

# Integrating Health Economics Into the Product Development Cycle: A Case Study of Absorbable Pins for Treating Hallux Valgus

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**Background.** The probability of reimbursement is a key factor in determining whether to proceed with or abandon a product during its development. The purpose of this article is to illustrate how the methods of iterative Bayesian economic evaluation proposed in the literature can be incorporated into the development process of new medical devices, adapting them to face the relative scarcity of data and time that characterizes the process. **Methods.** A 3-stage economic evaluation was applied: an early phase in which simple methods allow for a quick prioritization of competing products; a mid-stage in which developers synthesize the data into a decision model, identify the parameters for which more information is most valuable, and explore uncertainty; and a late stage, in which all relevant information is synthesized. A retrospective analysis was conducted of the case study of absorbable pins, compared with metallic

fixation, in 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 high probability. Late-stage analysis synthesizes evidence from a randomized controlled trial and informative priors, which are based on previous evidence. It also suggests that absorbable pins are the most cost-effective strategy, although the uncertainty in the model output increased considerably. **Conclusions.** This example illustrates how the method proposed allows decisions in the product development cycle to be based on the best knowledge that is available at each stage. **Key words:** cost utility analysis; evidence synthesis; Bayesian meta-analysis; priority setting for spending; orthopedics. (*Med Decis Making* 2011;31:596–610)

Some health care systems such as the National Health Service (NHS) in the United Kingdom increasingly make reimbursement decisions based

on both clinical and cost-effectiveness evidence of new therapies compared with standard care or alternative technologies. To this end, guidelines for technology appraisals have been developed by the National Institute for Health and Clinical Excellence (NICE).<sup>1</sup> In recognition of the inevitable uncertainty surrounding the measurement of costs and effectiveness of different strategies, the guidelines emphasize the use of methods that quantify the implications of parameter and methodological uncertainty for the results as well as methods that assess the value of conducting further research to reduce the uncertainty relating to the reimbursement decision. Therefore, methods such as probabilistic sensitivity analysis (PSA) and value-of-information (VOI) analyses are now increasingly incorporated into economic evaluations.

Recently, the potential value and practicality of incorporating Bayesian methods into the iterative framework of health technology assessment (HTA)

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have been described.<sup>2</sup> This builds 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.<sup>3</sup> The Bayesian approach is ideal for this since it facilitates combining prior information with more recent data to inform whether the technology appears cost-effective after all available information has been incorporated.

The iterative Bayesian approach to HTA can also be applied within the commercial or government-funded development of new products. The development cycle of new technologies often takes the form of a staged-decision making process that is regularly reviewed and in which decisions of whether to proceed with the innovation are made at several different time points.<sup>4</sup> Incorporating economic evaluations into such a stage-gated decision process from very early stages of the development could support internal investment decisions in order to prioritize potential products or prototypes to take forward and may 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 brought to market, formal analysis that aims to identify the parameters with the largest impact on the likely cost-effectiveness could direct internal research resources more efficiently.

In many cases data are scarce and the time to perform the analysis is likely to be short, particularly in the medical device industry, compared with those late-stage public sector evaluations for which the iterative Bayesian approach has been illustrated.<sup>2</sup> At early stages, a potentially large number of products in competing lines of development would need to be evaluated. Therefore, the methods need to be adapted to avoid undue delay in the innovative development process. To address these issues we propose starting with relatively simple economic evaluations at the very early stages that would provide a rapid indication of potential cost-effectiveness and then increasing the depth of analysis in later stages as more information becomes available and attention is centered on fewer products. The principal aim of the approach is to ensure that early-stage evaluations can be internally undertaken within the resources of even small medical device firms. This is not, however, intended to be a substitute for more sophisticated modeling where that is practical but it is intended as a way to ensure that informed decisions are made in all situations.

To illustrate the approach, we applied this method retrospectively to the case study of absorbable pins in osteotomy to treat hallux valgus. We evaluate what was known about the cost-effectiveness of this

fixation device compared with standard fixation methods from a very early stage of the development of the device, iteratively incorporating further information as it became available at later stages. At each step of the evaluation we explore the uncertainty of the decision and the parameters for which the model outcome is most sensitive.

The case study was based on the use of absorbable pins in the treatment of hallux valgus. Hallux valgus is defined as a deviation of the big toe (hallux) toward the midline of the foot. When the condition is first diagnosed, conservative treatment such as orthosis, night splints, or foot exercise may be attempted. Alternatively, surgical procedures are used 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, where the bone is divided surgically and repositioned. There are different methods to stabilize the osteotomy while the bone unites: bone suture, internal metallic fixation, and a more recent method, absorbable pins.

## METHODS

To illustrate the approach, we consider the case of a company that was developing an absorbable device and planning to sell it for use in osteotomies to treat hallux valgus (Orthosorb; Johnson & Johnson, New Brunswick, New Jersey). 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 a comparison with similar products; gate 2, in 1990 a competitor product entered the market; gate 3, the product received CE-Mark approval in 1995 (CE stands for *Conformité Européenne* and certifies that a product has met EU consumer safety, health, or environmental requirements); gate 4, from 1995, a series of postmarketing studies were conducted.

We apply a previously published<sup>5</sup> 3-stage economic evaluation approach as summarized in Figure 1. At each gate, economic evaluations are carried out using the information available at that time. A literature search was undertaken for each time period, and the articles identified for each analysis are reported in the appendix. The evaluation methods used vary in their complexity and the time required to conduct them, and different types of economic evaluation methods could be used at the same point in time to evaluate the product if needed. Early-stage analysis is conducted using the information prior to 1987 (gate 1). Subject to the results from the analysis a company

	Gates	Data	Methods
Early-stage	Gate 1 (... -1987)	Observational data on standard methods + assumptions	Headroom/Effectiveness gap method
Mid-stage	Gate 1 (... -1987) Gate 2 (1988-1990) Gate 3 (1991-1995)	Observational data on standard methods & absorbable pins + assumptions	Decision model (deterministic and probabilistic) + one-way SA
Late-stage	Gate 4 (1996 -...)	RCT + observational data on standard methods and absorbable pins	Decision model (deterministic and probabilistic) + VOI analysis

Note: RCT: Randomised Control trial; SA: Sensitivity Analysis; VOI: Value of Information

Figure 1 Stage-gates for iterative analysis of cost-effectiveness of absorbable pins.

could decide to proceed with the device and undertake a more formal evaluation. Therefore, mid-stage analyses that synthesize the data into a decision model are also conducted at gate 1. Such a model provides an ideal framework to update the results when new evidence becomes available in 1990 and 1995 (gate 2 and 3). At the late-stage analysis applied post 1995 (gate 4), the information collected previously is used to form prior distributions of parameters that are then updated with the findings from a randomized controlled trial (RCT) available at this stage.

