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Probability Elicitation to Inform Early Health Economic Evaluations of New Medical Technologies: A Case Study in Heart Failure Disease Management

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ABSTRACT

Objectives: Early estimates of the commercial headroom available to a new medical device can assist producers of health technology in making appropriate product investment decisions. The purpose of this study was to illustrate how this quantity can be captured probabilistically by combining probability elicitation with early health economic modeling. The technology considered was a novel point-of-care testing device in heart failure disease management. Methods: First, we developed a continuous-time Markov model to represent the patients’ disease progression under the current care setting. Next, we identified the model parameters that are likely to change after the introduction of the new device and interviewed three cardiologists to capture the probability distributions of these parameters. Finally, we obtained the probability distribution of the commercial headroom available per measurement by propagating the uncertainty in the model inputs to uncertainty in modeled outcomes. Results: For a willingness-to-pay value of €10,000 per life-year, the median headroom available per measurement was €1.64 (interquartile range €0.05-€3.16) when the measurement frequency was assumed to be daily. In the subsequently conducted sensitivity analysis, this median value increased to a maximum of €57.70 for different combinations of the willingness-to-pay threshold and the measurement frequency. Conclusions: Probability elicitation can successfully be combined with early health economic modeling to obtain the probability distribution of the headroom available to a new medical technology. Subsequently feeding this distribution into a product investment evaluation method enables stakeholders to make more informed decisions regarding to which markets a currently available product prototype should be targeted. Keywords: early health economic modeling, headroom analysis, heart failure disease management, probability elicitation.

Introduction

Investment in the research and development of new medical technology typically results in several promising product concepts. There is usually, however, insufficient funding to further develop each of these concepts into concrete products that can be brought to the market. This forces producers of medical technology and other stakeholders, such as venture capitalists and funding agencies, to already decide early during the product development process which of these concepts to abandon and which of them to push forward for further development [1–5].

In the current practice of product investment decision making, such decisions often seem to be based on potentially arbitrary representations of the expected improvements in outcomes and costs resulting from the use of the new technology. A factual representation of the current care situation and the specific changes that are likely to occur after the new technology has been fully adopted is generally not elaborated. Thus, decisions regarding the selection of suitable target markets for a currently available prototype technology are reached in a similarly arbitrary way. Early-stage health economic modeling has recently been suggested as a tool for supporting product investment decision making in a more formal way as it can provide insight into the maximum additional cost at which the intended clinical use of the new technology in a selected target market is still deemed cost-effective [3]. This upper bound on the technology’s maximum cost, also known as the commercial headroom available [4,6], can then be fed into an appropriate product investment evaluation method to determine whether further development of the prototype technology is likely to yield sufficient return on investment [7,8].

In early-stage health economic evaluations, there is usually only a limited amount of data available with regard to the performance of the new technology, leading to high uncertainty in the values of some of the model inputs [9]. Expert judgment therefore needs to be relied on to obtain initial estimates of those parameters for which sufficient clinical evidence is not yet available. Probability elicitation (PE) refers to a set of techniques for formulating one or more experts’ beliefs about the unknown parameters into a probability distribution of those parameters.

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Previous work already described how PE can be applied to handle parameter uncertainty in health economic models [12–14]. In this article, we take the use of this approach one step further by illustrating how PE can be combined with early health economic modeling to obtain the probability distribution of the commercial headroom available to a novel point-of-care testing (POCT) device, which is defined as laboratory testing at or near the patient, in the disease management of patients with heart failure (HF).

Methods

The approach that we used for combining PE with early health economic modeling is summarized in Figure 1. First, conceptual models of the current care setting (e.g., the health care setting in which the conventional disease management strategies are applied) and the new care setting (e.g., the health care setting in which the novel POCT device is introduced) were developed. Then, a continuous-time Markov model that appropriately reflects the disease progression in patients under the current care setting was developed. Next, the model parameters that are likely to change under the new care setting were identified. These served as the unknown Parameter(s) of Interest (uPoI) for which PE was subsequently conducted. Finally, the commercial headroom available was calculated and its uncertainty was captured probabilistically by propagating the uPoI distributions.

Fig. 1 – Schematic representation of the approach used in this article.

