Integrating Health Economics in the Development Cycle of Medical Devices: The Case Study of Absorbable Pins

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Abstract

Aims: The probability of reimbursement is a key factor to determining to proceed with or abandon a product during its process of development. Health economics analysis can help to anticipate the eventual outcome of the reimbursement decision from early stages of the development cycle. We aim to incorporate the methods of the iterative Bayesian economic evaluation proposed in the literature (Fenwick et al, 2006) into the development process of new medical devices, and adapt them to face the relative scarcity of data and time to perform the analyses that characterise the development stage.

Methods: We propose a three-stage economic evaluation, starting from an early phase where simple methods allow for a quick prioritisation of competing products. In a mid-stage, the data is synthesised into a decision model, the parameters for which more information is most valuable are identified, and the uncertainty surrounding the decision is explored. At the late-stage, all relevant information is synthesised to inform purchase decision. We analyse retrospectively the case-study of absorbable pins, as compared with metallic fixation, in metatarsal osteotomy to treat hallux valgus.

Results: The results from the early analysis suggest absorbable pins to be cost-effective under the beliefs and assumptions applied. The outputs from the models at the mid-stage analyses show the device to be cost-effective with a very high probability. Late-stage analysis synthesises evidence from a RCT and informative priors formed using previous evidence. It also suggests that absorbable pins are the most cost-effective strategy, although the uncertainty in the model output increased considerably.

Conclusions: We show that undertaking economic evaluation at early stages of medical devices is feasible, and how the estimates of expected cost-effectiveness can be updated, and the uncertainty can be explored. This methodology allows decisions in the product development cycle to be based on the best knowledge that is available at each stage.

1. Introduction

Ideally, healthcare technologies should not be widely adopted unless they have been shown to be cost-effective as compared to standard care or alternative technologies. Some health care systems such as the National Healthcare System (NHS) in the UK make

reimbursement decisions based on the clinical and cost-effectiveness evidence of new therapies. In this regard, guidelines for technology appraisals have been developed by the National Institute of Clinical Excellence (NICE) [1]. As a recognition that measurement of the costs and effectiveness of different strategies are inevitably estimated with a degree of imprecision, the guidelines emphasises the use of methods that quantify the implications of parameter and methodological uncertainty for the results, and also methods that assess the value of conducting further research to reduce the uncertainty relating to the reimbursement decision. Therefore, sophisticated methods such as probabilistic sensitivity analysis which allow for the uncertainty associated to all input parameter to be characterised in the analysis, and formal value-of-information (VOI) analysis which estimates the value for money for further research, are now increasingly incorporated in economic evaluations.

More recently, the value and practicality of incorporating Bayesian methods into the iterative framework of health technology assessment (HTA) has been argued [2]. This methodology relies on the idea that reimbursement decisions may be reviewed on the basis of new evidence that becomes available in the life cycle of a technology [3]. The Bayesian approach provides then an ideal framework where the prior information is combined with the recent data to inform whether the technology is considered to be cost-effective after incorporating all of the information available.

We believe that the iterative Bayesian approach to HTA can have a commercial appeal in the development of new products by incorporating such a methodology from a much early stage in the lifecycle of the technology: at its development phase. The commercial development cycle of new technologies often takes the form of a staged-decision making process which is regularly reviewed and decisions are taken as to whether or not to proceed with the innovation at different time points. Incorporating economic evaluations into such a stage-gated decision process from very early stages of development could support internal investment decisions in order to prioritise between a number of potential products or prototypes to take forward, and could avoid investing in technology that could never be cost-effective. In addition, given that at the development stage there is still scope for further research before the product is launched to the market, formal analysis that aims to identify the parameters with the largest impact on the likely cost-effectiveness could direct research resources more efficiently.

However, given that in this context the availability of data and time to perform the analysis is likely to be relatively scarce as compared with those evaluations for which the iterative Bayesian approach has generally been proposed, the methods need to be adapted appropriately to avoid unduly delaying innovation development process. To address these issues we suggest starting with relatively simple health economic evaluations at the very early stages which would provide a rapid indication of potential cost-effectiveness, and then

gaining greater depth of analysis in later stages as more information becomes available. Formal data regarding an innovation at early stages of development would be unavailable, and therefore the use of 'expert' assumptions based on similar products and/or elicitation of the believed impact of the new technology would be required.

To test out the approach, within a short time period, we applied this methodology retrospectively to the case study of absorbable pins in osteotomy to treat hallux valgus. We focused on a medical device rather than on a pharmaceutical product because for medical device companies demonstration of safety and performance is sufficient to receive CE-marking, and cost-effectiveness evidence is often not required. As a result, conducting or investing in economic evaluation is not a core activity in most medical device companies. However, due to the rapidly growing range and expense of new medical devices, manufacturers are increasingly being asked to demonstrate 'value for money' of their products, and thus incorporating such an approach may increase the marketability of the device. In addition, medical devices are characterised by short product development times and short product lifecycles, and therefore they could benefit more from the rapid early assessment suggested in the approach. Moreover, the constant flow of incremental product improvements characterising the medical device development means that relative good prior information on the performance of the device may be available from earlier studies on previous generations [4].

2. Proposed methodology

We propose a three-stage economic evaluation approach, where the type of evaluation is defined by the methods employed in the analysis (they have been detailed elsewhere [5]). We summarise the suggested methodology of the evaluation at each stage.

