SCENARIO ANALYSIS AND REAL OPTIONS MODELING OF HOME BRAIN MONITORING IN EPILEPSY PATIENTS

Martine Breteler

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Department of Health Technology & Services Research
University of Twente

Supervisors:

Prof. Maarten J. IJzerman
Health Technology and Services Research, MIRA institute for Biomedical Technology & Technical Medicine
University of Twente

Dr. Berend Roorda
Financial Engineering
University of Twente

Prof. dr. ir. Michel J.A.M. van Putten (external)
Clinical Neurophysiology, MIRA Institute for Biomedical Technology and Technical Medicine
Medisch Spectrum Twente

UNIVERSITEIT TWENTE.

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ABSTRACT

OBJECTIVES A lot of uncertainties exist when introducing new technologies to the healthcare market. The objective of this study is to explore the use of a real options approach to assess uncertainties of Home Brain Monitoring (HBM) in epilepsy patients and to construct different implementation scenarios of HBM in an early stage of its development. This method tries to show the (financial) consequences of different uncertainties on the option value of the HBM project to facilitate investment decisions in the future.

METHODS Individual semi-structured interviews were used to present (implementation) uncertainties to 18 epilepsy experts. Expert elicitation was used to collect beliefs regarding uncertainties of HBM and to estimate probabilities of 'success' of uncertainties. Scenarios were constructed, each of which describe a set of uncertainties. These uncertainties were resolved in order to obtain a production process with a certain expected option value. Finally, a real options model was developed that shows the influence of uncertainties on the total option value of the project. Sensitivity analysis was used to demonstrate the impact of different uncertainties.

RESULTS Obtained results indicated the importance of a proper estimation of the probabilities by experts. The most likely scenario of HBM which received the highest probability of success (14.3%) is scenario 3 of which HBM is being implemented after a negative first routine EEG together with a computer detection algorithm to analyze the results. Sensitivity analysis showed that uncertainty number 1, which refers to a very high diagnostic value, can increase the option value most when it is able to increase its probability of success in the future.

CONCLUSIONS The real options approach used in this study, Project Portfolio Option-Value (PPO) provides an innovative way to represent and value uncertainty of new projects early in its development. This study is the first to apply PPO on a new development in healthcare combined with simplified elicitation techniques and could be used in the future to guide new developments when the validity of the experts' estimations can be improved.

1. INTRODUCTION

In the Netherlands, approximately 5000-8100 new patients are diagnosed with epilepsy every year [1]. A very important diagnostic procedure for epilepsy is electroencephalography (EEG) which can detect interictal epileptiform discharges (IEDs). Although the detection of IEDs has high specificity for the diagnosis of epilepsy, the sensitivity of a standard routine EEG in epileptic patients is only about 20-56% [2-4].

To further improve sensitivity of EEG records, long-term EEG recordings (24-48h) are proposed due to the increased chance of detecting epileptiform abnormalities [5]. Therefore, 'in-Home Brain Monitoring' (HBM) is being developed as an alternative to routine diagnostics for patients evaluated for epilepsy. Questions arise about different uncertainties of HBM. For instance, where in the diagnostic path can it be implemented and what are the (financial) consequences of different uncertainties in terms of economic return? The objective of this study is to identify and evaluate a new technology early in its development to show the financial impact of different uncertainties of HBM.

1.1. HOME BRAIN MONITORING

Epilepsy is a serious brain condition, characterized by recurrent seizures that significantly affect quality of life. An EEG should be performed to support the diagnosis of epilepsy of which the clinical history suggests the seizure is likely to be epileptic [6]. An EEG can increase or decrease the likelihood of having epilepsy after a clinical suspicion of an epileptic disorder. However, the diagnosis of a first seizure is often not straightforward and subjected to inter-observer disagreement, with a misdiagnosis rate up to 23% [7].

A wrong diagnosis can be partly caused by the low sensitivity of current routine diagnostics. A routine EEG of 20 minutes shows only epileptiform abnormalities in as few as 20-56% of patients with epilepsy [3]. Repeated routine EEG studies can increase the sensitivity up to 77% [2, 4, 8]. A sleep deprived EEG after an initial negative routine EEG can increase the yield with 20-24% [9-11]. Overall, the specificity of EEGs is better, ranging between 78-98% [3, 12]. The variable sensitivity of the interictal EEGs depends on a number of factors such as seizure frequency [13], whether to record sleep [14] or not and the time between seizure and recording [8, 15].

HBM (Figure 1) is expected to improve the diagnostic process in epilepsy. In a retrospective study of Faulkner et al. [16], 180 consecutive epilepsy patients have undergone 96 hours of outpatient ambulatory EEG and they found that IEDs were recorded in 85% of the patients within 24 hours.

Figure 1: HBM-amplifier with electrodes.

HBM aims to significantly improve the effectiveness and reliability of the diagnostic process in epilepsy by making use of the assistance of a computer detection algorithm. With the algorithm that detects candidate epileptiform discharges, a sensitivity and specificity of >90% is pursued.

Besides the advantage of being able to measure for a longer time, it is expected to be more comfortable for patients to measure EEG at home instead of inpatient recordings. Also, the HBM device is small and easy to wear for patients.

At present, some hospitals and epilepsy centres already use ambulatory EEG for characterizing seizures in the home setting. The advantage of HBM over ambulatory EEG is the development of computer algorithms which will assist in the real-time detection of candidate-events of epileptiform abnormalities. Moreover, user-friendly software will be developed to improve efficiency in reviewing long EEG recordings and to assist physicians in interpreting data.

1.2. HEALTH TECHNOLOGY ASSESSMENT

The application of Health Technology Assessment (HTA) methodology to earlier stages of technology development is increasingly receiving attention. One of the objectives of HTA is to evaluate the application of a new technology to inform medical product developers on specific requirements to anticipate on future developments [17].

Different methods have been applied to collect evidence of health economic benefits and to predict potential clinical outcomes in an early stage [18, 19]. Early (Bayesian) health economic modeling can be used to support decision making by collecting evidence on the health economic benefits of a new medical technology. This is done by evaluating a new medical device in order to update existing information when new data becomes available [20, 21]. However, it has to deal with many uncertainties to foresee the likely application of a new medical product. This can be improved when more precise estimates of the model inputs are obtained. Expert elicitation showed to be a feasible method to estimate uncertain parameters [22, 23]. Other alternative methods for addressing structural uncertainty are for instance, multi-criteria decision analysis (MCDA) and real options analysis (ROA). MCDA assesses multiple (conflicting) criteria problems with a small number of alternatives, such as the analytical hierarchy process (AHP). Hilgerink et al. [24] used AHP to estimate the diagnostic performance of a new imaging technology with an expert panel. The advantage of AHP is the straightforward use of multiple pairwise comparisons to measure the impact and

importance of parameters [25] and its ability to check inconsistencies. However the disadvantage of this approach is the fact that these parameters are not directly assessed individually and therefore it is difficult to represent it as distributions to characterize its uncertainty as with expert elicitation. Moreover, AHP produces a unitless score [26], whereas ROA uses units with finance as the common basis.

1.3. REAL OPTIONS ANALYSIS

ROA is an approach for making optimal project selection decisions. It has been used as an investment evaluation tool that accounts for both uncertainty and the company's ability to react when new information becomes available. This information is incorporated in decisions which have to be made [27].

ROA emerged as a reaction to imperfections of cost-benefit analysis that is used commonly to evaluate investment decisions. In a cost-benefit analysis, the net present value of the project is determined using discounted cash flow analysis. Reliable forecasts of uncertain costs and benefits are therefore essential to the outcome. However, the standard discounted cash flow method often values investments wrongly and cannot value uncertainties properly [28, 29].

Despite the advantages of ROA, the method also has some shortcomings. ROA models are not very well suited for application in complex technology settings, because ROA tends to sacrifice transparency. This is primarily due to the fact that unrealistic assumptions are made when ROA models are used in a complex decision setting and thereby it does not fit in standard option models anymore.

To overcome these imperfections, a simplified method for valuing complex projects is developed by Wouters et al [30]. This method, called 'Project Portfolio Option-Value (PPO)' was used to discuss its application for a large project investment by Philips Lighting [30, 31]. An option value [30] is the ability to undertake action during a project and the managerial flexibility to retrieve information about uncertain project characteristics that has value in context of uncertainties of HBM.