Uncertainty is explored at the mid- and late-stage analyses. In the mid-stage analyses, all parameters were subjected to 1-way sensitivity analyses applying wide test ranges. In the decision-analytic models, PSA is undertaken by applying probability distributions to each parameter of the model and running 5000 iterations in the simulation. For completeness, value of information analyses are presented at each gate, although they are most relevant at the late-stage evaluation, which is aimed at informing external decision makers concerned with the societal perspective that underpins the VOI approach. In these analyses, the expected value of perfect information is calculated by estimating the number of operations in the United Kingdom over an assumed lifetime of the technology of 5 years, herewith accounting for the relatively short lifetime of medical devices compared with drugs or other medical technologies.

### Early-Stage Analysis

A company or government agency would conduct this analysis at the phase in the development when the product may still be just an idea or a concept and when a potentially large number of alternative technology developments are competing for research and

development resources. At this stage similar analyses would be undertaken for other products in competing lines of development. These analyses would be conducted under optimistic assumptions, making the tool quite sensitive for the detection of worthwhile ideas. However, these analyses can only be considered as indicative as they do not account for uncertainty. Recent work has focused on extending these methods to allow for uncertainty in early-stage valuations.<sup>6</sup>

### Methods

The first step is to identify the potential areas of improvement that the new device will have over the current technology (in terms of both cost savings and increased effectiveness) and estimate its monetary value. In the absence of data about the new technology, the analysis is based on the evidence concerning the current technology that the new product aims to substitute or will compete with, plus expert opinion and/or assumptions regarding the impact on cost and effectiveness of the new technology. The data are then analyzed using simple techniques based on the "effectiveness gap,"<sup>7</sup> which estimates the extent to which current practice is less than totally effective, or the "headroom method,"<sup>8</sup> which is based on the maximum additional cost of the new treatment over the comparator that has been proposed to establish a price ceiling. These methods will therefore provide bounds on the maximum reimbursable price that will then be compared with the expected cost of the device at this stage.

### Data

Before 1987, there was evidence of the successful use of synthetic absorbable materials for suturing and fracture fixation in malleolar fractures<sup>9,10</sup> and some promising results in distal femoral osteotomies in trials with rabbits.<sup>11</sup> However, no clinical evidence for its use in hallux valgus operations had yet

**Table 1** Early-Stage Analysis: Data and Result

	Metallic	Absorbable
Probability of		
Removal	1.0 <sup>a</sup>	0.0 <sup>a</sup>
Fracture	0.010 <sup>b</sup>	0.005 <sup>a</sup>
Infection	0.044 <sup>c</sup>	0.022 <sup>a</sup>
Cost of		
Removal	£464 <sup>e</sup>	
Fracture	£49 <sup>f</sup>	
Infection	£49 <sup>f</sup>	
Cost saving	£465	
Elicited quality of life	0.90 <sup>d</sup>	0.95 <sup>d</sup>
Overall headroom estimate	£21 306	

Sources (Bayesian random-effect meta-analysis, when more than 1 source of data, from articles reported in the appendix)

- a. Assumption: All metallic pins need removal, and the risks of fracture and infection after absorbable fixation are assumed to be half of those when using metallic pin.
- b. [9].
- c. [2,3,9].
- d. Expert opinion.
- e. National Health Service (NHS) reference cost, minor foot procedure for nontrauma category 2 without complications and comorbidities (CC).
- f. NHS reference cost, minor foot procedure for nontrauma category 2 with CC—NHS reference cost, minor foot procedure for nontrauma category 2 without CC.

been reported. Therefore, the evaluation at this stage is based on the data available on metallic devices and expert opinion and assumptions regarding the impact of the new device on cost and effectiveness.

**Probabilities.** Metallic fixation with a screw or percutaneous K-wire often requires removal at a later date and also carries a risk of refracture and infection. Theoretically, absorbable pins obviate removal surgery because they decompose gradually and the stress is transferred gradually to the healing tissue. It was thus assumed that absorbable devices would reduce the probability of stress fracture and wound infection by half compared with metallic devices and that they would completely avoid the need for removal surgery. The probabilities of these events after a metallic fixation were taken from the literature and are reported in Table 1.

**Costs.** Early-stage cost data reported in UK pounds (Table 1) were taken from the NHS Reference Cost 2006–2007<sup>12</sup> and deflated to 1987 (this data set had not been developed in the earlier years of the analyses; however, as the aim of this case study is to illustrate the method 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).

**Quality of life.** The predicted impact of the new technology on quality of life (QoL) was elicited from a group of manufacturers with experience with the standard and with the innovative devices to inform early analyses. This was a fairly crude elicitation exercise where a group of experts (n = 5) were asked to estimate the mean, minimum, and maximum quality-adjusted life year (QALY) weight (scale 0–1) for each strategy (i.e., absorbable pins and standard fixation). Given the retrospective nature of our analysis, these views represent the expectations of manufacturers at the time of development.

**Results**

Table 1 presents the results for the early-stage analysis. The assumptions applied on the risks of refracture, infection, and removal led to a cost saving of £465 per procedure compared with metallic devices. The elicited estimates of the QALY weights after treatment were 0.90 for metallic pins and 0.95 for absorbable pins. The difference was possibly attributable to increased stability, which decreases the risk of displacement and subsequent metatarsalgia (pain) and was assumed to last for the lifetime of the patient. Therefore, this provided an estimate of the incremental QALY of (0.95 – 0.90) = 0.05 per year; which given a £20 000 per QALY potential cost-effectiveness threshold translates into £20 000 \* 0.05 = £1000 per year. Individuals in the studies reviewed were mainly female (around 90%) and the mean age was 40 years. Considering a life expectancy of 38 years and discounted at 3.5%, the expected (discounted) benefit is £20 841 assuming that the effect lasts the remaining life expectancy of the individuals. The overall headroom estimate of the maximum reimbursable price is £21 306 (£465 + £20 841).

This sort of analysis would inform a company or government agency at an early stage of development that if absorbable pins were to have the effect on QoL believed by experts, then they would be cost-effective even if the incremental price of the device was very high (up to £21 306). Once the company estimates the potential cost of the new technology, this can help to prioritize resources in order to avoid proceeding with products that will never be more than marginally cost-effective. In the case study, the headroom estimate was far higher than the expected incremental cost of the technology (even with a generous allowance for the cost of development), and therefore the company, given this estimation, may decide to proceed in terms of the cost-effectiveness of the product.



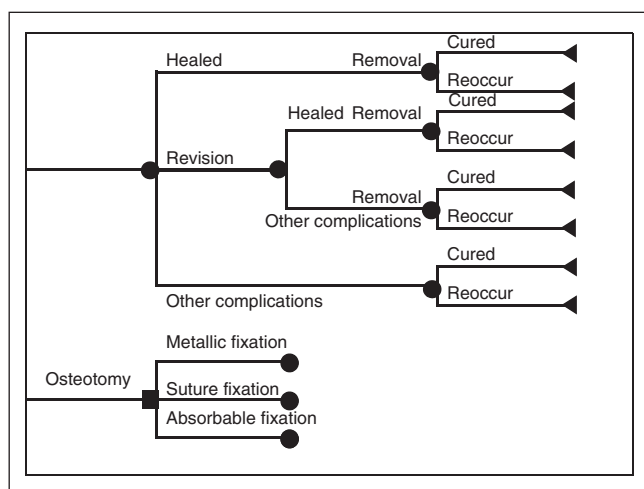


Figure 2 Simple decision tree for fixation methods.

