Support Services for the Management and Utilization of Monitoring and Assessment of the EIP - MAFEIP Tool

MD-Paedigree

Clinical Impact Assessment

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led by

in partnership with

funded by

Executive summary

Description of the intervention

The EU project MD-Paedigree aims to develop a set of reusable and adaptable multi-scale models for more predictive, individualised, effective and safer paediatric healthcare, being scientifically and technologically supported by one of the leading industrial actors in medical applications in Europe operating in conjunction with highly qualified SMEs and some of the most experienced research partners in the VPH community.

The concrete intervention explored in this use case is a model scenario for improved paediatric cardiomyopathy care – a set of chronic and often progressive diseases in which the heart muscle (myocardium) is abnormally enlarged, thickened and/or stiffened. 200 children with cardiovascular disease have been analysed in the project in order to provide clinical and cardiac structural, geometrical and functional data to build the heart model and to validate it afterwards.

Model input

Defining the health states and the transition probabilities

The MD-Paedigree project has used a 5-state Markov model with two more disease stages: mechanical support and transplant. This approach was adapted to the 3-state Markov model in MAFEIP by combining probabilities of some states. The project has collected the necessary data to populate the model with values for transition probabilities and relative risk for mortality.

Computing the costs

Annual fixed cost of making use of the MD Paedigree simulation and decision support services in the case of cardiomyopathy have been calculated. This does not account for the initial development and investment costs; here we assume that the EU funding of the research project and also follow-up clinical validation work will be absorbed by third party payers, and this is regarded as sunk costs not be included into the cost equation. The fixed amount is used to derive the cost p.a. per patient. Additional costs will arise each time the model is applied to a specific patient. Table 4 presents the total intervention costs per patient.

Data collected by the project team about costs of stay provides values for the healthcare and societal costs.

Utility

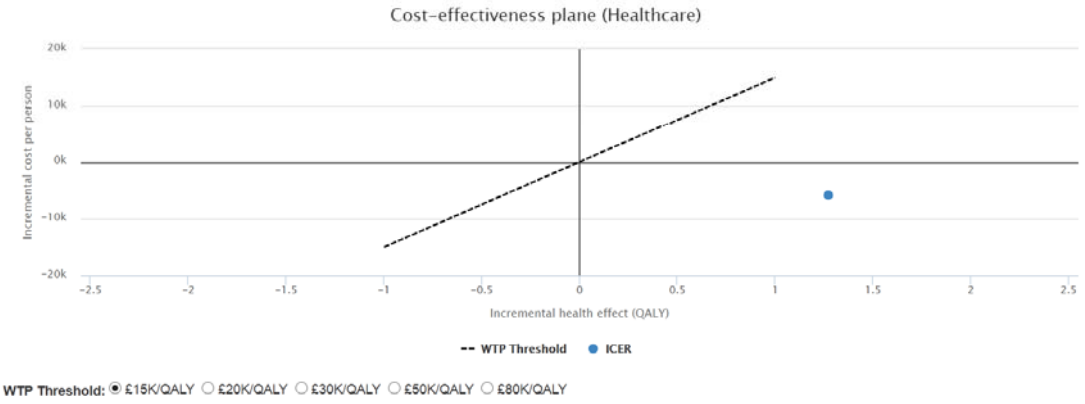
The project has not focused on utility calculations, but uses some secondary sources to provide moderate estimations. A sensitivity analysis will be most suitable to be performed on these values in order to see what the effect of the uncertainty is.

		Utility
Control	Baseline	0.5
	Deteriorated	0.3
Intervention	Baseline	0.5
	Deteriorated	0.4

Model output

The combination of the incremental cost and effects place the incremental cost-effectiveness ratio (ICER) in the lower-right quadrant. This means that the intervention is better (more effective) and cheaper than the current (standard) care, which makes it dominant. It this case it is accepted, because it is also below the Willingness to Pay (WTP) threshold.

