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Early Bayesian modeling of a potassium lab-on-a-chip for monitoring of heart failure patients at increased risk of hyperkalaemia

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ABSTRACT

Objectives: Innovative point-of-care (POC) diagnostics are likely to have a strong impact on health care. The aim of this study is to conduct an early assessment of a point-of-care chip for the detection of a pathological deviation of the potassium levels in patients at increased risk, specifically in patients with heart failure (HF) requiring diuretics and ACE inhibitors that can both interfere with potassium levels, which may lead to serious clinical complications. This study also identifies the key factors that determine the success of the application under study.
Methods: A Markov health state transition model was developed representing the disease process. Model parameters were obtained from various literature sources and estimated using interviews and related data. Simulation was carried out for 60 cycles of 1 month each. A discount rate of 3.5% was used, both for costs and utilities. In order to assess uncertainty a probabilistic sensitivity analysis was carried out from which a cost-effectiveness acceptability curve was derived.
Results: For an anticipated number of 121 measurements per year with a cost of €16.60 per chip, an incremental cost-effectiveness ratio (ICER) of 34,856 €/QALY was found. Sensitivity analysis revealed that the threshold for the costs per chip was €19.30 in order to maintain a positive net monetary benefit. Also, model results are very sensitive to the utility of hyperkalaemia and to the probability to develop severe hyperkalaemia.
Conclusions: The question whether or not a POC chip to measure potassium concentrations in order to avoid a severe potassium imbalance is likely to be cost-effective cannot be definitively answered with the information at our disposal. Further research should focus on heart failure patients at particularly high risk of severe life-threatening hyperkalaemia, for instance in the presence of significant renal dysfunction. It may be expected that the use of the chip in such patient populations may render this point-of-care application very cost-effective.

1. Introduction

Health Technology Assessment (HTA) was originally defined as "a policy research approach that examines the short- and long-term social consequences of the application or use of technology" [1]. Internationally different institutions have translated this definition to local contexts [2]. In this study the definition of the society for Health Technology Assessment International (HTAi) is used. HTAi defines HTA as "research-based, practice-oriented assessments of relevant available knowledge on the direct and intended consequences of technologies, as well as the indirect and unintended consequences" [3].

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Early assessment of a new technology is a difficult process in every kind of industry, but especially in the health care sector. This is because new technologies in this sector require extensive clinical trialing before they are approved, as well as the fact that this trialing is very difficult to perform without prototypes of the device or drug. As healthcare costs in many countries absorb a large part of the gross domestic product, early HTA receives increased attention from governments as well as industries [4,5]. By identifying, in an early development stage, those health care technologies that are most likely to generate 'value for money', manufacturers can steer their R&D more effectively. Governments have an interest in early HTA to anticipate on future coverage and reimbursement decisions as well as for steering their innovation funds toward those areas of medical technology development that are most likely to increase quality and decrease costs of care.

An excellent candidate for early HTA is point-of-care (POC) testing. This way of testing clinically important parameters at or near the site of patient care is a relatively new approach in healthcare. Decrease in therapeutic turnaround time, unnecessary testing, and hospitalization, as well as improvement in measurement accuracy are advantages of such patient care [6]. By providing patients and healthcare professionals with the possibility of performing decentralized measurements and even self monitoring, quality of life can be increased and costs can be reduced at the same time [7–9].

Park and Kricka [10] previously pointed out that POC testing, although taking advantage from rapid technological advances in the field, faces challenges during the implementation in the clinical environment. In fact, not only safety and user-friendliness of the new technology, but also health insurance issues and social acceptance codetermine the success of POC applications [11]. These factors are dependent on anticipated costs and effects. It is therefore of paramount importance to analyze both costs and effects of any POC application before proceeding with its construction. In this phase of development, many uncertainties exist regarding the parameters underlying cost-effectiveness of such an application. This study gives an example of how an early health technology assessment can provide POC developers and reimbursement agencies with valuable insight into the potential of this product in the market.

A novel POC application for self-testing is currently being developed at the University of Twente. This application operates using capillary electrophoresis with conductivity detection (CE–CD). Capillary electrophoresis separates substances based on their size to charge ratio in the interior of a small capillary filled with an electrolyte (see Fig. 1). First the sample is loaded into the sample well (injection stage). After this a current is applied on the capillary which separates the sample components (separation stage). Using conductivity detection, concentrations of a broad spectrum of substances in human blood and urine can now be determined. Examples of substances that can be detected using CE–CD are electrolytes, amino acids and peptides [12]. In the healthcare sector this technique enables measurements of substances outside the hospital laboratory.

The actual POC-application basically consists of two parts: a multi-reader and a disposable chip. The multi-reader is a measuring instrument and the interface for the user (Fig. 2). Furthermore it operates the chip and saves the measurement results. The disposable chip actually measures the concentration of the substance. In the near future, this application should be able to determine and display concentrations of a broad spectrum of substances in human blood and urine in less than 2 min.

This POC application can be a valuable addition to the wide range of high-tech products already present in the health care sector. However, as is the case with all technologies and their associated products, it is of eminent importance to develop the application for the market for which it creates the most, or at least sufficient value. This study models potential clinical as well as economical gains for one distinct patient population. With no comparable product yet on the market and no clinical trials yet underway, this research is a good example of early HTA.