Conceptual Models of the Two Health Care Settings

The current care comparator depends on the clinical setting in which the POCT device will be applied after it has been brought to the market. As this device could potentially be used in different clinical settings (e.g., outpatient clinic, home setting), we used semi-structured interviews to learn from the clinical experts in which the novel POCT device is introduced. Then, a continuous-time Markov model that appropriately reflects the disease progression in patients under the current care setting was developed. Next, the model parameters that are likely to change under the new care setting were identified. These served as the unknown Parameter(s) of Interest (uPoI) for which PE was subsequently conducted. Finally, the commercial headroom available was calculated and its uncertainty was captured probabilistically by propagating the uPoI distributions.

Markov Model

To estimate the expected health outcomes and costs under the current care setting, we developed a continuous-time Markov model with three health states (Fig. 2): discharged alive from hospital, HF-related hospital readmission, and death. For practical purposes, the transition intensities were assumed to be constant over time and independent of patient-related risk factors. We used the data collected during the Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH), one of the largest multicenter, randomized controlled trials of nurse-led disease management programs in HF [15,16], to estimate the current care model parameters. To be consistent with our description of the current care setting, we included all patients from COACH who received additional basic or intensive support from a nurse specialized in the disease management of patients with HF. This resulted in a total sample size of 684. To make the model of the current care setting probabilistic, simple random sampling with replacement was conducted to obtain 10,000 resamples of equal size to the original sample. For each bootstrap resample, the current care transition intensities were subsequently estimated by using the msm package for R [17], resulting in 10,000 realizations from the joint probability distribution of the current care transition intensities. Unit costs for outpatient visits and HF-related hospitalization were taken from Postmus et al. [18] and set to be equal to €110/visit and €769/d, respectively.

Probability Elicitation of the Unknown Model Parameters

The transition intensities of the continuous-time Markov model were identified as the uPoI for the new care setting. The three cardiologists who assisted in developing the conceptual models of the two health care settings were invited to take part in the face-to-face PE interviews. We took the suggestions from Soares et al. [13] and expressed the uPoI in terms of more directly observable quantities for which the experts’ beliefs were elicited. In particular, let $T_i$ denote the amount of time spent in health state $i$, let $F_i(t)$ denote the proportion of patients who have left health state $i$ by time $t_i$, and let $P_i$ denote the probability that...

Fig. 2 – Structure of the continuous-time Markov model.
when leaving state $i$ the next state will be state $j$. For a continuous-time Markov model, it holds that $T_i$ is exponentially distributed with mean value $1/\sum_{j \neq i} q_{ij}$, where $q_{ij}$ denotes the transition intensity between health states $i$ and $j$ [17,19]. This allows us to express $F(t_i)$ as follows:

$$F(t_i) = 1 - \exp(-\sum_{j \neq i} q_{ij} t_i) \quad (i=1, 2; j=1, 2, 3)$$

(1)

Similarly, the transition probabilities $P_{ij}$ can be expressed in terms of the transition intensities as follows:

$$P_{ij} = \frac{q_{ij}}{\sum_{j' \neq i} q_{ij'}} \quad (i=1, 2; j=1, 2, 3)$$

(2)

By combining Equations 1 and 2, the transition intensities $q_{ij}$ can be expressed as follows:

$$q_{ij} = -p_{ij} \log(1 - F(t_i)) / t_i \quad (i=1, 2; j=1, 2, 3; i \neq j)$$

(3)

To obtain the probability distributions of $q_{ij}$, we elicited point estimates of the transition probabilities $p_{ij}$ and used the fixed interval elicitation method [10,11] to capture the probability distributions of $F(t_i)$ ($i=1, 2$) at the time points $t_1=365$ days and $t_2=10$ days. Equation 3 was then used to capture the $q_{ij}$ distributions from the elicited $F(t_i)$ ($i=1, 2$) distributions and $p_{ij}$ values. A detailed description of the method of data capture and the distribution fitting is provided in Supplementary Material I found at http://dx.doi.org/10.1016/j.val.2013.02.008.