In contrast to ROA, PPO is designed for a complex setting of which many uncertainties exist about technology and the market. PPO is able to translate economical and technological uncertainty into financial consequences, which can be easily understood when criteria are compared. It is therefore a transparent way to help bringing together important information to guide decision making instead of ROA models which are perceived as difficult black boxes. Moreover, transparency is one of the important points when management need to be convinced when a model will be showed [32].

In the present study the use of a real options approach is explored to assess uncertainties of in-Home Brain Monitoring in an early stage of its development. This study will explore promising application scenarios of in-home brain monitoring in the diagnostic track of epilepsy patients and evaluate the value of these scenarios using a real options approach to determine the option value of these scenarios.

2. METHODS

In this study, the real options approach (PPO) used by Wouters et al. [30] serves as guidance to achieve the development of a model that shows the influence of uncertainties of HBM on the value of the project.

[redacted]

Wouters et al. [30] described this PPO model as the indirect effect of one project on other projects to support decision making at portfolio level. However, this study includes one project HBM and therefore the portfolio level is not applicable.

[redacted]

2.1. DEFINING DIAGNOSTIC PATHWAY

The diagnostic pathway of first-seizure patients is set up to be able to construct implementation possibilities of HBM. These implementation possibilities are needed to construct scenarios of HBM finally. Figure 3 shows a flowchart of the diagnostic pathway of first-seizure patients. The patients' medical history, including family history determines whether there is a suspicion of a first seizure.

Assumptions were made with regard to the diagnostic path of epilepsy. It is assumed that patients with a suspicion of a first seizure will not undergo more than two EEG recordings (where the second recording will be a routine EEG or a sleep deprived EEG). In practice, neurologists typically do not order more than two recordings. When these EEGs did not reveal anything, it is thought that the chance of having epilepsy is very small, but not excluded. Only in exceptional cases more recordings are performed. Often, also Magnetic Resonance Imaging (MRI) is indicated and blood samples are retrieved to exclude other disorders, but this is not shown here.

2.1.1. IMPLEMENTATION POSSIBILITIES

Two neurologists were asked during a pilot interview about uncertainties of HBM and important implementation possibilities. An implementation possibility is defined as a position in the diagnostic track of epilepsy where HBM could be implemented.

With the retrieved information from neurologists five implementation possibilities are identified and scenarios are identified afterwards. HBM can be implemented at two different stages in the diagnostic path of first-seizure patients:

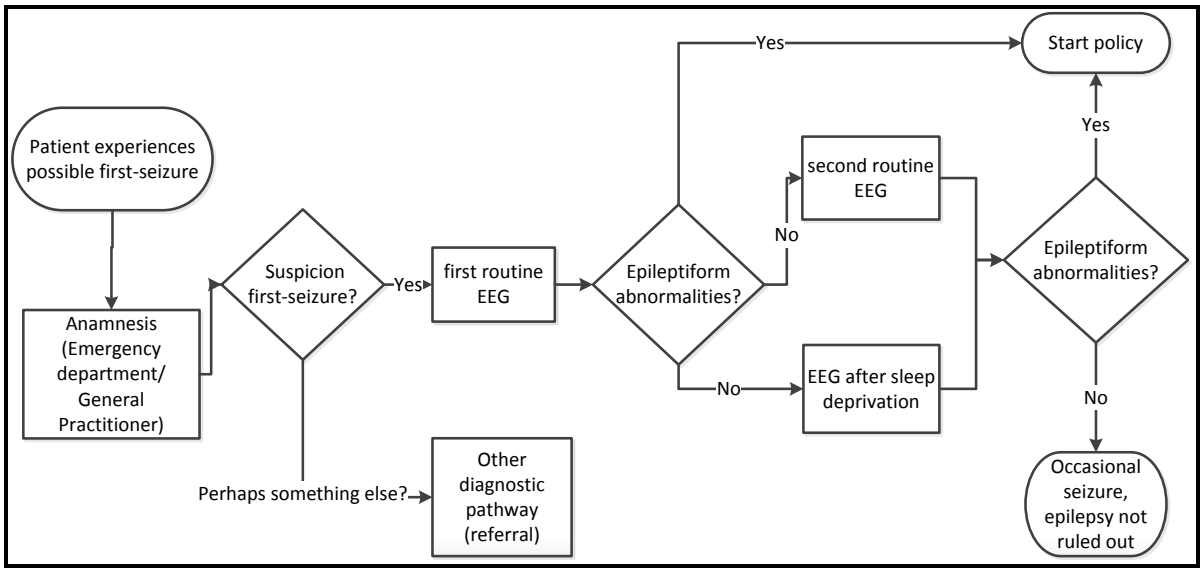


Figure 3: Diagnostic pathway first-seizure patients.

1. Immediately after the suspicion of a first seizure, based on seizure description and other relevant information. It substitutes the first routine EEG and possible subsequent recordings (second routine EEG or a sleep deprived EEG).
2. After the first routine EEG if it did not show epileptiform abnormalities. Thus, substituting a second routine EEG or an EEG after sleep deprivation.

HBM can also be implemented in patients who experienced a possible second-seizure:

3. When the patient presents unclear symptoms after the suspicion of a second seizure and the previous EEG recordings did not reveal anything. Possibly, a distinction between epilepsy and pseudo-epilepsy can be made.
4. In patients who experienced a second seizure which occurred more than 6 months after the first one and routine EEG did not show epileptiform abnormalities, while it is thought that those patients might have epilepsy since they experienced a possible second seizure.

Finally, HBM can be implemented as a treatment evaluation tool in patients already diagnosed with epilepsy for several years:

5. To evaluate whether treatment can be reduced or adapted when patients are seizure-free for a long time. Or to evaluate and adapt treatment when a patient had a recurrence while using medication.

2.1.2. IDENTIFICATION OF SCENARIOS

Every scenario describes a possible way to realize value by specifying a number of uncertainties that are required to have a successful outcome [30]. An example is given in Figure 2. The value of a scenario is expected to be realized given successful outcomes of the specified uncertainties. This value is expressed as the expected economic return when the development would be implemented immediately. In fact, each scenario describes a possible way to realize value in the project HBM.

Once uncertainties (represented with variable *U*) of HBM are solved, the scenario can generate the expected value. Each scenario has the potential to generate a value *V* if $U_i=1$ for $i = 1,\ldots K$, and zero otherwise. The probability that a scenario is having outcome *V* equals $q_1 \ldots q_k$. This probability only succeeds if all uncertainties are actually tried. However, a scenario will not only be chosen when all uncertainties have success, because it is possible that there is another feasible scenario of the project that is preferred when it generates a higher value. In fact this can be seen as the conditional probability that a scenario is feasible, given that some other scenarios failed.

The example in Figure 2 shows three scenarios. For each scenario, the corresponding set of uncertainties is indicated with a vector of ones. If the vector of ones for every uncertainty involved will be allocated differently, other feasible scenarios are developed. The order of the scenarios is always going from the highest to the lowest value.

2.2. DEFINING AND ELICITING UNCERTAINTIES

In the subsequent sections it is first described what uncertainties are defined, how uncertainties and implementation possibilities are elicited and in which way the implementation possibilities are used to calculate the probability of success of the uncertainties. Finally it is shown what scenarios are constructed in the results section.

2.2.1. FORMAT OF ELICITATION

The probability that a possible implementation is likely to occur is estimated first by experts. This information is used to derive the probabilities of success of different uncertainties afterwards.

2.2.1.1. PARTICIPATING EXPERTS

An expert is a person whose knowledge in a specific domain (e.g. epilepsy) is obtained gradually through a period of learning and experience and depends on the circumstances in which experience is gained [33]. These properties have influence on the analytical and judgmental behavior which is necessary to estimate probabilities [34]. A number of 18 neurologists were interviewed, which needs

to be sufficient according to a panel of expert elicitation experts [35]. Inclusion criteria for selecting experts are: they have to be neurologist specialized in the field of epilepsy or with a strong affiliation with it. Neurologists are seen as expert, since they have the appropriate knowledge, experience and expertise in the diagnosis of epilepsy. Most of these 18 experts were recruited through a list of epilepsy experts from a conference of epilepsy in the Netherlands, obtained from a neurologist. These neurologists can be seen as the best experts in the specialism of epilepsy in the Netherlands.

The neurologists were recruited from academic hospitals, non-academic hospitals and epilepsy centres. Academic hospitals were included since they are affiliated with research and therefore could have a more flexible attitude towards new technologies. Experts from epilepsy centres were included, because they are used to treat difficult epilepsy patients and often perform long-term EEG recordings.