2.1 'Early-stage analysis' is conducted at an early phase of development, when the product may still be just an idea or a concept, and when a potential large number of alternative directions to take forward the development of the technology are still open. Therefore, this type of evaluation is characterised by very limited availability of data, and limited research resources. Thus, simple methods that allow for a quick prioritisation of competing products are called for. In the absence of data about the new technology, the analysis is based on the evidence concerning the current technology that the new product aim to substitute or will compete with, and expert opinion and/or assumptions regarding the impact on cost and effectiveness of the new technology. The data is then analyse using simple techniques such as what has been described in the literature as the 'effectiveness gap' [6] or 'headroom method' [7] to place a bound on the maximum reimbursable price that will then be compared with the expected cost of the device at this stage.

2.2 'Mid-stage analysis'. At a mid-stage, typically, observational studies would provide some clinical evidence of the effect of the new technology, and some initial cost estimates would be available. Under these conditions, decision-analytical modelling techniques can be applied. Two important issues need to be addressed at this stage; 1) synthesising the evidence available, and 2) exploring the uncertainty in the parameters in the model in order to find the inputs with the largest impact on the model outcome. The former may require combining evidence from multiple sources of data, and using formal Bayesian evidence synthesis techniques will ensure that the uncertainty is incorporated appropriately [8]. We use random effect models that allow for between-studies variation and will provide more conservative confidence intervals than fixed effect models that assume each individual study to be estimating a true single effect. Algebraically, if Y_i is the observed effect in study i with variance V_i, the estimated study specific effect, δ_i , are allowed to be different from each other, and are assumed to be sample from a Normal distribution with mean d and variance τ^2. A Bayesian analysis requires a prior distribution for τ^2 as well as for d, which in the absence of evidence can be set to be vague uninformative distributions.

$Y_i \sim Normal(\delta_i, V_i)$

$i = 1,....Nstud$

$\delta_i \sim Normal(d, \tau^2)$

In order to identify the key parameters affecting the cost-effectiveness at this stage, we suggest starting with simple one-way sensitivity analysis, where each relevant parameter is varied one at a time to study their impact. These methods are easy and quick to undertake and to understand, and would provide some insights of whether changes in specific parameters are likely to make a meaningful impact on the model outcome and on the potential decision based upon it. Therefore, this information not only could direct research resources to areas with larger impact, but also if the development process allows for changes or improvements to be made in the new technology, this could inform to which specific changes in the technology the cost-effective estimate will be more sensitive. However, one-way sensitivity analysis has been regarded as an unsatisfactory approach to handle parameter uncertainty because the overall uncertainty in the cost-effective estimate depends on the combined variability in several factors [9]. As a result, probabilistic sensitivity analyses (PSA) are increasingly being used. In this type of analysis, probability distributions are applied to the parameters and samples are drawn at random from these distributions using simulation techniques. Therefore, in order to provide a full picture of the parameter uncertainty we also undertake probabilistic sensitivity analysis, and represent the results by

cost-effectiveness acceptability curves (CEAC) which show the probability that a given intervention is the most cost-effective strategy at different values of willingness-to-pay for a unit of effect.

2.3 'Late-stage analysis'. Health economic analyses undertaken in the late stage are typically designed to inform external decision makers (for example, health service payers) about the expected cost-effectiveness of the new technology, and so to make the case for reimbursement of the product. Although they would preferably be based on evidence provided by large randomised control trial (RCT), the need to incorporate all the relevant information in an appropriate way has also been argued [10]. Therefore, we form prior distributions of the parameters of interest using the previously collected data, which would typically be provided by observational studies, and combine it within the Bayesian framework with the data newly available. Parameter uncertainty is again explored by the means of PSA, and these results are used to quantify the societal cost of making the wrong decision about which technology to fund, both in terms of forgone health gain to patients and in terms of wasted resources. This represents the expected value of perfect information (EVPI), because if research could remove uncertainty, its value would be the cost of that uncertainty. In addition, the EVPI can be computed for different set of parameters to inform the specific consequences of the technology (e.g. impact on cost, utilities or health status) for which more information is most valuable. Note that this standard VOI analysis is related to a collective view of the value of this additional research for the society, and therefore would not be directly relevant in a commercial context. Thus, this analysis is only conducted in the final stage, which is aimed to inform external decision makers concerned with collective welfare.

3. An application of iterative Bayesian economic evaluation within the development of absorbable pins to treat hallux valgus.

3.1 Background

The case study utilised in this study is the use of absorbable pins in the treatment of hallux valgus. Hallux valgus is defined as a deviation of the big toe (hallux) towards the midline of the foot. Symptoms are highly variable and may not show until larger degrees of deformity are reached or when the pressure from footwear causes inflammation and development of a bursa. When the condition is first diagnosed, conservative treatment such as orthosis, night splints or foot exercise may be attempted. Alternatively, surgical procedures are carried when the deformity makes fitting footwear a problem or when the foot function is affected and the joint becomes painful. The most common procedure is the metatarsal osteotomy. There are different methods to stabilise the osteotomy such as bone suture, internal metallic fixation, and a more recent method, absorbable pins. Suture fixation is

related with a significant risk of displacement, while metallic fixation increases the risk of infection and fragmentation, and often necessitates removal at a later date [11]. Absorbable devices decompose gradually, and the stress is transferred gradually to the healing tissue, which may reduce the risk of fracture. Furthermore, they obviate removal surgery and so may reduce the total cost when compared to other devices.

