & 95+	0.7059	-	Nüesch et al. & CBS [40, 43]		
Female & 45-64	0.0050	-	Nüesch et al. & CBS [40, 43]		
Female & 65-80	0.0268	-	Nüesch et al. & CBS [40, 43]		
Female & 80-85	0.0768	-	Nüesch et al. & CBS [40, 43]		
Female & 85-90	0.1598	-	Nüesch et al. & CBS [40, 43]		
Female & 90-95	0.3150	-	Nüesch et al. & CBS [40, 43]		
Female & 95+	0.5872	-	Nüesch et al. & CBS [40, 43]		
<b>Probability TKA → D</b>	<b>Mean</b>	<b>Distribution</b>	<b>Source</b>		
45-64	0.0042	-	Zhou et al. & CBS [41, 43]		
65-80	0.0232	-	Zhou et al. & CBS [41, 43]		
80-85	0.0652	-	Zhou et al. & CBS [41, 43]		
85-90	0.1298	-	Zhou et al. & CBS [41, 43]		
90-95	0.2472	-	Zhou et al. & CBS [41, 43]		
95+	0.4499	-	Zhou et al. & CBS [41, 43]		
<b>Probability rTKA → D</b>	<b>Mean</b>	<b>Distribution</b>	<b>Source</b>		
45-64	0.0070	-	Inacio et al. & CBS [42, 43]		
65-80	0.0386	-	Inacio et al. & CBS [42, 43]		
80-85	0.1087	-	Inacio et al. & CBS [42, 43]		
85-90	0.2164	-	Inacio et al. & CBS [42, 43]		
90-95	0.4120	-	Inacio et al. & CBS [42, 43]		
95+	0.7498	-	Inacio et al. & CBS [42, 43]		

### Probability DMII

Beside the probabilities to progress or die, there were also probabilities implemented in the model to develop a comorbidity due to the KOA. This comorbidity was DMII as mentioned before. The probabilities to develop DMII was not restricted to the health state that was occupied by the patient. Instead, every cycle, the patient had a chance of developing the comorbidity. The probability of developing DMII was calculated using RR measures from the work of Rahman et al. in combination with Dutch population data [52, 53]. To calculate the probability that an obese, overweight or not overweight KOA patient would develop DMII, we needed the probabilities that a not exposed obese, overweight or not overweight individual would develop DMII. This latter probability would have to be multiplied by the RR to get the probability for a KOA patient. Then the model controls for each cycle whether, using stochastic assignment, someone will develop DMII. After that initial cycle where the patient develops DMII, they remain diabetic until death and keep incurring the DMII related costs and utilities.

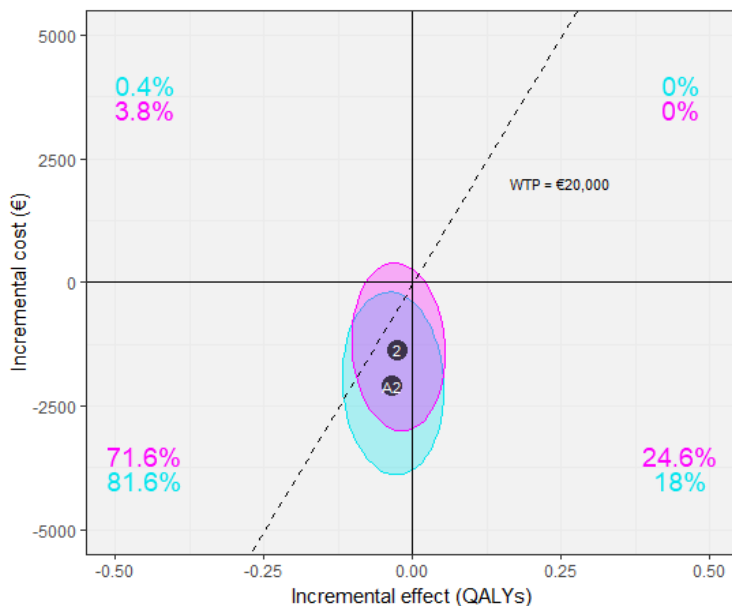
## Supplementary file B

Scenario 2A is an additional analysis to Scenario 2 regarding adherence. In Scenario 2A, the exact same population was tested for the intervention, but an adherence of 100% was assumed to explore the maximum potential effect of the e-health application. Therefore, all other parameters were the same as in Scenario 2.

The scenario analysis showed that there was an average effect loss of 0.04. This was 0.01 percent point lower than in Scenario 2, showing that full adherence is more effective in retaining KOA patients in the conservative phase of the model. At the same time average cost-savings of €2095 were observed in Scenario 2A. These cost-savings were €736 higher than in Scenario 2. The ICER and MAC both had increased compared to in Scenario 2 and were €59119 per QALY and €1386 per person per year, respectively.

The percentage of simulations that were dominant in Scenario 2A were the same as the percentage of simulations that were effective, namely 18%. This was 6.6 percent points lower than in Scenario 2. The probability of the scenario simulations being cost-saving had increased by 3.4 percent points, see supplementary Figure 1.

It had also been observed that the lifetime risk for a TKA and rTKA were 0.89 and 0.09, respectively, and that the reduction in TKAs and rTKAs were 1.6% and 6.2%, respectively.



Supplementary Figure 1. Graph showing PSA results of Scenario 2 in magenta and Scenario 2A in light blue.

## Supplementary file C

The code for the simulation Model consist of three parts. The first part entails the libraries necessary to run the code, standard model input parameters and all of the transition probabilities that will be called by certain functions when certain conditions are met. The basal layout of the code comes from the following source:

Krijkamp EM, Alarid-Escudero F, Enns EA, Jalal HJ, Hunink MGM, Pechlivanoglou P. Microsimulation modeling for health decision sciences using R: A tutorial. *Med Decis Making*. 2018;38(3):400–22.

```
rm(list = ls()) # remove any variables in R's memory
library(truncnorm) # Generate truncated normal distributions
library(ggplot2) # Data visualization
library(dampack) # Estimate Gamma and Beta distributions

## Model input ##
n.i <- 1000 # Number of simulated individuals
n.t <- 50 # Time horizon in years
v.n <- c("KL2", "KL3", "KL4", "TKA", "FB_pTKA", "NB_pTKA", "rTKA", "FB_prTKA", "NB_prTKA", "D") #
Model states
n.s <- length(v.n) # Number of health states
d.c <- 0.03 # Discounting of costs 3%
d.e <- 0.015 # Discounting of QALYs 1.5%
v_names_str <- c("SOC", "E.health") # Store the strategy names
n_str <- length(v_names_str) # Number of strategies
n_sim <- 500 # Number of PSA simulations
seed.all <- 1 # Identical seed for all random processes
RR_SC1 <- 0.95 # Relative risk used to reduce chance of KOA progression
RR.dm_SC1 <- 1 # Relative risk used to lower chance for DMII development

## Data analysis ##
# Annual mortality in general Dutch population. Based on CBS
p.male.45to65.mortality <- 0.0045335
p.female.45to65.mortality <- 0.00328725
p.male.65to80.mortality <- 0.025257
p.female.65to80.mortality <- 0.017613667
p.male.80to85.mortality <- 0.070285
p.female.80to85.mortality <- 0.05053
p.male.85to90.mortality <- 0.135232
p.female.85to90.mortality <- 0.105158
p.male.90to95.mortality <- 0.250561
p.female.90to95.mortality <- 0.207239
p.male.95tox.mortality <- 0.446796
p.female.95tox.mortality <- 0.386342

# Probability of dying in KL2 to KL4, age and sex specific.
SMR_M_KL <- 1.58 # Standardized mortality ratio for men. Based on: https://pubmed.ncbi.nlm.nih.gov/21385807/
SMR_F_KL <- 1.52 # Standardized mortality ratio for women. Based on: https://pubmed.ncbi.nlm.nih.gov/21385807/

p.KLtoD_45to65_M <- p.male.45to65.mortality * SMR_M_KL
p.KLtoD_45to65_F <- p.female.45to65.mortality * SMR_F_KL
p.KLtoD_65to80_M <- p.male.65to80.mortality * SMR_M_KL
p.KLtoD_65to80_F <- p.female.65to80.mortality * SMR_F_KL
p.KLtoD_80to85_M <- p.male.80to85.mortality * SMR_M_KL
p.KLtoD_80to85_F <- p.female.80to85.mortality * SMR_F_KL
p.KLtoD_85to90_M <- p.male.85to90.mortality * SMR_M_KL
p.KLtoD_85to90_F <- p.female.85to90.mortality * SMR_F_KL
p.KLtoD_90to95_M <- p.male.90to95.mortality * SMR_M_KL
p.KLtoD_90to95_F <- p.female.90to95.mortality * SMR_F_KL
p.KLtoD_95tox_M <- p.male.95tox.mortality * SMR_M_KL
p.KLtoD_95tox_F <- p.female.95tox.mortality * SMR_F_KL

# Annual probability of dying in revision TKA, age specific. Based on: https://pubmed.ncbi.nlm.nih.gov/30559011/ AND https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5528856/
```

```

SMR_rTKA <- 1.8 # Joint SMR for men and women
p.45to65.mortality <- 0.003910375
p.65to80.mortality <- 0.021435333
p.80to85.mortality <- 0.0604075
p.85to90.mortality <- 0.120195
p.90to95.mortality <- 0.2289
p.95tox.mortality <- 0.416569

p.rTKAtoD_45to65 <- p.45to65.mortality * SMR_rTKA
p.rTKAtoD_65to80 <- p.65to80.mortality * SMR_rTKA
p.rTKAtoD_80to85 <- p.80to85.mortality * SMR_rTKA
p.rTKAtoD_85to90 <- p.85to90.mortality * SMR_rTKA
p.rTKAtoD_90to95 <- p.90to95.mortality * SMR_rTKA
p.rTKAtoD_95tox <- p.95tox.mortality * SMR_rTKA

# Annual probability of dying in TKA, age specific. Based on: https://pubmed.ncbi.nlm.nih.gov/37279845/
SMR_TKA <- 1.08
p.TKAtoD_45to65 <- p.45to65.mortality * SMR_TKA
p.TKAtoD_65to80 <- p.65to80.mortality * SMR_TKA
p.TKAtoD_80to85 <- p.80to85.mortality * SMR_TKA
p.TKAtoD_85to90 <- p.85to90.mortality * SMR_TKA
p.TKAtoD_90to95 <- p.90to95.mortality * SMR_TKA
p.TKAtoD_95tox <- p.95tox.mortality * SMR_TKA

# Probability of being an obese dutch person stratified by age and sex. Based on:
# https://www.zorginzicht.nl/binaries/content/assets/zorginzicht/kwaliteitsinstrumenten/KNGF-richtlijn+Artrose+heup-knie.PDF AND
# https://www.vzinfo.nl/overgewicht/volwassenen
p.man <- 190400/546100 # probability of KOA patient being male.
p.OB.U65 <- 0.2 # Probability of being obese and under 65 years
p.OW.U65 <- 0.403 # Probability of being overweight and under 65 years
p.OB.O65 <- 0.159 # Probability of being obese and over 65 years
p.OW.O65 <- 0.383 # Probability of being overweight and over 65 years

# Developing diabetes, Based on
# https://www.cbs.nl/nl-nl/nieuws/2022/40/meer-obesitas-en-diabetes-bij-volwassenen-met-arm-oederisico#:~:text=In%202021%20had%205%20procent,zonder%20overgewicht%20\(2%20procent\).
# https://www.hindawi.com/journals/ijr/2014/620920/
rr.DM.O65 <- (0.99 + 1.32)/2 # averaged, because the report it stratified
rr.DM.U65 <- (1.32 + 1.52)/2 # averaged, because the report it stratified
p.DM.U65.OB <- rr.DM.U65 * 0.118 # probability of developing DM2 while under 65 years and obese
p.DM.U65.OW <- rr.DM.U65 * 0.059 # probability of developing DM2 while under 65 years and overweight
p.DM.U65.NW <- rr.DM.U65 * 0.020 # probability of developing DM2 while under 65 years and not overweight
p.DM.O65.OB <- rr.DM.O65 * 0.225 # probability of developing DM2 while over 65 years and obese
p.DM.O65.OW <- rr.DM.O65 * 0.140 # probability of developing DM2 while over 65 years and overweight
p.DM.O65.NW <- rr.DM.O65 * 0.063 # probability of developing DM2 while over 65 years and not overweight

# Dissatisfied patient cost factor
set.seed(seed.all)
ds_NB_pTKA <- mean(rnorm(100000, 21156.18, 137107.72)) / mean(rnorm(100000, 13453.84, 42446.40)) # https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9451500/
set.seed(NULL)

## Functions ##
gen_psa <- function(n_sim = n_sim, seed = seed.all){ # Function that generates input parameter distributions for PSA
  set.seed(seed)
  df_psa <- data.frame(