Incremental cost and HRQoL effects	
Incremental cost (Healthcare)	-5868.45
Incremental effects	1.275
Incremental cost-effectiveness ratio (Healthcare)	Dominant



WTP Threshold: ◉ £15K/QALY ○ £20K/QALY ○ £30K/QALY ○ £50K/QALY ○ £80K/QALY

Sensitivity analysis is further explored in this use case to show the effects of parameters, the values for which have uncertainty

1. Description of the intervention

The EU project MD-Paedigree aims to develop a set of reusable and adaptable multi-scale models for more predictive, individualised, effective and safer paediatric healthcare, being scientifically and technologically supported by one of the leading industrial actors in medical applications in Europe operating in conjunction with highly qualified SMEs and some of the most experienced research partners in the VPH community.

MD-Paedigree validates and brings to maturity patient-specific computer-based predictive models of various paediatric diseases, thus increasing their potential acceptance in the clinical and biomedical research environment by making them readily available not only in the form of sustainable models and simulations, but also as newly-defined workflows for personalised predictive medicine at the point of care. These tools can be accessed and used through an innovative model-driven infostructure powered by an established digital repository solution able to integrate multimodal health data, entirely focused on paediatrics and conceived of as a specific implementation of the VPH-Share project, planned to be fully interoperable with it and cooperating, through it, also with p-Medicine.

The concrete intervention explored in this use case is a model scenario for improved paediatric cardiomyopathy care. Cardiomyopathy is a summary term for a set of chronic and often progressive diseases in which the heart muscle (myocardium) is abnormally enlarged, thickened and/or stiffened. The condition typically begins in the walls of the heart's lower chambers (ventricles), and in more severe cases also affects the walls of the upper chambers (atria). The actual muscle cells as well as the surrounding tissues of the heart become damaged. Eventually, the weakened heart loses the ability to pump blood effectively and various types of severity of heart failure, or also irregular heartbeats (arrhythmias) may occur.

Cardiomyopathy is classified as either "ischemic" or "nonischemic". In ischaemic cardiomyopathy, ventricular dysfunction is a consequence of myocardial ischaemia and infarction related to coronary arteriosclerosis. Non-ischemic cardiomyopathy predominately involves the heart's abnormal structure and function. All cases related to children and teenagers are considered "nonischemic" cardiomyopathy. There are many potential causes of non-ischaemic cardiomyopathy (NICM), including haemodynamic pathology, infection, immunologic abnormalities, toxic injury, or genetic factors. Nonischemic cardiomyopathy can be broken down into: 1) "primary cardiomyopathy" where the heart is predominately affected and the cause may be due to infectious agents or genetic disorders and 2) "secondary cardiomyopathy" where the heart is affected due to complications from another disease affecting the body (i.e. HIV, cancer, muscular dystrophy or cystic fibrosis).

Unfortunately, there is no current cure or treatment that can return the heart to normal or guarantee long term survival. Although occasionally children with certain types of cardiomyopathy do improve, the vast majority do not show any recovery in heart function. If detected in the earlier stages, cardiomyopathy may be controlled with long-term drug therapy and placement of a pacemaker/ defibrillator. This may prevent the need for measures such as placement of a breathing tube (mechanical ventilator) and administration of medications intravenously (i.e. dobutamine, dopamine) to improve blood pressure and heart function. The MD Paedigree model aims to improve the care pathways so that the disease does not always have to only be diagnosed at an advanced stage.

In summary, in paediatric cardiovascular disease, predicting how patients will respond to treatments, which treatments to use and when to treat can be difficult to define due to small