In a market scan, a chip for the monitoring of potassium in patients suffering from heart failure was identified as potentially attractive to develop. In order to decide whether or not to develop this chip the decision maker may want to perform a cost-effectiveness analysis and subsequently decide on implementation depending on the cost-effectiveness outcome. However, there is limited data available on both costs as well as effectiveness of this application. This causes much uncertainty which makes it difficult to make a decision regarding development based on a formal cost-effectiveness analysis. Hence, in order to support the technology developer in the earliest development stages, a decision-support process is requested that focuses

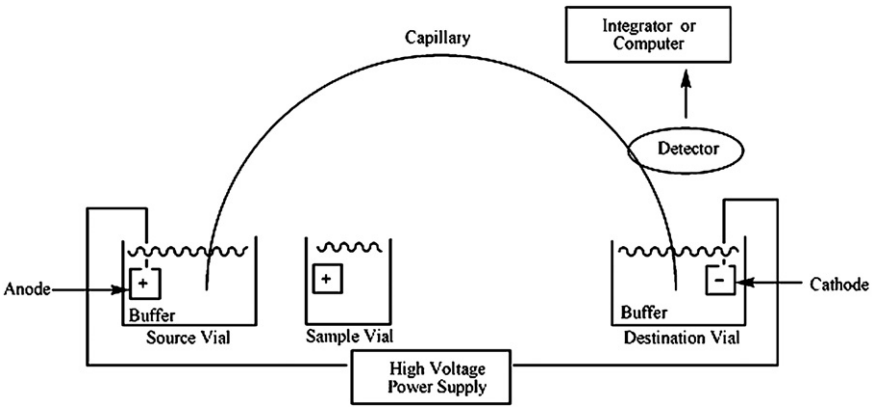

Fig. 1. Principle of chip capillary electrophoresis.

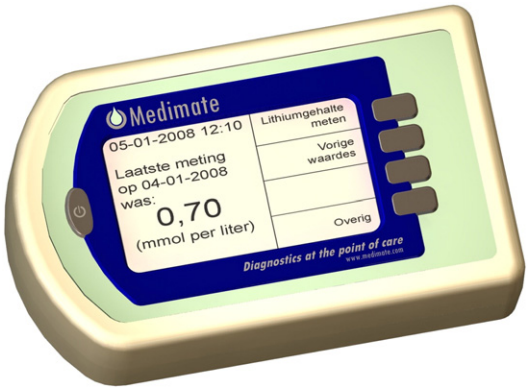

Fig. 2. Point of care multireader.

on identifying critical factors which determine the application's success as well as determining the added value of further research.

Consequently, in this study a method is developed that allows the technology developer to make an early-stage assessment of the cost-effectiveness of the potassium POC application. Because the technology is in its infant stages, many uncertainties exist regarding important parameters. We therefore propose a stepwise approach starting with simple methods and progressing to greater analytical depth based on the results of the previous step(s). This approach mainly aims at determining the expected economic viability of the chip and identifying the key variables that determine the cost-effectiveness of the application under study.

2. Materials and methods

2.1. Cost-effectiveness analysis (CEA) in health care

Due to the high costs associated with the diffusion of new medical technologies and therapies, implementation of cost-effective interventions in clinical practice is a crucial process in healthcare. Cost-effectiveness is determined by comparing the relative value of various clinical strategies or technologies. Ultimately a CEA produces an incremental cost-effectiveness ratio (ICER). The ICER is defined as the ratio of the change in costs of a therapeutic intervention (compared to an alternative, such as usual care or doing nothing) to the change in effects of the intervention. Effects are most commonly expressed as quality-adjusted life-years (QALY). The resulting ICER is made operational by linking the outcome to a range of reference values expressed as willingness-to-pay for a unit of effect. In healthcare economic evaluations, this willingness-to-pay (WTP) value reflects the amount of money society is willing to pay for one additional QALY. If the ICER is lower or equal than the WTP value, the new strategy is considered cost-effective.

2.2. Clinical case

In patients suffering from systolic heart failure, the heart is unable to adequately respond to physical activity by supplying the body with sufficient blood flow. In this situation, the human body activates various compensatory mechanisms (via the nervous system and hormonal control systems) which may lead to tachycardia, retention of sodium chloride and fluid, and vasoconstriction. Fluid retention and vasoconstriction result in an increase in hydrostatic pressure in the vasculature, which presses fluid out into the interstitial space of the surrounding tissue. Ultimately, this pathophysiological mechanism leads to the formation of edemas in the lower extremities, if the amount of interstitial fluid is critically increased.

These edemas can be relieved by diuretics, a class of drugs which increase renal water secretion of the body. However, an important side-effect of the mechanism of action of diuretics is their interaction with the body's potassium level. Depending on the class of diuretics used, they may be associated with loss or accumulation of potassium; as a side effect of treatment this can therefore lead to either hypo- or hyperkalaemia.

Besides using diuretics, which is a symptomatic treatment only, patients with heart failure are generally treated with several other drugs, most notably ACE inhibitors or AT blockers, beta blockers, and – in more advanced stages – aldosterone receptor antagonists [13]. Published in September 1999, the Randomized Aldactone Evaluation Study (RALES) demonstrated that treatment with spironolactone substantially reduced morbidity and mortality in patients with severe heart failure [14]. However, although spironolactone is inexpensive and generally well tolerated, it can provoke life-threatening hyperkalaemia when combined with ACE inhibitors [15–18]. Risks for developing hyperkalaemia are increased because physicians may neglect baseline attributes that predispose patients to hyperkalaemia (e.g., diabetes mellitus), and may overlook conditions that develop during therapy (e.g., renal dysfunction). Furthermore some patients may purposefully increase their dietary potassium intake, as is often recommended during treatment with diuretics such as furosemide [19].