### Mid-Stage Analysis

At a mid-stage, typically, observational studies may provide some clinical evidence of the effect of the new technology, and some initial cost estimates may be available. Under these conditions, decision-analytical modeling techniques can be applied and the uncertainty in the decision can be explored. We apply these methods to explore the decision at gate 1 (i.e., we re-run more formally the analysis previously undertaken using the early-stage techniques). This requires incorporating more information in order to populate the decision model. We then update the analysis with the information available in 1990 and 1995 (i.e., gate 2 and gate 3).

### Methods

We synthesize the data available in a decision-analytic model that takes the form of a decision tree. The model structure is presented in Figure 2. 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, may need revision surgery, or may suffer from other types of complications that do not require a new surgical procedure. Once the patient is healed, and depending on the type of fixation, some patients require surgery to remove the fixation device, after which the condition may be satisfactorily cured or may reoccur.

Two important issues are addressed at this stage: 1) synthesizing the evidence available, and 2) exploring the uncertainty around the parameters in the model in order to find the inputs with the largest

impact on the model outcome. Synthesizing the evidence available may require combining evidence from multiple sources of data, and using formal Bayesian evidence synthesis techniques will ensure that the uncertainty is incorporated appropriately.<sup>13</sup> When pooling data we use Bayesian meta-analysis models that allow for between-study variation with vague priors for the mean and variance of the study-specific effect sizes.

To assess the second issue of identifying the key parameters affecting the cost-effectiveness, we suggest starting with simple 1-way sensitivity analysis, where each relevant parameter is varied one at a time to study its impact. These methods are easy and quick to undertake and to understand, and they provide some insight into alternative values for specific parameters that could make a meaningful impact on the model outcome and on the potential decision based upon it. However, they have been criticized for not being able to account for the overall uncertainty from the combined variability of several factors.<sup>14</sup> This uncertainty can be explored via PSA. In PSA, probability distributions are applied to the parameters and samples are randomly drawn from these distributions using simulation techniques. Results can then be represented using cost-effectiveness acceptability curves (CEACs), 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 by future potential health care purchasers. PSA results can also be used to quantify the societal cost of making the wrong decision about which technology to fund. This represents the expected value of perfect information (EVPI). In addition, the EVPI can be computed for various sets 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. This is referred to as expected value of perfect partial information (EVPPI). Note that this standard VOI analysis is related to a collective view of the value of this additional research for the society, both in terms of forgone health gain to patients and in terms of wasted resources, and therefore would not be directly relevant in a commercial context. Thus, this analysis, although conducted at each gate, is only considered relevant in the final stage, which is aimed to inform external decision makers concerned with collective welfare.

### Data

Data for the mid-stage analyses are summarized in columns 1–3 of Table 2 and Table 3.

**Table 2** Probabilities (Standard Error) for Mid-Stage and Late-Stage Analyses

	Mid-Stage Analyses					Late-Stage Analyses		
	Gate 1 (1987 and Earlier)		Gate 2 (1988–1990)		Gate 3 (1991–1995)		Gate 4 (1996 Onward)	
	META	SUTUR	META	SUTUR	META	ABSOR	STN	ABSOR
Probabilities								
Revision	0.055 <sup>a</sup> (0.049)	0.025 <sup>b</sup> (0.005)	0.041 <sup>c</sup> (0.013)	0.034 <sup>d</sup> (0.006)	0.025 <sup>e</sup> (0.014)	0.014 <sup>f</sup> (0.07)	0.518 <sup>z</sup> (0.108)	0.417 <sup>z</sup> (0.081)
Other complications								
Fracture	0.010 <sup>g</sup> (0.005)	0.032 <sup>h</sup> (0.083)	0.010 <sup>g</sup> (0.005)	0.032 <sup>h</sup> (0.083)	0.004 <sup>i</sup> (0.002)	0.005 <sup>i</sup> (0.005)		
Avascular necrosis	0.015 <sup>k</sup> (0.004)	0.006 <sup>l</sup> (0.002)	0.015 <sup>k</sup> (0.004)	0.006 <sup>l</sup> (0.002)	0.015 <sup>k</sup> (0.004)	0.003 <sup>m</sup> (0.03)		
Infection	0.044 <sup>n</sup> (0.081)	0.025 <sup>o</sup> (0.018)	0.044 <sup>n</sup> (0.081)	0.025 <sup>o</sup> (0.018)	0.030 <sup>p</sup> (0.015)	0.008 <sup>q</sup> (0.005)		
Foreign-body reaction				0.065 <sup>r</sup> (0.031)		0.034 <sup>s</sup> (0.013)		
Irritation					0.107 <sup>t</sup> (0.014)			
Recurrence	0.082 <sup>u</sup> (0.074)	0.093 <sup>v</sup> (0.037)	0.081 <sup>w</sup> (0.040)	0.096 <sup>x</sup> (0.030)	0.081 <sup>u</sup> (0.040)	0.085 <sup>y</sup> (0.031)	0.176 <sup>z</sup> (0.092)	0.095 <sup>z</sup> (0.064)
Removal	1	0.02 <sup>aa</sup> (0.02)	1	0.02 <sup>aa</sup> (0.02)	1	0	0.177 <sup>z</sup> (0.090)	0

Note: ABSORB, absorbable pins; META, metallic fixation; STN, standard (i.e., both metallic pins and sutures); SUTUR, sutures.

a–z. Sources (Bayesian random-effect meta-analysis, when more than 1 source of data, from articles reported in the appendix):

- a. [1,2,3].
- b. [4,5,6,7].
- c. [1,2,3,20,21,22].
- d. [4,5,6,7,22].
- e. [1,2,3,20,21,22,24,25].
- f. [24,26,27,28,29,30].
- g. [9].
- h. [7,8,9].
- i. [9,24,25].
- j. [26,27,30,31].
- k. [1,2,9,10,11,12].
- l. [1,2,4,5,9,11,13,14].
- m. [26,28,32].
- n. [2,3,9].

aa. Assumptions: Absorbable pins are assumed to have the same probabilities in gate 1 and gate 2 than those reported for metallic devices, with the exception of the risk of fracture and infection, which are assumed to be half of those when using metallic pins. We assume all metallic devices need to be removed (in gates 1–3), whereas only 2% of sutures and absorbable devices require removal surgery (in gate 1 and gate 2).