In this study we explore retrospectively the cost-effectiveness of absorbable pins, as compared with other fixation methods, from an early stage of the development of the device for the treatment of hallux valgus, and iteratively, in later stages of the decision-making process that a company would have faced.

3.2 Methodology

To illustrate the approach, we consider the case of a company that is developing an absorbable device and planning to sell it for its use in osteotomies to treat hallux valgus (Orthosorb; Jonhson & Jonhson). The stage gates for this project are based on the following timeline: gate 1) the company received approval for conducting clinical trials in 1987 based on comparison with similar products; gate 2) then in 1990 a competitor product entered the market; gate 3) the product received CE-Mark approval in 1995; gate 4) after which post-marketing studies were continued to be conducted.

At each gate, economic evaluations are carried out using the information available at that time. A literature search was undertaken at each time-point, and the articles identified for each analysis are reported in Appendix 1. The evaluation methods used vary in the complexity and time required to conduct them as explained above. 'Early-stage analysis' is conducted using the information prior to 1987 (gate 1). Subjected to the results from this analysis a company could decide to proceed with the device and undertake a more formal evaluation. Therefore, 'mid-stage analyses' which synthesise the data into a decision model are also conducted at gate 1. Such model provides an ideal framework to update the results when new evidence becomes available in 1990 and 1994 (gate 2 and 3). At the 'late-stage analysis', gate 4, the information collected previously is used to form prior distributions of the parameters that are then updated with the findings from a RCT available at this stage.

To determine the impact of a change in model inputs on model outcomes, the following parameters were subjected to one-way sensitivity analysis: probability of reoccurrence, complications, revision, and removal for absorbable pins [range 0 to 1]; the impact of absorbable pins on quality of life (QoL) [decrement OR range 0 to 2]; the QALY weight for cured and reoccurrence states [range 0.7-1], the cost of absorbable pins [range £0 to £300]; cost of removal and revision surgery [range £0 to £1,000] and cost of complications [range £0 to £200]. In the decision-analytic models, PSA were undertaken by applying probability distributions to each parameter of the model and running 5,000 iterations in the

simulation. The value of information analysis at gate 4 is conducted considering a population-level EVPI by estimating the number of operations in the UK over an expected lifetime of the technology of 5 years, and applying a threshold value of £20,000 per QALY.

2.3 Data

2.3.1 Probabilities

The probabilities of any event after the surgery (reported in Table 1) such as the need of revision or other complications, and the reoccurrence of the condition were taken from the literature and synthesised using binomial models in WinBUGS™ (Windows-based Bayesian inference using Gibbs sampling). In the early and mid-stage analyses, uninformative prior distributions were used, and the data available at different stages were synthesised using Bayesian random-effect meta-analyses. In the late stage (gate 4) analysis, informative priors were formed using the results from these meta-analyses and updated with the data from the recent trial [11] using the following model:

$$r \sim Binomial(p, n)$$
$$p \sim Beta(alpha, beta)$$

Where, r is the number of events, n is the sample size of the trial, and p is the probability of the event that has a prior that follows a beta distribution where *alpha* and *beta* are computed to approximate the posterior from the meta-analysis of the previous evidence.

The WinBUGS synthesis was conducted with 20,000 burn-in iterations, followed by a further 20,000 iterations for each probability. Before 1991 there was no formal data on the use of absorbable pins; therefore, the probabilities are assumed to be the same as those for metallic, although some assumptions are applied with respect to its effect on the risk of fracture and infection. To incorporate those assumptions, we applied odd ratios (OR) to ensure that the probabilities lay between zero and one. The following formula was used:

$$P_{New} = \frac{OR \cdot \frac{P_{Base}}{1 - P_{Base}}}{1 + OR \cdot \frac{P_{Base}}{1 - P_{Base}}} \qquad (1)$$

where P_{Base} is the probability for the metallic device, OR is the odds ratio, and P_{New} is the probability when using absorbable pins.

Table 1. Probabilities (standard error), Cost data and Quality of Life data

	GATE 1 (… -1987)		GATE 2 (1988-1990)		GATE 3 (1991-1994)		GATE 4 (1995 - …)		Distrib.
	METAL	SUTUR	METAL	SUTUR	METAL	ABSOR	METAL	ABSOR	
Probabilities									**Beta**
Revision	0.055[a] (0.049)	0.025[b] (0.005)	0.041[c] (0.013)	0.034[d] (0.006)	0.025[e] (0.014)	0.014[f] (0.07)			
Other complications							0.518[¶] (0.108)	0.417[¶] (0.081)	
Fracture	0.010[g] (0.005)	0.032[h] (0.083)	0.010[i] (0.005)	0.032[j] (0.083)	0.004[k] (0.002)	0.005[l] (0.005)			
Avasc Necro	0.015[m] (0.004)	0.006[n] (0.002)	0.015[o] (0.004)	0.006[p] (0.002)	0.015[q] (0.004)	0.003[r] (0.03)			
Infection	0.044[s] (0.081)	0.025[t] (0.018)	0.044[u] (0.081)	0.025[v] (0.018)	0.030[w] (0.015)	0.008[x] (0.005)			
Foreign-body reaction				0.065[y] (0.031)		0.034[z] (0.013)			
Irritation					0.107[aa] (0.014)				
Reoccurrence	0.082[ab] (0.074)	0.093[ac] (0.037)	0.081[ad] (0.040)	0.096[ae] (0.030)	0.081[af] (0.040)	0.085[ag] (0.031)	0.176[¶] (0.092)	0.095[¶] (0.064)	
Removal	1	0.02 (0.02)	1	0.02 (0.02)	1	0	0.177 (0.090)	0	
Costs									**Gamma**
Procedure[ah]	£889		£1,039		£1383		£1543		
Complications[ai]	£49		£57		£76		£84		
Revision[aj]	£464		£542		£722		£805		
Removal[aj]	£464		£542		£722		£805		
Absorbable pins[ak]	£63		£74		£98		£140		
Metallic/sutures[al]	£4		£4		£6		£7		
Reoccurrence[am]	-		-		-		£74		
Quality of life									**Beta**
Successful surgery	0.981[an]		0.981[an]		0.986[ao]		0.929[ap]		
Reoccurrence	0.916[an]		0.916[an]		0.956[ao]		0.907[ap]		
Impact on QoL OR decrement	0.474[aq] (0.567)		0.474[aq] (0.567)		0.474[aq] (0.567)		1 (0.567)		**Log-normal**