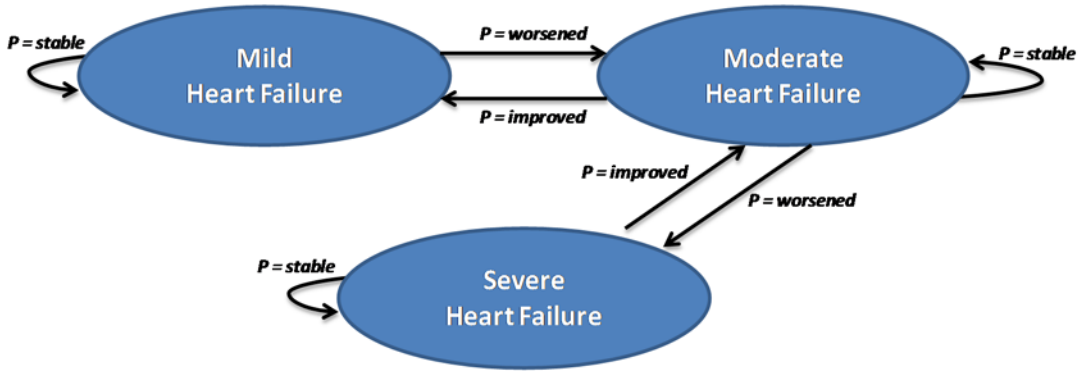
patient numbers and limited outcome data. When children present with cardiomyopathy or new onset heart failure, there are five possible outcomes: full recovery, dilated cardiomyopathy (DCM) requiring drug therapy, DCM requiring transplantation or mechanical support, another diagnosis (other forms of cardiomyopathy, metabolic disease), or death. At presentation, however, it is very difficult to predict which group any patient will end up in. Data suggests that good systolic function and younger age are good prognostic indicators for survival, but better prognosticators are necessary.

200 children with cardiovascular disease have been analysed in the project in order to provide clinical and cardiac structural, geometrical and functional data to build the heart model and to validate it afterwards.

2. Model input

2.1. Defining the health states and the transition probabilities

In the project, the generic Markov-chain disease states were derived from the care pathway and its three general disease states as reflected in the figure below.



For the purpose of calculating the incremental health gain and its impact on the costing model behind each of the disease states, however, the project work necessitated the addition of two more disease stages: mechanical support and transplant. The incremental health gain, in the definition of the project's generic clinical impact modelling framework, is the comparative measurement of impact between standard care and the care pathway facilitated by MD Paedigree technologies. The below figure summaries this 5-staged Markov model.

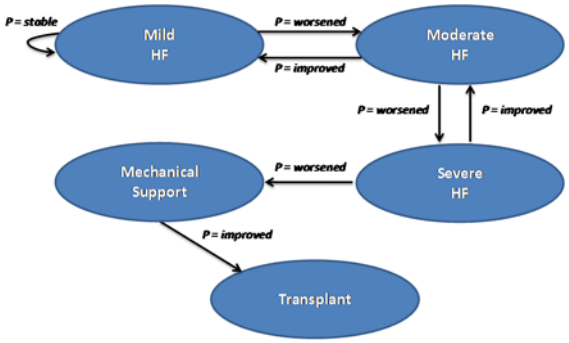


Table 1. Transition matrix with the standard pathway of care

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

Table 2. Transition matrix MD-Paedigree

Transition Matrix – MD Paedigree					
	Mild HF	Moderate HF	Severe HF	Mechanical Support	Transplant
Mild HF		0.50			
Moderate HF	0.70		0.30		
Severe HF		0.05		0.25	
Mechanical Support					0.80
Transplant					

The use case takes into account the three-state Markov model. A separate use case can be derived to observe the differences with a five-state Markov model. This means that in this case baseline health is mild heart failure, deteriorated health equals moderate heart failure, and under the death state we understand severe heart failure. The values from the table above provide the probabilities for the MAFEIP tool:

Table 3. Transition probabilities

	Incidence rate	Recovery rate
Intervention group	0.5	0.7
Control group	0.5	0.6

Regarding the risk for mortality in baseline health, the project does not collect data about the mortality probability of going from mild to severe HF, therefore the tool values are used (a value of 1 is entered for control and intervention). Relative risk of mortality in deteriorated health is estimated at 40% normally[1], and an improvement through MD-Paedigree leads to a reduction to 30%.

2.2. Computing the costs

Based on first estimates from the exploitation task, we assume at this stage that the annual fixed cost of making use of the MD Paedigree simulation and decision support services in the case of cardiomyopathy will amount to roughly € 60,000. This does not account for the initial development and investment costs; here we assume that the EU funding of the research project and also follow-up clinical validation work will be absorbed by third party payers, and this is regarded as sunk costs not be included into the cost equation.