**Table 3** Cost and Quality of Life Data for Mid-Stage and Late-Stage Analyses

	Mid-Stage Analyses			Late-Stage Analyses
	Gate 1 (1987 and Earlier)	Gate 2 (1988–1990)	Gate 3 (1991–1995)	Gate 4 (1996 Onward)
Costs				
Procedure <sup>a</sup>	£889	£1039	£1383	£1543
Complications <sup>b</sup>	£49	£57	£76	£84
Revision <sup>c</sup>	£464	£542	£722	£805
Removal <sup>c</sup>	£464	£542	£722	£805
Absorbable pins <sup>d</sup>	£63	£74	£98	£140
Metallic/sutures <sup>e</sup>	£4	£4	£6	£7
Reoccurrence <sup>f</sup>	—	—	—	£74
Quality of life				
Successful surgery	0.981 <sup>g</sup>	0.981 <sup>g</sup>	0.986 <sup>h</sup>	0.929 <sup>i</sup>
Reoccurrence	0.916 <sup>g</sup>	0.916 <sup>g</sup>	0.956 <sup>h</sup>	0.907 <sup>i</sup>
Impact on QoL OR decrement (s <sub>j</sub> )	0.474 <sup>j</sup> (0.567)	0.474 <sup>j</sup> (0.567)	0.474 <sup>j</sup> (0.567)	1 (0.567)

Sources (from articles reported in the appendix):

Note: OR, odds ratio; QoL, quality of life.

a. NHS reference cost, minor foot procedure for nontrauma category 2 without complications and comorbidities (CC).

b. NHS reference cost, minor foot procedure for nontrauma category 2 with CC—NHS reference cost, minor foot procedure for nontrauma category 2 without CC.

c. NHS reference cost, minor foot procedure for nontrauma category 2 without CC, day case.

d. Industry.

e. [37].

f. [38].

g. [2].

h. [35].

i. [38].

j. expert opinion based on a QALY weight of 0.90 for metallic pins and 0.95 for absorbable pins.

**Probabilities.** Data on the probability of any event after the surgery were taken from the literature and synthesized using WinBUGS (Windows-based Bayesian inference using Gibbs sampling). Uninformative prior distributions were used, and the data were synthesized using Bayesian random-effects meta-analyses.

Before 1991 there was no formal data on the use of absorbable pins, although data on probabilities after the use of metallic devices and sutures were available. The probabilities for absorbable devices were assumed to be the same as those for metallic, with the exception of the risk of fracture and infection, for which we applied the same assumption as in the early-stage analysis (i.e., we assumed these probabilities to be half of those when using metallic devices). To incorporate the uncertainty of those assumptions in the probabilistic analysis, we applied odd ratios (ORs) to ensure that the probabilities lay between zero and one.

In 1995, a number of observational studies provided evidence for the prognosis of patients treated surgically for hallux valgus with absorbable devices, and these data were used in the decision tree and summarized in Table 2. However, the use of sutures as a fixation method is no longer reported; therefore,

in this evaluation period, absorbable pins were only compared with metallic fixation.

We assumed that all metallic devices need to be removed (which corresponds to what is reported in the early literature, mainly because of the frequent use of percutaneous K-wires), whereas only 2% of sutures and absorbable devices require removal surgery.

**Costs.** We applied the costs from NHS reference costs data deflated to the year of interest (Table 3). The estimated cost of absorbable devices was provided by the company. We could not find contemporary published data on the cost of standard fixation methods for the early years of the analysis. Therefore, we used the price as published in 1997<sup>15</sup> for metallic pins, deflated this to the year of interest, and assumed this to be the same for suture fixation devices (in reality, however, a company is likely to have or be able to obtain information regarding the cost of the standard technology being used). Gamma distributions were applied to all cost estimates in the probabilistic sensitivity analysis, with their standard errors equal to the point estimate in the absence of further information.

**Quality of life.** Before 1991, there were no data on health-related QoL relative to hallux valgus, but

**Table 4** Data Used to Estimated Quality-Adjusted Life Year Weights Prior to 1991

	None	Mild Pain, No Functional Limitation	Moderate Pain, Occasional Functional Limitation	Severe Pain, Frequent Functional Limitation	Distrib
Proportions of patient in each category					Dirichlet
Preoperative	0.01	0.04	0.75	0.20	
Postoperative	0.67	0.25	0.07	0.01	
SF-6D <sup>a</sup> description	Constant only PAIN2		PAIN3, PF2	PAIN4, PF3, RL2	
QALY valuation	1	0.953	0.922	0.88	

Note: Distrib, parameter distribution.

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

estimates of pain and functioning were reported before and after the surgery<sup>16</sup> and we mapped these to QALYs using SF-6D valuations (see Table 4). For this purpose, the level for the pain, physical functioning, and role limitations dimensions (i.e., assumes no limitation for all other dimensions) was chosen according to the description of state, and then the utility was calculated. The severity categories were 1) no limitation, 2) mild pain and no functional limitation, 3) moderate pain and occasional functional limitation, and 4) severe pain and frequent functional limitation. The proportion of patients in each severity category was then used to estimate the overall QALY weight experience by patients before and after the surgery. We applied 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 patients in each severity category was computed using a Dirichlet distribution. At later stages, data on health-related QoL for individuals undergoing these procedures were available (see Table 3). We then applied beta distributions to the QoL weights in the probabilistic analyses.

Based on an elicited QALY weight of 0.90 for metallic pins and 0.95 following successful surgery after using an absorbable device, the QoL “decrement odds ratio” (difference from perfect health) was estimated to be 0.474 (i.e.,  $[0.05/0.95]/[0.1/0.9]$ ). We applied the formula of the decrement OR to the QALY weight of the cured state when absorbable devices are used. A log normal distribution was applied in the probabilistic analysis for this parameter. QALYs were computed for a life expectancy of 38 years and discounted at 3.5% per annum.

### Results

The deterministic results for each gate are shown in Table 5. We report the estimated expected

cost and expected QALY for each strategy and the incremental cost-effectiveness ratio (ICER) presented as comparisons of each strategy to the next less effective strategy after dominated strategies have been discarded. The use of absorbable pins led to better expected health outcomes compared with both sutures and metallic fixation, and the overall expected cost was lower than that of metallic fixation and slightly more expensive than using sutures. The ICER of absorbable pins versus suture fixation was £356 per QALY in both 1987 and 1990, whereas absorbable devices were found to dominate metallic fixation methods.

In the 1-way sensitivity analyses, the parameters for absorbable pins were varied using wide ranges that allowed the parameters to take extreme values and explore their individual effect on the cost-effectiveness results (0–1 for the probability of each event; 0–2 for the decrement OR; 0.7–1 for the QALY weights; £0–£1000 for the cost of revision and removal; £0–£300 for the cost of absorbable pins and complications). Only changes in the probability of recurrence and removal and in the impact of absorbable pins on QoL were found to have a meaningful impact on the model outcome; these are presented in Table 6. Absorbable pins no longer dominate but were still considered more cost-effective than metallic fixation if their probability of recurrence was 21% in gate 1 and gate 2 and 27% in gate 3 (compared with base values of around 8% at each gate). However, suture fixation would be regarded as the most cost-effective strategy for a threshold value of £20 000 per QALY. Regarding the impact on QoL, absorbable devices would no longer dominate metallic fixation if both were to have the same impact on QoL (OR = 1). Only if absorbable pins had a negative impact on the QALY weight compared with the standard methods (represented by a decrement OR higher than 1 compared with the base value of 0.474),



**Table 5** Deterministic Results for Mid-Stage and Late-Stage Analyses

	Mid-Stage						Late-Stage	
	Gate 1 (1987 and Earlier)		Gate 2 (1988–1990)		Gate 3 (1991–1995)		GATE 4 (1996 Onward)	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	Cost	QALYs
Strategy								
Sutures	£917	20.32	£1075	20.32	NA	NA	NA	NA
Absorbable	£989	20.52	£1148	20.52	£1494	20.64	£1694	19.32
Metallic	£1386	20.33	£1610	20.33	£2141	20.49	NA	NA
Standard	NA	NA	NA	NA	NA	NA	£1688	19.30
ICERs:								
Absorbable	£356 <sup>a</sup>		£356 <sup>a</sup>		—		£283 <sup>b</sup>	
Metallic	Dominated		Dominated		Dominated		NA	

Note: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; NA, not applicable.

a. ICER of absorbable pins versus sutures.

b. ICER of absorbable pins versus standard methods (include both sutures and metallic devices).