2.2.1.2. CALIBRATION OF EXPERTS

A calibration method is applied to weigh experts, since it is expected that neurologists vary in the performance of estimating probabilities. It was decided to use the clinical background of neurologists to apply weights to different experts (Table 1). Factors which reflect the performance of individual neurologists include (i) years of experience and (ii) the average number of EEGs examined per week. Another factor which may have influence is (iii) the availability to make long-term recordings in a hospital. This can influence the state of knowledge of experts regarding long-term monitoring of epilepsy patients.

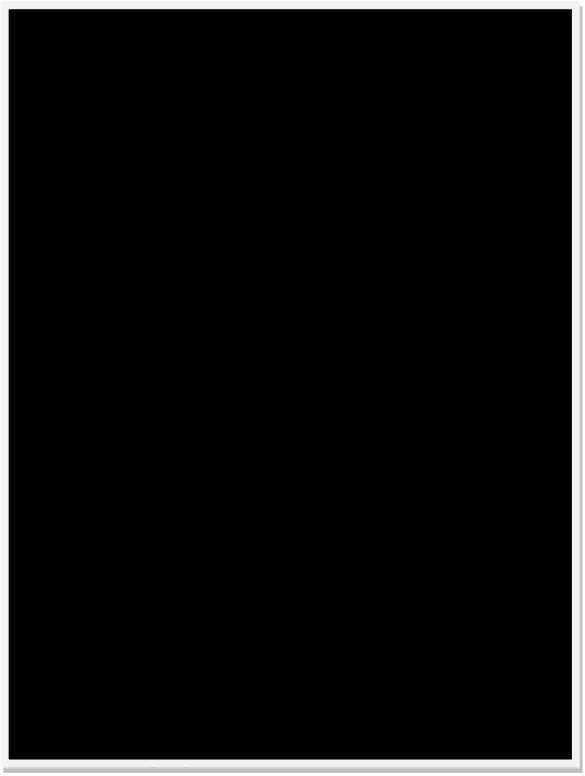
Table 1. Calibration process.

Years of experience		Number of EEGs examined per week		Ability to make long-term recordings	
< 5	1	< 5	1	No	1
≥ 5	2	5 a 10	2	Yes	2
		≥ 10	3		
Weight: 0,50		Weight : 0,30		Weight: 0,20	

Years of experience receives a weight of 0.50. Because it is expected that experience is most important when an expert tries to identify at what position HBM can be implemented. The factor 'average number of EEGs examined per week' receives a weight of 0.30, since this is important as well. But mostly, only clinical neurophysiologists examine EEGs, while specialists in epileptology have a proper knowledge of identifying epilepsy patients too. Therefore, the ability to make long-term recordings receives a weight of 0.20, since it is expected that experts can make better estimations about long-term monitoring when a similar form is used at their hospital.

2.2.1.3. FORMAT OF ELICITATION

A mathematical approach was used to produce combined probability distributions. This method is easier to conduct and avoids group polarization [36]. The variable method was applied where experts had to estimate the mode, the lower and the upper boundaries [23, 37]. It was believed that experts are able to accurately estimate the minimum and maximum, as well as the mode to define a beta distribution [38]. Also, it was expected that neurologists would indicate skewed distributions of which it is difficult to assess the mean and standard deviation. Therefore, estimating the mode was assumed reasonably accurate and is therefore chosen to estimate [39].



$$\mu = \frac{\min + 4*mode+max}{6} \quad (1)$$

$$\sigma = \frac{max-min}{6} \quad (2)$$

where min, mode and max are the subjective 'optimistic', 'most likely' and 'pessimistic' estimates respectively determined by experts. With these estimations, the shape parameters α and β of the beta distribution can be expressed as [40, 42]:

$$\alpha = \left(\frac{\mu-min}{max-min}\right) * \left(\frac{\mu-\min(max-\mu)}{\sigma^2}\right) \quad (3)$$

$$\beta = \left(\frac{max-\mu}{\mu-min}\right) * \alpha. \quad (4)$$

Individual telephonic semi-structured interviews of 15 minutes were carried out to show neurologists a presentation with information regarding HBM and the implementation possibilities. Afterwards, probabilities were elicited in an Excel spreadsheet. A presentation is used since it reduces diversity in which information is provided to different experts.

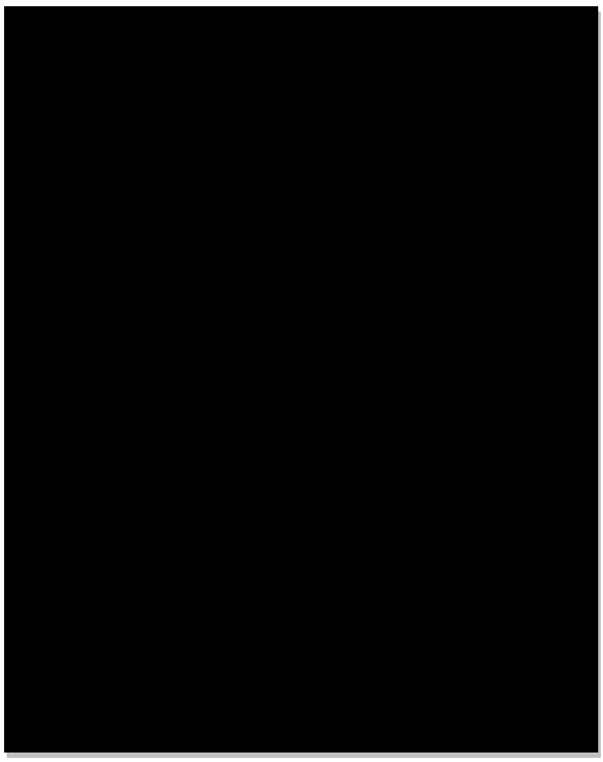
The questions of the interview were asked in the form of estimating the probability that neurologists will order HBM for (possible) patients at a certain point in the diagnostic path of epilepsy. It is assumed that the higher the chance of ordering HBM by neurologists, the better the implementation possibility of HBM will be. This chance to order HBM by neurologists is assumed to be indirectly related to the additional diagnostic usefulness of HBM compared to current available technologies. In general, neurologists are only prepared to order HBM if they believe the device is patient-friendly, diagnostic useful and reliable in detecting abnormalities. The elicitation estimates it in this way since it is not possible to estimate the diagnostic value directly, because the diagnostic performance of every implementation possibility cannot be compared with a current technology. But more important, this study is not interested in identifying the diagnostic performance of HBM directly, but it is interested in the uncertainty that a specific performance is likely to be achieved.

2.2.1.4. ELICITATION PROCEDURE

From the implementation possibilities in first-seizure patients, the sensitivity of the currently used (substituted) recordings is known. Moreover, Faulkner et al. [16] measured the latency of the first epileptiform discharge with ambulatory monitoring and they found that epileptiform abnormalities were found in 85% of the epilepsy patients within 24 hours. Both these facts about the current diagnostics and ambulatory monitoring were given to experts before they had to estimate. This is done to give the experts a certain reference, since it is expected that experts may be better in estimating unknown parameters if they are expressed relative to known data. Also, when neurologists were asked to estimate ranges of probabilities, a visual example of a probability function was given and explained.

During the interviews, feedback was provided to check whether questions were understood. Furthermore, it was tried to retrieve information about the neurologists' attitude towards new technologies, since this may affect the estimation of the probabilities of HBM. Background questions were asked including experience with doing research and whether there is faith or not in the additional diagnostic value of HBM in epilepsy.

2.2.2. DATA ANALYSIS: REPRESENTING EXPERTS' BELIEFS



2.2.3. IDENTIFICATION OF UNCERTAINTIES

An uncertainty is defined as an elementary success factor that is considered relevant for the value of the project [30]. In general, these uncertainties are of technical nature, but economical and social factors can also be included. For every uncertainty, only two outcomes can be considered: success or failure.

Important to note is the difference between these technical or economical uncertainties and the 'diagnostic uncertainty'. The diagnostic uncertainty represents whether HBM actually reaches a high sensitivity and high specificity to detect epileptiform abnormalities in epilepsy patients. While the technical, economical and other uncertainties represents that it is uncertain to which extent a certain goal will actually be achieved.

Formally, an uncertainty is defined as a binary variable U with outcome 1 ('success') and outcome 0 ('failure'). The probability of success is represented as q(U). It is assumed that all uncertainties in a scenario are mutually independent. Consequently, the probability of success of two uncertainties U_1, U_2, equals the joint probability of q_1, q_2.