Notes:

METAL: metallic fixation; SUTUR: sutures; ABSORB: absorbable pins; Distrib.: parameter distributions; Avasc Necro: Avascular necrosis; QoL: quality of life; OR: Odd ratio

Sources (Appendix 1):

a. [1,2,3], b. [4,5,6,7], c. [1,2,3,8,9,10], d. [4,5,6,7,10], e. [1, 2, 3, 8, 9, 10, 11, 12], f. [13, 14, 11, 15, 16, 17], g. i. [19], h. j. [18,19,7], k. [19, 11, 12], l. [13,20,14,17], m. o. q. [21,22,1,19,2,23], n. p. [4,24,19,25,2,5,22,1], r. [13,26,15], s. u. [3,2,19], t. v. [4,18,24,27,19,2], w. [3,2,19,28,12], x. [13,20,16,17], y. [29], z [29,13,26,20,30,16], aa. [12], ab. af. [31,32,22,1,19,33,3], ac. [4,18,34,24,19,25], ad. [31,32,22,1,19,33,3,8,9,10], ae. [4,18,34,24,19,25,10], ag. [13,14,15,17], ¶. [previuos data form prior distribution which update 35].

ah. NHS reference cost, minor foot procedure for non trauma category 2 without CC, ai. NHS reference cost, minor foot procedure for non trauma category 2 with CC - NHS reference cost, minor foot procedure for non trauma category 2 without CC, aj. NHS reference cost, minor foot procedure for non trauma category 2 without CC, day case; ak. Industry; al. [36]; am [37]

an. [2], ao, [38], ap[37], aq expert opinion based on a QALY weight of 0.90 for metallic pins and 0.95 for absorbable pins.

2.3.2 Costs

Cost data were taken from the NHS Reference Cost 2006-2007 [12] and deflated to the year of interest (see Table 1). This dataset was not yet developed at the earlier years of the analyses; however, as the aim of this case study is to illustrate the methodology that one would use to assess cost-effectiveness of technologies now being developed and the data is now routinely available, it is used in each stage of the analysis. Cost of absorbable devices

was taken as informed by the company (Johnson & Johnson, Orthopaedics, Bracknell). We could not find contemporaneous published data on the cost of standard fixation methods at the early years of the analysis. However, the company is likely to have or to be able to obtain relatively easily information regarding the cost of the standard technology being used. This was reported in one study published in 1997 [13] for metallic pins, and it was deflated to the year of interest and assumed to be the same for suture fixation devices. The 12-month cost for individuals with hallux valgus receiving no treatment or conventional treatment was reported in a study in 2001 [14], and it is included in the analysis as the cost of reoccurrence of the condition. This information is less likely to be available at the early stage of the development, and therefore, it was only included in the late-stage analysis. Gamma distributions were applied to all cost estimates in the probabilistic sensitivity analysis, with their standard error equal to the point estimate.

2.3.3 Quality of life

Quality of life data is also reported in Table 1. Before 1991, there was no data on health related quality of life relative to hallux valgus, but estimates of pain and functioning were reported before and after the surgery [15] and we mapped these to QALYs using SF-6D valuations (see Table 2). We apply the estimated QALY weight before the surgery to individuals for whom the condition reoccurs after the surgical intervention. When propagating the uncertainty, the proportion of individuals in different pain and functioning categories was computed using a dirichlet distribution. The believed impact of the new technology on quality of life was elicited from a group of manufacturers to inform early analyses. Based on a reported QALY weight of 0.90 for metallic pins and 0.95 following successful surgery after using an absorbable device, the quality of life decrement OR (difference from perfect health) was estimated to be 0.474. A log normal distribution was applied in the probabilistic analysis for this parameter.

Table 2. Data used to estimated QALY weights prior to 1991

	None		Mild Pain, No Functional Limitation		Moderate Pain, Occasional Functional Limitation		Severe Pain, Frequent Functional Limitation		Distrib
Proportions	Pre	Post	Pre	Post	Pre	Post	Pre	Post	**Dirichlet**
	0.01	0.67	0.03	0.25	0.75	0.07	0.20	0.01	
SF-6D* description	Constant only		PAIN2		PAIN3, PF2		PAIN4, PF3, RL2		
QALY valuation	1		0.953		0.922		0.88		

Note:

Pre: Preoperative; Post: Postoperative; Distrib: Parameter distribution.