**Table 6** 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)	
		Gate 1	Gate 2	Gate 3	Gate 1	Gate 2
Absorbable pins						
Probability reoccurrence	0–1	21%	21%	27%	21%	21%
Probability removal	0–1	85%	85%	89%	NA	NA
Decrement OR	0–2	1	1	1.03	1.05	1.05

Note: OR, odds ratio; QALY, quality-adjusted life year.

sutures would be the most cost-effective method in gate 1 and gate 2. The results were insensitive to the probability of removal of the absorbable pins in that more than 85% of the devices needed to be removed in order for absorbable pins to be not cost-effective, compared with 2% assumed in gate 1 and gate 2 and 0% reported in gate 3.

The probability that absorbable pins are the most cost-effective strategy increased over the 3 evaluation gates, as the CEACs show in Figure 3. In 1987, based on a willingness to pay per QALY higher than £1000 per QALY, the fixation method most likely to be the optimal was the absorbable device, with a probability of more than 70%, which was quite stable among the range of potential thresholds. This probability increased to more than 85% and to around 90% for the evaluations in 1990 and 1995. These high probabilities of success in terms of cost-effectiveness would have encouraged the company to continue with the device at each of the 3 decision gates. VOI analysis indicated that the most valuable parameter to collect further information about was QoL data. However, this is from a societal perspective and may not translate into the investment on

future research that would be worthwhile for a company.

### Late-Stage Analysis

Health economic analyses undertaken in the late stage are typically designed not just to inform internal decisions but to inform external decision makers (e.g., health service purchasers) about the expected cost-effectiveness of the new technology and so to make the case for reimbursement of the product. Although preferably they would be based on evidence provided by large RCTs, the need to incorporate all the relevant information in an appropriate way has also been argued.<sup>17</sup>

### Methods

At this stage, prior distributions for the parameters of interest are formed using the previously collected data and combined within the Bayesian framework with the newly available data. Parameter uncertainty is again explored by means of PSA, and these results are used to quantify the societal cost of making the wrong decision about which technology to fund.

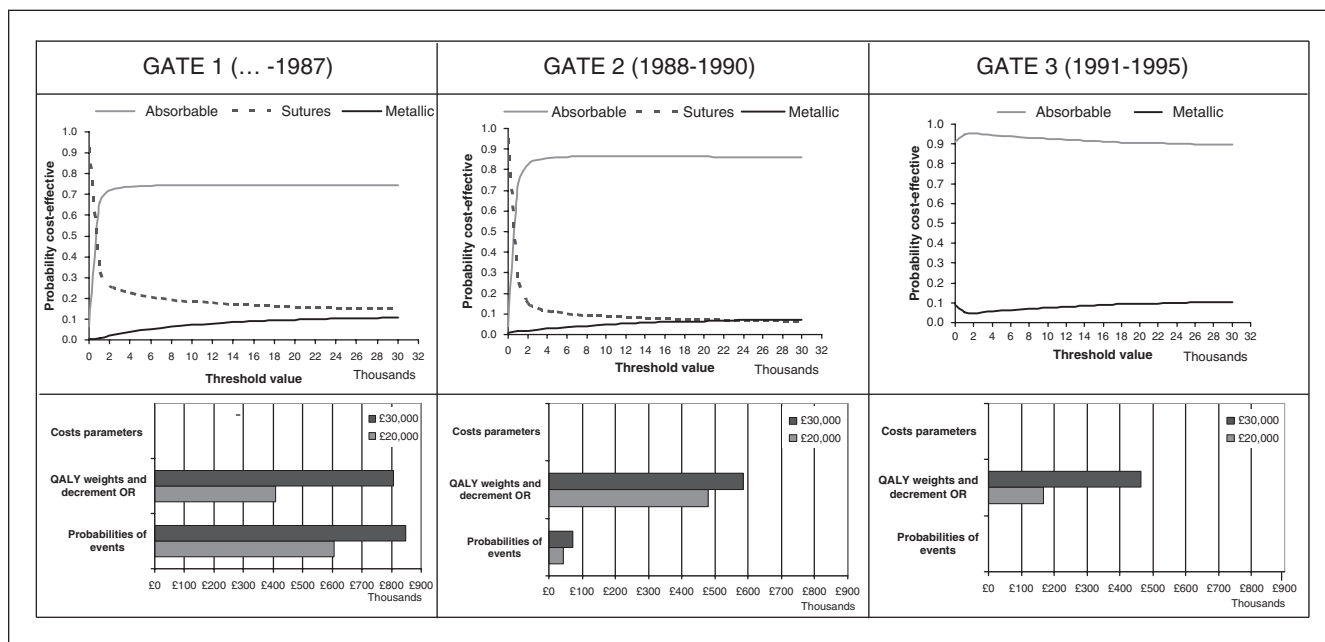


Figure 3 Cost-effectiveness acceptability curves and population expected value of perfect partial information at mid-stage analyses.

Data

The data for the late stage analyses are reported in the last column of Table 2 and Table 3. We use the data from a small RCT conducted in 1997 where patients undergoing osteotomy to treat hallux valgus were allocated to a treatment group (absorbable pins) or to a control group (using standard techniques, i.e., bone suture or metallic fixation).<sup>18</sup> Since both standard methods were combined in the trial, the comparison at this stage was absorbable pins against both sutures and metallic devices (which are referred to as “standard” in the analysis). The number of interventions in the study was 39 (28 patients), where 17 osteotomies were stabilized with standard fixation and 22 were internally fixed with absorbable pins.

*Probabilities.* In the RCT, no patients were reported to need a revision surgery (other than for the removal of metallic devices), and because of the different breakdown of complications in this study compared with previous literature, we pooled the data on all other complications. The small sample size of the trial prevented statistical analyses of the complications rates between the 2 groups. We used the data collected from the earlier analyses to form prior distributions of the recurrence risk and other complications and update those with the data from the trial using the following model:

$$r \sim \text{Binomial}(p, n)$$

$$p \sim \text{Beta}(\alpha, \beta)$$

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, which led to the same posterior distributions when different initial values were applied. We assume the events to be independent of one another.

The removal probability after standard fixation methods reported in this study was much lower than in the early literature but consistent with what was reported in other contemporaneous studies,<sup>19</sup> probably because of technology changes and the inclusion of suture together with metallic fixation as the control group.