Analysis of the Commercial Headroom Available

Let $e_0$ and $c_0$ be the expected survival time and cost derived from the current care model, and let $e_1$ and $c_1$ be the expected survival time and non-device-related cost derived from the new care model. The expected overall commercial headroom available to the new device can then be computed as follows:

$$h = \lambda t_e - \Delta c$$

(4)

where $\lambda$ denotes the willingness-to-pay per life-year, and $\Delta c = c_1 - c_0$ and $\Delta t_e = e_1 - e_0$ denote the expected incremental non-device-related cost and the expected improvement in survival time due to the use of the new technology (also known as the effectiveness gap [20]), respectively.

The POCT of circulating cardiac biomarkers involves placing a disposable containing a patient’s blood sample in an analyzer that is located at or near the patient. Denoting the cost of the analyzer by $c_{ana}$ and the cost of a disposable by $c_{dis}$, the total device-related cost can be expressed as follows:

$$c_{id} = c_{ana} + c_{dis} f_{in}$$

(5)

where $f_{in}$ and $t_{in}$ are the expected out-of-hospital days and the out-of-hospital measurement frequency (expressed in number of measurements per day), respectively. Assuming that the fully developed product will be applied in daily clinical practice only if its use is considered to be cost-effective, the commercial headroom available reflects the maximum price at which the POCT device can be sold on the market. Further development of the device into a tool for monitoring HF disease progression may therefore not be viable if the total device-related cost is likely to exceed this value. Equating 4 and 5 and dividing by the total number of measurements, this upper bound on the device-related cost can formally be expressed as follows:

$$c_{1dis} + c_{ana} / t_{in} f_{in} \leq \lambda t_e - \Delta c / t_{in} f_{in}$$

(6)

where the left-hand side denotes the average cost per measurement and the right-hand side the commercial headroom available per measurement.

Per expert, the uncertainty in the amount of headroom available per measurement was captured in a probabilistic way by propagating the uncertainty in the uPoI. This was achieved by repeatedly (10,000 times) sampling the current care transition intensities and the uPoI values from their corresponding probability distributions to obtain different values of $\lambda t_e$, $\Delta c$, and $t_{in}$ and then computing $(\lambda t_e - \Delta c) / t_{in} f_{in}$ for given values of $\lambda$ and $f_{in}$. For a given realization of the current care transition intensities and the uPoI, $\Delta c$ was estimated by taking the difference in the expected values of $c_1$ and $c_0$ and $\lambda t_e$ was estimated by taking the difference in the expected values of $e_1$ and $e_0$. The expected values of $c_0$, $c_1$, $c_{ana}$, $e_1$, and $e_0$ were obtained by taking the mean values of 10,000 first-order Monte Carlo simulation runs [21] from the two continuous-time Markov models, using a 5-year time horizon. This relatively short time period was selected to ensure that the assumption of constant transition intensities for the continuous-time Markov model would still be reasonable. As up to 70% of all patients with HF die within 5 years of their first hospital admission [22], this period should still be long enough to capture most of the health effects resulting from introducing the novel POCT device in this patient population. To combine multiple experts’ opinions into a single distribution of the commercial headroom available per measurement, we performed linear opinion pooling with equal experts' weighting [10,11].

Results

Current Care Model

After 18 months of follow-up in COACH, 270 (39%) patients reached the combined end point of HF hospitalization and death. Out of these patients, 176 (65%) had been readmitted to the hospital and 94 (35%) had died. In total, 242 HF hospitalizations were recorded for these patients, 176 (65%) had been readmitted to the hospital and the combined end point of HF hospitalization and death. Out of 242 HF hospitalizations, 94 (35%) had died. In total, 242 HF hospitalizations were recorded in the study cohort. The mean duration of hospital stay was 13 days, and the incidence of in-hospital mortality was 14%.

The estimated values of the transition intensities under the current care setting are provided in Table 1. Using Equation 2, the corresponding incidences of out-of-hospital and in-hospital mortality were 36% and 13%, respectively. The estimated mean hospital stay in the Markov model was 13 days. The event rates and mean hospital duration as predicted from the Markov model are close to the event rates and mean hospital duration as observed in COACH, showing that the current care model fitted the observed data well.