The fixed amount of € 60,000 would have to be divided by the number of patients who would undergo improved treatment due to the application of this new technology. If these were e.g. 20 patients, this would amount to € 500 p.a. per patient. We assume for a typical size of a specialised clinical setting like the one in OPBG some 6,000 patients annually enter the care pathway; as described earlier, only 20% of those initially enter the hospital ward (the moderate HF pathway). As a simplification, the fixed amount of € 60,000 Euro divided by 1200 patients leaves us with a service lump sum fee for MD Paedigree Cardio-Simulation Services per patient and cycle at €50.

[1] Lipshultz, Steven E et al. "Pediatric Cardiomyopathies: Causes, Epidemiology, Clinical Course, Preventive Strategies and Therapies." Future cardiology 9.6 (2013): 817–848. PMC. Web. 9 May 2017.

Furthermore, it is assumed that an additional cost per patient of roughly € 250 will arise each time the model is applied to a specific patient. This charge is due to the individual set-up, patient data entry, analysis and assessment of model output, and the health professional and IT specialist personnel costs involved.

Table 4. Intervention costs and healthcare and societal costs

Intervention one-off costs (per patient)	
Intervention one-off costs (per patient)	50
Intervention recurrent costs (per patient and year)	250
TOTAL	300

The healthcare and societal costs do not differentiate. They are calculated in the project and summarised as follows:

Mild HF				
	Unit Costs (€)	Lump sum fee ER (€)	Units (days)	Total (€)
Costs of Stay	250	500	~6	2,000
Moderate HF				
	Unit Costs (€)	Lump sum fee ER(€)	Units (days)	Total (€)
Costs of Stay	800	500	~21	17,300
Severe HF				
	Unit Costs (€)	Lump sum fee for ER(€)	Units (days)	Total (€)
Costs of Stay	1,200	500	~60	72,500
Mechanical Support				
	Lump sum fee (€)			Total (€)
Intervention costs	38,000			38,000
Transplant				
	Lump sum fee (€)			Total (€)
Intervention costs	66,300			66,300

Therefore, for healthcare costs baseline health we use 2,000, and for deteriorated health 17,300.

2.3. Utility

The project has not focused on utility calculations, but uses some secondary sources to provide moderate estimations. A sensitivity analysis will be most suitable to be performed on these values in order to see what the effect of the uncertainty is.

Table 5. Utility values

		Utility
Control	Baseline	0.5
	Deteriorated	0.3
Intervention	Baseline	0.5
	Deteriorated	0.4

3. Model output

The incremental costs by age are negative, implying that the intervention is cheaper than usual care (Figure 1). In this specific example, the age range observed is 0-18, and the values do not change much for this range.

The incremental effects are positive, with babies receiving 4 extra QALYs with the intervention (undiscounted values).