Figure 2 shows three uncertainties with each one outcome ('success, 1', or 'failure, 0') which makes the scenarios different from each other. The probability of success of each uncertainty is represented with a percentage, estimated by experts. The probability of success per scenario is the joint probability of each of the uncertainties with a 'successful outcome'. The difference between two consecutive scenarios is the availability of one or more uncertainties with 'failure' as outcome.

2.2.3.1. UNCERTAINTIES OF HOME BRAIN MONITORING

Table 2 shows the six important uncertainties which will distinguish the different scenarios of HBM and have to be solved.

Table 2. Uncertainties of HBM.

	Uncertainties	Type of uncertainty
1	Very high diagnostic value (Sensitivity >90%)	Implementation possibility
2	High diagnostic value (Sensitivity >85%)	Implementation possibility
3	Implementation of HBM at other positions	Implementation possibility
4	Detection algorithm	Technical uncertainty
5	Acceptation among patients	Uncertainty of society
6	Technical uncertainties	Technical uncertainty

These uncertainties were developed after studying literature and gathering information of different neurologists. The probability of success of uncertainty number 1, 2, 3 and 4 are derived from the estimated implementation possibilities during the interviews with neurologists. The probability of success of uncertainty 4 and 6 is estimated by other experts, because it is thought that neurologists are not able to estimate probabilities of technical origin. All probabilities can be expressed as the probability that an uncertainty is likely to occur.

Uncertainty 1 and 2 are dependent of the position of HBM in the diagnostic track. If HBM will be implemented as a substitution of all currently used EEG recordings, it needs to have a very high diagnostic value, because no information of EEGs is known yet. If there is information available of a first routine EEG, the diagnostic value of HBM needs to be high, but not as high when no routine EEG is present, since the information of a routine EEG already distinguishes the population. Therefore it is assumed that uncertainty 1 is linked to the implementation of HBM immediately without the yield of any EEG results, and uncertainty 2 is linked to the implementation of HBM after a first routine EEG with the corresponding extra information.

For uncertainty 1, a sensitivity of 90% is chosen since it is one of the targets of HBM. Uncertainty 2 assumes to have a sensitivity of >85% which is derived from the study of Faulkner et al. [16] where epileptiform abnormalities were detected in 85% of the epilepsy patients within 24 hours. An exception is made to include these two uncertainties which are dependent of each other. PPO assumed to exclude dependency between uncertainties, but this will be solved when the probability of the scenarios are calculated.

Uncertainty 3 is derived from the possibility to implement HBM in second-seizure patients or epilepsy patients. It is uncertain whether neurologists will order HBM at other positions in the diagnostic track when it is proven to be successful in first-seizure patients. The implementation in first-seizure patients (1 and 2, see table 3) includes the highest amount of patients, whereas the implementation of HBM at the other positions is only a small group. Therefore it is decided to take these implementation possibilities (3, 4 and 5) together and represent it as one uncertainty.

Uncertainty 4, the computer detection algorithm is an uncertainty, because it is uncertain whether it can detect seizure activity even better than an experienced neurophysiologist can.

From uncertainty 5 it is expected that patients are willing to be monitored at home and to wear EEG electrodes for 24 hours, but it is not sure whether all patients will choose for HBM instead of inpatient recordings.

Finally, the last uncertainty is about the technology. It represents the sustainability of EEG electrodes, the duration of the battery and not unimportant, the amplifier which amplifies the EEG signals with or without artifacts. This technological uncertainty might be even the most important point, cause if technology fails; the whole development is nothing worth anymore.

2.2.4. ELICITATION OF UNCERTAINTIES

As mentioned, a simplified form of expert elicitation is used to estimate the probability that an uncertainty is likely to occur. The information gained from experts serves as input for the PPO model.

Expert elicitation is the extraction of judgments from experts about uncertain parameters in the form of probability distributions [23]. By eliciting priors, synthesizing available knowledge and beliefs of experts can be made explicitly on a certain subject before conclusive scientific evidence becomes available [49].

Although expert elicitation has huge potential, their use in HTA has been minimal so far [50, 51]. Compared with other forms of evidence, expert elicitation forms a reasonably low cost source of collecting evidence. However, before propagating the collected evidence as input through the real options model, the potential bias in eliciting uncertainties need not to be ignored [51].

2.3. DEFINING RETURN ON INVESTMENT

2.3.1. ROI ANALYSIS

The PPO method is capable of modeling the potential of HBM and makes it visible in such a way that informed investment decisions can be made through the project management.

Return on investment (ROI) analysis is a performance measure to evaluate the efficiency of an investment such as HBM. ROI can be expressed as a percentage of the return of an investment divided by the costs of the investment. However for good investment decision making, this definition of ROI given above is not complete due to the uncertainties in the assumptions made to calculate the ROI.

In the present study, the economic return of the investment HBM is calculated from hospital's perspective. What amount of money can be saved annually by hospitals in the Netherlands when HBM will be implemented immediately? It is assumed to calculate the economic return of every scenario separately when HBM is being implemented.

The following expression will be used to express the value of every scenario:

*Value = (number of EEGs * (cost-price routine EEG or SD – cost-price HBM) + savings made with HBM) * distribution key*

The value of every scenario is defined as the expected revenue for hospitals per year when HBM will be implemented at this moment. The expected revenue is calculated with the number of EEG recordings ordered times the difference in costs between using HBM and currently used epilepsy diagnostics. Moreover, the expected increased efficiency of using HBM is represented as the saving of 1 repeating consultation to the neurologist per patient.

The ROI is expressed in this way to show the relative return of using HBM with respect to the initial costs when HBM is not being used for a specific scenario. It is not a percentage what will be calculated, but a value which is used to show the differences in scenarios.

2.3.2. SENSITIVITY ANALYSIS

In this study, sensitivity analysis is concerned with the understanding how changes in uncertainties influence the option value of the project. Parameters are varied (probabilities of success), from worse case to best case, and the option value is recalculated.

To perform this, a deterministic analysis can be employed to evaluate sensitivity or alternatively, a probabilistic analysis, using Bayesian frameworks. A review of Andronis et al. [52] reveals that both forms of sensitivity analysis have their supporters and detractors. This study will use deterministic sensitivity analysis (univariate) whereby input values for the uncertainties are varied one at a time, while the remaining uncertainties are held at their baseline values. An assessment of the impact of the change on the results is provided finally [53].

The strength of deterministic sensitivity analysis with respect to probabilistic analysis is its simplicity to provide insight into the uncertainty regarding a parameter, and it draws attention to key parameters [54]. Moreover, to use probability sensitivity analysis properly, it is necessary to make decent estimates of the underlying probability distributions. While this study estimates probability functions by experts of which it is expected to vary much among them.

2.4. OPTION VALUE ESTIMATION

To calculate the option value of HBM, an assumption is made with regards to the order of the scenarios, namely that the most profitable scenario is chosen first, and only if this fails the one with the highest value among the remaining ones is chosen. This means that it is expected that the generated value is in general higher than the R&D costs. Differences in costs will be assigned to different scenarios. Therefore, a project can be defined as a list of scenarios (Sc_1,…Sc_N) ordered after their value, with $V(Sc_1) \geq V(Sc_2) \geq \ldots \geq V(Sc_N) > 0$.

Here, a project can be perceived as a random variable that takes value $V(Sc_i)$ with probability $P(Sc_i)$, where $P(Sc_i)$ is the probability that scenario Sc_i is successful. The probability that a scenario Sc_j is successful is given by:

$$P(Sc_j) = q(Sc_j) * (1 - (P(Sc_{j-1}) + \cdots + P(Sc_1)) \quad (1)$$

Where $q(Sc_j)$ is the conditional probability that Sc_j is feasible, given the failure of the scenarios preferred. The success probability $P(Sc_j)$ can be further formulated as:

$$P(Sc_j) = q(Sc_j) * (1 - q(Sc_{j-1}) * \ldots * 1 - q(Sc_1)) \quad (2)$$

This expresses that a scenario is successful if it is successfully tried after the subsequent failure of preferred scenarios. For example, the probability of scenario 3 is feasible if all higher scenarios (scenario 1 and 2 with a higher value) have failed. This can be expressed as follows. Every scenario denotes a set of uncertainties, which can be seen as a vector of ones for every uncertainty involved (Figure 2). The model developed aggregates the probabilities of all vectors of outcomes of the uncertainties for which every scenario Sc_j will be feasible and all scenarios Sc_{j-1}…Sc_1 which are not feasible.