```

```

p.adh = rbeta(n_sim, 184, 100), # Distribution for probability of being adherent to the intervention
c.DMII = rgamma(n_sim, shape = 99.40388, scale = 60.48054), # Distribution for costdata when a patient is diabetic

p.t1_M_40to59 = rbeta(n_sim, 4, 412), # Distribution for probability to transition to TKA after 1 year of symptoms when 40-59 year old man
p.t2to5_M_40to59 = (rbeta(n_sim, 152, 264) / 4), # Distribution for probability to transition to TKA after 2-5 year of symptoms when 40-59 year old man
p.t6to9_M_40to59 = (rbeta(n_sim, 91, 325) / 4), # Distribution for probability to transition to TKA after 6-9 year of symptoms when 40-59 year old man
p.t10tox_M_40to59 = rbeta(n_sim, 169, 247), # Distribution for probability to transition to TKA after 10+ year of symptoms when 40-59 year old man

p.t1_M_60to80 = rbeta(n_sim, 77, 4741), # Distribution for probability to transition to TKA after 1 year of symptoms when 60-80 year old man
p.t2to5_M_60to80 = (rbeta(n_sim, 2355, 2463) / 4), # Distribution for probability to transition to TKA after 2-5 year of symptoms when 60-80 year old man
p.t6to9_M_60to80 = (rbeta(n_sim, 1237, 3581) / 4), # Distribution for probability to transition to TKA after 6-9 year of symptoms when 60-80 year old man
p.t10tox_M_60to80 = rbeta(n_sim, 1149, 3669), # Distribution for probability to transition to TKA after 10+ year of symptoms when 60-80 year old man

p.t1_M_80tox = rbeta(n_sim, 7, 521), # Distribution for probability to transition to TKA after 1 year of symptoms when 80+ year old man
p.t2to5_M_80tox = (rbeta(n_sim, 332, 196) / 4), # Distribution for probability to transition to TKA after 2-5 year of symptoms when 80+ year old man
p.t6to9_M_80tox = (rbeta(n_sim, 109, 419) / 4), # Distribution for probability to transition to TKA after 6-9 year of symptoms when 80+ year old man
p.t10tox_M_80tox = rbeta(n_sim, 80, 448), # Distribution for probability to transition to TKA after 10+ year of symptoms when 80+ year old man

p.t1_F_40to59 = rbeta(n_sim, 14, 814), # Distribution for probability to transition to TKA after 1 year of symptoms when 40-59 year old woman
p.t2to5_F_40to59 = (rbeta(n_sim, 409, 419) / 4), # Distribution for probability to transition to TKA after 2-5 year of symptoms when 40-59 year old woman
p.t6to9_F_40to59 = (rbeta(n_sim, 204, 624) / 4), # Distribution for probability to transition to TKA after 6-9 year of symptoms when 40-59 year old woman
p.t10tox_F_40to59 = rbeta(n_sim, 201, 627), # Distribution for probability to transition to TKA after 10+ year of symptoms when 40-59 year old woman

p.t1_F_60to80 = rbeta(n_sim, 100, 5249), # Distribution for probability to transition to TKA after 1 year of symptoms when 60-80 year old woman
p.t2to5_F_60to80 = (rbeta(n_sim, 2987, 2362) / 4), # Distribution for probability to transition to TKA after 2-5 year of symptoms when 60-80 year old woman
p.t6to9_F_60to80 = (rbeta(n_sim, 1278, 4071) / 4), # Distribution for probability to transition to TKA after 6-9 year of symptoms when 60-80 year old woman
p.t10tox_F_60to80 = rbeta(n_sim, 984, 4365), # Distribution for probability to transition to TKA after 10+ year of symptoms when 60-80 year old woman

p.t1_F_80tox = rbeta(n_sim, 22, 747), # Distribution for probability to transition to TKA after 1 year of symptoms when 80+ year old woman
p.t2to5_F_80tox = (rbeta(n_sim, 520, 249) / 4), # Distribution for probability to transition to TKA after 2-5 year of symptoms when 80+ year old woman
p.t6to9_F_80tox = (rbeta(n_sim, 132, 637) / 4), # Distribution for probability to transition to TKA after 6-9 year of symptoms when 80+ year old woman
p.t10tox_F_80tox = rbeta(n_sim, 95, 674), # Distribution for probability to transition to TKA after 10+ year of symptoms when 80+ year old woman

# Probability of +1 KL
p.KL_M_0 = rbeta(n_sim, 15.77727, 112.9117), # Probability to transition 1 KL-stage when male and obese
p.KL_F_0 = rbeta(n_sim, 15.54264, 158.1182), # Probability to transition 1 KL-stage when female and obese

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```

    p.KL_M = rbeta(n_sim, 15.16028, 256.5293), # Probability to transition 1 KL-stage when male and not obese
    p.KL_F = rbeta(n_sim, 15.01735, 360.4163), # Probability to transition 1 KL-stage when female and not obese

    # Probability TKA to FB_pTKA (NBp = 1-p)
    p.TKA_FBp_M_45to60 = rbeta(n_sim, 344, 75), # Probability TKA to FB_pTKA for 45 to 60 year old men
    p.TKA_FBp_F_45to60 = rbeta(n_sim, 657, 174), # Probability TKA to FB_pTKA for 45 to 60 year old women
    p.TKA_FBp_M_60to80 = rbeta(n_sim, 3971, 876), # Probability TKA to FB_pTKA for 60 to 80 year old men
    p.TKA_FBp_F_60to80 = rbeta(n_sim, 4466, 935), # Probability TKA to FB_pTKA for 60 to 80 year old women
    p.TKA_FBp_M_80tox = rbeta(n_sim, 440, 91), # Probability TKA to FB_pTKA for 80+ year old men
    p.TKA_FBp_F_80tox = rbeta(n_sim, 645, 139), # Probability TKA to FB_pTKA for 80+ year old women

    # Probability rTKA to FB_prTKA (NBpr = 1-p)
    p.rTKA_FBpr_M_45to60 = rbeta(n_sim, 19, 7), # Probability rTKA to FB_prTKA for 45 to 60 year old men
    p.rTKA_FBpr_F_45to60 = rbeta(n_sim, 25, 10), # Probability rTKA to FB_prTKA for 45 to 60 year old women
    p.rTKA_FBpr_M_60to80 = rbeta(n_sim, 134, 51), # Probability rTKA to FB_prTKA for 60 to 80 year old men
    p.rTKA_FBpr_F_60to80 = rbeta(n_sim, 158, 43), # Probability rTKA to FB_prTKA for 60 to 80 year old women
    p.rTKA_FBpr_M_80tox = rbeta(n_sim, 23, 5), # Probability rTKA to FB_prTKA for 80+ year old men
    p.rTKA_FBpr_F_80tox = rbeta(n_sim, 30, 8), # Probability rTKA to FB_prTKA for 80+ year old women

    # Probability FB or NB post primary TKA to revision TKA
    p.FB.NBp_rTKA_M_45to65 = 1 - ((1 - rbeta(n_sim, 1274, 11553))^(1/6)), # Probability FB or NB post primary TKA to revision TKA for 45 to 60 year old men
    p.FB.NBp_rTKA_F_45to65 = 1 - ((1 - rbeta(n_sim, 1937, 35293))^(1/6)), # Probability FB or NB post primary TKA to revision TKA for 45 to 60 year old women
    p.FB.NBp_rTKA_M_65to80 = 1 - ((1 - rbeta(n_sim, 1190, 37484))^(1/6)), # Probability FB or NB post primary TKA to revision TKA for 60 to 80 year old men
    p.FB.NBp_rTKA_F_65to80 = 1 - ((1 - rbeta(n_sim, 2415, 72613))^(1/6)), # Probability FB or NB post primary TKA to revision TKA for 60 to 80 year old women
    p.FB.NBp_rTKA_M_80tox = 1 - ((1 - rbeta(n_sim, 118, 6103))^(1/6)), # Probability FB or NB post primary TKA to revision TKA for 80+ year old men
    p.FB.NBp_rTKA_F_80tox = 1 - ((1 - rbeta(n_sim, 352, 18505))^(1/6)), # Probability FB or NB post primary TKA to revision TKA for 80+ year old women
  )
  return(df_psa)
}

# Function to Look-up transition probability from conservative health stages to TKA based on duration of symptoms, sex and age
# tx, where x is the number of years with symptoms before surgery
# M = male; F = Female
# x1tox2, where x1 and x2 describe the age category
prob_t <- function(i){
  df_l_2TKA <- expand.grid(Age = c(45:150), Sex = c(0,1), Cycle = c(1:n.t))
  df_l_2TKA$Probability <- NA

  df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 40:60 & df_l_2TKA$Sex == 1 & df_l_2TKA$Cycle == 1)] <- df_psa_input_SC1$p.t1_M_40to59[i]
  df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 60:80 & df_l_2TKA$Sex == 1 & df_l_2TKA$Cycle == 1)] <- df_psa_input_SC1$p.t1_M_60to80[i]
  df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 80:150 & df_l_2TKA$Sex == 1 & df_l_2TKA$Cycle == 1)] <- df_psa_input_SC1$p.t1_M_80tox[i]
}

```



```

df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 40:60 & df_l_2TKA$Sex == 0 & df_l_2TKA$C
ycle == 1)] <- df_psa_input_SC1$p.t1_F_40to59[i]
df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 60:80 & df_l_2TKA$Sex == 0 & df_l_2TKA$C
ycle == 1)] <- df_psa_input_SC1$p.t1_F_60to80[i]
df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 80:150 & df_l_2TKA$Sex == 0 & df_l_2TKA$C
ycle == 1)] <- df_psa_input_SC1$p.t1_F_80tox[i]

df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 40:60 & df_l_2TKA$Sex == 1 & df_l_2TKA$C
ycle %in% 2:5)] <- df_psa_input_SC1$p.t2to5_M_40to59[i]
df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 60:80 & df_l_2TKA$Sex == 1 & df_l_2TKA$C
ycle %in% 2:5)] <- df_psa_input_SC1$p.t2to5_M_60to80[i]
df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 80:150 & df_l_2TKA$Sex == 1 & df_l_2TKA$C
ycle %in% 2:5)] <- df_psa_input_SC1$p.t2to5_M_80tox[i]

df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 40:60 & df_l_2TKA$Sex == 0 & df_l_2TKA$C
ycle %in% 2:5)] <- df_psa_input_SC1$p.t2to5_F_40to59[i]
df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 60:80 & df_l_2TKA$Sex == 0 & df_l_2TKA$C
ycle %in% 2:5)] <- df_psa_input_SC1$p.t2to5_F_60to80[i]
df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 80:150 & df_l_2TKA$Sex == 0 & df_l_2TKA$C
ycle %in% 2:5)] <- df_psa_input_SC1$p.t2to5_F_80tox[i]

df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 40:60 & df_l_2TKA$Sex == 1 & df_l_2TKA$C
ycle %in% 6:9)] <- df_psa_input_SC1$p.t6to9_M_40to59[i]
df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 60:80 & df_l_2TKA$Sex == 1 & df_l_2TKA$C
ycle %in% 6:9)] <- df_psa_input_SC1$p.t6to9_M_60to80[i]
df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 80:150 & df_l_2TKA$Sex == 1 & df_l_2TKA$C
ycle %in% 6:9)] <- df_psa_input_SC1$p.t6to9_M_80tox[i]

df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 40:60 & df_l_2TKA$Sex == 0 & df_l_2TKA$C
ycle %in% 6:9)] <- df_psa_input_SC1$p.t6to9_F_40to59[i]
df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 60:80 & df_l_2TKA$Sex == 0 & df_l_2TKA$C
ycle %in% 6:9)] <- df_psa_input_SC1$p.t6to9_F_60to80[i]
df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 80:150 & df_l_2TKA$Sex == 0 & df_l_2TKA$C
ycle %in% 6:9)] <- df_psa_input_SC1$p.t6to9_F_80tox[i]

df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 40:60 & df_l_2TKA$Sex == 1 & df_l_2TKA$C
ycle %in% 10:n.t)] <- df_psa_input_SC1$p.t10tox_M_40to59[i]
df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 60:80 & df_l_2TKA$Sex == 1 & df_l_2TKA$C
ycle %in% 10:n.t)] <- df_psa_input_SC1$p.t10tox_M_60to80[i]
df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 80:150 & df_l_2TKA$Sex == 1 & df_l_2TKA$C
ycle %in% 10:n.t)] <- df_psa_input_SC1$p.t10tox_M_80tox[i]

df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 40:60 & df_l_2TKA$Sex == 0 & df_l_2TKA$C
ycle %in% 10:n.t)] <- df_psa_input_SC1$p.t10tox_F_40to59[i]
df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 60:80 & df_l_2TKA$Sex == 0 & df_l_2TKA$C
ycle %in% 10:n.t)] <- df_psa_input_SC1$p.t10tox_F_60to80[i]
df_l_2TKA$Probability[which(df_l_2TKA$Age %in% 80:150 & df_l_2TKA$Sex == 0 & df_l_2TKA$C
ycle %in% 10:n.t)] <- df_psa_input_SC1$p.t10tox_F_80tox[i]

return(df_l_2TKA)
}

Probs <- function(M_it, Trt, i, t, RR_SC1){
  p.KL2_3 <- p.KL3_4 <- ifelse(df_Char_SC1$male[i] == 1 & df_Char_SC1$Obese[i] == "Obese",
p.KL_M_0,
  ifelse(df_Char_SC1$male[i] == 0 & df_Char_SC1$Obese[i] == "Obese",
p.KL_F_0,
  ifelse(df_Char_SC1$male[i] == 1 & df_Char_SC1$Obese[i] != "Obese",
p.KL_M, p.KL_F))) # Probability to progress 1 KL state based on sex and BMI

  p.KL_D <- ifelse(m.AGE_SC1[i, t] < 65 & df_Char_SC1$male[i] == 1, p.KLtoD_45to65_M,
  ifelse(m.AGE_SC1[i, t] < 80 & m.AGE_SC1[i, t] >= 65 & df_Char_SC1$male[i] == 1,
p.KLtoD_65to80_M,

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        ifelse(m.AGE_SC1[i, t] < 85 & m.AGE_SC1[i, t] >= 80 & df_Char_SC1$male[i] == 1,
p.KLtoD_80to85_M,
        ifelse(m.AGE_SC1[i, t] < 90 & m.AGE_SC1[i, t] >= 85 & df_Char_SC1$male[i] == 1,
p.KLtoD_85to90_M,
        ifelse(m.AGE_SC1[i, t] < 95 & m.AGE_SC1[i, t] >= 90 & df_Char_SC1$male[i] == 1,
p.KLtoD_90to95_M,
        ifelse(m.AGE_SC1[i, t] >= 95 & df_Char_SC1$male[i] == 1, p.KLtoD_95tox_M,
        ifelse(m.AGE_SC1[i, t] < 65 & df_Char_SC1$male[i] == 0, p.KLtoD_45to65_F,
        ifelse(m.AGE_SC1[i, t] < 80 & m.AGE_SC1[i, t] >= 65 & df_Char_SC1$male[i] == 0,
p.KLtoD_65to80_F,
        ifelse(m.AGE_SC1[i, t] < 85 & m.AGE_SC1[i, t] >= 80 & df_Char_SC1$male[i] == 0,
p.KLtoD_80to85_F,
        ifelse(m.AGE_SC1[i, t] < 90 & m.AGE_SC1[i, t] >= 85 & df_Char_SC1$male[i] == 0,
p.KLtoD_85to90_F,
        ifelse(m.AGE_SC1[i, t] < 95 & m.AGE_SC1[i, t] >= 90 & df_Char_SC1$male[i] == 0,
p.KLtoD_90to95_F, # Probability to die from KL stages
p.KLtoD_95tox_F))))))))))

p.TKA_FBP <- ifelse(m.AGE_SC1[i, t] <= 60 & df_Char_SC1$male[i] == 1, p.TKA_FBP_M_45to60,
        ifelse(m.AGE_SC1[i, t] <= 80 & m.AGE_SC1[i, t] > 60 & df_Char_SC1$male[i] ==
1, p.TKA_FBP_M_60to80,
        ifelse(m.AGE_SC1[i, t] > 80 & df_Char_SC1$male[i] == 1, p.TKA_FBP_M_80tox,
        ifelse(m.AGE_SC1[i, t] <= 60 & df_Char_SC1$male[i] == 0, p.TKA_FBP_F_45to60,
        ifelse(m.AGE_SC1[i, t] <= 80 & m.AGE_SC1[i, t] > 60 & df_Char_SC1$male[i] ==
0, p.TKA_FBP_F_60to80, p.TKA_FBP_F_80tox)))) # Probability to experience full benefit post
-TKA based on sex and age

p.TKA_D <- p.FBP_D <- p.NBP_D <- ifelse(m.AGE_SC1[i, t] < 65, p.TKAtD_45to65,
        ifelse(m.AGE_SC1[i, t] < 80 & m.AGE_SC1[i, t] >= 65, p.T
KAtoD_65to80,
        ifelse(m.AGE_SC1[i, t] < 85 & m.AGE_SC1[i, t] >= 80, p.T
KAtoD_80to85,
        ifelse(m.AGE_SC1[i, t] < 90 & m.AGE_SC1[i, t] >= 85, p.T
KAtoD_85to90,
        ifelse(m.AGE_SC1[i, t] < 95 & m.AGE_SC1[i, t] >= 90, p.T
KAtoD_90to95, p.TKAtD_95tox)))) # Probability to die from primary surgical stages based o
n age

p.KL2_TKA <- p.KL3_TKA <- p.KL4_TKA <- df_prob_t_SC1$Probability[df_prob_t_SC1$Sex == df_
Char_SC1$male[i] & df_prob_t_SC1$Age == m.AGE_SC1[i, t] & df_prob_t_SC1$Cycle == t]

p.TKA_FBP <- p.TKA_FBP - (p.TKA_FBP * p.TKA_D)
p.TKA_NBP <- 1 - p.TKA_FBP - p.TKA_D

p.FBP_rTKA <- p.NBP_rTKA <- ifelse(m.AGE_SC1[i, t] <= 65 & df_Char_SC1$male[i] == 1, p.FB
.NBP_rTKA_M_45to65,
        ifelse(m.AGE_SC1[i, t] <= 80 & m.AGE_SC1[i, t] > 65 & df_Char
_SC1$male[i] == 1, p.FB.NBP_rTKA_M_65to80,
        ifelse(m.AGE_SC1[i, t] > 80 & df_Char_SC1$male[i] == 1, p.FB.
NBP_rTKA_M_80tox,
        ifelse(m.AGE_SC1[i, t] <= 65 & df_Char_SC1$male[i] == 0, p.FB
.NBP_rTKA_F_45to65,
        ifelse(m.AGE_SC1[i, t] <= 80 & m.AGE_SC1[i, t] > 65 & df_Char
_SC1$male[i] == 0, p.FB.NBP_rTKA_F_65to80,
        p.FB.NBP_rTKA_F_80tox)))) # Probability to need revision TKA
based on sex and age

p.rTKA_FBpr <- ifelse(m.AGE_SC1[i, t] <= 60 & df_Char_SC1$male[i] == 1, p.rTKA_FBpr_M_45t
o60,
        ifelse(m.AGE_SC1[i, t] <= 80 & m.AGE_SC1[i, t] > 60 & df_Char_SC1$male[i]
== 1, p.rTKA_FBpr_M_60to80,
        ifelse(m.AGE_SC1[i, t] > 80 & df_Char_SC1$male[i] == 1, p.rTKA_FBpr_M_80to
x,
        ifelse(m.AGE_SC1[i, t] <= 60 & df_Char_SC1$male[i] == 0, p.rTKA_FBpr_F_45t
o60,