Figure 1. Incremental cost by age

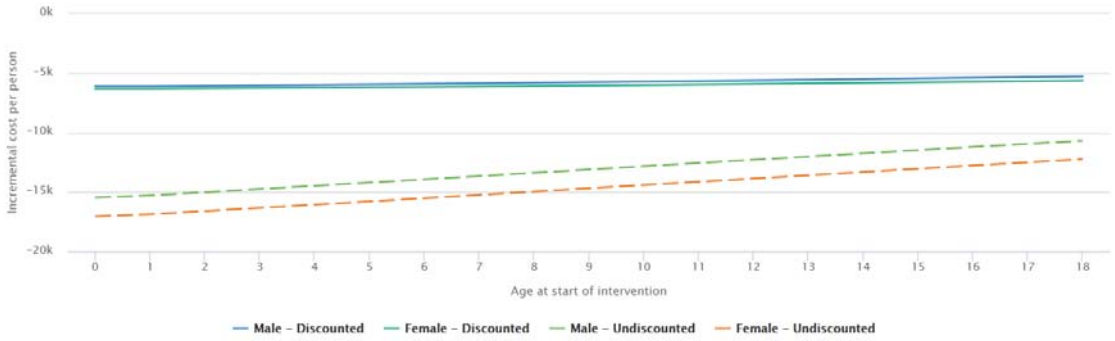


Figure 2. Incremental effects by age

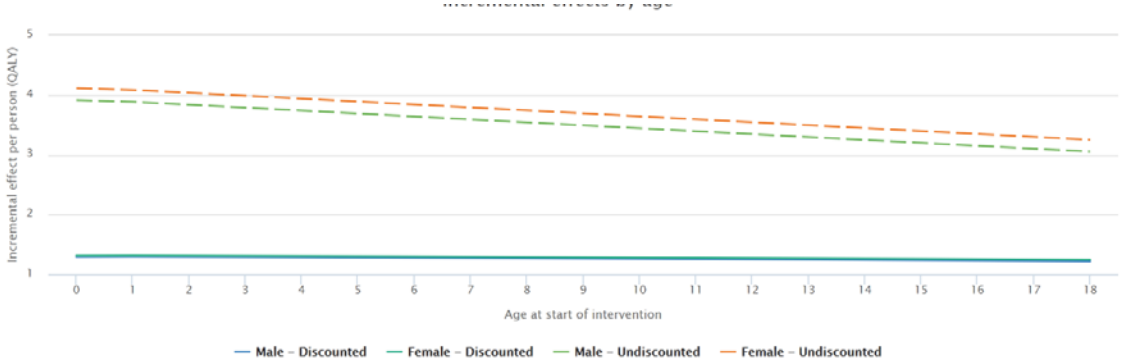