Patients with potassium imbalance may experience – besides other symptoms – muscle weakness and respiratory problems. However, most patients remain asymptomatic until the potassium level is severely disturbed which may cause cardiac arrhythmias and even cardiac arrest [20]. In this paper we study both forms of potassium imbalance: severe hypokalaemia (defined as a serum potassium level of less than 2.5 mmol/L) and severe hyperkalaemia (defined as a serum potassium level of more than 6.5 mmol/L) [20].

Regular and frequent monitoring of the potassium level will greatly prevent the occurrence of a severe potassium imbalance. Therefore an application which can provide patients suffering from heart failure with the possibility of frequent check-ups of their potassium levels at their GP, an outpatient clinic, or even by using self-monitoring could significantly increase both safety and quality of life and provide a valuable asset to current treatment.

2.3. Early assessment methods

A Bayesian approach [21] is adopted for early assessment of the potential cost-effectiveness of the POC chip. First, a cost-effectiveness gap analysis is performed to identify the maximum reimbursable price of the chip. Basically, this analysis considers the economic viability of a new technology, from the producer's point of view, by comparing the expectations about the chip's cost-effectiveness against the prevailing willingness-to-pay threshold for one unit of additional effectiveness (in this study QALYs). Such analysis can help to decide whether or not to take the concept of a POC chip in development. In fact, it provides a first assessment to test the application in which failure will result in a strong advice to discontinue the development of the technology. In other words, the development of the chip should (rationally) only proceed if the expected unit cost (including development costs) of one POC chip is smaller than the anticipated cost-effectiveness gap (or 'headroom'). Suffice to say, abandoning development of the chip is indicated when its expected unit cost exceeds this 'headroom'. A price margin exists to the extent that the expected unit costs of one chip are lower than the anticipated 'headroom'.

If the POC chip successfully passes this first early assessment, subsequently, a simple health economic model is developed that combines all available evidence regarding costs and effects. This model aims to support decision-making regarding prototype development and identifies the parameters for which the cost-effectiveness estimate is most sensitive. At this stage, the analysis identifies the parameters (e.g. costs or effectiveness) that cause the greatest decision-uncertainty. Yet, in this early development stage the prototype chip design or some of its functions may still be eligible for alteration and doing so can positively influence the parameters that drive the chip's expected cost-effectiveness. Such early assessment may thus lead to better and more affordable POC chips at the end of the development cycle.

2.4. Cost-effectiveness gap analysis

The cost-effectiveness gap analysis relies on optimistic assumptions for the performance of the POC chip to derive maximum headroom for its commercial prospects. The health benefit turns on avoiding disutility associated with severe hypo- or hyperkalaemia (ΔU). In addition, potential cost savings of avoiding severe hypo- and hyperkalaemia treatment are identified (ΔC). The calculation assumes the prevailing willingness-to-pay threshold for one additional QALY, which is €30,000, with the benefits extending over an (undiscounted) average patient life-expectancy of 5 years. Following this, the headroom can be calculated using Eq. (1.1):

$$€30,000 * 5 * \Delta U + \Delta C \tag{1.1}$$

2.5. Model structure

In order to determine cost-effectiveness a Markov model was constructed. A Markov model describes several discrete health states in which a person can be at time t, as well as the health states into which the person may move at time $t+1$. The progression from t to $t+1$ is called a cycle. All clinically important events are modeled as transitions from one state to another state. Each transition between two states has an associated probability; these are termed transition probabilities. Each transition probability is a function of the health state and the treatment. Each health state is assigned a cost (in Euros) and a utility (in QALYs), and the overall contribution of these costs and utilities depends on the length of time spent in the health state. Expected clinical and economic outcomes can be determined as a probability-weighted sum of costs and outcomes occurring beyond the initial treatment decision. The time horizon of the model is set at the remaining life expectancy which is 5 years and the perspective of the analysis is that of the healthcare system.

In the Markov state diagram shown below, each state is represented by an oval. Arrows represent transitions and numbers along the arrows indicate the transition probabilities. Based on the clinical problem three health states were identified. Fig. 3 displays the model for patients suffering from heart failure with a distinction made for the presence or absence of edema. Although the basic model only has three states, each state consists of multiple dependent transitions. For example, a patient that moves from the health state "HF; edema" to the state "Death" can die of heart failure or hypokalaemia.