Equation 2 is used to calculate the probabilities of success of scenarios (Figure 2). As a consequence of the success of one scenario, other scenarios with lower value are blocked.

3. RESULTS

This section describes the results of applying the PPO model. First an overview is given how to convert the probabilities of the implementation possibilities to uncertainties and how this is applied in the scenarios constructed.

3.1. EXPERTS INCLUDED

In total, 18 neurologists were included from epilepsy centres and both academic and non-academic hospitals. None of the participants were excluded. Three neurologists preferred to give a point estimate instead of a range of likely probabilities.

Table 3 shows the type of specialization of each neurologist and the weight factors applied based on the calibration characteristics (*section 2.2.1.2. Calibration of Experts*). The weight factor applied is a relative weight with respect to other neurologists since it is being normalized at 1. In total, 4 neurologists were included from academic hospitals, 8 from non-academic hospitals and 6 from epilepsy centres.

3.2. IMPLEMENTATION POSSIBILITIES

The five implementation possibilities of HBM (*section 2.1.1. Implementation possibilities*) are shown in Figure 4. These implementation possibilities were implemented in the current diagnostic pathway of first-seizure patients, second-seizure patients and epilepsy patients.

Experts were asked to estimate the most likely probability, lower and upper boundary of these implementation possibilities. Moreover, they were asked to estimate the chance that patients are likely to accept to wear a portable EEG device at home instead of receiving inpatient recordings.

Table 3. Experts characteristics and calibration of weight factor applied.

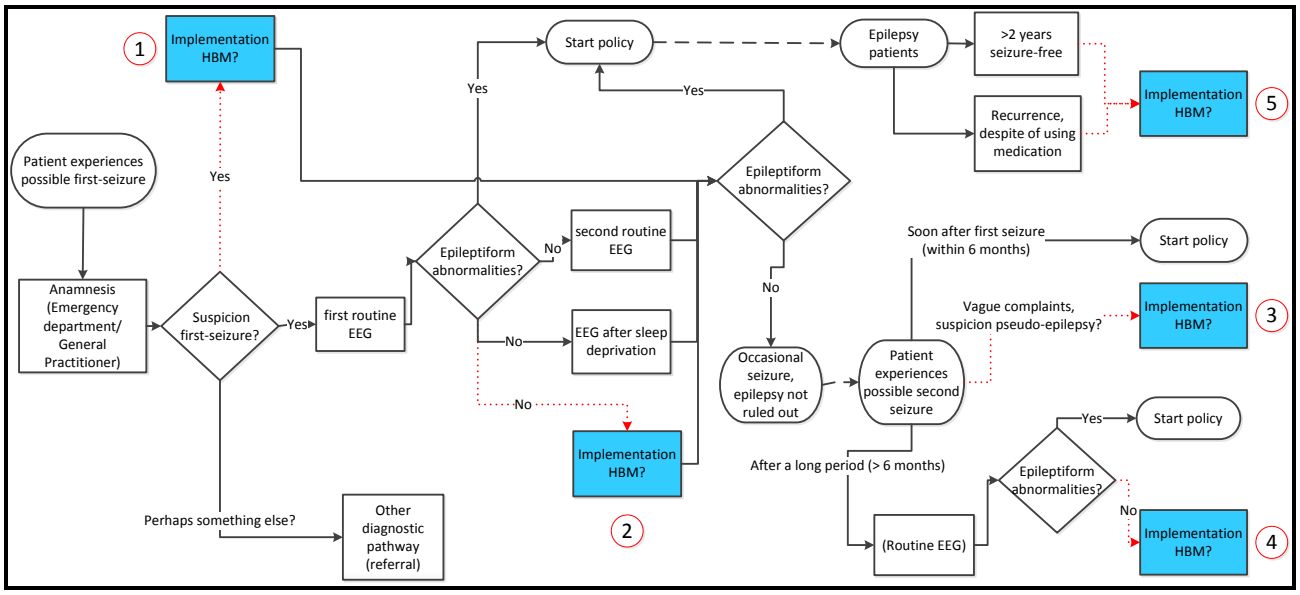


Figure 4: implementation possibilities of HBM.

Table 4. Estimated probabilities and standard deviation + confidence interval of probability distributions experts

	Implementation possibility	Min.	Mode	Max.	Standard deviation	95% confidence interval
1	Immediately after the suspicion of a first seizure (substitution first routine EEG + subsequent recordings)	16,49	28,56	44,04	23,01	[18,50;39,76]
2	After a first routine EEG (substitution second routine EEG or EEG after sleep deprivation)	34,42	49,8	63,28	24,87	[37,99; 60,97]
3	When patient presents unclear symptoms and a possible distinction between pseudo-epilepsy and epilepsy could be made	46,27	57,11	67,52	29,23	[43,53; 70,55]
4	In patients who experienced a second seizure after a long period (>6 months)	29,3	40,4	51,05	27,79	[27,47; 53,15]
5	To evaluate treatment in epilepsy patients	18,07	27,81	35,23	18,26	[18,99; 35,86]
6	Acceptation among patients	71,73	81,2	89,99	17,39	[73,05; 89,12]

Table 4 shows the estimated probabilities of experts. The implementation of HBM in patients with unclear symptoms indicating either pseudo-epilepsy or epilepsy receives the highest probability to be implemented (about 57%). An important factor which contributes to this high probability is the fact that if there is a suspicion of pseudo-epilepsy, the currently used EEG diagnostics are unable to detect it. Only a small number of neurologists suggested video monitoring instead of HBM, but a lot of hospitals do not have this opportunity or it is seen often as too expensive.

The implementation of HBM in epilepsy patients receives the lowest probability of success (28%). Neurologists mention that it is nonsense to evaluate epilepsy patients when they are seizure free for a long time or experienced a recurrence; overdiagnosis may occur. However, some of the neurologists think that it may still be ordered by neurologists elsewhere when it is available.

Just as low is the implementation of HBM immediately after the suspicion of a first seizure (29%). Neurologists note the importance of the information retrieved when a first routine EEG is performed. Moreover, from a 'positive' first routine EEG the chance of a recurrence is known and policy is being adapted on it, while it is not known what the clinical consequences are likely to be when epileptiform abnormalities are found on a 24 hours EEG.

The implementation of HBM after a first negative routine EEG is much higher. Experts estimated that it is about 50% likely that neurologists will order HBM in first-seizure patients after a negative first routine EEG. This seems to be a likely implementation possibility for HBM, also because the important information from a first routine EEG is included.

The probability of success of implementation number 4 in patients who experienced a second seizure after a long time is estimated at 40%. Neurologists mention the importance of the duration in time between two possible seizures; often policy will be started without further diagnostics if the symptoms seem clear.