*Costs.* We applied the NHS reference costs data deflated to the year of interest. The 12-month cost for individuals with hallux valgus receiving no treatment or conventional treatment was reported in a study in 2001,<sup>20</sup> and it was included in the analysis as the cost of recurrence of the condition.

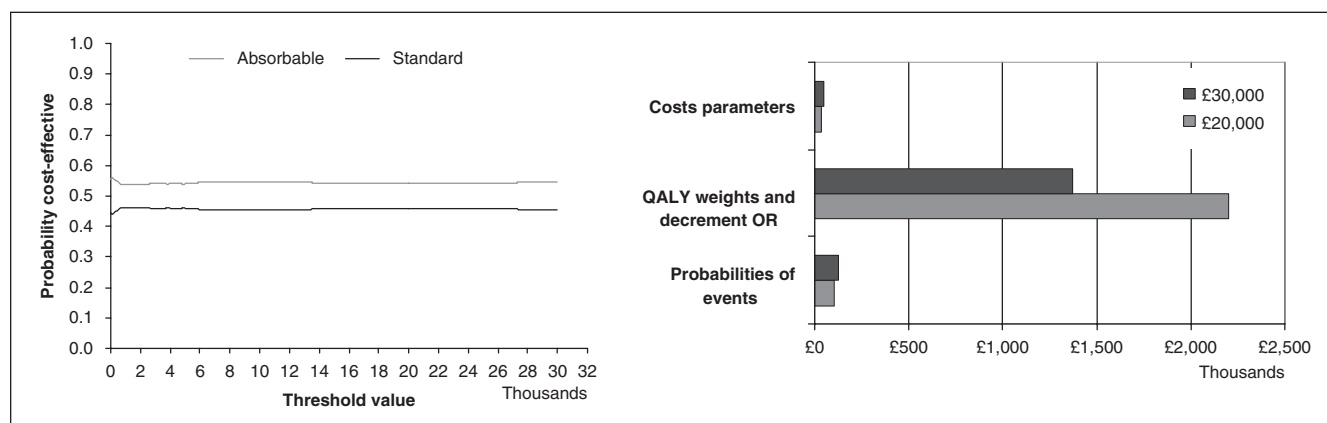


Figure 4 Cost-effectiveness acceptability curves (CEAC) and population expected value of perfect partial information (EVVPI) at late-stage analysis.

**Quality of life.** Contrary to what was included in previous stages of analysis and based on the elicited expert opinion, the RCT found no significant differences between the 2 groups in any of the preoperative and postoperative radiological and clinical measures including pain (metatarsalgia), walking ability, footwear choice, and cosmetic appearance. Therefore, the impact on QoL assumed in earlier analyses was no longer included in the model. The health-related QoL index for individuals undergoing hallux valgus surgery was measured before and after the intervention in a study in 2001,<sup>20</sup> and these values were applied to the recurrence and cured states, respectively.

## Results

The results are presented in Table 5. The expected cost for absorbable pins was slightly higher than for standard fixation, although absorbable pins result in a better expected health outcome. The ICER was £283 per QALY. The CEAC at this stage is presented in Figure 4. The method of fixation most likely to be cost-effective was absorbable pins with a probability of just above 55% at any threshold value. This probability was considerably lower than the analogous probabilities at earlier stages. The population-EVPI for different sets of parameters (cost parameters, QALY weights and impact on QoL, and probabilities of each event) shows that the information with the greatest value was related to the QALY weights and impact on QoL for a threshold value of £20 000 and £30 000 per QALY.

## DISCUSSION

We applied an iterative Bayesian approach to the early assessment of cost-effectiveness of a medical

device during its development process by evaluating the potential cost-effectiveness of the device at 4 different decision points.

Starting with simple methods such as the effectiveness gap analysis or headroom estimate, the device appeared to be cost-effective based on the assumptions applied and the elicited impact on QoL from experts. Given this positive outcome, manufacturers may decide to continue with the product development and run a more formal analysis at this point, that is, synthesizing the evidence into a decision model. This required incorporating more information in the analysis in order to populate the decision tree used for the evaluation. Compared with the headroom analysis (where the maximum reimbursable price for absorbable pins was estimated as high as £21 306), the decision model at the same stage estimates absorbable pins to be cost-effective with a probability of around 70% at a much lower cost of the device (£63). Therefore, the early-stage analysis would suggest continuation of the technology at the realized price. The outcomes of the early-stage analysis and the first mid-stage evaluation undertaken at the same time period in gate 1 are not easily comparable. The differences between them are mainly due to the fact that the headroom analysis is driven by the elicited QALY weights after the use of absorbable and metallic fixation of 0.95 and 0.90, respectively. However, in the decision model we require information on the QALY weight of individuals who recovered and that of individuals whose condition reoccurred after the surgery, which were derived from Table 4 using information from Merkel and others (1983). The resulting QALY weight after a successful surgery is 0.981, which

leads to a QALY weight of 0.991 when applying the decrement OR (difference from perfect health) derived from the elicited QALY weights for absorbable pins. The incremental effectiveness was therefore much lower than that reported in the elicitation exercise and provided less optimistic results. As a result, the probability that absorbable pins are cost-effective at the maximum reimbursable price derived from the early-stage analysis (£21 306) is estimated to be close to zero in the mid-stage analysis.

We populated the decision tree using information available in 1987, 1990, and 1995. We found that 1) absorbable devices were the most cost-effective strategy in osteotomy for a conventional cost-effectiveness threshold of £20 000 per QALY, 2) the parameters with the largest impact on model outcomes were the probability of recurrence and the impact on QoL, and 3) the PSA showed a high probability (between 70% and 90% in the first 3 gates) of the device being cost-effective after accounting for all the parameter uncertainty.

At the late-stage analysis, previously collected data were used to form the prior distributions of some parameters that were updated with the evidence from an RCT. Absorbable devices appeared to remain the most cost-effective strategy, although the probability after addressing uncertainty fell to just above 55%. The principal reasons for this drop were the reduced effect on QoL of absorbable pins over standard methods found in the RCT and the technological changes related to metallic devices that resulted in a reduced risk of removal of this type of device. The VOI analysis shows that the parameters for which further information would be most valuable were those related to the QALY weights and the impact of absorbable pins on QoL.

The use of a retrospective study to illustrate the concepts was necessary given the elapsed time involved in a prospective study and the difficulty of access to, and publication of, a commercially sensitive ongoing development. Given the retrospective nature of the case study analysis, the elicitation and application of assumptions in the early stages of the evaluation were the weakest part of this study. The results show that the believed impact on the elicited QoL weights and the assumptions regarding complication rates were too optimistic, compared with the data later available. This optimism may be a common occurrence in the early evaluations of new products, and also companies may not anticipate the technical progress of competitors. Furthermore, in our retrospective example, the elicitation could only involve a very crude elicitation exercise, which did not provide reliable data. Therefore, these assumptions and elicited effects were not included in the priors at later

stages when additional evidence became available, as they may have contaminated the results rather than adding any information. This limitation would be overcome in a context where the analysis is undertaken prospectively and therefore good quality prior information can be properly elicited using more robust methods for the parameters for which there is no evidence. Although the elicitation methods are nontrivial, there is a growing body of research on how to elicit expert knowledge accurately and reliably.<sup>21</sup> In a context of a small RCT, such as in this example, elicited information if based on a body of expert opinion can enhance the evidence from the trials.