* Only pain (PAIN), physical functioning (PF) and role limitations (RL) were considered relevant to hallux valgus (excludes social functioning, mental health and vitality).

3.4 Results

3.4.1 Early analysis

The use of absorbable materials for suturing and fracture fixation has been under investigation since the early 1960 and commercially available since 1970 [16]. Before 1987, there is evidence of its successful use in malleolar fractures [17, 18], and some promising results in distal femoral osteotomies in trials with rabbits [19]. However, no clinical evidence for its use in hallux valgus operations has been reported.

In the absence of such data, the first analysis, based on the available evidence before 1987, concerns the current technology that the new device aims to substitute for or compete with, and expert opinion and assumptions regarding the impact of the new device on cost and effectiveness. We analyse the data available for metallic fixation and compare it with the believed effect of absorbable pins. The probabilities of complications using a metallic device are reported in the second column in Table 1.

It was assumed that absorbable devices would reduce the probability of stress fracture and wound infection by half as compared with metallic devices, and that they would completely avoid the need for removal surgery. This leads to a cost saving of £465 per procedure compared with metallic devices. Expert opinion on the quality of life of individuals following successful surgery was sought to estimate the difference between metallic and absorbable fixation from a group of manufacturers with experience with the standard and with the innovative devices. The quality of life impact was estimated from a QALY weight of 0.90 for metallic pins to 0.95 for absorbable pins, possibly due to increased stability which decreases the risk of displacement and subsequent metatarsalgia (pain), which is assumed to last for the lifetime of the patient.

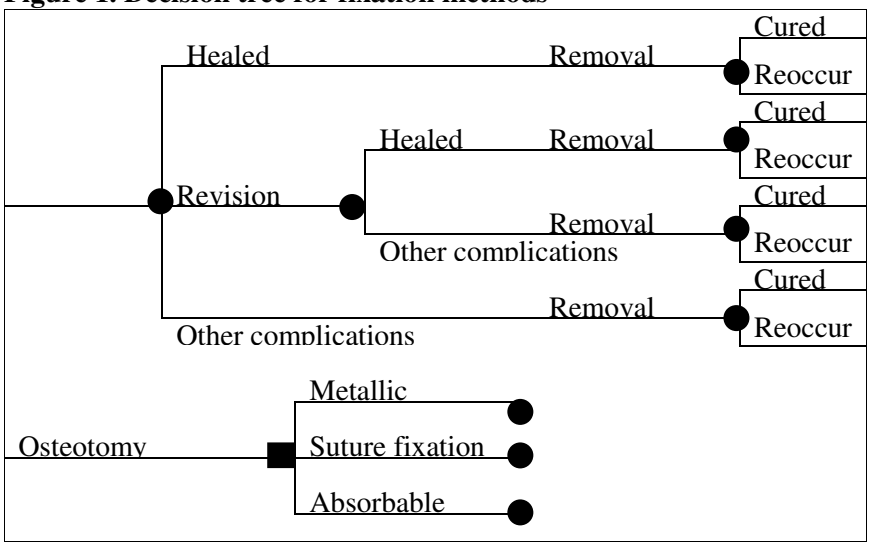
Therefore, this provides an estimate of the incremental QALY of: (0.95-0.90) = 0.05 per year; which considering the £20,000 potential threshold is translated into: £20,000 * 0.05 = £1,000 per year. Individuals in the studies reviewed are mainly female (around 90%) and the mean age is 40. Considering a life expectancy of 38 years and discounted at 3.5%, the expected benefit is £20,841 when assuming that the effect lasts the remaining life expectancy of the individuals.

This sort of analysis would inform a company in an early stage of development that if absorbable pins were to have the effect on quality of life believed by experts then they would be cost-effective if the incremental price of the device was up to £21,306. Once the company has worked out the potential cost of the new technology, this can help to prioritise in order to avoid proceeding with products that will never be more than marginally cost-effective. In the case of absorbable fixation devices, the headroom estimate is far higher than the expected incremental price of the technology, and therefore the company, based on this estimation, would decide to proceed at least in terms of the cost-effectiveness of the product.

3.4.2 Mid-analysis

At this stage, we synthesised the data available in a decision-analytic model that takes the form of a decision tree. The model structure is presented in Figure 1. For each method of fixation, the tree represents the pathways that the patients may follow. After the surgery, a patient undergoing an osteotomy may heal with no complications, need revision surgery, or suffer other type of complications, such as fracture, infection, avascular necrosis, etc., which do not require a new surgical procedure. Once the patient is healed, and depending on the type of fixation, there is a probability of needing removal surgery of the fixation device, after which the condition can be satisfactorily cured, or it may reoccur.

Figure 1. Decision tree for fixation methods



We populate this model with the data available in 1987, 1990, and in 1994 (i.e. gates 1, 2, and 3). Therefore, we rerun in a more formal analysis the evaluation undertaken at gate 1 in the early stage analysis. The assumptions in the model include the following ones: in gate 1 and 2, there is no trial data on absorbable pins and therefore, the probabilities of events are assumed to be the same as after metallic fixation, with the exception of the rates of fracture and infection which are assumed to be half of those (by applying ORs to those probabilities using formula (1)). We assume all metallic devices need to be removed (which corresponds to what is reported in the early literature), while only 2% of suture and absorbable devices require removal surgery. In the model, the impact of absorbable pins on the quality of life estimates is included as a decrement OR (difference from perfect health) and applied to the QALY weight of the cured state when absorbable devices are used. QALYs are computed for a life expectancy of 38 years and discounted at 3.5%.