Figure 3. Cumulative incremental cost

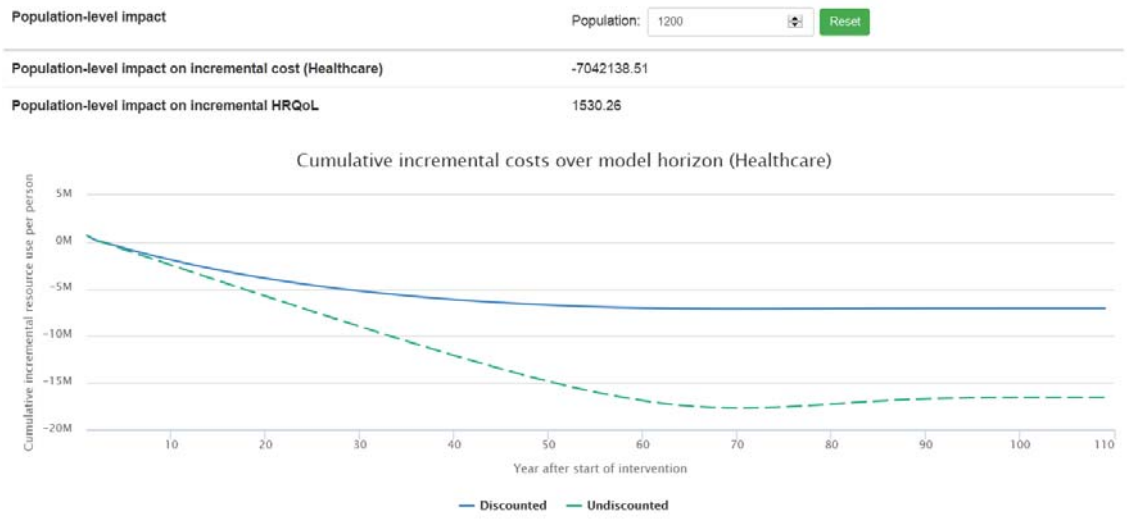
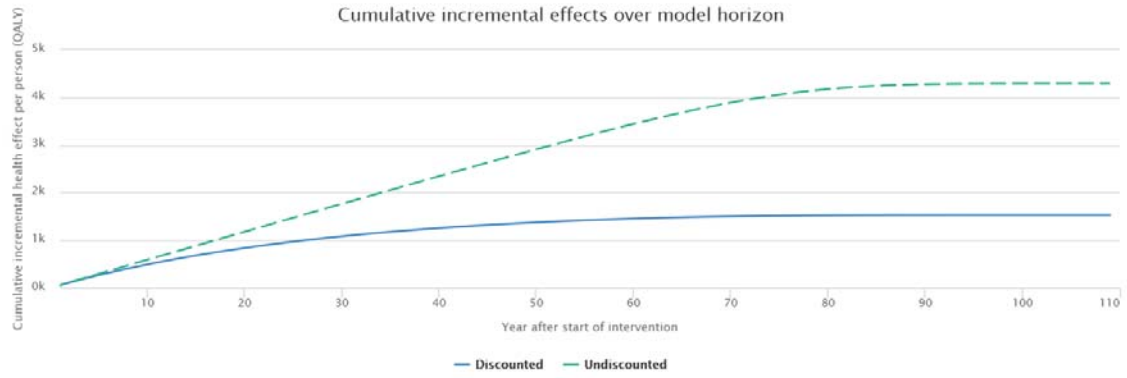
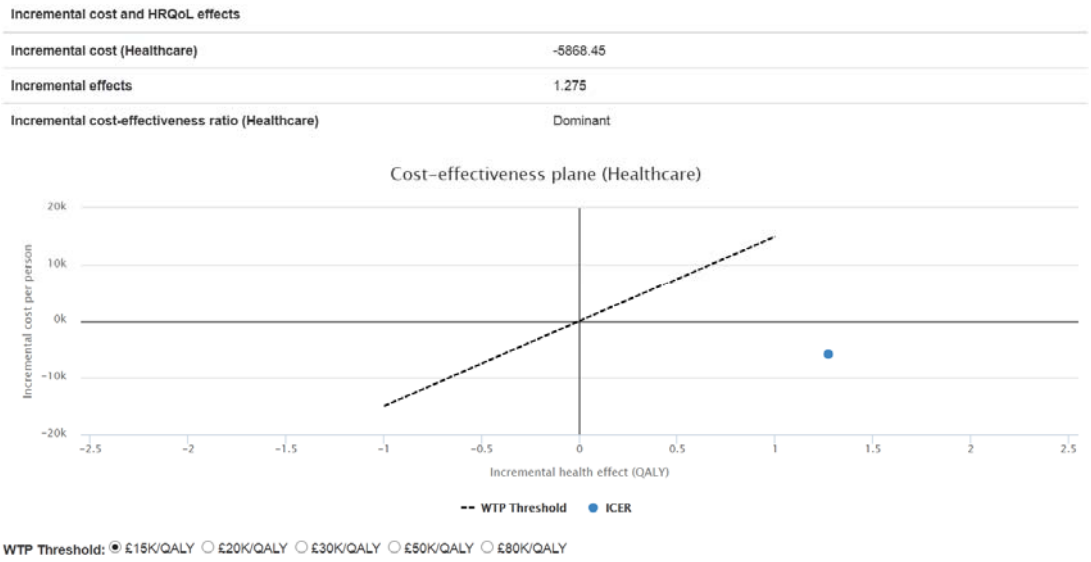