Patients start either in the health state "HF; edema" or "HF; No edema", which means they are suffering from heart failure, with or without edemas, respectively. For all patients suffering from heart failure, medical treatment is prescribed that bears the risk of severe hyperkalaemia, which is considered a complication in the model. Patients that develop hyperkalaemia will

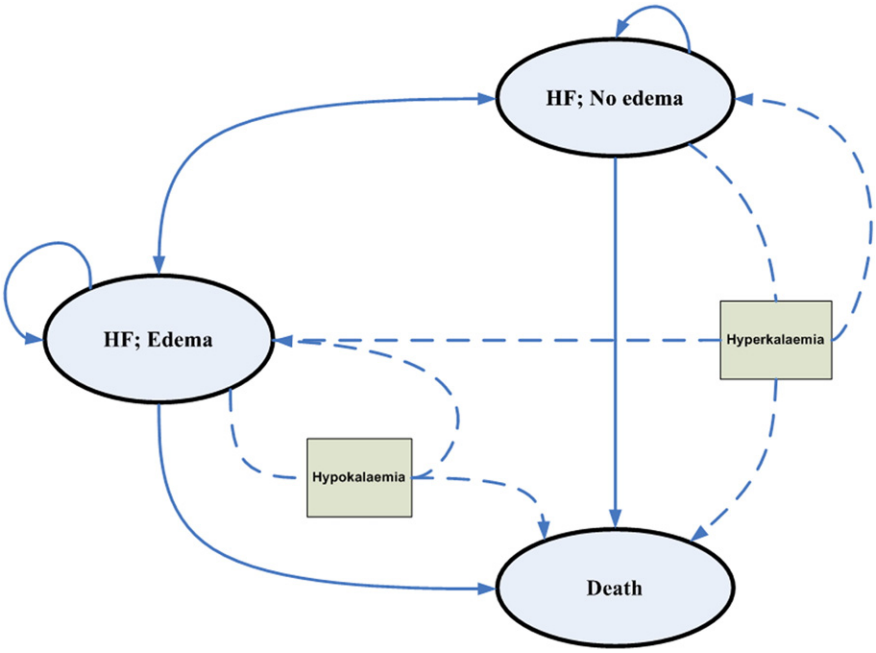

Fig. 3. Markov model for patients suffering from heart failure using non-potassium sparing diuretics.

return to their original health state or die. Applying non potassium-sparing diuretics to patients suffering from edemas can lead to severe hypokalaemia. The probability to develop severe hypokalaemia during treatment is independent of diuretic effectiveness. If this complication occurs, diuretic treatment must be halted immediately which will cause the edemas to either stay or reappear, causing the patient to stay in the health state "HF; edema", or die. However, if the diuretic treatment is effective and severe potassium imbalances do not occur, the diuretics can help to relieve the edemas which means that the patient moves from the health state "HF; edema" to "HF; no edema". If the treatment is not effective, treatment modifications will be applied. Consequently, the patient remains in the "HF; edema" state. There is also the possibility that a patient will die due to heart failure. In our model it is assumed that this possibility is independent of the effectiveness of the diuretics, as diuretics are a symptomatic therapy. This means that we assume that diuretics increase the patient's quality of life but do not prolong it, hereby neglecting potentially fatal cardiovascular events associated with fluid overload. This is a somewhat conservative assumption, as not taking into account this gain in life years will decrease the effectiveness gain of the innovation.

2.6. Parameter estimation

As the technology is new for this kind of application and no existing therapy is replaced, there is no data available from clinical trials. Most transition probabilities as well as costs and utilities could be obtained from different sources of literature. In addition, some parameters were estimated using related literature data and interviews.

The probability to develop hyperkalaemia while using non potassium-sparing diuretics was assumed to be zero, as these class of diuretics promote potassium excretion from the body. The probabilities to develop severe potassium imbalances were estimated from data obtained in hospitalized patients, as data on outpatients was neither available in the literature nor available from other sources. Costs for edema therapy were estimated assuming an average of four treatments per month. Costs for severe potassium imbalances were estimated using cost data for life-threatening ventricular arrhythmias, the most abundant consequence of this condition.

It was assumed that the development of either a severe hypokalaemia or hyperkalaemia would lead to an average reduction in quality of life for 1 month of 50%. This assumption was made based on the fact that the immediate consequence of a severe cardiac arrhythmia is a drop in utility to almost zero. This condition will improve rapidly (unless the patient dies), but still it is assumed that the patient will need 1 month to get back to the utility value present before the hypo- or hyperkalaemia. The probability for dying represents an average for heart failure patients over all age categories, not taking into account NYHA classification.

2.7. Defining probability distributions

Transition probabilities follow a Dirichlet distribution (i.e. the multinomial version of the beta-distribution) which was employed to generate random probabilities for all Markov transitions in the model [22].

As costs are confined between zero at the lower end and positive infinity at the upper end, and are usually skewed to the right, a gamma distribution was fitted to generate random cost estimations [23]. Utilities are confined between one at the upper end

and negative infinity at the lower end, and therefore a beta distribution was used to generate random utility values [23]. Standard deviations (SD) were set at 10% for costs and 20% for utilities.

The parameters of the distributions were solved using analytic methods (method-of-moments [23]). Method-of-moments fitting involves equating the mean and SE observed in the trial data to the expressions for the mean and SE of the relevant distribution. The parameters of the distribution (α, β) can then be solved analytically.

2.8. Introducing the POC chip in the model

When the chip is introduced, changes will occur in the current disease process. In order to introduce these changes in the model for the current situation, two adaptations are needed: First, the probability to develop severe potassium imbalances is assumed to become zero and second, the costs for using the POC application are added to the health state "edema present".

The increase in costs is determined by using cost data obtained from a similar application for the monitoring of lithium level in patients suffering from MDI. The model assumes that a patient can use the multireader for 5 years, leading to a yearly cost of €130 for this device. Costs per chip are estimated at €16.60, based on information provided by the technology developer.