In 1995, a number of observational studies provide evidence of the prognosis of patients treated surgically for hallux valgus with absorbable devices, and therefore this data is

now applied in the decision tree. However, the use of sutures as a fixation method is no longer reported; therefore absorbable pins are only compared with metallic fixation. Also new information regarding the QALY weights for individuals undergoing chiropody interventions is available [20], and is included in the model.

The deterministic results for each gate are shown in Table 3. We report the estimated expected cost and expected QALY for each strategy and the incremental cost-effectiveness ratio (ICER) which tells us the cost per QALY of two competing strategies. The use of absorbable pins leads to better expected health outcomes as compared with both sutures and metallic fixation, and the overall expected cost is lower than the expected cost after metallic fixation, and slightly more expensive than using sutures. The incremental cost-effectiveness ratios (ICER) when compared with suture fixation are £356 in 1987, and 1990 respectively, while absorbable devices are found to dominate metallic fixation methods.

Table 3. Deterministic results at Gate 1, Gate 2 and Gate 3

	GATE 1 (… -1987)		GATE 2 (1988-1990)		GATE 3 (1991-1994)	
Strategy	Cost	QALYs	Cost	QALYs	Cost	QALYs
Sutures	£917	20.32	£1,075	20.32	-	-
Metallic	£1,386	20.33	£1,610	20.33	£2,141	20.49
Absorbable	£989	20.52	£1,148	20.52	£1,494	20.64
ICERs:						
Absorbable vs Metallic	(Dominates)		(Dominates)		(Dominates)	
Absorbable vs Sutures	£356		£356		-	

In the one-way sensitivity analyses, the parameters for absorbable pins were varied using the ranges reported in Table 4. Only changes in the probability of recurrence and in the impact on quality of life were found to have a meaningful impact on the model outcome. Absorbable pins would not longer dominate metallic fixation if their probability of reoccurrence were 21% (compared with base values of 8.2% and 8.1% in gate 1 and gate 2, respectively), but they would still be considered to be cost-effective as compared with metallic devices since the cost per QALY is always lower than the recommended threshold of £20-30k. However, suture fixation could then be regarded as the most cost-effective strategy, with a cost per QALY for absorbable pins higher than £20k. In gate 3, absorbable pins would not longer dominate metallic fixation at a probability of recurrence of 27% (compared with based value of 8.5%). As regard to the impact of changes of the effect on quality of life, only in the case that absorbable pins were to have a lower impact on the QALY weight as compared with the standard methods (represented by an decrement OR higher than 1 compared with the base value of 0.474), will sutures be the most cost-effective method in gate 1 and gate 2. Absorbable devices would not longer dominate metallic fixation if both were to have the same impact on quality of life (OR =1). The probability of removal of the absorbable

pins would only have a small impact in the extreme case than over 85% of the devices needed to be removed, as compared with 2% assumed in gate 1 and gate 2, and 0% reported in gate 3.

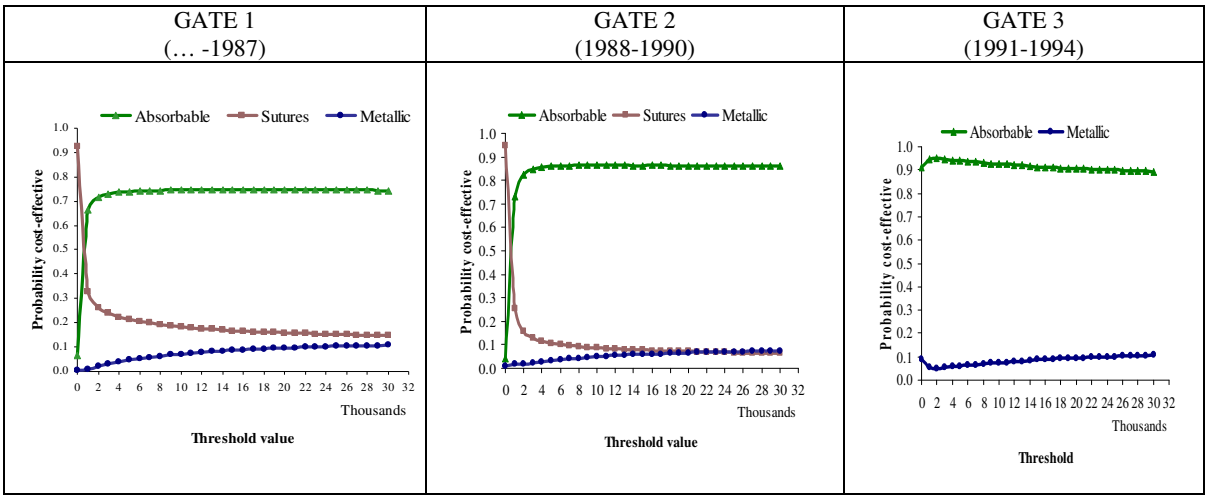
Table 4: Break even points as estimated from the one -way sensitivity analyses