```

```

        ifelse(m.AGE_SC1[i, t] <= 80 & m.AGE_SC1[i, t] > 60 & df_Char_SC1$male[i]
== 0, p.rTKA_FBpr_F_60to80,
        p.rTKA_FBpr_F_80tox)))) # Probability to experience full benefit post-rTK
A

p.rTKA_D <- p.NBpr_D <- p.FBpr_D <- ifelse(m.AGE_SC1[i, t] < 65, p.rTKAtoD_45to65,
ifelse(m.AGE_SC1[i, t] < 80 & m.AGE_SC1[i, t] >= 65,
p.rTKAtoD_65to80,
ifelse(m.AGE_SC1[i, t] < 85 & m.AGE_SC1[i, t] >= 80,
p.rTKAtoD_80to85,
ifelse(m.AGE_SC1[i, t] < 90 & m.AGE_SC1[i, t] >= 85,
p.rTKAtoD_85to90,
ifelse(m.AGE_SC1[i, t] < 95 & m.AGE_SC1[i, t] >= 90,
p.rTKAtoD_90to95,
p.rTKAtoD_95tox)))) # Probability to die after revis
ion TKA stages

p.rTKA_FBpr <- p.rTKA_FBpr - (p.rTKA_FBpr * p.rTKA_D)
p.rTKA_NBpr <- 1 - p.rTKA_FBpr - p.rTKA_D

p.KL2_TKA <- RR_SC1 * p.KL2_TKA #readjusting of probabilities based on RR
p.KL3_TKA <- RR_SC1 * p.KL3_TKA #readjusting of probabilities based on RR
p.KL4_TKA <- RR_SC1 * p.KL4_TKA #readjusting of probabilities based on RR
p.KL2_3 <- RR_SC1 * p.KL2_3 #readjusting of probabilities based on RR
p.KL3_4 <- RR_SC1 * p.KL3_4 #readjusting of probabilities based on RR

p.KL2_2 <- 1 - p.KL2_3 - p.KL2_TKA - p.KL_D
p.KL3_3 <- 1 - p.KL3_4 - p.KL3_TKA - p.KL_D
p.KL4_4 <- 1 - p.KL4_TKA - p.KL_D
p.FBpr_FBpr <- 1 - p.FBpr_D
p.NBpr_NBpr <- 1 - p.NBpr_D

v.p.it <- rep(NA, n.s)
names(v.p.it) <- v.n

v.p.it[M_it == "KL2"] <- c(p.KL2_2, p.KL2_3, 0, p.KL2_TKA, 0, 0, 0, 0, 0, p.KL_D)
v.p.it[M_it == "KL3"] <- c(0, p.KL3_3, p.KL3_4, p.KL3_TKA, 0, 0, 0, 0, 0, p.KL_D)
v.p.it[M_it == "KL4"] <- c(0, 0, p.KL4_4, p.KL4_TKA, 0, 0, 0, 0, 0, p.KL_D)
v.p.it[M_it == "TKA"] <- c(0, 0, 0, 0, p.TKA_FBpr, p.TKA_NBpr, 0, 0, 0, p.TKA_D)
v.p.it[M_it == "FB_pTKA"] <- c(0, 0, 0, 0, (1-p.FBpr_rTKA-p.FBpr_D), 0, p.FBpr_rTKA, 0, 0, p.FBpr_D)
v.p.it[M_it == "NB_pTKA"] <- c(0, 0, 0, 0, (1-p.NBpr_rTKA-p.NBpr_D), p.NBpr_rTKA, 0, 0, p.NBpr_D)
v.p.it[M_it == "rTKA"] <- c(0, 0, 0, 0, 0, 0, 0, p.rTKA_FBpr, p.rTKA_NBpr, p.rTKA_D)
v.p.it[M_it == "FB_prTKA"] <- c(0, 0, 0, 0, 0, 0, 0, p.FBpr_FBpr, 0, p.FBpr_D)
v.p.it[M_it == "NB_prTKA"] <- c(0, 0, 0, 0, 0, 0, 0, p.NBpr_NBpr, p.NBpr_D)
v.p.it[M_it == "D"] <- c(0, 0, 0, 0, 0, 0, 0, 0, 0, 1)
ifelse(all.equal(sum(v.p.it), 1), return(v.p.it), print("Probabilities do not sum to 1"))
}

# Calculation of costs associated with each health state
Costs <- function (M_it, Trt = FALSE, c.KL2, c.KL3, c.KL4, c.TKA, c.TKA.prod, c.FB_pTKA, c.
NB_pTKA, c.rTKA) {
  c.it <- 0
  c.it[M_it == "KL2"] <- c.KL2/0.75
  c.it[M_it == "KL3"] <- c.KL3/0.75
  c.it[M_it == "KL4"] <- c.KL4/0.75
  c.it[M_it == "TKA"] <- c.TKA + c.TKA.prod
  c.it[M_it == "FB_pTKA"] <- c.FB_pTKA
  c.it[M_it == "NB_pTKA"] <- c.NB_pTKA * ds_NB_pTKA
  c.it[M_it == "rTKA"] <- c.rTKA + (1.5 * c.TKA.prod)
  c.it[M_it == "FB_prTKA"] <- 1.5 * c.FB_pTKA
  c.it[M_it == "NB_prTKA"] <- 1.5 * c.NB_pTKA * ds_NB_pTKA
  c.it[M_it == "D"] <- 0

  return(c.it)
}

```

```

}

# Calculation of effects associated with each health state
Effs <- function(M_it, Trt = FALSE, c1 = 1, u.KL2, u.KL3, u.KL4, u.TKA, u.FB_pTKA, u.NB_pTKA, u.rTKA, u.FB_prTKA, u.NB_prTKA) {
  u.it <- 0
  u.it[M_it == "KL2"] <- u.KL2
  u.it[M_it == "KL3"] <- u.KL3
  u.it[M_it == "KL4"] <- u.KL4
  u.it[M_it == "TKA"] <- u.TKA
  u.it[M_it == "FB_pTKA"] <- u.FB_pTKA
  u.it[M_it == "NB_pTKA"] <- u.NB_pTKA
  u.it[M_it == "rTKA"] <- u.rTKA
  u.it[M_it == "FB_prTKA"] <- u.FB_prTKA
  u.it[M_it == "NB_prTKA"] <- u.NB_prTKA
  u.it[M_it == "D"] <- 0
  QALYs <- u.it * c1
  return(QALYs)
}

# Function to keep track of patient age
AGE <- function(M_it, i, t) {
  age <- df_Char_SC1$age[i]
  age <- if (M_it != "D") {
    age + t # each year age grows with 1 year
  } else {
    0 # age remains unchanged if M_it is "D"
  }
  return(age)
}

# Function that determines whether someone develops DMII or has DMII based on age and BMI
DMII_func <- function(M_it, i, t, RR.dm_SC1){
  DM2_present <- ifelse((m.AGE_SC1[i, t + 1] < 65) & (df_Char_SC1$Obese[i] == "Obese") & (runif(1) < (RR.dm_SC1 * p.DM.U65.OB)) | m.DMII_SC1[i, t] == 1, 1,
    ifelse((m.AGE_SC1[i, t + 1] < 65) & (df_Char_SC1$Obese[i] == "Overweight") & (runif(1) < (RR.dm_SC1 * p.DM.U65.OW)) | m.DMII_SC1[i, t] == 1, 1,
    ifelse((m.AGE_SC1[i, t + 1] < 65) & (df_Char_SC1$Obese[i] == "Not overweight") & (runif(1) < (RR.dm_SC1 * p.DM.U65.NW)) | m.DMII_SC1[i, t] == 1, 1,
    ifelse((m.AGE_SC1[i, t + 1] >= 65) & (df_Char_SC1$Obese[i] == "Obese") & (runif(1) < (RR.dm_SC1 * p.DM.O65.OB)) | m.DMII_SC1[i, t] == 1, 1,
    ifelse((m.AGE_SC1[i, t + 1] >= 65) & (df_Char_SC1$Obese[i] == "Overweight") & (runif(1) < (RR.dm_SC1 * p.DM.O65.OW)) | m.DMII_SC1[i, t] == 1, 1,
    ifelse((m.AGE_SC1[i, t + 1] >= 65) & (df_Char_SC1$Obese[i] == "Not overweight") & (runif(1) < (RR.dm_SC1 * p.DM.O65.NW)) | m.DMII_SC1[i, t] == 1, 1, 0))))))

  if (M_it == "D") {DM2_present <- 0}
  return(DM2_present)
}

# Generate patient characteristics table
set.seed(seed.all)
df_Char_SC1 <- data.frame(male = ifelse(runif(n.i) < p.man, 1, 0), # Gender:
  1 = Male, 0 = Female
  age = round(rtruncnorm(n.i, a = 45, mean = 53.2, sd = 7.4))) # Generate population based on Hermans et al., which used Dutch patients
set.seed(NULL)

# Function that performs the patient simulations and stores costs, effects and other outcomes
MicroSim <- function(n.i, n.t, v.n, X = NULL, d.c, d.e, TR.out = FALSE, TS.out = FALSE, Trt = FALSE, seed = seed.all, RR_SC1, drawn_values_SC1, RR.dm_SC1) {
  set.seed(seed)
  v.dwc <- 1 / ((1 + d.c) ^ (0:n.t))
  v.dwe <- 1 / ((1 + d.e) ^ (0:n.t))

```

```

# create the matrix capturing the state name/costs/health outcomes for all individuals at
each time point
m.DMII_SC1 <- m.AGE_SC1 <- m.M_SC1 <- m.C_SC1 <- m.E_SC1 <- matrix(nrow = n.i, ncol
= n.t + 1,
                                                                    dimnames = list(p
aste("ind", 1:n.i, sep = " "),
                                                                    p
aste("cycle", 0:n.t, sep = " ")))
#####
# Complement the patient characteristics table
df_Char_SC1$Obese <- ifelse((df_Char_SC1$age >= 65) & (runif(n.i) < p.OB.065), "Obese",
                           ifelse((df_Char_SC1$age >= 65) & (runif(n.i) < p.OW.065), "O
verweight",
                           ifelse((df_Char_SC1$age < 65) & (runif(n.i) < p.OB.U6
5), "Obese",
                           ifelse((df_Char_SC1$age < 65) & (runif(n.i) <
p.OW.U65), "Overweight",
                           "Notoverweight"))))
df_Char_SC1$u.DMII <- qbeta(drawn_values_SC1, 3425.909, 910.6847)
#####
m.M_SC1[, 1] <- rep("KL2", n.i) # ALL patients start at KL2
m.DMII_SC1[, 1] <- rep(0, n.i) # ALL patients start without DMII

for (i in 1:n.i) { # Run simulation for every individual
  set.seed(seed + i) # set the seed for every individual for the random number generator
  m.AGE_SC1[i, 1] <- df_Char_SC1$age[i]
  m.E_SC1[i, 1] <- Effs(m.M_SC1[i, 1], Trt, u.KL2 = df_ut_SC1$u.KL2[i], u.KL3 = df_ut_SC
1$u.KL3[i], u.KL4 = df_ut_SC1$u.KL4[i],
                      u.TKA = df_ut_SC1$u.TKA[i], u.FB_pTKA = df_ut_SC1$u.FB_pTKA[i],
u.NB_pTKA = df_ut_SC1$u.NB_pTKA[i], u.rTKA = df_ut_SC1$u.rTKA[i],
                      u.FB_prTKA = df_ut_SC1$u.FB_prTKA[i], u.NB_prTKA = df_ut_SC1$u.N
B_prTKA[i])
  m.C_SC1[i, 1] <- Costs(m.M_SC1[i, 1], Trt, c.KL2 = df_ct_SC1$c.KL2[i], c.KL3 = df_ct_S
C1$c.KL3[i], c.KL4 = df_ct_SC1$c.KL4[i],
                      c.TKA = df_ct_SC1$c.TKA[i], c.TKA.prod = df_ct_SC1$c.TKA.prod[i
], c.FB_pTKA = df_ct_SC1$c.FB_pTKA[i],
                      c.NB_pTKA = df_ct_SC1$c.NB_pTKA, c.rTKA = df_ct_SC1$c.rTKA)

  for (t in 1:n.t) { # For Loop stepping through each cycle
    if (Trt == TRUE & m.p.adh_SC1$p.adh[i] == 1) { # For 100% adherence, remove 2nd condit
ion
      v.p <- Probs(m.M_SC1[i, t], Trt, i, t, RR_SC1)
    } else {
      v.p <- Probs(m.M_SC1[i, t], Trt, i, t, RR_SC1 = 1)
    }

    m.M_SC1[i, t + 1] <- sample(v.n, prob = v.p, size = 1)
    m.AGE_SC1[i, t + 1] <- AGE(m.M_SC1[i, t + 1], i, t)
    m.E_SC1[i, t + 1] <- Effs(m.M_SC1[i, t + 1], Trt, u.KL2 = df_ut_SC1$u.KL2[i], u.KL3
= df_ut_SC1$u.KL3[i], u.KL4 = df_ut_SC1$u.KL4[i],
                          u.TKA = df_ut_SC1$u.TKA[i], u.FB_pTKA = df_ut_SC1$u.FB_pT
KA[i], u.NB_pTKA = df_ut_SC1$u.NB_pTKA[i], u.rTKA = df_ut_SC1$u.rTKA[i],
                          u.FB_prTKA = df_ut_SC1$u.FB_prTKA[i], u.NB_prTKA = df_ut_
SC1$u.NB_prTKA[i])
    m.C_SC1[i, t + 1] <- Costs(m.M_SC1[i, t + 1], Trt, c.KL2 = df_ct_SC1$c.KL2[i], c.KL3
= df_ct_SC1$c.KL3[i], c.KL4 = df_ct_SC1$c.KL4[i],
                          c.TKA = df_ct_SC1$c.TKA[i], c.TKA.prod = df_ct_SC1$c.TKA.
prod[i], c.FB_pTKA = df_ct_SC1$c.FB_pTKA[i],
                          c.NB_pTKA = df_ct_SC1$c.NB_pTKA, c.rTKA = df_ct_SC1$c.rTK
A)

  } # close the loop for the time points
  if(i/100 == round(i/100,0)) { # display the progress of the simulation