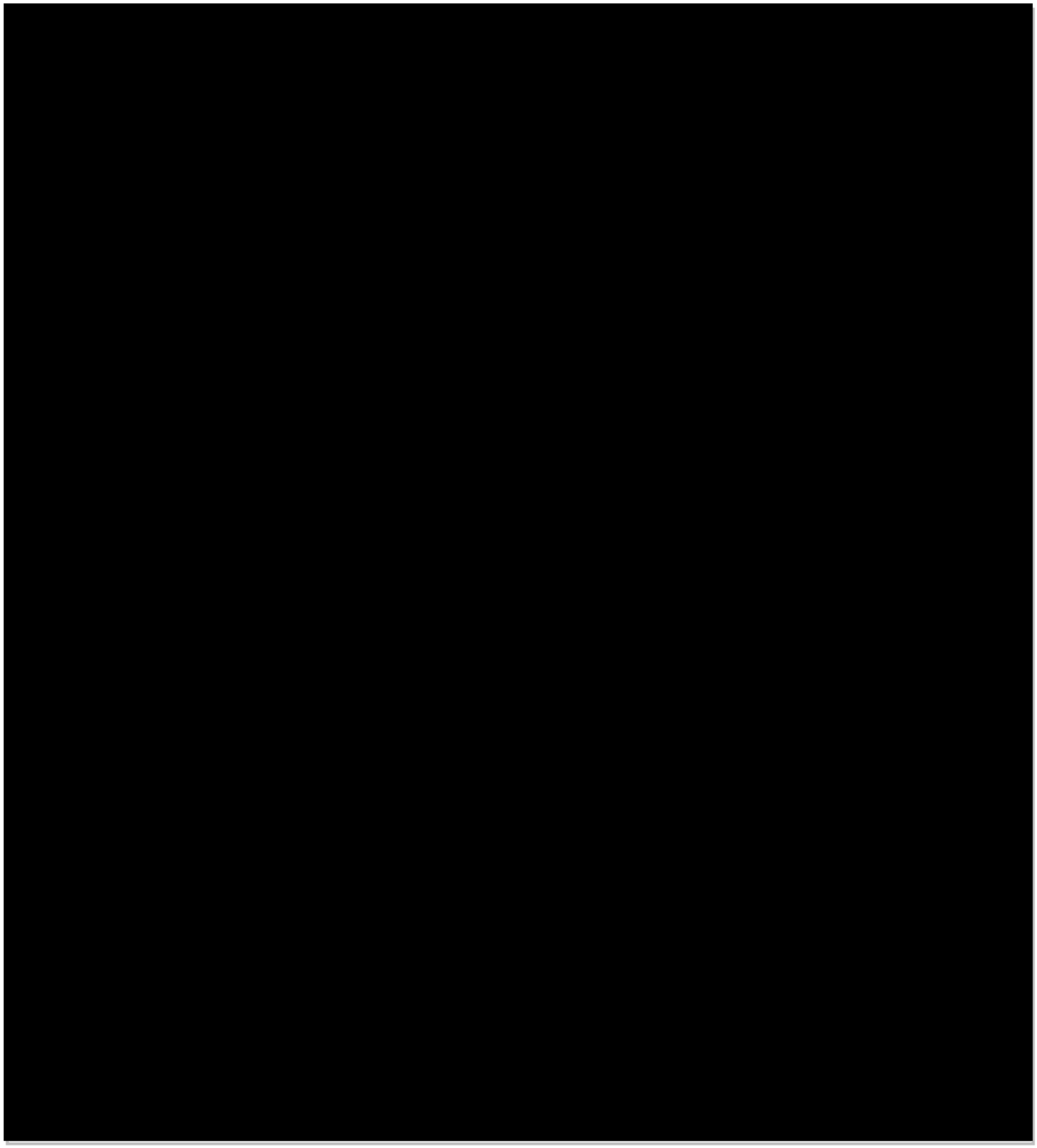


Figure 5: Probability distribution functions of the five implementation possibilities and the acceptation among patients.

From each of the weighted estimates of table 4 a PDF is calculated. Figure 5 on the previous page shows these estimated PDFs of the five implementation possibilities and the PDF of the acceptation among patients. To estimate the probabilities it is assumed that HBM is available immediately (no waiting list) and the technique will be reimbursed. Three neurologists preferred to give a point estimate instead of a range of probabilities and therefore their distribution could not be calculated and is not shown in Figure 5. But their point estimate is included in the black line in all graphs that represent the weighted average of all experts which corresponds with the results of table 5.

The PDFs 1-5 of Figure 5 show the estimated probabilities that HBM will be ordered by neurologists at the specific implementation possibilities. The dispersion among experts of especially PDFs 1-4 is considerably. The standard deviation and confidence interval in table 4 conforms this. Consequently, experts are not unambiguous in estimating the probabilities of implementation possibility 1-4. The dispersion among experts of implementation number 5 is a little bit less. Just as the PDF of the acceptation among patients. Experts generally agree that patients are very willing to accept the use of HBM instead of inpatient recordings.

The implementation of HBM at different stages in the diagnostic track shows that a lot of variation exists among experts. In particular, implementation numbers 1, 2, 3 and 4.

3.3. UNCERTAINTIES THAT HAVE TO BE RESOLVED

Six uncertainties were defined in Table 2. The weighted probability distributions of Figure 5 (upper point of the black lines) were used to retrieve the highest probability with the associated probability percentage.

Table 5 shows the results of the estimated probabilities of success. From uncertainty 4 and 6 no probability distribution can be calculated, since only a small number of experts were asked and no range is being asked. The other four uncertainties were estimated with expert elicitation and a probability distribution can be calculated.

The probability that a 'very high diagnostic value with a sensitivity of >90%' will be successful is estimated at 29%. The probability of uncertainty 2; 'high diagnostic value with a sensitivity of >85%' has a higher chance to be successful, which is estimated at 50%. This seems logical due to the achievement of a lower sensitivity level. Both uncertainty 1 and 2 are linked to the implementation of HBM in the diagnostic track (as mentioned in *section 2.2.3.1. Uncertainties of Home Brain Monitoring*).

Uncertainty number 3 to implement HBM at other positions was derived from the implementation possibilities in second-seizure patients and epilepsy patients. These are implementation possibilities 3, 4 and 5 of Table 5. The probability of success of these 3 possibilities is summed up and divided by three. The estimated probability of success of ordering HBM at other positions is then calculated at 42%.

Finally the probability of the acceptance among patients to wear a portable EEG device for 24 hours instead of inpatient recordings is estimated at 82%. In general, it is expected (but do we have to verify?) that patients are very willing to carry a portable EEG device when the choice can be made to measure an EEG at home or at the hospital.

The probability that a computer detection algorithm is able to detect candidate events of epileptiform abnormalities, even better than a neurologist is estimated at 85%. Up to now, there are no well-accepted automated algorithms to aid the neurologist. Particularly due to the high number of false detections which have been detected often so far. There is a correlation between the sensitivity of the algorithm and the number of false positives. If a neurologist wants to reach the detection of all patients with epileptiform abnormalities, the rate of false positives increases too [55]. The new detection algorithm which is being developed for HBM is proposed to improve the quality of interpretations of neurologists.

The probability of success of the technical uncertainties is very high (98%). This is merely due to the fact that the durability of the electrodes and amplifier of HBM is high. Moreover, the amplifier of HBM is being developed in such a way that it will not be disturbed by electric fields in the environment. But it stays unavoidable that EEG signals are lost when electrodes are scratched off by the patient itself.

Table 5. Uncertainties and their probability of success

	Uncertainties	Probability of success
1	Very high diagnostic value (Sensitivity >90%)	29%
2	High diagnostic value (Sensitivity > 85%)	50%
3	Implementation of HBM at other positions	42%
4	Detection algorithm	85%
5	Acceptation among patients	82%
6	Technical uncertainties	98%

3.4. SCENARIOS HBM

Together with the implementation possibilities and the probabilities of success of the uncertainties of HBM which are previously explained, five scenarios were constructed. Every scenario is a collection of uncertainties (a vector with ones) which have to be dealt in order to have a successful outcome. These scenarios are shown in Figure 6. As mentioned before in the method section, the scenario with the highest value is preferred.

Scenario 1 represents the implementation of HBM in first-seizure patients without making any EEG recordings (substitution of first routine EEG + subsequent recordings). This scenario includes also the implementation of HBM at other positions (e.g. epilepsy patients and second-seizure patients).

Scenario 2 represents almost the same implementation as scenario 1, but without the use of HBM at other positions.

Scenario 3 represents the implementation of HBM in first-seizure patients after a nondiagnostic first routine EEG (subsitution second routine EEG or EEG after sleep deprivation)

Scenario 4 represents the same implementation as scenario 3, but without the use of computer detection algorithm.

Scenario 5 represents a scenario when it is not likely to implement HBM, because of technical failure.

3.5. ROI ANALYSIS AND OPTION VALUE ESTIMATION

To calculate the contribution of every scenario to the option value, the values of all scenarios are determined first.

First, the number of requested EEGs in one year with the question 'epileptiform abnormalities?' needs to be known. To find out these numbers, the database of all requested EEGs in 2010 from the Medisch Spectrum Twente (MST) hospital has been used. In total, 1070 EEGs were ordered in 2010, of which 684 related to epilepsy diagnostics. Table 6 shows for all specific implementation possibilities what number of EEGs have been ordered by neurologists. These numbers are not completely certain, since for example it is not specifically known what and when exactly a first seizure can be defined. The suspicion is sometimes unclear.

The numbers of implementation possibility 1 and 2 are quite indicative, but the other numbers of HBM at other positions are more uncertain. Especially of the number of patients from which there is a suspicion of pseudo-epilepsy, the number of three seems low. This might be explained by the fact that those patients often do not receive a routine EEG, since the suspicion of epilepsy is low. Moreover, no background information of patient files is used.

Now the number of requested EEGs per year of one hospital is known. To calculate the savings for a hospital, the cost-price of routine EEG and sleep deprivation is used. For HBM, an estimation of the cost-price has been made. Table 7 shows the results. Cost-prices were retrieved from the MST and are allocated based on direct time and cost locations. These values are fictitious, but indicative for the difference in costs between HBM and routine EEG or SD.