Figure 4. Cumulative incremental effects



The combination of the incremental cost and effects place the incremental cost-effectiveness ratio (ICER) in the lower-right quadrant. This means that the intervention is better (more effective) and cheaper than the current (standard) care, which makes it dominant. It this case it is accepted, because it is also below the Willingness to Pay (WTP) threshold.

Figure 5. Cost-effectiveness plane



The following figures (Figure 6, Figure 7) reflect the simulation results based on the transition probabilities identified earlier. The probability of death for this intervention and with this age group is not big.

Figure 6. Patient flow through model states (Alive states)

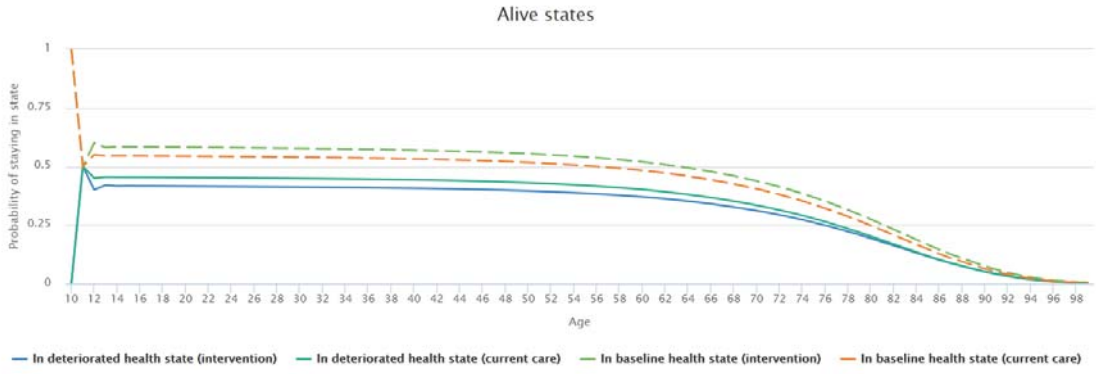
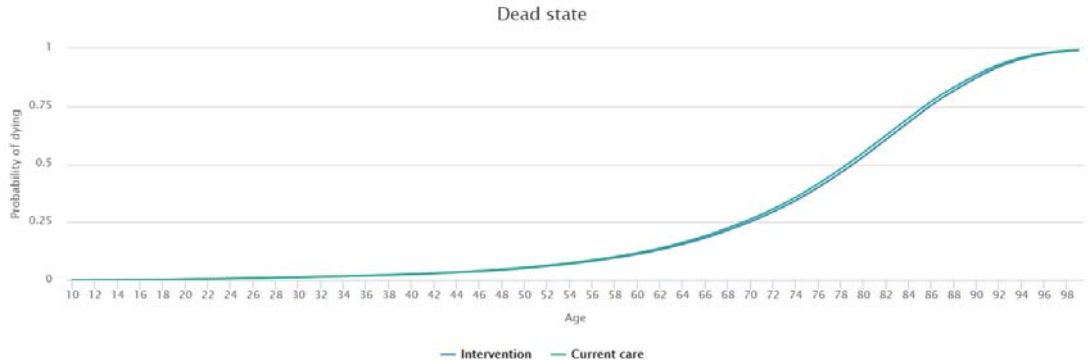
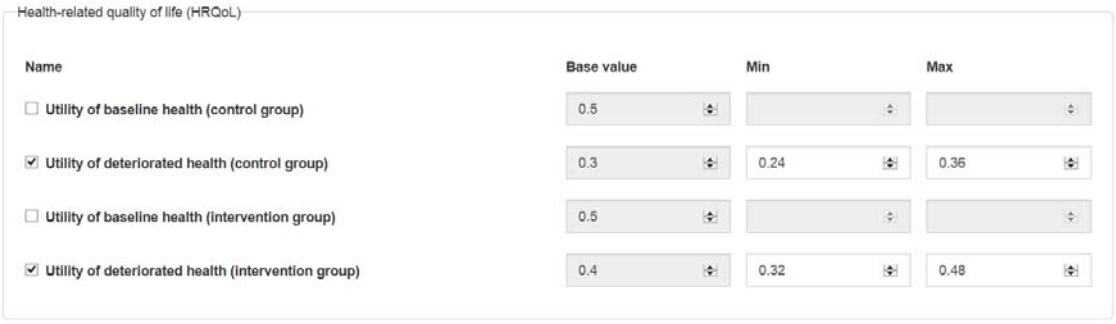


Figure 7. Patient flow through model states (Dead state)



The sensitivity analysis is applied with focus on exploring the impact of the utility values on the overall model, because the project did not have solid sources and high certainty. We vary the utility in deteriorated health for both control and intervention by approx. ±20% as seen in the figure below.



The results show that although uncertain, the dominating state of the intervention does not change when taking this uncertainty into account. This may be because other parameters like the costs and transition probabilities have much higher impact in this specific case.

Raising the uncertainty level even more (±50%) indicates that the intervention may enter a different quadrant and become less effective but cheaper. In this case one should look at the WTP – if it is below the threshold, the intervention will still be preferred. If however the values are above the threshold, the intervention will not be accepted. Therefore, a high uncertainty in the utility values should be backed by real data as it becomes available.