```

```

    cat('\r', paste(i/n.i * 100, "% done", sep = ""))
  }
} # close the loop for the individuals

# After all the dataframes are filled, a separate loop is started to readjust costs and effects based on DMII status
for (i in 1:n.i) {
  for (t in 1:n.t) {

    if (Trt == TRUE & m.p.adh_SC1$p.adh[i] == 1) {# For 100% adherence, remove 2nd condition
      m.DMII_SC1[i, t + 1] <- DMII_func(m.M_SC1[i, t + 1], i, t, RR.dm_SC1 = RR.dm_SC1)
    } else {
      m.DMII_SC1[i, t + 1] <- DMII_func(m.M_SC1[i, t + 1], i, t, RR.dm_SC1 = 1)
    }

    if (m.DMII_SC1[i, t + 1] == 1){
      m.C_SC1[i, t + 1] <- m.C_SC1[i, t + 1] + c.DMII
      m.E_SC1[i, t + 1] <- m.E_SC1[i, t + 1] * df_Char_SC1$u.DMII[i]
    }else{
      m.C_SC1[i, t + 1] <- m.C_SC1[i, t + 1]
      m.E_SC1[i, t + 1] <- m.E_SC1[i, t + 1]
    }
  }
}

tc_SC1 <- m.C_SC1 %>% v.dwc      # total (discounted) cost per individual
te_SC1 <- m.E_SC1 %>% v.dwe      # total (discounted) QALYs per individual

tc_hat_SC1 <- mean(tc_SC1)      # average (discounted) cost
te_hat_SC1 <- mean(te_SC1)      # average (discounted) QALYs

if (TS.out == TRUE) { # create a matrix of transitions across states
  TS_SC1 <- paste(m.M_SC1, cbind(m.M_SC1[, -1], NA), sep = "->") # transitions from one state to the other ###
  TS_SC1 <- matrix(TS, nrow = n.i)
  rownames(TS_SC1) <- paste("Cycle", 0:n.t, sep = " ") # name the rows of the matrix
  colnames(TS_SC1) <- paste("Ind", 1:n.s, sep = " ") # name the columns of the matrix
} else {
  TS_SC1 <- NULL
}

if (TR.out == TRUE) { # create a trace from the individual trajectories
  TR_SC1 <- t(apply(m.M_SC1, 2, function(x) table(factor(x, levels = v.n, ordered = TRUE))))
  TR_SC1 <- TR_SC1 / n.i # create a distribution trace
  rownames(TR_SC1) <- paste("Cycle", 0:n.t, sep = " ") # name the rows of the matrix
  colnames(TR_SC1) <- v.n # name the columns of the matrix
} else {
  TR_SC1 <- NULL
}

results <- list(RR.dm_SC1 = RR.dm_SC1, m.AGE_SC1 = m.AGE_SC1, m.DMII_SC1 = m.DMII_SC1, m.M_SC1 = m.M_SC1, m.C_SC1 = m.C_SC1, m.E_SC1 = m.E_SC1, tc_SC1 = tc_SC1, te_SC1 = te_SC1, tc_hat_SC1 = tc_hat_SC1, te_hat_SC1 = te_hat_SC1, TS_SC1 = TS_SC1, TR_SC1 = TR_SC1, RR_SC1 = RR_SC1, drawn_values_SC1 = drawn_values_SC1) # store the results from the simulation in a list
return(results) # return the results
}

calculate_ce_out_SC1 <- function(n_wtp_SC1 = 100000){
  ## create empty vectors to store total utilities and costs
  v_tot_qaly_SC1 <- v_tot_cost_SC1 <- vector(mode = "numeric", length = n_str)
  names(v_tot_qaly_SC1) <- names(v_tot_cost_SC1) <- v_names_str
}

```

```

v_tot_qaly_SC1[1] <- sim_no_scrn_SC1$te_hat_SC1
v_tot_qaly_SC1[2] <- sim_scrn_SC1$te_hat_SC1
v_tot_cost_SC1[1] <- sim_no_scrn_SC1$tc_hat_SC1
v_tot_cost_SC1[2] <- sim_scrn_SC1$tc_hat_SC1

## Vector with discounted net monetary benefits (NMB)
v_nmb_SC1 <- v_tot_qaly_SC1 * n_wtp_SC1 - v_tot_cost_SC1

## data.frame with discounted costs, effectiveness and NMB
df_ce_SC1 <- data.frame(Strategy = v_names_str,
                        Cost      = v_tot_cost_SC1,
                        Effect    = v_tot_qaly_SC1,
                        NMB       = v_nmb_SC1)

return(df_ce_SC1)
}

##### Running the psa model #####
#####
df_psa_input_SC1 <- gen_psa(n_sim = n_sim) # Store PSA input parameters

df_c_SC1 <- df_e_SC1 <- df_TKA_SC1 <- df_rTKA_SC1 <- as.data.frame(matrix(0,
                                                                    nrow = n_sim,
                                                                    ncol = n_str))
colnames(df_c_SC1) <- colnames(df_e_SC1) <- colnames(df_TKA_SC1) <- colnames(df_rTKA_SC1) <-
v_names_str
df_dm_count_SC1 <- df_dm_avg_y_SC1 <- as.data.frame(matrix(0,
                                                                    nrow = n_sim,
                                                                    ncol = 4))
colnames(df_dm_count_SC1) <- colnames(df_dm_avg_y_SC1) <- c("mean SOC", "sd SOC", "mean e-h
ealth", "sd e-health")
df_FB_pTKA_SC1 <- df_NB_pTKA_SC1 <- df_FB_prTKA_SC1 <- df_NB_prTKA_SC1 <- df_KL2_SC1 <- df_
KL3_SC1 <- df_KL4_SC1 <- as.data.frame(matrix(0,
                                                                    nrow = n_sim,
                                                                    ncol = 6))
colnames(df_FB_pTKA_SC1) <- colnames(df_NB_pTKA_SC1) <- colnames(df_FB_prTKA_SC1) <- colnam
es(df_NB_prTKA_SC1) <- colnames(df_KL2_SC1) <- colnames(df_KL3_SC1) <- colnames(df_KL4_SC1)
<- c("count_soc", "mean_SOC", "sd_SOC", "count_E", "mean_E", "sd_E")

l_int_health_states_SC1 <- l_soc_health_states_SC1 <- l_int_DMII_SC1 <- l_soc_DMII_SC1 <- l
ist()

start.time_SC1 <- Sys.time() # track computation time
for(i in 1:n_sim){ # start simulation
  for(j in 1:ncol(df_psa_input_SC1)){
    assign(colnames(df_psa_input_SC1)[j],df_psa_input_SC1[i,j])
  }
  set.seed(seed.all)
  df_prob_t_SC1 <-< prob_t(i)
  m.p.adh_SC1 <- data.frame(p.adh = ifelse(runif(n.i) < df_psa_input_SC1$p.adh[i], 1, 0)) #
determine each simulation who is adherent based on drawn value from adherence distribution
  norm_distr_SC1 <- rnorm(n.i, mean = 0, sd = 1)
  percentiles_SC1 <- ecdf(norm_distr_SC1) # calculate percentiles for respective normal dis
tribution
  drawn_values_SC1 <- percentiles_SC1(norm_distr_SC1) # drawn values
  drawn_values_SC1[drawn_values_SC1 == 1] <- 0.9999
  df_ut_SC1 <- data.frame(Patient = 1:n.i,
                          Percentile = drawn_values_SC1,
                          u.KL2 = qbeta(drawn_values_SC1, 323.3098, 138.5613),
                          u.KL3 = qbeta(drawn_values_SC1, 323.3098, 138.5613),
                          u.KL4 = qbeta(drawn_values_SC1, 624.4044, 576.3733),

```

```

        u.TKA =      qbeta(drawn_values_SC1, 624.4044, 576.3733),
        u.FB_pTKA = qbeta(drawn_values_SC1, 56604.54, 12425.39),
        u.NB_pTKA = qbeta(drawn_values_SC1, 4388.031, 3310.269),
        u.rTKA =     qbeta(drawn_values_SC1, 564.9103, 812.9196),
        u.FB_prTKA = qbeta(drawn_values_SC1, 1687.618, 562.5394),
        u.NB_prTKA = qbeta(drawn_values_SC1, 112.6213, 149.2887)) # Draw
utilities based on percentile scores
df_ct_SC1 <- data.frame(Patient = 1:n.i,
                        Percentile = drawn_values_SC1,
                        c.KL2      = qgamma(drawn_values_SC1, shape = 0.1225 , scale =
16000 ),
                        c.KL3      = qgamma(drawn_values_SC1, shape = 0.168970 , scale =
13197.59),
                        c.KL4      = qgamma(drawn_values_SC1, shape = 0.332136 , scale =
7105.519),
                        c.TKA.prod = qgamma(drawn_values_SC1, shape = 2.334613 , scale =
643.3744),
                        c.FB_pTKA  = qgamma(drawn_values_SC1, shape = 2.25078 , scale =
2577.12 ),
                        c.NB_pTKA  = qgamma(drawn_values_SC1, shape = 2.25078 , scale =
2577.12 ),
                        c.TKA       = qgamma(drawn_values_SC1, shape = 84.75009 , scale =
172.3184),
                        c.rTKA      = qgamma(drawn_values_SC1, shape = 234.6973 , scale =
103.708 )) # Draw costs based on percentile scores

##
sim_no_scrn_SC1 <- MicroSim(n.i, n.t, v.n, X = v.x, d.c, d.e, TS.out = FALSE, TR.out = FA
LSE, Trt = FALSE, RR_SC1 = 1, seed = seed.all, drawn_values_SC1, RR.dm_SC1 = 1) # run for n
o treatment
sim_scrn_SC1    <- MicroSim(n.i, n.t, v.n, X = v.x, d.c, d.e, TS.out = FALSE, TR.out = FA
LSE, Trt = TRUE, RR_SC1 = RR_SC1, seed = seed.all, drawn_values_SC1, RR.dm_SC1 = RR.dm_SC1)
# run for treatment
df_ce_psa_SC1 <- calculate_ce_out_SC1() #calculate and save the outcomes
df_c_SC1[i, ] <- df_ce_psa_SC1$Cost # take the cost from the PSA run and store in df_c
df_e_SC1[i, ] <- df_ce_psa_SC1$Effect # take the QALY from the PSA run in store in df_e

## List of dataframes containing all the health states status and DMII status
l_int_health_states_SC1[[i]] <- sim_scrn_SC1$m.M_SC1
l_soc_health_states_SC1[[i]] <- sim_no_scrn_SC1$m.M_SC1
l_int_DMII_SC1[[i]] <- sim_scrn_SC1$m.DMII_SC1
l_soc_DMII_SC1[[i]] <- sim_no_scrn_SC1$m.DMII_SC1

## Display simulation progress
if(i/(n_sim/10) == round(i/(n_sim/10),0)) { # display progress every 10%
  cat('\r', paste(' ', 'Overall progress: ', i/n_sim * 100, "% done",
                sep = " "))
}
}
elapsed.time_SC1 <- Sys.time() - start.time_SC1 # total computation time
elapsed.time_SC1

## Analysis
sim_stats_KL2_SC1 <- sim_stats_KL3_SC1 <- sim_stats_KL4_SC1 <-
sim_stats_TKA_SC1 <- sim_stats_FBpTKA_SC1 <- sim_stats_NBpTKA_SC1 <-
sim_stats_rTKA_SC1 <- sim_stats_FBprTKA_SC1 <- sim_stats_NBprTKA_SC1 <- as.data.frame(mat
rix(0,
nrow = n_sim,
ncol = 4))
colnames(sim_stats_KL2_SC1) <- colnames(sim_stats_KL3_SC1) <- colnames(sim_stats_KL4_SC1) <-
-
colnames(sim_stats_TKA_SC1) <- colnames(sim_stats_FBpTKA_SC1) <- colnames(sim_stats_NBpTK
A_SC1) <-