The inclusion of more information in the analysis did not reduce the uncertainty in the decision as one would hope but in fact did the opposite. This may be a common circumstance if the new data obtained do not confirm but instead challenge some of the previous beliefs, assumptions, or data, making the choice between 2 alternatives less clear as is the case in our example. There is also a well-documented tendency to underestimate uncertainty about the knowledge of quantitative information.<sup>22</sup> This may generate reported prior distributions from expert opinion that are far too tight, and, therefore, new collected information might often fall outside the error bars of the elicited data. This would also have consequences for the value of information analysis, as it may be biased downward if the elicited priors do not represent the “true uncertainty” about the parameters.<sup>23</sup> In our example, the expected value of perfect partial information for the QALY weights and the impact on QoL increased considerably at the late-stage analysis, when information from the elicited expert opinion was no longer included in the analysis.

The main advantage of the proposed approach is that it could support internal decision making in order to prioritize the alternative products to be developed and avoid investing in a product that could never be cost-effective. However, as the exemplar product achieved commercial success anyway, it is difficult to prove whether such analysis, if it had been undertaken, would have been commercially beneficial. It may have encouraged the acceleration of the development process or the setting of a higher price (subject to expectations about competitive responses), or the final-stage analysis may have speeded an increased market penetration. Further research based upon a product that failed in the market would be valuable.

There are potentially broader benefits related to the proposed approach compared with undertaking a late-stage analysis alone. First, introducing formally the cost-effectiveness criterion as a variable into the



product development process means that commercial decisions are in line with policy requirements. This could support the development of more cost-effective products that would eventually be brought to the market. Second, collecting and synthesizing data from early stages and identifying the parameters for which more information would be valuable when there is scope for further research could facilitate more accurate estimates in the economic evaluation undertaken at a late stage. Third, late-stage public sector economic evaluations may be costly. The stage-evaluation approach conducted internally ensures the collection of data and provision of evidence, which would reduce the cost of the late-stage public sector economic evaluation usually undertaken when the product is ready for market launch.

Finally, standard VOI analysis takes a societal perspective. Although this approach is useful for government agencies considering funding the development of products, the approach is problematic in a commercial setting. Ideally, in this context, the method of VOI analysis should 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 such case, the wrong decision would be to abandon (proceed with) the product when the eventual purchase decision is (not) to reimburse it. Further research on the commercial perspective in this context would be valuable.

We have illustrated the potential use and the challenges involved in applying iterative economic evaluation to inform commercial investment decisions concerning the development of a new product by anticipating the eventual purchase decisions. 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 used in the evaluation, we ensure that the methods undertaken at each stage take into account the availability of data and resources, in terms of both time and money, that characterize each development phase.

#### APPENDIX Studies Identified in the Literature Review at Each Gate

##### Gate 1.

1. Meier P, Kenzora J. The risks and benefits of distal first metatarsal osteotomies. *Foot Ankle*. 1985;6:7-17.

2. Merkel K, Katoh Y, Johnson E, Chao E. Mitchell osteotomy for hallux valgus: long-term follow-up and gait analysis. *Foot Ankle*. 1983;3(4):189-96.

3. Bishop J, Kahn A, Turba J. Surgical correction of the splayfoot: the Giannestras procedure. *Clin Orthop*. 1980;146:234-8.

4. Austin DW, Leventen EO. A new osteotomy for hallux valgus. *Clin Orthop*. 1981;157:25-30.

5. Wu K. Mitchell bunionectomy: an analysis of four hundred and thirty personal cases plus a review of the literature. *J Foot Surg*. 1987;26(4):277-92.

6. Gibson J, Piggot H. Osteotomy of the neck of the first metatarsal in the treatment of hallux valgus. *J Bone Joint Surg*. 1962;44-B:349-55.

7. Donovan J. Results of bunion correction using Mitchell osteotomy. *J Foot Surg*. 1982;21(3):181-5.

8. Lewis R, Feffer H. Modified Chevron osteotomy of the first metatarsal. *Clin Orthop*. 1981;157:105-9.

9. Miller J. Distal first metatarsal displacement osteotomy. *J Bone Joint Surg*. 1974;56:923-31.

10. Meisenhelder D, Harkless L, Patterson J. Avascular necrosis after first metatarsal head osteotomies. *J Foot Surg*. 1984;23(6):429-35.

11. Hatstrup S, Johnson K. Chevron osteotomy: analysis of factors in patient's dissatisfaction. *Foot Ankle*. 1985;5(6):327-32.

12. Haddad R. Hallux Valgus and metatarsus primus varus treated by bunionectomy and proximal metatarsal osteotomy. *South Med J*. 1975;68(6):684-6.

13. Glynn M, Dunlop, J, Fitzpatrick D. The mitchell distal metatarsal osteotomy for hallux valgus. *J Bone Joint Surg*. 1980;62-B:188-91.

14. Shapiro F, Heller L. The Mitchel distal metatarsal osteotomy in the treatment of hallux valgus. *Clin Orthop*. 1975;107:225-31.

15. Carr C, Boyd B. Correctional osteotomy for metatarsus primus varus and hallux valgus. *J Bone Joint Surg*. 1968;50-A:1353-69.

16. Bonney G, McNab I. Hallux valgus and hallux rigidus: a critical survey of operative results. *J Bone Joint Surg*. 1952;34-B(3):366-87.

17. Goldner J, Gaines R. Adult and juvenile hallux valgus: analysis and treatment. *Orthop Clin North Am*. 1976;7:863.

18. Lindgren U, Turan I. A new operation for hallux valgus. *Clin Orthop Rel Res*. 1983;175:179-83.

19. Mitchell C, Fleming J, Allen R, Clenney C, Sanford G. Osteotomy-bunionectomy for hallux valgus. *J Bone Joint Surg*. 1958;40-A:41-58.

##### Gate 2.

20. Ramanathan EBS, Heywood-Waddington MB. Plaster support after Wilson's osteotomy for hallux valgus. *J Bone Joint Surg*. 1988;70-B:412-4.

21. O'Doherty DP, Lowrie IG, Magnussen PA, Gregg PJ. The management of the painful first metatarsophalangeal joint in the older patient. *J Bone Joint Surg.* 1990;72-B:839–42.  
 22. Grace D, Hughes J, Klenerman L. A comparison of Wilson and Hohmann osteotomies in the treatment of hallux valgus. *J Bone Joint Surg.* 1988;70-B:236–41.  
 23. Bostman O, Hirvensalo E, Makinen J, Rokkanen P. Foreign-body reactions to fracture fixation implants of biodegradable synthetic polymers. *J Bone Joint Surg.* 1990;72-B:592–6.

Gate 3.