2.9. Simulation and assessing cost-effectiveness uncertainty

Simulation was carried out using the health care module of TreeAge Pro 2009™. A 5-year cohort analysis for 1000 patients suffering from heart failure as well as a Monte Carlo simulation with 200,000 trials was carried out. This number of trials roughly corresponds to the number of patients suffering from heart failure in the Netherlands [24]. Effectiveness was expressed in Quality Adjusted Life Years (QALYs) and costs in Euros. The changes in outcomes between the current treatment and treatment using the POC chip were expressed by the incremental cost-effectiveness ratio. The willingness-to-pay (WTP) value was set at €40,000 [25]. Costs and QALYs were discounted at 3.5% rate [26]. In order to represent the uncertainty in the costs and effects of the treatment a scatter plot of simulated incremental costs and effectiveness pairs on the cost-effectiveness plane was drawn. Subsequently, a cost-effectiveness acceptability curve (CEAC) was constructed to obtain more information about the probability that the treatment using the POC chip will be cost-effective [27,28].

2.10. Sensitivity analysis and expected value of information

Sensitivity analyses were carried out to identify the parameters most crucial to the application's cost-effectiveness outcomes. One-way sensitivity analyses were carried out to analyze costs per chip (range: €6–€26), quality of life measures for developing severe hyperkalaemia (range: 0.1–0.4) and probability to develop this complication (range: 0.001–0.01). Hyperkalaemia has a significantly higher incidence combined with a higher mortality rate than hypokalaemia which is why only this complication is analyzed (this is confirmed by a two-way sensitivity analysis on utility hyperkalaemia vs. utility hypokalaemia). Costs per chip were chosen because it is, apart from being of utmost importance for commercial success, also considered to be influenceable by the technology developer. This parameter therefore represents uncertainty in the developmental process, as opposed to post market uncertainties that were also analyzed [29]. These include 1) quality of life measures of hyperkalaemia which were analyzed because these parameters had to be estimated, which makes them uncertain by definition and 2) information regarding the probabilities to develop potassium imbalances in usual care that was considered to be less reliable because this information was obtained in hospitalized patients, which are not the main target group of the application under study.

In addition, probabilistic sensitivity analysis (PSA), using second order Monte-Carlo simulation techniques, was employed to handle parameter uncertainty in the model as described by the distributions of costs, health outcomes and the resulting cost-effectiveness estimates. The benefit of propagating distributions through the model, instead of using a single point estimate, is that the cost-effectiveness results indicate the uncertainty surrounding the decision, rather than the uncertainty surrounding a single input. The PSA randomly selects values from each of the parameter distributions, and evaluates the model results for that combination of parameter values. This process was repeated 20,000 times to obtain a representative range of cost and effect pairs for the two strategies and hence a distribution of incremental costs and effects (QALYs). These estimates are then presented graphically on a cost-effectiveness plane, to show the estimated joint distribution of incremental costs against incremental effects. To avoid potential problems with interval estimates for incremental cost-effectiveness ratios (ICERs), net benefit analysis was performed. This involves the calculation of a net benefit (NB) statistic for each of the 20,000 simulations, from the formula $NMB = \lambda\Delta E - \Delta C$, where λ is the societal willingness-to-pay for one additional unit of effect and ΔE and ΔC are the incremental differences in effectiveness (QALYs) and costs, respectively. A positive monetary net benefit indicates that a strategy is cost effective for a given value of λ. A cost-effectiveness acceptability curve [24] is obtained by plotting the proportion of the 20,000 simulations that have positive net benefits as a function of λ.

Apart from identifying those parameters crucial to the application's cost-effectiveness it is also vital for the technology developer to know for which specific parameters more or better data is needed. In other words, in addition to reducing the uncertainty as a consequence of uncertain individual parameters influencing model outcomes as is done in sensitivity analysis, there is also a need to reduce the uncertainty surrounding the ultimate decision whether or not to continue developing the innovation. The latter is done using value of information analysis. In order to inform the technology developer about the expected value of conducting more research to better support the decision instead of making the decision to proceed with the chip's development with the information available today, an estimation of the partial expected value of perfect information (pEVPI) was determined [30]. The pEVPI is

Table 1
One-month transition probabilities HF patients.

Transition	Probability standard care	Source	Probability after chip introduction
HF; edema => HF; no edema	0.7916	Estimated[a]	0.7933
HF; edema => HF; edema	0.1979	Estimated[a]	0.1984
HF; edema => severe hypokalaemia | HF; edema	0.0022	[32]	0
HF; edema => death	0.0083	[34]	0.0083
HF; no edema => HF; edema	0.1990	Estimated[a]	0.2001
HF; no edema => HF; no edema	0.7877	Estimated[a]	0.7916
HF; no edema => severe hyperkalaemia | HF; no edema	0.0050	[32]	0
HF; no edema => death	0.0083	[34]	0.0083
Severe hyperkalaemia | HF; no edema => HF; no edema	0.6936	[33]	NA
Severe hyperkalaemia | HF; edema => HF; edema	0.6936	[33]	NA
Severe hyperkalaemia | HF; edema => death	0.3064	[33]	NA
Severe hyperkalaemia | HF; no edema => death	0.3064	[33]	NA
Severe hypokalaemia | HF; edema => HF; edema	0.7960	[32]	NA
Severe hypokalaemia | HF; edema => death	0.2040	[24]	NA

[a] Estimates corrected for other probabilities at the same node.

based on the results of the PSA. It is the maximum price that one would be willing to pay in order to gain access to perfect information (i.e. no decision uncertainty) regarding a specific parameter of the model. If the costs of acquiring the additional information are lower than the pEVPI, the rational decision would be to do so. If, however, the costs of acquiring additional information would be higher than the expected value of that information, the rational decision would be either to decide today based on available information, or focus the future research to other uncertain parameters and as such reduce the costs of future studies below the expected value of information as can be obtained from these studies. The choice was made to obtain pEVPI values for the parameters that in sensitivity analyses were proven to be vital to the cost-effectiveness outcome.