```



```

colnames(sim_stats_rTKA_SC1) <- colnames(sim_stats_FBprTKA_SC1) <- colnames(sim_stats_NBprTKA_SC1) <- c("count_of_patients_ehealth", "mean_ehealth", "count_of_patients_soc", "mean_soc")

for (i in 1:n_sim) {
  sim_stats_KL2_SC1[i, ] <- c((sum(rowSums(l_int_health_states_SC1[[i]] == "KL2") > 0)),
  (mean(rowSums(l_int_health_states_SC1[[i]] == "KL2")[rowSums(l_int_health_states_SC1[[i]] == "KL2") != 0], na.rm = TRUE)),
  (sum(rowSums(l_soc_health_states_SC1[[i]] == "KL2") > 0)),
  (mean(rowSums(l_soc_health_states_SC1[[i]] == "KL2")[rowSums(l_soc_health_states_SC1[[i]] == "KL2") != 0], na.rm = TRUE)))
  sim_stats_KL3_SC1[i, ] <- c((sum(rowSums(l_int_health_states_SC1[[i]] == "KL3") > 0)),
  (mean(rowSums(l_int_health_states_SC1[[i]] == "KL3")[rowSums(l_int_health_states_SC1[[i]] == "KL3") != 0], na.rm = TRUE)),
  (sum(rowSums(l_soc_health_states_SC1[[i]] == "KL3") > 0)),
  (mean(rowSums(l_soc_health_states_SC1[[i]] == "KL3")[rowSums(l_soc_health_states_SC1[[i]] == "KL3") != 0], na.rm = TRUE)))
  sim_stats_KL4_SC1[i, ] <- c((sum(rowSums(l_int_health_states_SC1[[i]] == "KL4") > 0)),
  (mean(rowSums(l_int_health_states_SC1[[i]] == "KL4")[rowSums(l_int_health_states_SC1[[i]] == "KL4") != 0], na.rm = TRUE)),
  (sum(rowSums(l_soc_health_states_SC1[[i]] == "KL4") > 0)),
  (mean(rowSums(l_soc_health_states_SC1[[i]] == "KL4")[rowSums(l_soc_health_states_SC1[[i]] == "KL4") != 0], na.rm = TRUE)))
  sim_stats_TKA_SC1[i, ] <- c((sum(rowSums(l_int_health_states_SC1[[i]] == "TKA") > 0)),
  (mean(rowSums(l_int_health_states_SC1[[i]] == "TKA")[rowSums(l_int_health_states_SC1[[i]] == "TKA") != 0], na.rm = TRUE)),
  (sum(rowSums(l_soc_health_states_SC1[[i]] == "TKA") > 0)),
  (mean(rowSums(l_soc_health_states_SC1[[i]] == "TKA")[rowSums(l_soc_health_states_SC1[[i]] == "TKA") != 0], na.rm = TRUE)))
  sim_stats_FBprTKA_SC1[i, ] <- c((sum(rowSums(l_int_health_states_SC1[[i]] == "FB_pTKA") > 0)),
  (mean(rowSums(l_int_health_states_SC1[[i]] == "FB_pTKA")[rowSums(l_int_health_states_SC1[[i]] == "FB_pTKA") != 0], na.rm = TRUE)),
  (sum(rowSums(l_soc_health_states_SC1[[i]] == "FB_pTKA") > 0)),
  (mean(rowSums(l_soc_health_states_SC1[[i]] == "FB_pTKA")[rowSums(l_soc_health_states_SC1[[i]] == "FB_pTKA") != 0], na.rm = TRUE)))
  sim_stats_NBprTKA_SC1[i, ] <- c((sum(rowSums(l_int_health_states_SC1[[i]] == "NB_pTKA") > 0)),
  (mean(rowSums(l_int_health_states_SC1[[i]] == "NB_pTKA")[rowSums(l_int_health_states_SC1[[i]] == "NB_pTKA") != 0], na.rm = TRUE)),
  (sum(rowSums(l_soc_health_states_SC1[[i]] == "NB_pTKA") > 0)),
  (mean(rowSums(l_soc_health_states_SC1[[i]] == "NB_pTKA")[rowSums(l_soc_health_states_SC1[[i]] == "NB_pTKA") != 0], na.rm = TRUE)))
  sim_stats_rTKA_SC1[i, ] <- c((sum(rowSums(l_int_health_states_SC1[[i]] == "rTKA") > 0)),
  (mean(rowSums(l_int_health_states_SC1[[i]] == "rTKA")[rowSums(l_int_health_states_SC1[[i]] == "rTKA") != 0], na.rm = TRUE)),
  (sum(rowSums(l_soc_health_states_SC1[[i]] == "rTKA") > 0)),
  (mean(rowSums(l_soc_health_states_SC1[[i]] == "rTKA")[rowSums(l_soc_health_states_SC1[[i]] == "rTKA") != 0], na.rm = TRUE)))
  sim_stats_FBprTKA_SC1[i, ] <- c((sum(rowSums(l_int_health_states_SC1[[i]] == "FB_prTKA") > 0)),
  (mean(rowSums(l_int_health_states_SC1[[i]] == "FB_prTKA")[rowSums(l_int_health_states_SC1[[i]] == "FB_prTKA") != 0], na.rm = TRUE)),
  (sum(rowSums(l_soc_health_states_SC1[[i]] == "FB_prTKA") > 0)),
  (mean(rowSums(l_soc_health_states_SC1[[i]] == "FB_prTKA")[rowSums(l_soc_health_states_SC1[[i]] == "FB_prTKA") != 0], na.rm = TRUE)))
  sim_stats_NBprTKA_SC1[i, ] <- c((sum(rowSums(l_int_health_states_SC1[[i]] == "NB_prTKA") > 0)),
  (mean(rowSums(l_int_health_states_SC1[[i]] == "NB_prTKA")[rowSums(l_int_health_states_SC1[[i]] == "NB_prTKA") != 0], na.rm = TRUE)),
  (sum(rowSums(l_soc_health_states_SC1[[i]] == "NB_prTKA") > 0)),
  (mean(rowSums(l_soc_health_states_SC1[[i]] == "NB_prTKA")[rowSums(l_soc_health_states_SC1[[i]] == "NB_prTKA") != 0], na.rm = TRUE)))
}

summary_table_KL2_SC1 <- c((mean(sim_stats_KL2_SC1$mean_ehealth)), (sqrt(var(sim_stats_KL2_SC1$mean_ehealth)/n_sim)), (mean(sim_stats_KL2_SC1$mean_soc)), (sqrt(var(sim_stats_KL2_SC1$mean_soc)/n_sim)))
summary_table_KL3_SC1 <- c((mean(sim_stats_KL3_SC1$mean_ehealth)), (sqrt(var(sim_stats_KL3_SC1$mean_ehealth)/n_sim)), (mean(sim_stats_KL3_SC1$mean_soc)), (sqrt(var(sim_stats_KL3_SC1$mean_soc)/n_sim)))

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SC1$mean_soc)/n_sim))
summary_table_KL4_SC1 <- c((mean(sim_stats_KL4_SC1$mean_ehealth)), (sqrt(var(sim_stats_KL4_SC1$mean_ehealth)/n_sim)), (mean(sim_stats_KL4_SC1$mean_soc)), (sqrt(var(sim_stats_KL4_SC1$mean_soc)/n_sim)))
summary_table_TKA_SC1 <- c((mean(sim_stats_TKA_SC1$mean_ehealth)), (sqrt(var(sim_stats_TKA_SC1$mean_ehealth)/n_sim)), (mean(sim_stats_TKA_SC1$mean_soc)), (sqrt(var(sim_stats_TKA_SC1$mean_soc)/n_sim)))
summary_table_FBpTKA_SC1 <- c((mean(sim_stats_FBpTKA_SC1$mean_ehealth)), (sqrt(var(sim_stats_FBpTKA_SC1$mean_ehealth)/n_sim)), (mean(sim_stats_FBpTKA_SC1$mean_soc)), (sqrt(var(sim_stats_FBpTKA_SC1$mean_soc)/n_sim)))
summary_table_NBpTKA_SC1 <- c((mean(sim_stats_NBpTKA_SC1$mean_ehealth)), (sqrt(var(sim_stats_NBpTKA_SC1$mean_ehealth)/n_sim)), (mean(sim_stats_NBpTKA_SC1$mean_soc)), (sqrt(var(sim_stats_NBpTKA_SC1$mean_soc)/n_sim)))
summary_table_rTKA_SC1 <- c((mean(sim_stats_rTKA_SC1$mean_ehealth)), (sqrt(var(sim_stats_rTKA_SC1$mean_ehealth)/n_sim)), (mean(sim_stats_rTKA_SC1$mean_soc)), (sqrt(var(sim_stats_rTKA_SC1$mean_soc)/n_sim)))
summary_table_FBprTKA_SC1 <- c((mean(sim_stats_FBprTKA_SC1$mean_ehealth)), (sqrt(var(sim_stats_FBprTKA_SC1$mean_ehealth)/n_sim)), (mean(sim_stats_FBprTKA_SC1$mean_soc)), (sqrt(var(sim_stats_FBprTKA_SC1$mean_soc)/n_sim)))
summary_table_NBprTKA_SC1 <- c((mean(sim_stats_NBprTKA_SC1$mean_ehealth)), (sqrt(var(sim_stats_NBprTKA_SC1$mean_ehealth)/n_sim)), (mean(sim_stats_NBprTKA_SC1$mean_soc)), (sqrt(var(sim_stats_NBprTKA_SC1$mean_soc)/n_sim)))

names(summary_table_KL2_SC1) <- names(summary_table_KL3_SC1) <- names(summary_table_KL4_SC1) <-
) <-
  names(summary_table_TKA_SC1) <- names(summary_table_FBpTKA_SC1) <-
  names(summary_table_NBpTKA_SC1) <- names(summary_table_rTKA_SC1) <-
  names(summary_table_FBprTKA_SC1) <- names(summary_table_NBprTKA_SC1) <- c("mean_ehealth",
"se_ehealth", "mean_soc", "se_soc")

## DMII
sim_stats_DMII_SC1 <- as.data.frame(matrix(0,
                                         nrow = n_sim,
                                         ncol = 4))
colnames(sim_stats_DMII_SC1) <- c("count_of_patients_ehealth", "mean_ehealth", "count_of_patients_soc", "mean_soc")
for (i in 1:n_sim) {
  sim_stats_DMII_SC1[i, ] <- c((sum(rowSums(l_int_DMII_SC1[[i]] == 1) > 0)), (mean(rowSums(l_int_DMII_SC1[[i]] == 1)[rowSums(l_int_DMII_SC1[[i]] == 1) != 0], na.rm = TRUE)),
  (sum(rowSums(l_soc_DMII_SC1[[i]] == 1) > 0)), (mean(rowSums(l_soc_DMII_SC1[[i]] == 1)[rowSums(l_soc_DMII_SC1[[i]] == 1) != 0], na.rm = TRUE)))
}
summary_table_DMII_SC1 <- c((mean(sim_stats_DMII_SC1$count_of_patients_ehealth)), (mean(sim_stats_DMII_SC1$mean_ehealth)), (sqrt(var(sim_stats_DMII_SC1$mean_ehealth)/n_sim)), (mean(sim_stats_DMII_SC1$count_of_patients_soc)), (mean(sim_stats_DMII_SC1$mean_soc)), (sqrt(var(sim_stats_DMII_SC1$mean_soc)/n_sim)))
names(summary_table_DMII_SC1) <- c("N_DMII_ehealth", "mean_ehealth", "se_ehealth", "N_DMII_soc", "mean_soc", "se_soc")

## Create PSA object for dampack
mean_TKA_SC1 <- data.frame(SOC = mean(df_TKA_SC1$SOC),
                          E.health = mean(df_TKA_SC1$E.health))
t.test(df_TKA_SC1$SOC, df_TKA_SC1$E.health)
mean_rTKA_SC1 <- data.frame(SOC = mean(df_rTKA_SC1$SOC),
                          E.health = mean(df_rTKA_SC1$E.health))
t.test(df_rTKA_SC1$SOC, df_rTKA_SC1$E.health)

l_psa_SC1 <- make_psa_obj(cost = df_c_SC1,
                        effectiveness = df_e_SC1,
                        parameters = df_psa_input_SC1,
                        strategies = v_names_str,
                        currency = "€")

df_incr_SC1 <- data.frame(Incr_cost = df_c_SC1$E.health - df_c_SC1$SOC,

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      Incr_effect = df_e_SC1$E.health - df_e_SC1$SOC)
avg_effect_SC1 <- mean(df_incr_SC1$Incr_effect)
avg_cost_SC1 <- mean(df_incr_SC1$Incr_cost)

MAC_SC1 <- (avg_effect_SC1 * 20000) - avg_cost_SC1

# Create a ggplot object with your data
p_SC1 <- ggplot(df_incr_SC1, aes(x = Incr_effect, y = Incr_cost)) +
  geom_point(color = "red", size = 2, alpha = 0.3) +
  xlim(-0.25, 0.25) +
  ylim(-5000, 5000) +
  labs(x = "Incremental effect", y = "Incremental costs") +
  theme_minimal() +
  geom_hline(yintercept = 0, linetype = "solid", color = "black", size = 0.5) +
  geom_vline(xintercept = 0, linetype = "solid", color = "black", size = 0.5) +
  geom_abline(intercept = 0, slope = 10000, color = "black", size = 0.5) +
  geom_abline(intercept = 0, slope = 20000, color = "black", size = 0.5) +
  geom_point(data = data.frame(x=avg_effect_SC1, y=avg_cost_SC1), aes(x=x, y=y), color = "black", size = 4, alpha = 0.7)
print(p_SC1)
# Add an ellipse around the data points
p_SC1 + stat_ellipse(level = 0.95, geom = "polygon", fill = NA, linetype = "dashed", color = "black", size = 0.5)

v_wtp <- seq(0, 100000, by = 20000)

## 09.3.1 ICER
# use dampack to calculate the ICER
df_cea_psa_SC1 <- calculate_icers(cost      = df_ce_psa_SC1$Cost,
                                effect    = df_ce_psa_SC1$Effect,
                                strategies = df_ce_psa_SC1$Strategy)

## 09.3.2 Cost-Effectiveness Acceptability Curves (CEAC) and Frontier (CEAF)
out_ceaf_SC1 <- ceac(v_wtp, l_psa_SC1)
plot(out_ceaf_SC1)
#
#df_icer_wtp_test_SC1 <- as.data.frame(matrix(0,
#                                           nrow = n_sim,
#                                           ncol = length(v_wtp)))
#colnames(df_icer_wtp_test_SC1) <- v_wtp
#df_icer_wtp_test_SC1 <- sapply(v_wtp, function(wtp){
#  (df_incr_SC1$Incr_cost < df_incr_SC1$Incr_effect * wtp) & (df_incr_SC1$Incr_effect >= 0)
#})
#proportions_ehealth_SC1 <- colMeans(df_icer_wtp_test_SC1)
#proportions_soc_SC1 <- 1 - proportions_ehealth_SC1
#
#out_SOC_SC1 <- data.frame(WTP = v_wtp,
#                          Strategy = "SOC",
#                          Proportion = proportions_soc_SC1)
#out_E.health_SC1 <- data.frame(WTP = v_wtp,
#                               Strategy = "E.health",
#                               Proportion = proportions_ehealth_SC1)
#out_ceaf_SC1 <- rbind(out_SOC_SC1, out_E.health_SC1)
#out_ceaf_SC1 <- out_ceaf_SC1 %>%
#  group_by(WTP) %>%
#  mutate(On_Frontier = Proportion == max(Proportion)) %>%
#  ungroup()
#
#figure4_1 <- ggplot(out_ceaf_SC1, aes(x=WTP, y=Proportion, color = Strategy)) +
#  geom_line() +
#  geom_point(size = 1.5) +
#  geom_rect(data=subset(out_ceaf_SC1, On_Frontier), aes(xmin=WTP-1000, xmax=WTP+1000, ymin=Proportion-0.05, ymax=Proportion+0.05), fill="transparent", color="black") +
#  scale_x_continuous(breaks = unique(out_ceaf_SC1$WTP), labels = function(x) x/1000, expand = c(0, 0))+

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# scale_y_continuous(limits = c(0, 1), breaks = seq(0, 1, 0.25), expand = c(0, 0)) +
# scale_color_manual(values = c("SOC" = "tomato3", "E.health" = "turquoise4")) +
# labs(
#   x = "WTP in €1000/QALY",
#   y = "Pr cost-effective"
# ) +
# theme_bw() +
# theme(
#   axis.title.x = element_text(size = 7),
#   axis.title.y = element_text(size = 7),
#   legend.position = "none")

## 09.3.3 Cost-Effectiveness Scatter plot
plot(l_psa_SC1)

## 09.4 Expected value of perfect information (EVPI)
evpi_SC1 <- calc_evpi(wtp = v_wtp, psa = l_psa_SC1) # calculate EVPI
plot(evpi_SC1, effect_units = "QALY") # EVPI plot

write.csv(df_psa_input_SC1, "C:/Users/shoai/OneDrive/Bureaublad/R_afstuderen/R_afstudeeropdracht/psa_input_data_SC1.csv", row.names = FALSE)
write.csv(df_c_SC1, "C:/Users/shoai/OneDrive/Bureaublad/R_afstuderen/R_afstudeeropdracht/pa_results_costs_SC1.csv", row.names = FALSE)
write.csv(df_e_SC1, "C:/Users/shoai/OneDrive/Bureaublad/R_afstuderen/R_afstudeeropdracht/pa_results_effects_SC1.csv", row.names = FALSE)

## Paper figures ##

library(ggplot2)
library(gridExtra)
library(grid)
library(SAVI)
library(dplyr)
library(tidyr)
library(tibble)

##
total_points <- n_sim
f1_nw_SCF1 <- sum(df_incr_SCF1$Incr_effect < 0 & df_incr_SCF1$Incr_cost > 0) / total_points
f1_nw_SCF2 <- sum(df_incr_SCF2$Incr_effect < 0 & df_incr_SCF2$Incr_cost > 0) / total_points
f1_nw_SCF3 <- sum(df_incr_SCF3$Incr_effect < 0 & df_incr_SCF3$Incr_cost > 0) / total_points
f1_ne_SCF1 <- sum(df_incr_SCF1$Incr_effect > 0 & df_incr_SCF1$Incr_cost > 0) / total_points
f1_ne_SCF2 <- sum(df_incr_SCF2$Incr_effect > 0 & df_incr_SCF2$Incr_cost > 0) / total_points
f1_ne_SCF3 <- sum(df_incr_SCF3$Incr_effect > 0 & df_incr_SCF3$Incr_cost > 0) / total_points
f1_sw_SCF1 <- sum(df_incr_SCF1$Incr_effect < 0 & df_incr_SCF1$Incr_cost < 0) / total_points
f1_sw_SCF2 <- sum(df_incr_SCF2$Incr_effect < 0 & df_incr_SCF2$Incr_cost < 0) / total_points
f1_sw_SCF3 <- sum(df_incr_SCF3$Incr_effect < 0 & df_incr_SCF3$Incr_cost < 0) / total_points
f1_se_SCF1 <- sum(df_incr_SCF1$Incr_effect > 0 & df_incr_SCF1$Incr_cost < 0) / total_points
f1_se_SCF2 <- sum(df_incr_SCF2$Incr_effect > 0 & df_incr_SCF2$Incr_cost < 0) / total_points
f1_se_SCF3 <- sum(df_incr_SCF3$Incr_effect > 0 & df_incr_SCF3$Incr_cost < 0) / total_points

f2_nw_SCF4 <- sum(df_incr_SCF4$Incr_effect < 0 & df_incr_SCF4$Incr_cost > 0) / total_points
f2_nw_SCF5 <- sum(df_incr_SCF5$Incr_effect < 0 & df_incr_SCF5$Incr_cost > 0) / total_points
f2_nw_SCF6 <- sum(df_incr_SCF6$Incr_effect < 0 & df_incr_SCF6$Incr_cost > 0) / total_points
f2_ne_SCF4 <- sum(df_incr_SCF4$Incr_effect > 0 & df_incr_SCF4$Incr_cost > 0) / total_points
f2_ne_SCF5 <- sum(df_incr_SCF5$Incr_effect > 0 & df_incr_SCF5$Incr_cost > 0) / total_points
f2_ne_SCF6 <- sum(df_incr_SCF6$Incr_effect > 0 & df_incr_SCF6$Incr_cost > 0) / total_points
f2_sw_SCF4 <- sum(df_incr_SCF4$Incr_effect < 0 & df_incr_SCF4$Incr_cost < 0) / total_points
f2_sw_SCF5 <- sum(df_incr_SCF5$Incr_effect < 0 & df_incr_SCF5$Incr_cost < 0) / total_points
f2_sw_SCF6 <- sum(df_incr_SCF6$Incr_effect < 0 & df_incr_SCF6$Incr_cost < 0) / total_points
f2_se_SCF4 <- sum(df_incr_SCF4$Incr_effect > 0 & df_incr_SCF4$Incr_cost < 0) / total_points
f2_se_SCF5 <- sum(df_incr_SCF5$Incr_effect > 0 & df_incr_SCF5$Incr_cost < 0) / total_points
f2_se_SCF6 <- sum(df_incr_SCF6$Incr_effect > 0 & df_incr_SCF6$Incr_cost < 0) / total_points

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## adherence
f3_ne_SCF2 <- sum(df_incr_SCF2$Incr_effect > 0 & df_incr_SCF2$Incr_cost > 0) / total_points
f3_nw_SCF2 <- sum(df_incr_SCF2$Incr_effect < 0 & df_incr_SCF2$Incr_cost > 0) / total_points
f3_se_SCF2 <- sum(df_incr_SCF2$Incr_effect > 0 & df_incr_SCF2$Incr_cost < 0) / total_points
f3_sw_SCF2 <- sum(df_incr_SCF2$Incr_effect < 0 & df_incr_SCF2$Incr_cost < 0) / total_points

figure_adh <- ggplot() +
  stat_ellipse(data = df_incr_SCF2, aes(x = Incr_effect, y = Incr_cost), level = 0.95, geom = "polygon", alpha = 0.3, fill = "turquoise2", color = "turquoise2", size = 0.5) +
  stat_ellipse(data = df_incr_SCF2, aes(x = Incr_effect, y = Incr_cost), level = 0.95, geom = "polygon", alpha = 0.3, fill = "magenta", color = "magenta", size = 0.5) +
  xlim(-0.5, 0.5) +
  ylim(-5000,5000) +
  labs(x = "Incremental effect (QALYs)", y = "Incremental cost (€)") +
  theme_minimal() +
  geom_hline(yintercept = 0, linetype = "solid", color = "black", size = 0.5) +
  geom_vline(xintercept = 0, linetype = "solid", color = "black", size = 0.5) +
  geom_abline(intercept = 0, linetype = "dashed", slope = 20000, color = "black", size = 0.5) +
  geom_point(data = data.frame(x=avg_effect_SCF2, y=avg_cost_SCF2), aes(x=x, y=y), color = "black", size = 5, alpha = 0.7, shape = 16) +
  geom_point(data = data.frame(x=avg_effect_SCF2, y=avg_cost_SCF2), aes(x=x, y=y), color = "black", size = 5, alpha = 0.7, shape = 16) +
  geom_text(data = data.frame(x = avg_effect_SCF2, y = avg_cost_SCF2), aes(x = x, y = y, label = "2"), color = "white", size = 3, vjust = 0.5, hjust = 0.5) +
  geom_text(data = data.frame(x = avg_effect_SCF2, y = avg_cost_SCF2), aes(x = x, y = y, label = "A2"), color = "white", size = 3, vjust = 0.5, hjust = 0.5) +
  annotate("text", x = -0.45, y = 3500, color = "magenta", size = 5, label = paste0(round(f1_nw_SCF2 * 100, 1), "%")) +
  annotate("text", x = -0.45, y = -3500, color = "magenta", size = 5, label = paste0(round(f1_sw_SCF2 * 100, 1), "%")) +
  annotate("text", x = 0.45, y = 3500, color = "magenta", size = 5, label = paste0(round(f1_ne_SCF2 * 100, 1), "%")) +
  annotate("text", x = 0.45, y = -3500, color = "magenta", size = 5, label = paste0(round(f1_se_SCF2 * 100, 1), "%")) +
  annotate("text", x = -0.45, y = 4000, color = "turquoise2", size = 5, label = paste0(round(f3_nw_SCF2 * 100, 1), "%")) +
  annotate("text", x = -0.45, y = -4000, color = "turquoise2", size = 5, label = paste0(round(f3_sw_SCF2 * 100, 1), "%")) +
  annotate("text", x = 0.45, y = 4000, color = "turquoise2", size = 5, label = paste0(round(f3_ne_SCF2 * 100, 1), "%")) +
  annotate("text", x = 0.45, y = -4000, color = "turquoise2", size = 5, label = paste0(round(f3_se_SCF2 * 100, 1), "%")) +
  annotate("text", x = 0.25, y = 2000, size = 3, color = "black", label = paste0("WTP = €20,000")) +
  theme_bw() +
  theme(panel.background = element_rect(fill = "gray95"))

##
figure1 <- ggplot() +
  geom_point(data = df_incr_SCF3, aes(x = Incr_effect, y = Incr_cost), shape = 19, color = "turquoise2", size = 2, alpha = 0.2) +
  geom_point(data = df_incr_SCF2, aes(x = Incr_effect, y = Incr_cost), shape = 19, color = "magenta", size = 2, alpha = 0.2) +
  geom_point(data = df_incr_SCF1, aes(x = Incr_effect, y = Incr_cost), shape = 19, color = "yellow2", size = 2, alpha = 0.2) +
  xlim(-0.5, 0.5) +
  ylim(-5000,5000) +
  labs(x = "Incremental effect", y = "Incremental cost") +
  theme_minimal() +

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geom_hline(yintercept = 0, linetype = "solid", color = "black", size = 0.5) +
geom_vline(xintercept = 0, linetype = "solid", color = "black", size = 0.5) +
geom_abline(intercept = 0, linetype = "dashed", slope = 20000, color = "black", size = 0.5) +
geom_point(data = data.frame(x=avg_effect_SCF3, y=avg_cost_SCF3), aes(x=x, y=y), color = "black", size = 5, alpha = 0.7, shape = 16) +
geom_point(data = data.frame(x=avg_effect_SCF2, y=avg_cost_SCF2), aes(x=x, y=y), color = "black", size = 5, alpha = 0.7, shape = 16) +
geom_point(data = data.frame(x=avg_effect_SCF1, y=avg_cost_SCF1), aes(x=x, y=y), color = "black", size = 5, alpha = 0.7, shape = 16) +
geom_text(data = data.frame(x = avg_effect_SCF3, y = avg_cost_SCF3),
  aes(x = x, y = y, label = "3"),
  color = "white", size = 3, vjust = 0.5, hjust = 0.5) +
geom_text(data = data.frame(x = avg_effect_SCF2, y = avg_cost_SCF2),
  aes(x = x, y = y, label = "2"),
  color = "white", size = 3, vjust = 0.5, hjust = 0.5) +
geom_text(data = data.frame(x = avg_effect_SCF1, y = avg_cost_SCF1),
  aes(x = x, y = y, label = "1"),
  color = "white", size = 3, vjust = 0.5, hjust = 0.5) +
annotate("text", x = -0.45, y = 3000, color = "yellow3", size = 5, label = paste0(round(
f1_nw_SCF1 * 100, 1), "%")) +
annotate("text", x = -0.45, y = -3000, color = "yellow3", size = 5, label = paste0(round(
f1_sw_SCF1 * 100, 1), "%")) +
annotate("text", x = 0.45, y = 3000, color = "yellow3", size = 5, label = paste0(round(
f1_ne_SCF1 * 100, 1), "%")) +
annotate("text", x = 0.45, y = -3000, color = "yellow3", size = 5, label = paste0(round(
f1_se_SCF1 * 100, 1), "%")) +
annotate("text", x = -0.45, y = 3500, color = "magenta", size = 5, label = paste0(
round(f1_nw_SCF2 * 100, 1), "%")) +
annotate("text", x = -0.45, y = -3500, color = "magenta", size = 5, label = paste0(
round(f1_sw_SCF2 * 100, 1), "%")) +
annotate("text", x = 0.45, y = 3500, color = "magenta", size = 5, label = paste0(
round(f1_ne_SCF2 * 100, 1), "%")) +
annotate("text", x = 0.45, y = -3500, color = "magenta", size = 5, label = paste0(
round(f1_se_SCF2 * 100, 1), "%")) +
annotate("text", x = -0.45, y = 4000, color = "turquoise2", size = 5, label = paste
0(round(f1_nw_SCF3 * 100, 1), "%")) +
annotate("text", x = -0.45, y = -4000, color = "turquoise2", size = 5, label = paste
0(round(f1_sw_SCF3 * 100, 1), "%")) +
annotate("text", x = 0.45, y = 4000, color = "turquoise2", size = 5, label = paste
0(round(f1_ne_SCF3 * 100, 1), "%")) +
annotate("text", x = 0.45, y = -4000, color = "turquoise2", size = 5, label = paste
0(round(f1_se_SCF3 * 100, 1), "%")) +
annotate("text", x = 0.25, y = 2000, size = 3, color = "black", label = paste0("WTP = €
20,000")) +
theme_bw() +
theme(panel.background = element_rect(fill = "gray95")) +
annotate("text", x = Inf, y = Inf, label = "A", size = 4, hjust = 1.1, vjust = 1.1)

figure2 <- ggplot() +
geom_point(data = df_incr_SCF6, aes(x = Incr_effect, y = Incr_cost), shape = 19, color =
"orange", size = 2, alpha = 0.2) +
geom_point(data = df_incr_SCF5, aes(x = Incr_effect, y = Incr_cost), shape = 19, color =
"purple", size = 2, alpha = 0.2) +
geom_point(data = df_incr_SCF4, aes(x = Incr_effect, y = Incr_cost), shape = 19, color =
"green", size = 2, alpha = 0.2) +
xlim(-0.5, 0.5) +
ylim(-5000, 5000) +
labs(x = "Incremental effect", y = "Incremental cost") +
theme_minimal() +
geom_hline(yintercept = 0, linetype = "solid", color = "black", size = 0.5) +
geom_vline(xintercept = 0, linetype = "solid", color = "black", size = 0.5) +
geom_abline(intercept = 0, linetype = "dashed", slope = 20000, color = "black", size = 0.5) +
geom_point(data = data.frame(x=avg_effect_SCF6, y=avg_cost_SCF6), aes(x=x, y=y), color =
"black", size = 5, alpha = 0.7, shape = 16) +