Assumptions were made with regards to HBM. The costs of specialists, personnel and room used are halved compared with SD, since the time needed to execute HBM is 1.5 hours instead of 3 hours. Also, the costs of material, equipment and pharmacy are assumed to be the same. Moreover, the cost price does not include the time spend by specialists and therefore honoraria of specialists are included.

The honoraria of routine EEG and sleep deprivation are based on fixed prices of the Dutch Healthcare Authority (NZa). HBM is given the same honorarium prices since it is expected that the examination time is about the same as sleep deprivation, if the detection algorithm is used. It is expected that the examination time of HBM without detection algorithm (scenario 4) will be 3 hours, which increases the cost-price of HBM to 267 euro.

Table 6. Overview of requested EEGs of one year.

Table 7. Cost prices (fictitious values)

	Routine EEG	Sleep deprivation	Home Brain Monitoring*
Time:			
Total time needed (time at hospital)	45 minutes	3 hours	1.5 hour
Time EEG recording	20 minutes	1.5 hour	24 hours
Examination time	10 minutes	30 minutes	30 minutes
Costs:			
Specialists (supporting)	5	24	12
Personnel	23	63	31,5
Room used	3	12	6
Material	11	17	17
Equipment	6	8	8
Pharmacy	6	6	6
Cost-price	54	130	80,5
Fee specialist (honorarium)**	15,65	26,67	26,67
Total cost-price (include fee specialist)	**69,65**	**156,67**	**107,17**

* With algorithm

** Fixed prices of NZa

Table 8. Distribution key.

	Academic	General	Total
Number of hospitals in the Netherlands	8	82	90
Bed capacity*	8186	42356	50542
Number of beds MST			1070
Number of beds MST with respect to total			1070/50542 = 0,02117
Distribution key			1/0,02117 = **48**

It remains difficult to estimate the expected savings when HBM will be used instead of the current used diagnostics. HBM proposes to diagnose epilepsy patients earlier and more reliable. Consequently, patients may need less consultations and the number of true positives may be increased.

Therefore, more patients are treated correctly which finally decreases costs. To calculate the value, it is assumed that the diagnosis can be made earlier which results in the saving of one (repeating) consultation to the neurologist per patient. The effect of a higher reliability is not taken into account due to the difficulty in expressing it.

Finally, to calculate the value representative for all hospitals in the Netherlands, a distribution key is calculated (Table 8). Bed capacity is used to express the number of epilepsy related EEGs of the MST hospital converted to the other hospitals in the Netherlands, since it is expected that a hospital with a higher amount of beds probably may perform more EEGs. The calculated value of the MST is multiplied with 48.

3.6. CONTRIBUTION SCENARIO TO OPTION VALUE

The probability per scenario and the contribution to the option value are calculated as follows. For scenario 1, the probability is the product of the probabilities of success of all involved uncertainties. In the template of Figure 6, this is 8.4 percent. The contribution of scenario 1 to the option value is the product of the probability of the scenario and the estimated value of scenario 1 which is 8.4% of 460.000, 38.640 euro. Scenario 2 only contributes if scenario 1 fails and all uncertainties in scenario 2 are successful. Consequently, uncertainty 1, 2, 4, 5 and 6 are successful and uncertainty 3 is not successful. The probability of scenario 2 is 11.4 percent. The third scenario only contributes if scenario 1 and 2 fail and scenario 3 is feasible, and this also applies for

the subsequent scenarios. Finally, the total option value (sum of all contributed scenarios) of the project Home Brain Monitoring equals 103.105 euro.

The results (Figure 6) show that the probability to succeed is highest for scenario 3. This means that HBM is most successful when it will be implemented after a non-diagnostic first routine EEG. But if scenario 2 is chosen, the highest contribution to the option value is generated.

Scenario 4 and 5 are having a negative value, because no money will be saved when the detection algorithm of HBM is not functioning or when the technique fails to monitor. These values are shown in Figure 6, but do not contribute to the option value. In fact, these scenarios do not generate value and should not be considered, but merely to show the effect.

		Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Value:		460000	391000	139100	-175800	-295800
Uncertainties:	Estimated probability of success					
1 Very high diagnostic value	29%					
2 High diagnostic value	50%					
3 Implementation of HBM at other positions	42%					
4 Detection algorithm	85%					
5 Acceptation among patients	82%					
6 Technical uncertainties	98%					
Probability per scenario:		8,40%	11,40%	14,30%	6,00%	0,80%
Contribution to option value:		38640	44574	19891,3	0	0
Option value:		103105,3				

Figure 6: Template for HBM (values are fictitious).

3.7. SENSITIVITY ANALYSIS

Figure 7 shows graphically what happens to the total option value when the probability of success for a particular uncertainty slightly increases (+10%) and decreases (-10%) and when it becomes 0 or 100 percent. The left side of each bar illustrates the decrease in the option value of the project if the probability of success goes to zero, while the right side represents the increase in the option value if the probability of success of that uncertainty increases.

Figure 7 immediately shows what impact success or failure of some uncertainties has on the option value of the project. Uncertainty 1 (very high diagnostic value) will greatly increase the value of the project when the probability of success can be increased. Important to note is the dependency between uncertainty 1 and 2. In fact, when the probability of success of uncertainty 1 increases, uncertainty 2 should increase too due to the dependency, but this is not visible in Figure 7. If uncertainty 2 goes to zero probability, uncertainty 1 need to follow and the option value will decrease to zero.

The uncertainty to implement HBM at other positions is not very sensitive; the value will not increase or decrease much when the probability of success is changed.

If the probability of success of the very high diagnostic value can be increased, the option value of the project HBM will increase much. It seems logical that the value increases more when the probability of success of uncertainty 1 increases instead of uncertainty 2. It is expected that a higher diagnostic value increases the chance to detect epilepsy patients earlier and more reliable, and is associated with a higher value of the project HBM. No value is generated anymore when the probability of success of uncertainty 4, 5 and 6 decreases to 0%. While the value does not increase much if the probability of success will be increased.

It is not likely that the probabilities of the uncertainties will decrease to zero or become 100% and therefore Figure 7 also represents the option value when the probabilities increase or decrease a bit. These values are more representative than the former ones.

With the information of Figure 7, managers can put effort on different uncertainties to increase the probability of success and thereby increasing the value of the project. It can also help to guide priorities during the remainder of the development program of HBM. During the early development phase of HBM, probabilities are quite uncertain. As a consequence of this, effort is necessary to improve the probabilities for uncertainties that have the highest potential effect on the option value. In a later stage of development, some uncertainties and scenarios already have a high probability of success and the option value cannot increase that much anymore, but effort needs to be put into this to finally realize its success.

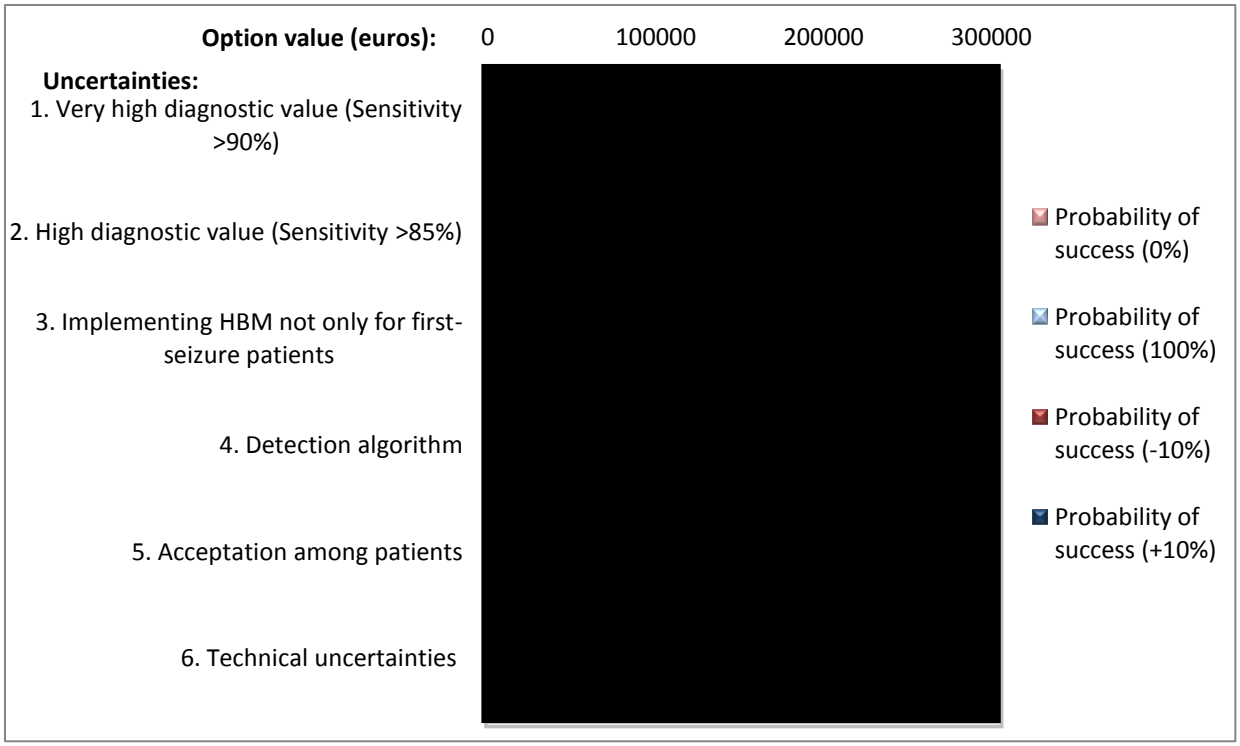


Figure 7: Sensitivity analysis uncertainties HBM.