3. Results

3.1. Cost-effectiveness gap analysis

The difference in costs (ΔC) and the difference in utility (ΔU) following introduction of the POC chip in (otherwise) usual care are optimistically estimated at €752 (cost associated to treating severe potassium imbalance; Table 2) and $0.51 - 0.225 = 0.285$ (instantaneous utility decrement for potassium imbalance additional to edema; Table 2), respectively. Yet, given the low probabilities for severe potassium imbalance of 0.005 (severe hyperkalaemia) and 0.0022 (severe hypokalaemia) per cycle (see Table 2) a patient is assumed to spend maximum 0.142 ($= 60$ cycles $* 0.007$) days per 5 years in a state of severe potassium imbalance. The expected utility decrement is therefore maximum $0.285 * 0.142 = 0.04$. Following Eq. (1.1) this leads to a headroom of: €30,000 $* 5 * 0.04 +$ €752 = €6752. Although no opinion on the precision of the estimates was elicited, the total headroom of €6752 is considered to offer good prospects for a commercially viable price since unit costs (including development costs) are unlikely to exceed this value. Therefore, the economic evaluation was continued.

3.2. Markov model analysis

3.2.1. Transition probabilities

One-month transition probabilities are displayed in Table 1. The probability that a patient with heart failure develops severe hyperkalaemia is approximately 0.5%, assuming a mean frequency of two cases of severe hyperkalaemia for patients who experience hyperkalaemia at least once [31]. However, this is only the case for patients who are not using non potassium-sparing diuretics. Patients using non potassium-sparing diuretics have a probability to develop severe hypokalaemia which is approximately 0.22% [32]. Chances of dying of severe hypokalaemia are 20.4% [32], for severe hyperkalaemia this is 30.64% [33].

Table 2
Estimated costs and utilities of health states with associated complications and therapy.

Markov health state	Costs (€)	Source	Utility	Source
HF; edema	173	[35]	0.51	Estimated
Severe hypokalaemia	752	[38]	0.255	Estimated
Non potassium-sparing diuretics	37	[36]	NA	
Edema therapy	156	[37]	NA	
HF; no edema	173	[35]	0.77	[39]
Severe hyperkalaemia	752	[38]	0.255	Estimated
Death	0	Assumed	0	Assumed

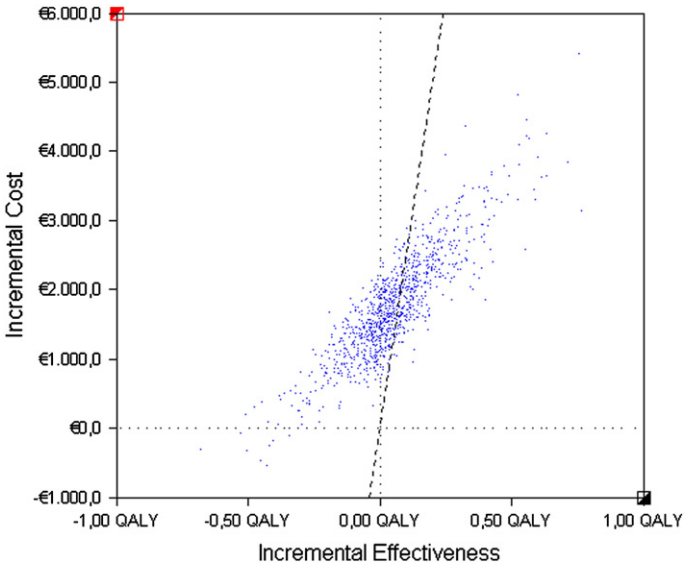

Fig. 4. Incremental cost-effectiveness scatter plot for treatment using a POC chip vs. current treatment for a simulation horizon of 5 years.

3.2.2. Costs and utilities

Average monthly costs for heart patients are €173.33 [35]. Average costs for non potassium-sparing diuretics, edema therapy and severe hypokalaemia were €37.42 [36], €156 [37] and €752 [38], respectively. Utility values range from 0.77 [39] for patients without edema to 0.255 for patients with severe potassium imbalances (Table 2).

3.2.3. Cost-effectiveness

Cohort simulation yielded an ICER of €35,000/QALY for 10 measurements per month at a cost of €16.60 per chip. Fig. 4 shows incremental costs and effectiveness of the treatment using the POC chip compared to the current treatment. On the horizontal axis the differences in effectiveness are depicted between the current treatment as baseline scenario and treatment using the POC chip. On the vertical axis the differences in costs are depicted for the treatment using the POC chip vs. current treatment. The oblique dotted line represents the WTP threshold.