```

```

geom_point(data = data.frame(x=avg_effect_SCF5, y=avg_cost_SCF5), aes(x=x, y=y), color =
"black", size = 5, alpha = 0.7, shape = 16) +
geom_point(data = data.frame(x=avg_effect_SCF4, y=avg_cost_SCF4), aes(x=x, y=y), color =
"black", size = 5, alpha = 0.7, shape = 16) +
geom_text(data = data.frame(x = avg_effect_SCF6, y = avg_cost_SCF6),
aes(x = x, y = y, label = "6"),
color = "white", size = 3, vjust = 0.5, hjust = 0.5) +
geom_text(data = data.frame(x = avg_effect_SCF5, y = avg_cost_SCF5),
aes(x = x, y = y, label = "5"),
color = "white", size = 3, vjust = 0.5, hjust = 0.5) +
geom_text(data = data.frame(x = avg_effect_SCF4, y = avg_cost_SCF4),
aes(x = x, y = y, label = "4"),
color = "white", size = 3, vjust = 0.5, hjust = 0.5) +
annotate("text", x = -0.45, y = 4000, color = "green", size = 5, label = paste0(round(f2
_nw_SCF6 * 100, 1), "%")) +
annotate("text", x = -0.45, y = -4000, color = "green", size = 5, label = paste0(round(f2
_sw_SCF6 * 100, 1), "%")) +
annotate("text", x = 0.45, y = 4000, color = "green", size = 5, label = paste0(round(f2
_ne_SCF6 * 100, 1), "%")) +
annotate("text", x = 0.45, y = -4000, color = "green", size = 5, label = paste0(round(f2
_se_SCF6 * 100, 1), "%")) +
annotate("text", x = -0.45, y = 3500, color = "purple", size = 5, label = paste0(round(f
2_nw_SCF5 * 100, 1), "%")) +
annotate("text", x = -0.45, y = -3500, color = "purple", size = 5, label = paste0(round(f
2_sw_SCF5 * 100, 1), "%")) +
annotate("text", x = 0.45, y = 3500, color = "purple", size = 5, label = paste0(round(f
2_ne_SCF5 * 100, 1), "%")) +
annotate("text", x = 0.45, y = -3500, color = "purple", size = 5, label = paste0(round(f
2_se_SCF5 * 100, 1), "%")) +
annotate("text", x = -0.45, y = 3000, color = "orange", size = 5, label = paste0(round(
f2_nw_SCF4 * 100, 1), "%")) +
annotate("text", x = -0.45, y = -3000, color = "orange", size = 5, label = paste0(round(
f2_sw_SCF4 * 100, 1), "%")) +
annotate("text", x = 0.45, y = 3000, color = "orange", size = 5, label = paste0(round(
f2_ne_SCF4 * 100, 1), "%")) +
annotate("text", x = 0.45, y = -3000, color = "orange", size = 5, label = paste0(round(
f2_se_SCF4 * 100, 1), "%")) +
annotate("text", x = 0.25, y = 2000, size = 3, color = "black", label = paste0("WTP = €
20,000")) +
theme_bw() +
theme(panel.background = element_rect(fill = "gray95")) +
annotate("text", x = Inf, y = Inf, label = "B", size = 4, hjust = 1.1, vjust = 1.1)

```

```

grid.arrange(figure1, figure2, ncol = 2)

```

```

scenarios <- c("RR_a = 0.95 & RR_b = 1", "RR_a = 0.90 & RR_b = 1", "RR_a = 0.85 & RR_b = 1"
,
"RR_a = 0.95 & RR_b = 0.95", "RR_a = 0.90 & RR_b = 0.95", "RR_a = 0.85 & RR_
b = 0.95")
delta_cost <- c(avg_cost_SCF1, avg_cost_SCF2, avg_cost_SCF3, avg_cost_SCF4, avg_cost_SCF5,
avg_cost_SCF6)
delta_eff <- c(avg_effect_SCF1, avg_effect_SCF2, avg_effect_SCF3, avg_effect_SCF4, avg_effe
ct_SCF5, avg_effect_SCF6)
MAC <- c(MAC_SCF1, MAC_SCF2, MAC_SCF3, MAC_SCF4, MAC_SCF5, MAC_SCF6)
UCL_cost <- c((avg_cost_SCF1 + (1.96 * (sd(df_incr_SCF1$Incr_cost ) / sqrt(n_sim)))) , (a
vg_cost_SCF2
+ (1.96 * (sd(df_incr_SCF2$Incr_cost ) / sqrt(n_sim))))),
(avg_cost_SCF3 + (1.96 * (sd(df_incr_SCF3$Incr_cost ) / sqrt(n_sim)))) , (a
vg_cost_SCF4
+ (1.96 * (sd(df_incr_SCF4$Incr_cost ) / sqrt(n_sim))))),
(avg_cost_SCF5 + (1.96 * (sd(df_incr_SCF5$Incr_cost ) / sqrt(n_sim)))) , (a
vg_cost_SCF6
+ (1.96 * (sd(df_incr_SCF6$Incr_cost ) / sqrt(n_sim))))
LCL_cost <- c((avg_cost_SCF1 - (1.96 * (sd(df_incr_SCF1$Incr_cost ) / sqrt(n_sim)))) , (a
vg_cost_SCF2
- (1.96 * (sd(df_incr_SCF2$Incr_cost ) / sqrt(n_sim))))),
(avg_cost_SCF3 - (1.96 * (sd(df_incr_SCF3$Incr_cost ) / sqrt(n_sim)))) , (a