4. CONCLUSION

This study showed that it is possible to apply a real options approach in an early stage of product development. PPO turned out to be an innovative way to represent and value uncertainty of new projects. This study is the first to apply the PPO method on a new development in healthcare combined with simplified elicitation techniques in order to generate probability distributions which serves as input for the PPO model. Finally, not only the impact of different uncertainties on the project is calculated, but this study also shows the most likely scenario for implementing HBM. Theoretically, the information gathered with this method can be used in early health economic models to help inform investment decisions.

Results obtained from this study indicated the importance of a proper estimation of probabilities of success by experts. However, it is striking that most experts vary considerably in their estimated probability distributions of the implementation possibilities. When more information regarding HBM is available, the uncertainty of the estimated probability functions is expected to decrease.

Scenarios were set up after identifying uncertainties and using implementation possibilities of HBM. The most likely scenario of HBM which received the highest probability of success (14.3%) is scenario 3 of which HBM is being implemented in first-seizure patients after a negative first routine EEG together with a computer detection algorithm to analyze the results. While this scenario does not contribute most to the option value, still about 20.000 euro can be saved by the hospitals annually. This value will be even more when the consequences of a higher reliability of HBM will be taken into account. Scenario 2, which represents the implementation of HBM in first-seizure patients immediately after entry, contributes most to the option value of the project HBM. About 45.000 euro can be saved annually by hospitals when HBM will be applied for this scenario. But the probability for this scenario to succeed (11.40%) is less than scenario 3.

The evaluation of five implementation possibilities of HBM with neurologists indicated that the most appropriate position to implement HBM will be the implementation in patients with unclear symptoms and a suspicion of pseudo-epilepsy (58%). This

implementation is, however, differently perceived among all experts. An even more likely implementation possibility is the implementation in first-seizure patients after a negative first routine EEG. This may be due to the fact that HBM is being developed primarily to diagnose first-seizure patients. The probability of success of this implementation was estimated at 50%.

Sensitivity analysis showed that uncertainty 1 has the highest impact on the option value. If it is possible to increase the probability of success of this very high diagnostic value, the option value may increase much. Whereas uncertainty number 3 (implementing HBM not only for first-seizure patients) is not very sensitive for changes in the probability of success.

In an early stage of new medical developments in general, PPO is able to identify key uncertainties which have a large impact on the option value of a project. Further, PPO is able to identify the uncertainty surrounding the estimated probability distributions and the dispersion among experts' beliefs. This information can indicate whether these parameters need to be further investigated.

To improve the validity of the experts' aggregated estimations in the future, it may be desirable to obtain the estimated probabilities of the uncertainties with group discussions to achieve consensus among experts instead of dispersed results. The results obtained in this study are indicative for the future of HBM, however; further clinical trials and information are needed to indicate whether these results are accurate. Therefore, the use of PPO in health economic modeling requires careful consideration until more conclusive information is known.

5. DISCUSSION

The goal of this study was to explore the use of a real options approach to assess uncertainties of HBM in an early stage of its development. PPO cannot be seen as a perfect valuation model, but rather as a model that provides a not too detailed, but comprehensive view of key criteria for success of certain developments. In this study, PPO was able to provide a clear overview of the impact of different uncertainties of HBM. Furthermore, it is thought that the scenarios presented in this study are feasible and representative for the future of HBM.

There are some limitations to this method; no opportunity costs of employing resources for one scenario over another were taken into account. Moreover, very detailed decision making is not supported such as allocating resources differently to scenarios. Anyway, sensitivity analysis can help guide priorities by simulating the impact of a higher probability of uncertainties than originally estimated. And it shows in particular for which uncertainty more effort is needed to increase the option value.

To execute PPO properly, a number of assumptions needed to be made. Most important was to define representative uncertainties of HBM and retrieving the probabilities of success of these uncertainties very accurately. Therefore the method how to ask experts is very important. This study asked experts individually, but assessing the probabilities in group sessions with experts to retrieve consensus is an option too. However, estimations of experts could then be too much converged.

PPO assumes to exclude dependency between uncertainties. In contrast, this study allowed the dependency between uncertainty 1 and 2 and relates them to two different implementation possibilities. It is questionable whether the sensitivity percentages of 90 and 85 percent of uncertainty 1 and 2 respectively are possible to reach. But at least the outcomes of the probability of success of these uncertainties (29% vs. 50%) are indicative for the difference between uncertainty 1 and 2.

Different calibration characteristics were used to represent the difference in quality among experts to estimate. It is debatable which weight factors need to be applied to calibrate experts, since it influences the results. All estimated probabilities of success were collected in one weighted probability distribution function to show the results of different implementation possibilities, but other methods to visualize results may be applicable as well [23].

The potential option value of a scenario is represented as the savings made for hospitals in the Netherlands when HBM is being implemented immediately. It is debatable what prices, distribution keys and savings need to be taken into account and how they need to be calculated. The estimated cost-price of HBM is uncertain, but is at least indicative for the difference between HBM and SD or routine EEG. The potential savings of a scenario when HBM is being implemented is expressed as the saving of one repeated consultation to the neurologist. Other expressions for the savings of HBM could have been used to indicate the potential option value. However, the estimated option value seems not unrealistic, neither too overconfident. When a high diagnostic value is actually reached, other savings are made as well, such as better treatment and a lower misdiagnosis rate which results in less unnecessary costs. But it turned out to be difficult to translate this into a certain saving.

5.1. RECOMMENDATIONS FOR FURTHER RESEARCH

The real options approach discussed in this study makes the potential of HBM visible in such a way that management could make better investment decisions. The application of PPO on a new development in healthcare is the first time, but it has been applied once by Philips Lighting [30]. Wouters et al. [30] used workshops to discuss the opportunities of the new technology with experts and to consider each other's probability estimates in order to gather data to be included in the analysis. This study recommends the use of group discussions to discuss the uncertain quantities about which their beliefs are to be elicited and to seek a consensus view. Consequently, the results will not be dispersed that much anymore between experts.

The estimated success of probabilities from experts which were needed to produce the results can be used differently to optimize probability distributions in the future. A statistical method could be applied which randomly retrieves a large number of values from the probability distribution and repeat it a number of times to optimize the probability distribution functions. However, it is questionable whether this actually will decrease the uncertainty of the retrieved probability estimates, since it is not known whether the data of experts is valid enough. Therefore, the manner how to ask experts to estimate probabilities of success is even more important to decrease the uncertainty of the results.

This study used a deterministic sensitivity analysis instead of a probabilistic analysis because its simplicity to provide insight into the uncertainty regarding a parameter. Probabilistic sensitivity analysis is recommended if the uncertainty underlying the experts' estimates will decrease in the future. Probabilistic sensitivity analysis allows the uncertainty of parameters to be characterized trough the use of probability distributions to reflect their imprecision [56]. Instead of simple sensitivity analysis, it will give a more accurate and comprehensive view of the importance of uncertainty of a parameter for the results [57]. Moreover, it can take into account how likely it will be that an uncertain parameter will take a specific value within a specified range [54].

Future research is needed to obtain a better understanding when PPO is most applicable and how this method can be optimized. This method seems to be a very useful and easy way to represent and value criteria of success for different new products in development, especially when the elicitation of probabilities of success of uncertainties can be improved in the future.

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