Approximately 50% of the data points are located below the WTP threshold, which represents cost effectiveness. This means there is a high uncertainty regarding cost-effectiveness. A cost-effectiveness acceptability curve (CEAC) confirms this. Fig. 5 presents the CEAC for WTP values ranging from 0 to €100,000/QALY. It can be seen that if the value placed on a life year is

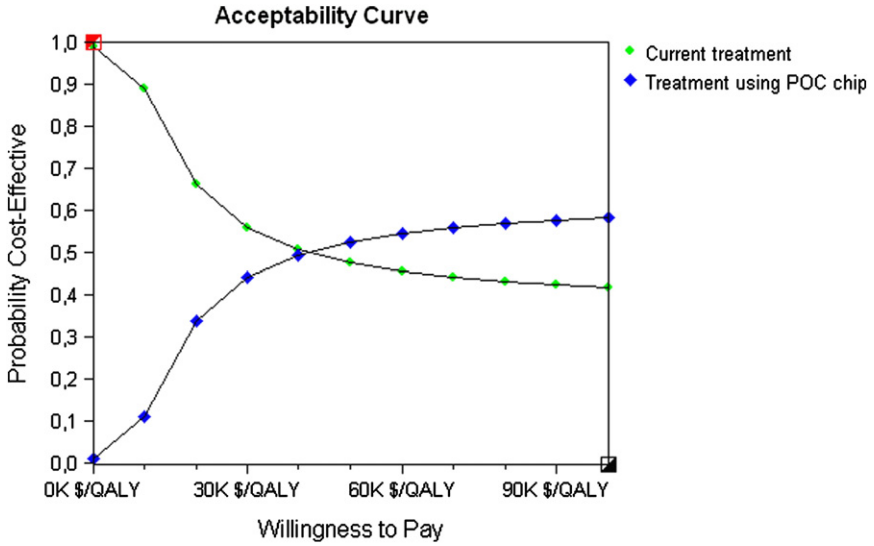

Fig. 5. Cost-effectiveness acceptability curves for the current treatment and treatment using POC chip.

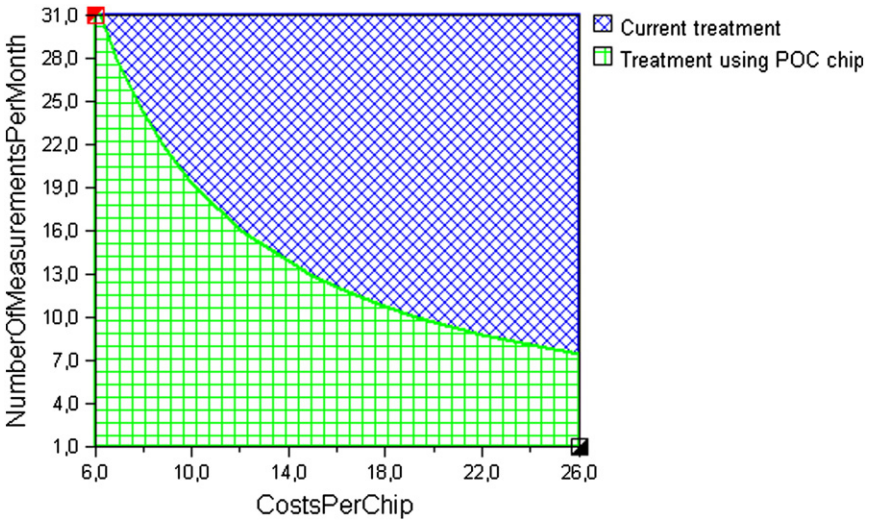

Fig. 6. Two-way sensitivity analysis on costs per chip versus number of measurements.

€40,000, as is the WTP, the probability that the current treatment compared with the chip is cost-effective is approximately 50%, as 50% of the simulated ICERS fall below this threshold.

3.2.4. Sensitivity analysis and pEVPI

A one-way sensitivity analysis was carried out on costs per chip. The cost-effectiveness threshold for the costs per chip was €19.30. This means that if the technology developer decides to raise the costs per chip to this value, the chip will still be cost-effective. Regarding the number of measurements per month 1-way sensitivity analysis showed that the application fails to be cost-effective when there are over 11 measurements necessary per month. Fig. 6 below displays a 2-way sensitivity analysis on costs per chip versus number of measurements per month. The technology developer can use this plot to make an assessment of the expected profit when the number of measurements varies. This is a good example of a developmental uncertainty (price per chip) versus a post market uncertainty (number of measurements). If development of the POC application proceeds, the model can be updated just prior to market implementation by more accurate estimates for the costs per chip [29].

Sensitivity analysis furthermore revealed that the results are very sensitive to the utility of hyperkalaemia as a rise from 0.26 (ICER = €34,000/QALY) to 0.28 (ICER = €42,000/QALY) leads to an ICER above the WTP threshold. Furthermore results are also sensitive to the probability to develop severe hyperkalaemia while not using a chip: a decrease in probability to 0.004 leads to a cost-inefficient outcome. Partial EVPI values for the utility of hyperkalaemia and probability to develop hyperkalaemia were €53 and €539 per patient, respectively. These values represent the costs for the health system to obtain perfect information about these parameters and consequently to make a better founded decision.