One–way sensitivity analysis	Range	Metallic (break even so absorbable do not dominate metallic)			Sutures (break-even absorbable cost per QALY >£20,000)	
Absorbable pins		Gate 1	Gate 2	Gate 3	Gate 1	Gate 2
Probability reoccurrence	0-1	21%	21%	27%	21%	21%
Probability revision	0-1	NA	NA	NA	NA	NA
Probability complications	0-1	NA	NA	NA	NA	NA
Probability removal	0-1	85%	85%	89%	NA	NA
Decrement OR	0-2	1	1	1.03	1.05	1.05
QALY cured	0.7-1	NA	NA	NA	NA	NA
QALY reoccurrence	0.7-1	NA	NA	NA	NA	NA
Cost absorbable	£0-£300	NA	NA	NA	NA	NA
Cost revision	£0-£1000	NA	NA	NA	NA	NA
Cost removal	£0-£1000	NA	NA	NA	NA	NA
Cost Complications	£0-£200	NA	NA	NA	NA	NA

* NA = Not applicable, indicating no break even point is reached within the test range

The probability that absorbable pins are the most cost-effective strategy is increasing over the three evaluation times, as the cost-effectiveness acceptability curves (CEAC) show in Figure 2. In 1987, considering a willingness to pay per QALY higher than £1,000, the fixation method more likely to be the optimal is the absorbable device, with a probability of over 70% which is quite stable among the range of potential thresholds. This probability increases to over 85%, and to around 90% in the next evaluations in 1990 and 1994. These high probabilities of success in terms of cost-effectiveness should encourage the company to continue with the device at each of the three decision gates.

Figure 2. Cost-effectiveness acceptability curves at Gate 1, Gate 2 and Gate 3.



3.4.3 Late analysis

We use the data from a small RCT of fixation methods where patients undergoing osteotomy to treat hallux valgus were allocated to a treatment group (Orthosorb absorbable pins) or to a control group (using standard techniques, i.e. bone suture or k wire fixation) [11]. Since both standard methods were combined in the trial, the comparison at this stage is absorbable pins against standard fixation methods (both sutures and metallic devices). The number of interventions in the study was 39, where seventeen osteotomies were stabilised with standard fixation, and 22 were fixated with absorbable pins. They found no significant differences between the two groups in any of the preoperative and postoperative radiological and clinical measures including pain, metatarsalgia, walking ability, shoewear choice and cosmetic appearance. Therefore, the impact on quality of life assumed in earlier analyses is no longer included in the model. The small sample of the trial prevented statistical analyses of the complications rates between the two groups. We used the data collected from the earlier analyses to form prior distribution of the recurrence risk and other complications, and update those with the data from the trial. The removal probability after standard fixation methods reported in this study is much lower than in the early literature, probably due to technology changes, and consistent with what is also reported in by Calder et al., 1999 [21] that compared suture and screw fixation in osteotomy and found that just 13% of the patients required removal of the screw fixation device. A study published in 2001 [14] provide estimates of 12-month costs for patients with hallux valgus receiving conservative treatment (orthosis) or not treatment, which on average was £74. We use this estimate for the cost of patients for which the condition reoccurs after the surgery (previously assumed to be zero). Also in this study, the health related quality of life index for individuals undergoing hallux valgus surgery was measured before and after the intervention, and those were applied to the reoccurrence and cured states, respectively.

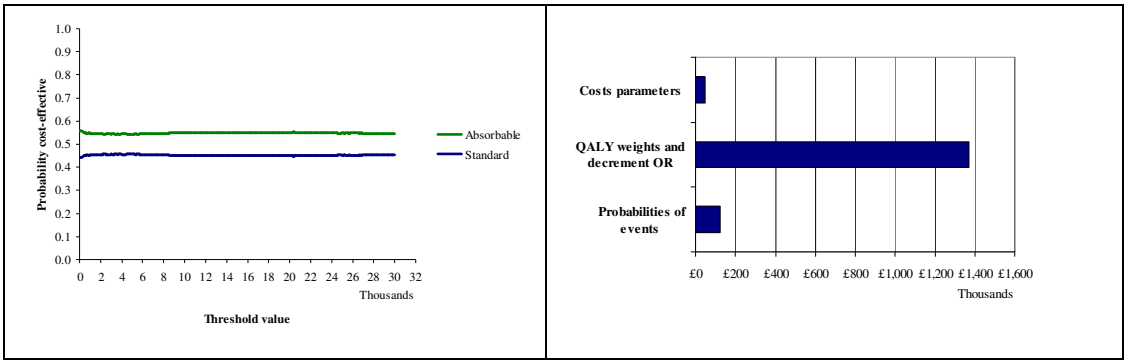
The results are presented in Table 5. Absorbable pins do not dominate the standard fixation methods since they are slightly more expensive, although they result in a better health outcome. The ICER is £283, which represents a cost per QALY much lower to what decision makers are typically willing to pay.

Table 5. Deterministic results at Gate 4

	GATE 4 (1995 - …)	
Strategy	Cost	QALYs
Standard	£1,688	19.30
Absorbable	£1,694	19.32
ICERs:		
Absorbable vs Standard	£283	

The CEAC at this stage are presented in Figure 3. The method of fixation most likely of being cost-effective is, at any threshold value, absorbable pins with a probability of just above 55%. The population-EVPI for different set of parameters (cost parameters, QALY weights and impact on quality of life, and probabilities of each event) show that the information with greatest value is related with the QALY weights and impact on QoL, while, the value of additional research on probabilities of events is relatively low, and more information to reduce uncertainty in the cost parameters has little value.