```

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vg_cost_SCF4 - (1.96 * (sd(df_incr_SCF4$Incr_cost ) / sqrt(n_sim))),
  (avg_cost_SCF5 - (1.96 * (sd(df_incr_SCF5$Incr_cost ) / sqrt(n_sim)))) , (a
vg_cost_SCF6 - (1.96 * (sd(df_incr_SCF6$Incr_cost ) / sqrt(n_sim))))
UCL_eff<- c((avg_effect_SCF1 + (1.96 * (sd(df_incr_SCF1$Incr_effect) / sqrt(n_sim)))) , (a
vg_effect_SCF2 + (1.96 * (sd(df_incr_SCF2$Incr_effect) / sqrt(n_sim))))),
  (avg_effect_SCF3 + (1.96 * (sd(df_incr_SCF3$Incr_effect) / sqrt(n_sim)))) , (a
vg_effect_SCF4 + (1.96 * (sd(df_incr_SCF4$Incr_effect) / sqrt(n_sim))))),
  (avg_effect_SCF5 + (1.96 * (sd(df_incr_SCF5$Incr_effect) / sqrt(n_sim)))) , (a
vg_effect_SCF6 + (1.96 * (sd(df_incr_SCF6$Incr_effect) / sqrt(n_sim))))
LCL_eff <- c((avg_effect_SCF1 - (1.96 * (sd(df_incr_SCF1$Incr_effect) / sqrt(n_sim)))) , (a
vg_effect_SCF2 - (1.96 * (sd(df_incr_SCF2$Incr_effect) / sqrt(n_sim))))),
  (avg_effect_SCF3 - (1.96 * (sd(df_incr_SCF3$Incr_effect) / sqrt(n_sim)))) , (a
vg_effect_SCF4 - (1.96 * (sd(df_incr_SCF4$Incr_effect) / sqrt(n_sim))))),
  (avg_effect_SCF5 - (1.96 * (sd(df_incr_SCF5$Incr_effect) / sqrt(n_sim)))) , (a
vg_effect_SCF6 - (1.96 * (sd(df_incr_SCF6$Incr_effect) / sqrt(n_sim))))
ICER <- delta_cost/delta_eff

summary_results <-
  data.frame(Scenario = scenarios,
    Mean_incremental_cost = delta_cost,
    UCL_cost = UCL_cost,
    LCL_cost = LCL_cost,
    Mean_incremental_effect = delta_eff,
    UCL_effect = UCL_eff,
    LCL_effect = LCL_eff,
    ICER = ICER,
    MAC = MAC)
#View(summary_results)

figure3 <- ggplot() +
  stat_ellipse(data = df_incr_SCF3, aes(x = Incr_effect, y = Incr_cost), level = 0.95, geom
= "polygon", alpha = 0.3, fill = "turquoise2", color = "turquoise2", size = 0.5) +
  stat_ellipse(data = df_incr_SCF2, aes(x = Incr_effect, y = Incr_cost), level = 0.95, geom
= "polygon", alpha = 0.3, fill = "magenta", color = "magenta", size = 0.5) +
  stat_ellipse(data = df_incr_SCF1, aes(x = Incr_effect, y = Incr_cost), level = 0.95, geom
= "polygon", alpha = 0.3, fill = "yellow2", color = "yellow3", size = 0.5) +
  xlim(-0.5, 0.5) +
  ylim(-5000, 5000) +
  labs(x = "Incremental effect (QALYs)", y = "Incremental cost (€)") +
  geom_hline(yintercept = 0, linetype = "solid", color = "black", size = 0.5) +
  geom_vline(xintercept = 0, linetype = "solid", color = "black", size = 0.5) +
  geom_abline(intercept = 0, linetype = "dashed", slope = 20000, color = "black", size = 0.
5) +
  geom_point(data = data.frame(x = avg_effect_SCF3, y = avg_cost_SCF3), aes(x = x, y = y),
color = "black", size = 5, alpha = 0.7, shape = 16) +
  geom_point(data = data.frame(x = avg_effect_SCF2, y = avg_cost_SCF2), aes(x = x, y = y),
color = "black", size = 5, alpha = 0.7, shape = 16) +
  geom_point(data = data.frame(x = avg_effect_SCF1, y = avg_cost_SCF1), aes(x = x, y = y),
color = "black", size = 5, alpha = 0.7, shape = 16) +
  geom_text(data = data.frame(x = avg_effect_SCF3, y = avg_cost_SCF3),
  aes(x = x, y = y, label = "3"),
  color = "white", size = 3, vjust = 0.5, hjust = 0.5) +
  geom_text(data = data.frame(x = avg_effect_SCF2, y = avg_cost_SCF2),
  aes(x = x, y = y, label = "2"),
  color = "white", size = 3, vjust = 0.5, hjust = 0.5) +
  geom_text(data = data.frame(x = avg_effect_SCF1, y = avg_cost_SCF1),
  aes(x = x, y = y, label = "1"),
  color = "white", size = 3, vjust = 0.5, hjust = 0.5) +
  annotate("text", x = -0.45, y = 5000, size = 3, color = "turquoise2", label = paste0(rou
nd(f1_nw_SCF3 * 100, 1), "%")) +
  annotate("text", x = -0.45, y = -5000, size = 3, colour = "turquoise2", label = paste0(ro
und(f1_sw_SCF3 * 100, 1), "%")) +
  annotate("text", x = 0.45, y = 5000, size = 3, colour = "turquoise2", label = paste0(ro
und(f1_ne_SCF3 * 100, 1), "%")) +
  annotate("text", x = 0.45, y = -5000, size = 3, colour = "turquoise2", label = paste0(ro
und(f1_se_SCF3 * 100, 1), "%")) +

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  annotate("text", x = -0.45, y = 4000, size = 3, color = "magenta", label = paste0(round(
f1_nw_SCF2 * 100, 1), "%")) +
  annotate("text", x = -0.45, y = -4000, size = 3, colour = "magenta", label = paste0(round
(f1_sw_SCF2 * 100, 1), "%")) +
  annotate("text", x = 0.45, y = 4000, size = 3, colour = "magenta", label = paste0(round
(f1_ne_SCF2 * 100, 1), "%")) +
  annotate("text", x = 0.45, y = -4000, size = 3, colour = "magenta", label = paste0(round
(f1_se_SCF2 * 100, 1), "%")) +
  annotate("text", x = -0.45, y = 3000, size = 3, color = "yellow3", label = paste0(round(
f1_nw_SCF1 * 100, 1), "%")) +
  annotate("text", x = -0.45, y = -3000, size = 3, colour = "yellow3", label = paste0(round
(f1_sw_SCF1 * 100, 1), "%")) +
  annotate("text", x = 0.45, y = 3000, size = 3, colour = "yellow3", label = paste0(round
(f1_ne_SCF1 * 100, 1), "%")) +
  annotate("text", x = 0.45, y = -3000, size = 3, colour = "yellow3", label = paste0(round
(f1_se_SCF1 * 100, 1), "%")) +
  annotate("text", x = 0.25, y = 2000, size = 3, color = "black", label = paste0("WTP = €
20,000")) +
  theme_bw() +
  theme(plot.margin = unit(c(0.2,2.3,0.2,0.2), "lines"),
        panel.background = element_rect(fill = "gray95")) +
  annotate("text", x = Inf, y = Inf, label = "A", size = 4, hjust = 1.1, vjust = 1.1)

figure4 <- ggplot() +
  stat_ellipse(data = df_incr_SCF6, aes(x = Incr_effect, y = Incr_cost), level = 0.95, geom
= "polygon", alpha = 0.3, fill = "orange", color = "orange", size = 0.5) +
  stat_ellipse(data = df_incr_SCF5, aes(x = Incr_effect, y = Incr_cost), level = 0.95, geom
= "polygon", alpha = 0.3, fill = "purple", color = "purple", size = 0.5) +
  stat_ellipse(data = df_incr_SCF4, aes(x = Incr_effect, y = Incr_cost), level = 0.95, geom
= "polygon", alpha = 0.3, fill = "green", color = "green", size = 0.5) +
  xlim(-0.5, 0.5) +
  ylim(-5000, 5000) +
  labs(x = "Incremental effect (QALYs)",
       y = "Incremental cost (€)") +
  geom_hline(yintercept = 0, linetype = "solid", color = "black", size = 0.5) +
  geom_vline(xintercept = 0, linetype = "solid", color = "black", size = 0.5) +
  geom_abline(intercept = 0, linetype = "dashed", slope = 20000, color = "black", size = 0.
5) +
  geom_point(data = data.frame(x = avg_effect_SCF6, y = avg_cost_SCF6), aes(x = x, y = y),
color = "black", size = 5, alpha = 0.7, shape = 16) +
  geom_point(data = data.frame(x = avg_effect_SCF5, y = avg_cost_SCF5), aes(x = x, y = y),
color = "black", size = 5, alpha = 0.7, shape = 16) +
  geom_point(data = data.frame(x = avg_effect_SCF4, y = avg_cost_SCF4), aes(x = x, y = y),
color = "black", size = 5, alpha = 0.7, shape = 16) +
  geom_text(data = data.frame(x = avg_effect_SCF6, y = avg_cost_SCF6),
           aes(x = x, y = y, label = "6"),
           color = "white", size = 3, vjust = 0.5, hjust = 0.5) +
  geom_text(data = data.frame(x = avg_effect_SCF5, y = avg_cost_SCF5),
           aes(x = x, y = y, label = "5"),
           color = "white", size = 3, vjust = 0.5, hjust = 0.5) +
  geom_text(data = data.frame(x = avg_effect_SCF4, y = avg_cost_SCF4),
           aes(x = x, y = y, label = "4"),
           color = "white", size = 3, vjust = 0.5, hjust = 0.5) +
  annotate("text", x = -0.45, y = 5000, size = 3, color = "orange", label = paste0(round(f
2_nw_SCF6 * 100, 1), "%")) +
  annotate("text", x = -0.45, y = -5000, size = 3, colour = "orange", label = paste0(round(
f2_sw_SCF6 * 100, 1), "%")) +
  annotate("text", x = 0.45, y = 5000, size = 3, colour = "orange", label = paste0(round(
f2_ne_SCF6 * 100, 1), "%")) +
  annotate("text", x = 0.45, y = -5000, size = 3, colour = "orange", label = paste0(round(
f2_se_SCF6 * 100, 1), "%")) +
  annotate("text", x = -0.45, y = 4000, size = 3, color = "purple", label = paste0(round(f
2_nw_SCF5 * 100, 1), "%")) +
  annotate("text", x = -0.45, y = -4000, size = 3, colour = "purple", label = paste0(round(
f2_sw_SCF5 * 100, 1), "%")) +
  annotate("text", x = 0.45, y = 4000, size = 3, colour = "purple", label = paste0(round(

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f2_ne_SCF5 * 100, 1), "%")) +
  annotate("text", x = 0.45, y = -4000, size = 3, colour = "purple", label = paste0(round(
f2_se_SCF5 * 100, 1), "%")) +
  annotate("text", x = -0.45, y = 3000, size = 3, color = "green", label = paste0(round(f2
_nw_SCF4 * 100, 1), "%")) +
  annotate("text", x = -0.45, y = -3000, size = 3, colour = "green", label = paste0(round(f
2_sw_SCF4 * 100, 1), "%")) +
  annotate("text", x = 0.45, y = 3000, size = 3, colour = "green", label = paste0(round(f
2_ne_SCF4 * 100, 1), "%")) +
  annotate("text", x = 0.45, y = -3000, size = 3, colour = "green", label = paste0(round(f
2_se_SCF4 * 100, 1), "%")) +
  annotate("text", x = 0.25, y = 2000, size = 3, color = "black", label = paste0("WTP = €
20,000")) +
  theme_bw() +
  theme(plot.margin = unit(c(0.2,2.3,0.2,0.2), "lines"),
        panel.background = element_rect(fill = "gray95")) +
  annotate("text", x = Inf, y = Inf, label = "B", size = 4, hjust = 1.1, vjust = 1.1)

figure1_1 <- ggplot(out_ceaf_SCF1, aes(x=WTP, y=Proportion, color = Strategy)) +
  geom_line() +
  geom_point(size = 1.5) +
  geom_rect(data=subset(out_ceaf_SCF1, On_Frontier), aes(xmin=WTP-1000, xmax=WTP+1000, ymin
=Proportion-0.05, ymax=Proportion+0.05), fill="transparent", color="black") +
  scale_x_continuous(breaks = unique(out_ceaf_SCF1$WTP), labels = function(x) x/1000, expan
d = c(0, 0))+
  scale_y_continuous(limits = c(0, 1), breaks = seq(0, 1, 0.25), expand = c(0, 0)) +
  scale_color_manual(values = c("SOC" = "tomato3", "E.health" = "turquoise4")) +
  labs(
    x = "WTP in €1000/QALY",
    y = "Pr cost-effective",
    title = "Scenario 1"
  ) +
  theme_bw() +
  theme(
    axis.title.x = element_text(size = 10),
    axis.title.y = element_text(size = 10),
    plot.margin = unit(c(0.2,1.5,0.2,0.2), "lines"),
    panel.background = element_rect(fill = "gray95"),
    plot.title = element_text(size = 10)) +
  annotate("text", x = Inf, y = Inf, label = "C", size = 4, hjust = 1.1, vjust = 1.1)

figure4_1 <- ggplot(out_ceaf_SCF4, aes(x=WTP, y=Proportion, color = Strategy)) +
  geom_line() +
  geom_point(size = 1.5) +
  geom_rect(data=subset(out_ceaf_SCF4, On_Frontier), aes(xmin=WTP-1000, xmax=WTP+1000, ymin
=Proportion-0.05, ymax=Proportion+0.05), fill="transparent", color="black") +
  scale_x_continuous(breaks = unique(out_ceaf_SCF4$WTP), labels = function(x) x/1000, expan
d = c(0, 0))+
  scale_y_continuous(limits = c(0, 1), breaks = seq(0, 1, 0.25), expand = c(0, 0)) +
  scale_color_manual(values = c("SOC" = "tomato3", "E.health" = "turquoise4")) +
  labs(
    x = "WTP in €1000/QALY",
    y = "Pr cost-effective",
    title = "Scenario 4"
  ) +
  theme_bw() +
  theme(
    axis.title.x = element_text(size = 10),
    axis.title.y = element_text(size = 10),
    plot.margin = unit(c(0.2,1.5,0.2,0.2), "lines"),
    panel.background = element_rect(fill = "gray95"),
    plot.title = element_text(size = 10)) +
  annotate("text", x = Inf, y = Inf, label = "F", size = 4, hjust = 1.1, vjust = 1.1)

figure2_1 <- ggplot(out_ceaf_SCF2, aes(x=WTP, y=Proportion, color = Strategy)) +

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geom_line() +
geom_point(size = 1.5) +
geom_rect(data=subset(out_ceaf_SCF2, On_Frontier), aes(xmin=WTP-1000, xmax=WTP+1000, ymin
=Proportion-0.05, ymax=Proportion+0.05), fill="transparent", color="black") +
scale_x_continuous(breaks = unique(out_ceaf_SCF2$WTP), labels = function(x) x/1000, expan
d = c(0, 0))+
scale_y_continuous(limits = c(0, 1), breaks = seq(0, 1, 0.25), expand = c(0, 0)) +
scale_color_manual(values = c("SOC" = "tomato3", "E.health" = "turquoise4")) +
labs(
  x = "WTP in €1000/QALY",
  y = "Pr cost-effective",
  title = "Scenario 2"
) +
theme_bw() +
theme(
  axis.title.x = element_text(size = 10),
  axis.title.y = element_text(size = 10),
  plot.margin = unit(c(0.2,1.5,0.2,0.2), "lines"),
  panel.background = element_rect(fill = "gray95"),
  plot.title = element_text(size = 10)) +
annotate("text", x = Inf, y = Inf, label = "D", size = 4, hjust = 1.1, vjust = 1.1)