4. Discussion

POC applications are promising to be valuable additions to the wide range of high-tech products already present in the health care sector. However, as is the case with all technologies and their associated products, it is of eminent importance to develop the applications for the markets for which they create the most, or at least sufficient value. This study modeled the potential clinical as well as economical gains for a POC chip for one distinct patient population (i.e. severe heart failure). The initial cost-effectiveness gap analysis showed sufficient 'headroom' for recouping the development costs of the chip after market launch. Subsequently, with a simple health economic model that was populated with the preliminary data available and expert opinions, even in this early development stage an estimation could be obtained regarding the likely cost-effectiveness of the chip—which will increasingly be a factor determining market success. As the expected incremental cost-effectiveness of the POC chip versus standard medical treatment without such a chip lies below the prevailing cost-QALY threshold, a positive advice could be given to continue developing this technology. However, as these estimates are uncertain, the identification of key parameters influencing the cost-effectiveness of the chip seems more valuable at this pre-development stage. A valuable addition to the identification of these key parameters is the determination of the expected value of information of doing further research to obtain better estimates for these parameters. This in turn helps the technology developer direct future R&D efforts to further optimize the cost-effectiveness of the chip at a time when there is still room for making changes in the design or functionality of the product. This is considered one of the core strengths of early assessment; as such changes are impossible at the latest stages of development.

4.1. Assumptions and limitations

As this paper was an early HTA exercise, this will inevitably bring about several assumptions that can have a major impact on model outcomes. When looking at the method, data selection is an important point of concern. Considering the limited amount of research into POC applications, not all data is available from literature. Especially, utility values are hard to assess when they are not yet investigated in existing cost-effectiveness studies. Furthermore, certain costs cannot be uniformly calculated but should instead be based on estimations. Good examples of this are the costs for hypo- or hyperkalaemia, since treatment is not uniform because there are different degrees of severity and different kinds of symptoms associated with these complications. Therefore, costs will vary over a broad range. Using sensitivity analysis, the influence of these estimations can be assessed.

Another very important issue is the patient population under consideration. In this study it was assumed that the patients were not suffering from other diseases. This means that for comorbidities that increase the risk of developing potassium imbalances our model provides an underestimation of the cost-effectiveness of the POC application. For example, many patients with heart failure also suffer from renal failure. These patients have a much greater risk to develop severe hyperkalaemia. Therefore, we can say that the outcomes of our model provide the technology developer with a lower bound of the cost-effectiveness of the innovation under study. Given the uncertainty surrounding the innovation, a lower bound seems appropriate as for example revenues for the technology developer can be lower than anticipated.

It is obvious that this kind of modeling does not give enough information on which the decision maker can solely base the decision whether or not to adopt and/or reimburse the technology under study. Apart from that, the model does not anticipate on the use of potassium supplements which can minimize the probability to develop hypokalaemia. However, as the most important population seems to be hyperkalaemia patients, this limitation will have minor consequences. Furthermore external factors like implementation costs, learning effects and acceptation of the new technology by the physicians are not taken into account as these factors are very hard to quantify. Also, the probabilities to develop severe potassium imbalances had to be obtained from estimates for hospitalized patients. Hospitalized patients are likely to have more complications, and thus a higher probability to develop either hyper- or hypokalaemia. This may give biased estimations on these particular parameters and thus on model outcomes. Perhaps the most important limitation of this study is that the frequency of measurements cannot be analyzed. After consulting experts in the field it was determined that for ten measurements per month the probability to develop potassium severe imbalances is reduced to zero. However, this remains an educated guess which affects the costs per month using the POC application.

4.2. Implications for existing technologies

As the chip in this study has the potential to measure other substances in the blood and urine as well, this innovation can potentially be quite disruptive as it has the potential to shift a significant portion of the production of the hospital laboratory either extramural or to a specific department in the hospital. Because it is very likely that high-volume laboratory tests will be major candidates for point-of-care applications outside of the hospital, diseconomies of scale and scope will inevitably arise for hospital laboratories. Diseconomies of scale refer to the relationship of average costs with volume of production and will arise when marginal costs of production get, with increasing volume of production, higher than average cost. Diseconomies of scope are conceptually similar to diseconomies of scale but refer to the multipurpose use of capital investments. It can be readily seen that the use of point of care technology introduces diseconomies of scope as demand for specific laboratory tests will decrease. Hence, in the short run, the hospital laboratory can no longer operate at minimal cost levels. This prospect can be a reason for the laboratory to prevent or abandon the implementation of potentially cost-effective point of care technology, both in-hospital as for outpatient care. Therefore it is important that any diseconomies are quantified in order to assess their influence on outcomes of economic evaluations. This will help to obtain a more realistic assessment of the cost-effectiveness of the point-of-care application, and might also assist the hospital laboratories in the development of an optimal implementation strategy.

5. Conclusions

This study did not intend to provide a final judgment about the economic viability of the technology under study. Instead, it aimed to explain the methodology to use early health technology assessment to give an advice whether or not to continue with the development of a technology when limited data is available on both the technology itself as well as its intended market. This paper indeed demonstrates that this kind of early stage modeling can be very useful in the early development stages of a new medical technology and that the technology developer can be provided with a comprehensive advice based on accumulating data about the further actions to be taken in anticipation of a final (reimbursement) assessment of the emerging technology.

For patients suffering from heart failure, the question whether or not a POC chip to help avoid a severe potassium imbalance is likely to be cost-effective cannot be definitively answered with the information at our disposal. This conclusion is supported by the ICER as well as CEAC which shows that a relatively small decrease in WTP reduces the probability that the application is cost-effective to below 50%. One-way sensitivity analysis revealed that the chip's cost-effectiveness is highly dependent on the probability to develop hyperkalaemia and the corresponding utility of this complication. Value of information analysis provides

the technology developer with the necessary information on which he can decide whether or not to do more extensive research into these parameters.

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