Figure 8. Univariate sensitivity analysis with a ±20% change in utility in deteriorated health for the control group

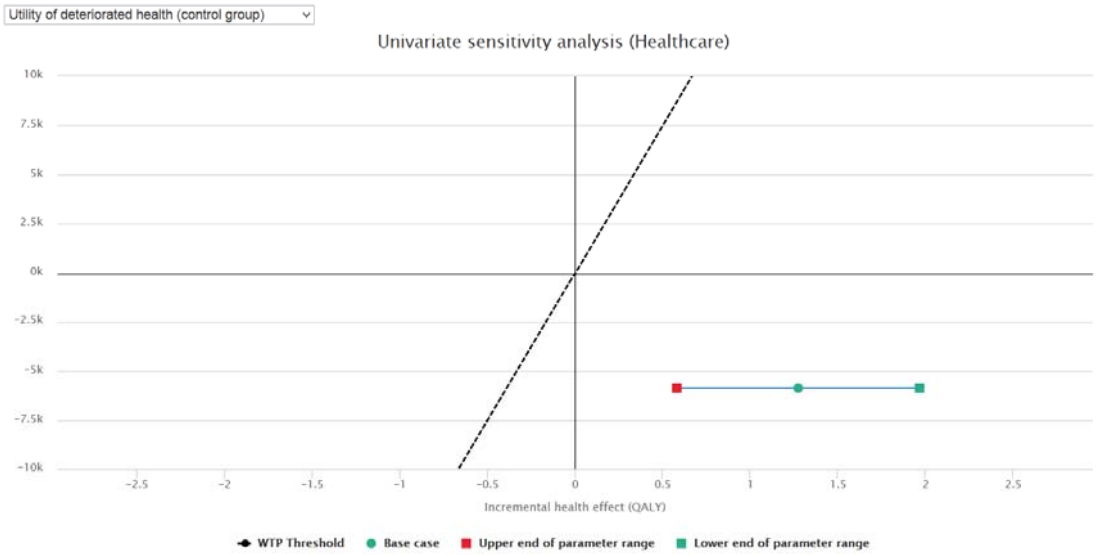
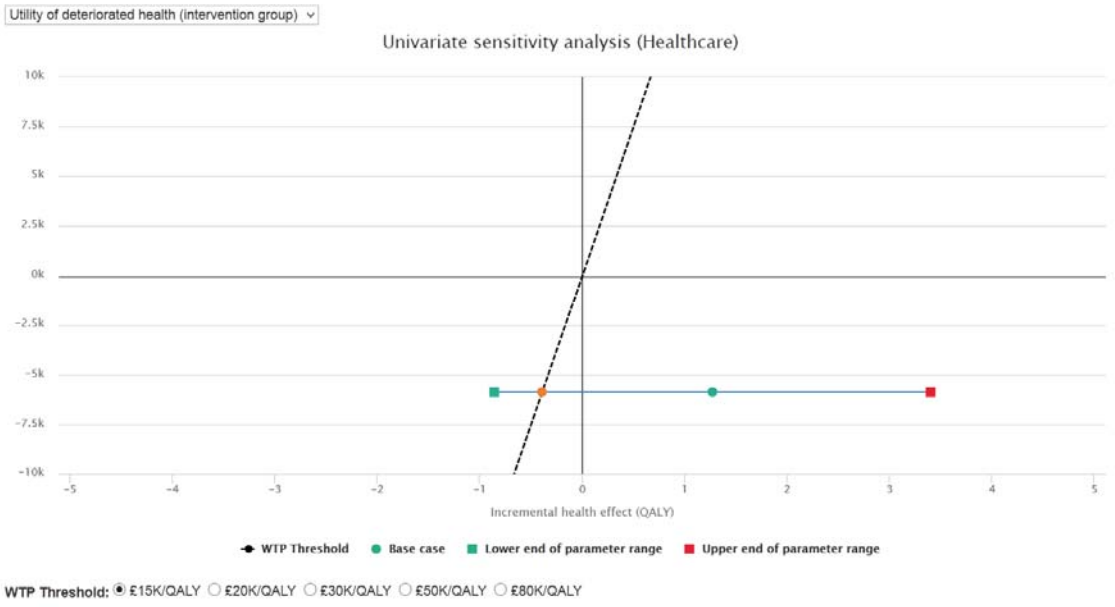


Figure 9. Univariate sensitivity analysis with a ±50% change in utility in deteriorated health for the intervention group



4. Lessons learned

This use case is a great example of how MAFEIP can be used for assessing the effects of interventions on different populations, in this case in children. The use case also indicates the importance of the values provided. If there are not (or not yet) values available, one should always perform a sensitivity analysis to see how this uncertainty affects the overall result.