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```

figure5_1 <- ggplot(out_ceaf_SCF5, aes(x=WTP, y=Proportion, color = Strategy)) +
  geom_line() +
  geom_point(size = 1.5) +
  geom_rect(data=subset(out_ceaf_SCF5, On_Frontier), aes(xmin=WTP-1000, xmax=WTP+1000, ymin
=Proportion-0.05, ymax=Proportion+0.05), fill="transparent", color="black") +
  scale_x_continuous(breaks = unique(out_ceaf_SCF5$WTP), labels = function(x) x/1000, expan
d = c(0, 0))+
  scale_y_continuous(limits = c(0, 1), breaks = seq(0, 1, 0.25), expand = c(0, 0)) +
  scale_color_manual(values = c("SOC" = "tomato3", "E.health" = "turquoise4")) +
  labs(
    x = "WTP in €1000/QALY",
    y = "Pr cost-effective",
    title = "Scenario 5"
  ) +
  theme_bw() +
  theme(
    axis.title.x = element_text(size = 10),
    axis.title.y = element_text(size = 10),
    plot.margin = unit(c(0.2,1.5,0.2,0.2), "lines"),
    panel.background = element_rect(fill = "gray95"),
    plot.title = element_text(size = 10)) +
  annotate("text", x = Inf, y = Inf, label = "G", size = 4, hjust = 1.1, vjust = 1.1)

```

```

figure3_1 <- ggplot(out_ceaf_SCF3, aes(x=WTP, y=Proportion, color = Strategy)) +
  geom_line() +
  geom_point(size = 1.5) +
  geom_rect(data=subset(out_ceaf_SCF3, On_Frontier), aes(xmin=WTP-1000, xmax=WTP+1000, ymin
=Proportion-0.05, ymax=Proportion+0.05), fill="transparent", color="black") +
  scale_x_continuous(breaks = unique(out_ceaf_SCF3$WTP), labels = function(x) x/1000, expan
d = c(0, 0))+
  scale_y_continuous(limits = c(0, 1), breaks = seq(0, 1, 0.25), expand = c(0, 0)) +
  scale_color_manual(values = c("SOC" = "tomato3", "E.health" = "turquoise4")) +
  labs(
    x = "WTP in €1000/QALY",
    y = "Pr cost-effective",
    title = "Scenario 3"
  ) +
  theme_bw() +
  theme(
    axis.title.x = element_text(size = 10),
    axis.title.y = element_text(size = 10),
    plot.margin = unit(c(0.2,1.5,0.2,0.2), "lines"),

```







```

data_EVPPPI_SCF2 <- data_EVPPPI_SCF2[data_EVPPPI_SCF2$PopulationEVPPPI != 0, ]
plot_evppi_SCF2 <- ggplot(data_EVPPPI_SCF2, aes(x = reorder(Parameter, PopulationEVPPPI), y =
PopulationEVPPPI)) +
  geom_bar(stat = "identity", width = 0.1) +
  coord_flip() +
  labs(title = "Population EVPPPI, Scenario 2",
       x = "Parameter",
       y = "Population EVPPPI") +
  theme_bw()

data_EVPPPI_SCF1 <- data.frame(
  Parameter = c("p.adh", "c.DMII", "p.t1_M_40to59", "p.t2to5_M_40to59", "p.t6to9_M_40to59", "p.t
10tox_M_40to59",
              "p.t1_M_60to80", "p.t2to5_M_60to80", "p.t6to9_M_60to80", "p.t10tox_M_60to80", "
p.t1_M_80tox",
              "p.t2to5_M_80tox", "p.t6to9_M_80tox", "p.t10tox_M_80tox", "p.t1_F_40to59", "p.t
2to5_F_40to59",
              "p.t6to9_F_40to59", "p.t10tox_F_40to59", "p.t1_F_60to80", "p.t2to5_F_60to80", "
p.t6to9_F_60to80",
              "p.t10tox_F_60to80", "p.t1_F_80tox", "p.t2to5_F_80tox", "p.t6to9_F_80tox", "p.t
10tox_F_80tox",
              "p.KL_M_0", "p.KL_F_0", "p.KL_M", "p.KL_F", "p.TKA_FBp_M_45to60", "p.TKA_FBp_F_4
5to60", "p.TKA_FBp_M_60to80",
              "p.TKA_FBp_F_60to80", "p.TKA_FBp_M_80tox", "p.TKA_FBp_F_80tox", "p.rTKA_FBpr_M
_45to60", "p.rTKA_FBpr_F_45to60",
              "p.rTKA_FBpr_M_60to80", "p.rTKA_FBpr_F_60to80", "p.rTKA_FBpr_M_80tox", "p.rTKA
_FBpr_F_80tox", "p.FB.NBp_rTKA_M_45to65",
              "p.FB.NBp_rTKA_F_45to65", "p.FB.NBp_rTKA_M_65to80", "p.FB.NBp_rTKA_F_65to80",
"p.FB.NBp_rTKA_M_80tox", "p.FB.NBp_rTKA_F_80tox"),
  PopulationEVPPPI = c(0,0,0,0,61550,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,185800,0,0,0,0,0,0,0,64940,0,
414500,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0))
data_EVPPPI_SCF1 <- data_EVPPPI_SCF1[order(-data_EVPPPI_SCF1$PopulationEVPPPI), ]
data_EVPPPI_SCF1 <- data_EVPPPI_SCF1[data_EVPPPI_SCF1$PopulationEVPPPI != 0, ]
plot_evppi_SCF1 <- ggplot(data_EVPPPI_SCF1, aes(x = reorder(Parameter, PopulationEVPPPI), y =
PopulationEVPPPI)) +
  geom_bar(stat = "identity", width = 0.1) +
  coord_flip() +
  labs(title = "Population EVPPPI, Scenario 1",
       x = "Parameter",
       y = "Population EVPPPI") +
  theme_bw()

data_EVPPPI_Mix <- data.frame(
  Parameter = c("p.adh", "c.DMII", "p.t1_M_40to59", "p.t2to5_M_40to59", "p.t6to9_M_40to59", "p.t
10tox_M_40to59",
              "p.t1_M_60to80", "p.t2to5_M_60to80", "p.t6to9_M_60to80", "p.t10tox_M_60to80", "
p.t1_M_80tox",
              "p.t2to5_M_80tox", "p.t6to9_M_80tox", "p.t10tox_M_80tox", "p.t1_F_40to59", "p.t
2to5_F_40to59",
              "p.t6to9_F_40to59", "p.t10tox_F_40to59", "p.t1_F_60to80", "p.t2to5_F_60to80", "
p.t6to9_F_60to80",
              "p.t10tox_F_60to80", "p.t1_F_80tox", "p.t2to5_F_80tox", "p.t6to9_F_80tox", "p.t
10tox_F_80tox",
              "p.KL_M_0", "p.KL_F_0", "p.KL_M", "p.KL_F", "p.TKA_FBp_M_45to60", "p.TKA_FBp_F_4
5to60", "p.TKA_FBp_M_60to80",
              "p.TKA_FBp_F_60to80", "p.TKA_FBp_M_80tox", "p.TKA_FBp_F_80tox", "p.rTKA_FBpr_M
_45to60", "p.rTKA_FBpr_F_45to60",
              "p.rTKA_FBpr_M_60to80", "p.rTKA_FBpr_F_60to80", "p.rTKA_FBpr_M_80tox", "p.rTKA
_FBpr_F_80tox", "p.FB.NBp_rTKA_M_45to65",
              "p.FB.NBp_rTKA_F_45to65", "p.FB.NBp_rTKA_M_65to80", "p.FB.NBp_rTKA_F_65to80",
"p.FB.NBp_rTKA_M_80tox", "p.FB.NBp_rTKA_F_80tox"),
  PopulationEVPPPI_Scenario1 = data_EVPPPI_SCF1$PopulationEVPPPI,
  PopulationEVPPPI_Scenario2 = data_EVPPPI_SCF2$PopulationEVPPPI,
  PopulationEVPPPI_Scenario3 = data_EVPPPI_SCF3$PopulationEVPPPI,
  PopulationEVPPPI_Scenario4 = data_EVPPPI_SCF4$PopulationEVPPPI,
  PopulationEVPPPI_Scenario5 = data_EVPPPI_SCF5$PopulationEVPPPI,

```

```

PopulationEVVPI_Scenario6 = data_EVVPI_SCF6$PopulationEVVPI)
data_long <- tidyr::pivot_longer(data_EVVPI_Mix, cols = c(PopulationEVVPI_Scenario1, Popula
tionEVVPI_Scenario2, PopulationEVVPI_Scenario3, PopulationEVVPI_Scenario4, PopulationEVVPI_
Scenario5, PopulationEVVPI_Scenario6),
                                names_to = "Scenario", values_to = "PopulationEVVPI")
data_long <- data_long %>%
  arrange(Scenario, desc(PopulationEVVPI))
data_long <- data_long %>%
  group_by(Scenario) %>%
  mutate(Parameter = factor(Parameter, levels = rev(unique(Parameter)))) %>%
  ungroup() %>%
  filter(PopulationEVVPI != 0)

plot_mix <- ggplot(data_long, aes(x = PopulationEVVPI, y = Parameter, fill = Scenario)) +
  geom_bar(stat = "identity", position = position_dodge2(preserve = "single", width = 3, pa
dding = 0), width = 1) +
  scale_x_continuous(labels = function(x)x / 1000000, limits = c(0, 4000000), breaks = seq(
0, 4000000, 500000)) +
  scale_y_discrete(expand = c(0.1, 0)) +
  labs(title = "Annual popEVVPI by Parameter",
        x = "Annual popEVVPI (million €)",
        y = "Parameter",
        fill = "Scenario") +
  theme_bw() +
  theme(plot.title = element_text(size = 10)) +
  annotate("text", x = Inf, y = Inf, label = "G", size = 4, hjust = 1.1, vjust = 1.1)
plot(plot_mix)
##
evpi_SCF1 <- calc_evpi(wtp = seq(0, 100000, by = 10000), psa = l_psa_SCF1)
evpi_SCF2 <- calc_evpi(wtp = seq(0, 100000, by = 10000), psa = l_psa_SCF2)
evpi_SCF3 <- calc_evpi(wtp = seq(0, 100000, by = 10000), psa = l_psa_SCF3)
evpi_SCF4 <- calc_evpi(wtp = seq(0, 100000, by = 10000), psa = l_psa_SCF4)
evpi_SCF5 <- calc_evpi(wtp = seq(0, 100000, by = 10000), psa = l_psa_SCF5)
evpi_SCF6 <- calc_evpi(wtp = seq(0, 100000, by = 10000), psa = l_psa_SCF6)

evpi_SCF1$pop <- evpi_SCF1$EVPI * 762700
evpi_SCF2$pop <- evpi_SCF2$EVPI * 762700
evpi_SCF3$pop <- evpi_SCF3$EVPI * 762700
evpi_SCF4$pop <- evpi_SCF4$EVPI * 762700
evpi_SCF5$pop <- evpi_SCF5$EVPI * 762700
evpi_SCF6$pop <- evpi_SCF6$EVPI * 762700

evpi1 <- ggplot(evpi_SCF1, aes(WTP, pop)) +
  geom_line(size = 0.5) +
  geom_vline(xintercept = 20000, linetype = "dashed", color = "red", size = 0.5) +
  geom_hline(yintercept = 182397666, linetype = "dashed", color = "red", size = 0.5) +
  scale_y_continuous(labels = function(x)x / 1000000, limits = c(0, 1000000000), breaks = s
eq(0, 1000000000, 400000000)) +
  theme_bw() +
  theme(panel.grid = element_blank(),
        plot.title = element_text(size = 10)) +
  labs(
    x = "WTP",
    y = "popEVVPI (million €)",
    title = "Annual popEVVPI, Scenario 1"
  ) +
  annotate("text", x = Inf, y = Inf, label = "A", size = 4, hjust = 1.1, vjust = 1.1)

evpi2 <- ggplot(evpi_SCF2, aes(WTP, pop)) +
  geom_line(size = 0.5) +
  geom_vline(xintercept = 20000, linetype = "dashed", color = "red", size = 0.5) +
  geom_hline(yintercept = 118755905, linetype = "dashed", color = "red", size = 0.5) +
  scale_y_continuous(labels = function(x)x / 1000000, limits = c(0, 1000000000), breaks = s
eq(0, 1000000000, 400000000)) +
  theme_bw() +

```



```

theme(panel.grid = element_blank(),
      plot.title = element_text(size = 10)) +
labs(
  x = "WTP",
  y = "popEVPI (million €)",
  title = "Annual popEVPI, Scenario 2"
) +
annotate("text", x = Inf, y = Inf, label = "B", size = 4, hjust = 1.1, vjust = 1.1)

evpi3 <- ggplot(evpi_SCF3, aes(WTP, pop)) +
  geom_line(size = 0.5) +
  geom_vline(xintercept = 20000, linetype = "dashed", color = "red", size = 0.5) +
  geom_hline(yintercept = 52300339, linetype = "dashed", color = "red", size = 0.5) +
  scale_y_continuous(labels = function(x)x / 1000000, limits = c(0, 1000000000), breaks = s
eq(0, 1000000000, 400000000)) +
  theme_bw() +
  theme(panel.grid = element_blank(),
        plot.title = element_text(size = 10)) +
  labs(
    x = "WTP",
    y = "popEVPI (million €)",
    title = "Annual popEVPI, Scenario 3"
  ) +
  annotate("text", x = Inf, y = Inf, label = "C", size = 4, hjust = 1.1, vjust = 1.1)

evpi4 <- ggplot(evpi_SCF4, aes(WTP, pop)) +
  geom_line(size = 0.5) +
  geom_vline(xintercept = 20000, linetype = "dashed", color = "red", size = 0.5) +
  geom_hline(yintercept = 228411797, linetype = "dashed", color = "red", size = 0.5) +
  scale_y_continuous(labels = function(x)x / 1000000, limits = c(0, 1000000000), breaks = s
eq(0, 1000000000, 400000000)) +
  theme_bw() +
  theme(panel.grid = element_blank(),
        plot.title = element_text(size = 10)) +
  labs(
    x = "WTP",
    y = "popEVPI (million €)",
    title = "Annual popEVPI, Scenario 4"
  ) +
  annotate("text", x = Inf, y = Inf, label = "D", size = 4, hjust = 1.1, vjust = 1.1)

evpi5 <- ggplot(evpi_SCF5, aes(WTP, pop)) +
  geom_line(size = 0.5) +
  geom_vline(xintercept = 20000, linetype = "dashed", color = "red", size = 0.5) +
  geom_hline(yintercept = 120020818, linetype = "dashed", color = "red", size = 0.5) +
  scale_y_continuous(labels = function(x)x / 1000000, limits = c(0, 1000000000), breaks = s
eq(0, 1000000000, 400000000)) +
  theme_bw() +
  theme(panel.grid = element_blank(),
        plot.title = element_text(size = 10)) +
  labs(
    x = "WTP",
    y = "popEVPI (million €)",
    title = "Annual popEVPI, Scenario 5"
  ) +
  annotate("text", x = Inf, y = Inf, label = "E", size = 4, hjust = 1.1, vjust = 1.1)

evpi6 <- ggplot(evpi_SCF6, aes(WTP, pop)) +
  geom_line(size = 0.5) +
  geom_vline(xintercept = 20000, linetype = "dashed", color = "red", size = 0.5) +
  geom_hline(yintercept = 33387720.8, linetype = "dashed", color = "red", size = 0.5) +
  scale_y_continuous(labels = function(x)x / 1000000, limits = c(0, 1000000000), breaks = s
eq(0, 1000000000, 400000000)) +

```

```

theme_bw() +
theme(panel.grid = element_blank(),
      plot.title = element_text(size = 10)) +
labs(
  x = "WTP",
  y = "popEVPI (million €)",
  title = "Annual popEVPI, Scenario 6"
) +
annotate("text", x = Inf, y = Inf, label = "F", size = 4, hjust = 1.1, vjust = 1.1)

grid.arrange(
  arrangeGrob(evpi1, evpi4, evpi2,
             evpi5, evpi3, evpi6, ncol = 2, nrow = 3),
  arrangeGrob(plot_mix, ncol = 1,
             nrow = 2,
             heights = c(2,1)
  )
)

```