Table 1 – Mean values (95% confidence intervals) of the transition intensities under the current care setting

<table>
<thead>
<tr>
<th>$q_{1}$</th>
<th>$q_{2}$</th>
<th>$q_{3}$</th>
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<tbody>
<tr>
<td>$q_{1}$</td>
<td>0.00078</td>
<td>0.00043</td>
</tr>
<tr>
<td>$q_{2}$</td>
<td>0.06810</td>
<td>0.00069</td>
</tr>
<tr>
<td>$q_{3}$</td>
<td>0</td>
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</table>
The resulting probability distributions of $q_{ij}$ together with the corresponding probability distributions of these parameters under the current care setting are depicted in Figure 3. Both experts believed that the introduction of the POCT device would not have a profound impact on the number of transitions from the discharged alive to the death state, but they had different opinions on how the use of this device would affect the number of hospital readmissions. The first expert believed that individually tailored drug doses in response to the observed biomarker trajectories would result in fewer hospital readmissions. The second expert believed that the repeated biomarker measurements would increase admission rates among patients with less severe clinical signs and symptoms. This explains why, compared with the current care setting, the mode of the distribution of $q_{12}$ is shifted to the left for expert 1 and to the right for expert 2. The first expert also believed that the introduction of the POCT device would not affect the transition intensities out of the hospital readmission state. For this expert, we therefore assumed that the probability distributions of the transition intensities out of the hospital readmission state under the new care setting were equal to the probability distributions of these intensities under the current care setting. The second expert, in contrast, believed that because of the increased admission rates among patients with less severe clinical signs and symptoms, the average length of stay in the hospital would decrease and the proportion of patients discharged alive would increase. This explains why, compared with the current care setting, the mode of the distribution of $q_{21}$ is shifted to the right while the mode of the distribution of $q_{23}$ is shifted to the left.

**Headroom Analysis**

Figure 4 summarizes the distributions of the commercial headroom available per measurement based on separate and pooled experts’ opinions for the base-case scenario of a willingness-to-pay threshold of €10,000 per life-year and a daily measurement frequency as suggested by one of the cardiologists. The corresponding pooled lower quartile, median, and upper quartile were €0.05, €1.64, and €3.16 per measurement, respectively.
How this median value is affected by different assumptions for the willingness-to-pay threshold and the measurement frequency is depicted in Figure 5. In comparison to the base-case value of €1.64, the median commercial headroom available per measurement increased to €11.48 when the measurement frequency was decreased to weekly and increased to €8.24 when the willingness-to-pay threshold was increased to €80,000 per life-year. When both these parameters were simultaneously set to their most favorable values, the commercial headroom available per measurement further increased to €57.70.

Discussion

Early-stage health economic evaluations are characterized by evidence scarcity because data from clinical research are usually still missing. This lack of clinical evidence leads to high uncertainty in some of the model inputs, which can generally be resolved only by incorporating expert opinion. In this article, experts’ beliefs were first elicited through semi-structured interviews to develop appropriate conceptual models of the health care settings without and with the use of a new medical technology. PE was then applied to quantitatively capture experts’ beliefs in a probabilistic way to handle parameter uncertainty in the subsequently constructed mathematical models. Finally, Monte Carlo simulation was applied to propagate the uncertainty in the model inputs to uncertainty in the modeled outcomes and to obtain a probability distribution of the amount of headroom available per measurement.

Technology-driven innovation consists of several phases, ranging from idea generation and application selection to the commercialization and launching of the developed products [23]. Given the specific characteristics of such projects, the use of early-stage health economic evaluation as a tool for informing product investment decision making seems especially useful at the intersection between “investigation and technology transfer” and “development and validation,” where it has to be decided to which markets the currently available prototype technology is being targeted, if any. For the case study considered in this article, the prototype technology was a novel POCT device for measuring one or more circulating biomarkers, and the market considered was the disease management of patients with HF. For this application of the prototype technology, the median (inter-quartile range) of the commercial headroom available per measurement was found to be equal to €1.64 (€0.05–€3.16) for a willingness-to-pay threshold of €10,000 per life-year and a daily measurement frequency. Further development of the device into a tool for monitoring HF disease progression may therefore not be viable if the average cost per measurement is expected to be much larger than these values, which can be assessed more formally by feeding the obtained distribution of the commercial headroom available into the product investment evaluation method proposed by Girling et al. [7]. This involves comparing the projected postmarket cash flows resulting from selling the analyzer and the disposable at a price that puts the average cost per measurement just below the commercial headroom available per measurement to the expected development cost to determine whether further development of the prototype technology into a commercial product for HF disease management is likely to yield sufficient return on investment.