Figure 3. Cost-effective Acceptability curves (CEAC) and population Expected Value of Perfect Partial Information (EVPPI) at Gate 4.



4. Discussion

We have applied the iterative Bayesian approach to early assessment of cost-effectiveness of a medical device during its development process, evaluating the potential cost-effectiveness of the device at four different decision points.

Starting with simple methods such as the effectiveness gap analysis or headroom estimate, the device appears to be cost effective based on the assumptions applied and the elicited impact on quality of life from experts. Synthesising the evidence into a decision model we found that, 1) absorbable devices were the most cost-effective strategy in osteotomy, 2) the parameters with largest impact on model outcomes are the probability of reoccurrence and the impact on QoL, and 3) the PSA shows a large probability (between 70%-90% in the first 3 gates of analysis) of the device being cost-effective after accounting for all the parameters uncertainty. At the late stage analysis, previously collected data are used to form prior distribution of some parameters that are updated with the evidence from a RCT. Absorbable devices appears to be cost-effective, although the probability after addressing uncertainty is lowered to just above 55%. The VOI analysis shows that the parameters with highest value are those related to the QALY weights and the impact of absorbable pins on QoL.

This analysis has involved the use of assumptions and beliefs about the potential effect of the technology elicited from a group of experts, synthesising evidence from a

number of different sources, identifying the parameters with largest impact on model outcome, addressing the overall parameter uncertainty, and exploring the value of additional research for separated set of parameters. We now move to discuss some of the difficulties or limitations of each of these methods highlighted in this study.

Given the retrospective nature of the analysis, the elicitation and application of assumptions for early stages of the evaluation is the weakest part of this study. The results show that the believed impact on QoL elicited, and the assumptions applied to the probabilities of complication rates were too optimistic, as compared with the data later available. This optimism may be a common occurrence in the early evaluations. Therefore, these assumptions are dropped at later stages when evidence became available, and although the outcome of the model is the same, the probability that the product is cost-effective becomes considerably lower. This limitation could be overcome in a context were the analysis is undertaken prospectively, and therefore good quality prior information can be elicited for the parameters for which there is no evidence. Although those are non-trivial methods, there is growing body of research on how to elicit expert's knowledge accurately and reliably [22].

The Bayesian methods for evidence synthesis have been argued to provide a number of advantages over traditional methods [8]. We opted in our models for Bayesian random-effect meta-analyses with uninformative priors to combine the observational evidence available at each of the first 3 gates. This involves making a number of decisions relating to the initial values used in the simulation, and also relating to the prior distribution of the between-studies variability parameter, to which the results can be sensitive to. We tried to address the first issue by choosing ourselves the initial values rather than allowing WinBUGS to do so, exploring the differences of selecting extreme different values, and running the simulation during a long number of iterations. It also worth noting that WinBUGS is not currently very user-friendly, which could impose restrictions in the practicality of this approach. The development of simple yet robust software is needed if these methods are to be extended to wider groups of users.

Although one-way sensitivity analyses have been criticised for not being able to account for the overall uncertainty that results from the combined variability of several parameters, we believe that they can be as helpful to provide a good indication of the parameters with largest impact on model outcomes as relatively more sophisticated methods. The reason is that at early stages of evaluation one is more likely to have a fairly better idea of reasonable ranges for the value of parameters, rather than being able to apply probability distributions to parameters for which evidence may still not be available. This brings us to the complication of running probabilistic sensitivity analysis at early stages, given that they are quite demanding in terms of data and also in terms of the expertise and time required to conduct them. The appropriate probability distributions to represent uncertainty is typically

given by the type of parameter being consider such as costs, utilities, probabilities and ORs [23]. Although those may be quite straightforward to apply, difficulties may come when the parameters are not independent of each other, or where heterogeneity between group of patients needs to be explored. Nevertheless, characterising overall uncertainty in a model where uncertainty is likely to play an important role is critical. Also, being able to express that uncertainty on a straightforward message such as the overall probability of reimbursement as based on the cost-effectiveness of the product, have a great value to support the investment decisions of whether or not to proceed with the new technology. However, this contributions will always depend on how well specified the probabilistic analysis is.

Finally, value-of-information analyses are increasingly being used to answer the question of whether or not to fund additional research to reduce uncertainty relating the reimbursement decision. As we already mentioned, this standard VOI analysis takes a social perspective and has therefore little relevance in a commercial setting. Ideally, in this context, the methodology of VOI analysis could be adapted to inform the value to a company of conducting further research internally to reduce uncertainty, and therefore to reduce the cost of making a wrong investment decision. In this case the wrong decision would be to abandon (proceed with) the product when the eventual reimbursement decision is (not) to reimburse it. More work needs to be done to account for this commercial perspective in this context.

5. Conclusions

Iterative economic evaluation can inform investment decision within the development of a new product in order to anticipate the eventual reimbursement decision, and avoid investing in technologies that could never be cost effective. The most influential parameters affecting the outcome of the decision can be identified from these early stages in order to direct research resources, and the uncertainty of the decision can be explored. By gradually increasing the complexity of the techniques employed in the evaluation, we assure that the methods undertaken at each stage take into account the availability of data and resources, both in terms of time and money, that characterise each development phase.

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