24. Friend G, Grace K, Stone HA. Cortical screws versus absorbable pins for fixation of the short z-bunionectomy. *J Foot Ankle Surg.* 1994;33(4):411–8.  
 25. Macuso JE, Abramow SP, Bloom WB. Smooth Kirschner (K) wire fixation of distal metaphyseal osteotomy bunionectomies: a 10-year retrospective survey. *J Foot Surg.* 1992;31(3):276–84.  
 26. Hirvensalo E, Bostman O, Tormala P, Vainionpaa S, Rokkanen P. Chevron osteotomy fixed with absorbable polyglycolide pins. *Foot Ankle.* 1991;11(4):211–8.  
 27. Friend G, Grace K, Stone HA. L-Osteotomy with absorbable fixation for correction of Taylor's bunion. *J Foot Ankle Surg.* 1993;32(1):94–124.  
 28. Hetherington VJ, Shields S, Wilhelm KR. Absorbable fixation of first ray osteotomies. *J Foot Ankle Surg.* 1994;33(3):290–4.  
 29. Burns AE. Biofix fixation techniques and results in foot surgery. *J Foot Ankle Surg.* 1995;34(3):276–82.  
 30. Small HN, Braly G. Fixation of the Chevron osteotomy utilizing absorbable polydioxanon pins. *Foot Ankle Int.* 1995;16(6):346–50.  
 31. Gerbert J. Effectiveness of absorbable fixation devices in Austin bunionectomies. *J Am Podiatr Med Assoc.* 1992;82(4):289–95.  
 32. Brunetti VA, Trepal MJ, Jule KT. Fixation of the Austin osteotomy with bioresorbable pins. *J Foot Surg.* 1991;30(1):56–65.  
 33. Goel AR, Vogel BI. The off-set v osteotomy with screw fixation for correction of hallux valgus: a retrospective study. *J Foot Ankle Surg.* 1993;32(3):305–10.  
 34. Miketa JP, Prigoff MM. Foreign-body reactions to absorbable implant fixation of osteotomies. *J Foot Ankle Surg.* 1994;33(6):623–7.  
 35. Bryan S, Parkin D, Donaldson C. Chiropody and the QALY: a case study in assigning categories of disability and distress to patients. *Health Policy.* 1991;18:169–85.

Gate 4.

36. Prior TD, Grace DL, MacLean JB, Allen PW, Chapman PG, Day A. Correction of hallux abductus valgus by Michell's metatarsal osteotomy: comparing standard

fixation methods with absorbable polydioxanone pins. *Foot.* 1997;7:121–5.  
 37. Juutilainen T, Patiala H, Ruuskanen M, Rokkanen P. Comparison of costs in ankle fractures treated with absorbable or metallic fixation devices. *Arch Orthop Trauma Surg.* 1997;116:204–8.  
 38. Torkki M, Malmivaara A, Seitsalo S, Hoikka V, Laippala P, Paavolainen P. Surgery vs orthosis vs watchful waiting for hallux valgus. *JAMA.* 2001;285(19):2474–80.

REFERENCES

1. National Institute for Clinical Excellence. Guide to the Methods of Technology Appraisal. London: NICE; 2008.  
 2. Fenwick E, Palmer S, Claxton K, et al. An iterative Bayesian approach to health technology assessment: application to a policy of preoperative optimization for patients undergoing major elective surgery. *Med Decis Making.* 2006;26(5):480–96.  
 3. Banta HD, Thacker SB. The case for reassessment of health care technology: once is not enough. *JAMA.* 1990;265:235–40.  
 4. Cooper RG. *Winning at New Products: Accelerating the Process From Idea to Launch.* 3rd ed. New York: Perreus; 2001.  
 5. Vallejo-Torres L, Steuten L, Buxton M, Girling A, Lilford R, Young T. Integrating health economics modelling in the product development cycle of medical devices: a Bayesian approach. *Int J Technol Assess Health Care.* 2008; 24(4):459–64.  
 6. Girling A, Young T, Bronw C, Lilford R. Early-stage valuation of medical devices: the role of developmental uncertainty. *Value Health.* Forthcoming 2010.  
 7. Sculpher M, Drummond M, Buxton MJ. The iterative use of economic evaluation as part of the process of health technology assessment. *J Health Serv Res Policy.* 1997;2(1):26–30.  
 8. Cosh E, Girling A, Lilford R, McAteer H, Young T. Investing in new medical technologies: a decision framework. *J Commer Biotechnol.* 2007;13:263–71.  
 9. Bostman O, Vainionpaa, S, Hirvensalo E, et al. Biodegradable internal fixation for malleolar fractures: a prospective randomised trial. *J Bone Joint Surg.* 1987;69-B(4):615–9.  
 10. Rokkanen P, Bostman O, Vainionpaa S, et al. Biodegradable implants in fracture fixation: early results of treatment of fractures of the ankle. *Lancet.* 1985;(8443):1422–4.  
 11. Vainionpaa S, Vihtonen K, Mero M, et al. Fixation of experimental osteotomies of the distal femur of rabbits with biodegradable material. *Arch Orthop Trauma Surg.* 1986;106(1):1–4.  
 12. Department of Health, UK. NHS reference costs 2006–07. Available from: URL: [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_082571](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_082571)  
 13. Sutton A, Abrams KR. Bayesian methods in meta-analysis and evidence synthesis. *Stat Methods Med Res.* 2001;10:277–303.  
 14. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. *Methods for the Evaluation of Health Care Programmes.* 3rd ed. Oxford (UK): Oxford University Press; 2005.  
 15. Juutilainen T, Patiala H, Ruuskanen M, Rokkanen P. Comparison of costs in ankle fractures treated with absorbable or metallic fixation devices. *Arch Orthop Trauma Surg.* 1997;116:204–8.  
 16. Merkel K, Katoh Y, Johnson E, Chao E. Mitchell osteotomy for hallux valgus: long-term follow-up and gait analysis. *Foot Ankle.* 1983;3(4):189–96.

17. Sculpher M, Claxton K, Drummond M, McCabe C. Whither trial-based economic evaluation for health care decision making? *Health Econ.* 2006;15(7):677–87.
18. Prior TD, Grace DL, MacLean JB, Allen PW, Chapman PG, Day A. Correction of hallux abductus valgus by Michell's metatarsal osteotomy: comparing standard fixation methods with absorbable polydioxanone pins. *Foot.* 1997;7:121–5.
19. Calder JDF, Hollingdale JP, Pearse MF. Screw versus suture fixation of Michell's osteotomy. *J Bone Joint Surg.* 1999;81-B(4):621–4.
20. Torkki M, Malmivaara A, Seitsalo S, Hoikka V, Laippala P, Paavolainen P. Surgery vs orthosis vs watchful waiting for hallux valgus. *JAMA.* 2001;285(19): 2474–80.
21. O'Hagan A, Buck CE, Daneshkhah A, et al. *Uncertain Judgements—Eliciting Experts' Probabilities.* London: Wiley; 2006.
22. Hammitt JK, Shlyakhter AI. The expected value of information and the probability of surprise. *Risk Analysis.* 1999;19(1): 135–52.
23. Hammitt JK. Can more information increase uncertainty? *Chance.* 1995;8(3):15–17, 36.