An important prerequisite of the use of elicitation in early health economic modeling is that experts need to be able or willing to provide values for the unknown model parameters. The method can therefore not be applied when experts do not want to speculate about the clinical impact of a not yet fully developed product. This problem was also encountered in our case study and led to the dropout of one of the cardiologists from participating in the elicitation exercise. Attempts to support product investment decision making through early health economic modeling may therefore not be successful when the impact of introducing the new technology in a selected clinical setting is difficult to perceive by the participating experts. Also, at the start of the product development process, there are typically many technological solution principles and/or target markets left to choose from, giving rise to a large variety of potential products. Other, more qualitative approaches are then required to perform an initial screening of the generated product concepts.
In previous applications of early health economic modeling, expert beliefs were mostly incorporated by eliciting point estimates of the uPoI as well as their minimum and maximum values to facilitate a subsequent sensitivity analysis [24–27]. Although this so-called deterministic value elicitation approach is easier to use than the PE approach applied in this article, it does not allow the parameter uncertainty to be explicitly represented and assessed regarding its impact. Propagating the uncertainty in the model inputs to uncertainty in the modeled outcomes is nevertheless essential if one wants to support product investment decision making through the use of formal decision support methods, such as the one described previously. A downside of using PE is that attaching likelihoods to the values of unknown parameters is not straightforward. Care must therefore be taken to parameterize the uPoI in terms of quantities that still have a clear interpretation. For the Markov model considered in this article, the transitions out of the two transient health states are subjected to competing risks, meaning that the overall effect of the POCT device on the number of transitions from state i to state j depends not only on the effect of this device on qij but also on its effect on the other transition intensity out of state i [28]. We therefore decided not to use hazard ratios to parameterize the transition intensities of the new care model in terms of the transition intensities of the current care model. Instead, we followed the approach taken by Soares et al. [15] and parameterized the transition intensities of the new care model in terms of two directly observable quantities and elicited their absolute values and their uncertainty conditional on the mean values of these quantities under the current care setting. The mean values of these quantities under the current setting therefore served as reference values based on which the experts’ opinions were elicited. As the elicitation exercise was not repeated for different reference values, the underlying assumption of our approach is that an expert’s opinion on the new care transition intensities does not depend on the specific values of these intensities under the current care setting. Our approach may therefore not be valid when experts believe that there is a large correlation between the current care and the new care transition intensities.

In specifying the Markov model, we assumed that the transition intensities were homogeneous (e.g., independent of time) and constant across patients. One way to relax these assumptions would be to include time and patient characteristics as regressors within the same model structure [29]. This would also result, however, in many more parameters to elicit and therefore seems less suitable for early-stage health economic modeling. In addition, there were only two experts who participated in the PE interviews. The resulting pooled distribution of the commercial headroom available may therefore not represent consensuses among a larger group of experts. A final important decision that has to be taken when combining PE with early health economic modeling is when the pooling of the different experts’ opinions has to be conducted. In our study, the probability distributions of the uPoI served as intermediate outcomes that were transformed into a probability distribution of the commercial headroom available per measurement, the main outcome of interest. We therefore decided to not directly pool the distributions of the uPoI but to postpone the pooling until the uncertainty in the model inputs was propagated to uncertainty in the modeled outcomes, resulting in both individual and aggregated distributions of the commercial headroom available per measurement.

To conclude, this study illustrated by means of a case study how PE can be combined with early health economic modeling to obtain the probability distribution of the commercial headroom available to a new medical technology. By subsequently feeding this distribution in a formal product investment evaluation method, the decision to which markets a currently available prototype technology should be targeted, if any, can be taken in a more informed way, which should ultimately result in higher return on investment for all stakeholders.

**Acknowledgments**

We thank the three cardiologists who participated in the elicitation interviews.

**Supplemental Materials**

Supplemental material accompanying this article can be found in the online version as a hyperlink at [dx.doi.10.1016/j.jval.2013.02.008](http://dx.doi.org/10.1016/j.jval.2013.02.008) or, if a hard copy of article, at [www.valueinhealthjournal.com/issues](http://www.valueinhealthjournal.com/issues) (select volume, issue, and article).

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