The Application of Portfolio Management Techniques to Resource Allocation Issues in the Health Care Environment

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Summary

Risk, complexity and uncertainty define the business environment of the 1990s, but few have suggested a framework for managing risk or a set of tools to help cope with uncertainty. Portfolio management techniques have been used by decision-makers within organisations to maximise returns and benefits from a given portfolio of projects while reducing the magnitude of uncertainties and risks associated with developing the projects. This paper investigates the application of portfolio management techniques to issues in the field of health care. Firstly, a selection of portfolio management techniques are identified and briefly described. The paper then suggests and illustrates the potential application of these techniques to two diverse situations: R&D investment prioritisation decisions faced by senior executives in pharmaceutical firms, and resource allocation decisions faced by health care policymakers. Finally some recommendations are given and areas for future research identified.

1. Introduction

The objective of portfolio management is to create the most value from a given portfolio of projects. It attempts to ensure that the current set of projects meets the strategic goals of the business by determining which projects are to be funded and at what levels. Concurrently, portfolio management also sets out to achieve the right balance in the portfolio between risky projects which will give an organisation a competitive and strategic advantage in the future, and those projects which are considered incremental and will be sufficient to maintain the competitiveness of the organisation.

Risk can be defined as a measure of the potential changes in value that will be experienced in the portfolio as a result of differences in the environment between now and some future point in time. Used extensively in many industry sectors to analyse highly complex long-term cause and effect problems, portfolio management techniques enable the user to assess the impact of a variety of portfolio investment decisions against a range of commercial and regulatory scenarios in order to fully understand the impact, both short- and long-term, of these decisions.

To illustrate the concept of portfolio management, we will use the following analogy. It is analogous to packing a suitcase with various objects each with a differing value and volume, such that the value of the suitcase is maximised (Bergman et al.,1985). In portfolio management, the suitcase would be some resource constraint such as the size of the research and development (R&D) budget, the objects would be the individual projects, the volume of each object would be the R&D cost associated with each project, and the value of each object would be the potential reward for each project.

The aim of this paper is to describe and investigate the application of two portfolio management techniques in the field of health care. Two follow-up papers will involve empirical testing of these techniques and further papers will consider other portfolio management techniques in-turn. The paper is divided into four sections. Section 2 describes in detail the Monte-Carlo simulation technique and the Pearson Index method. Section 3 illustrates the application of these techniques to R&D project selection in the pharmaceutical industry, and resource allocation problems faced by health care policymakers. The paper concludes with some recommendations and suggestions for further research.

2. Portfolio Management Techniques

Portfolio management techniques encompass a family of methods. Two such approaches involve the use of Monte-Carlo simulation and the Pearson Index which are explored further in this paper. However, it is worth briefly mentioning a number of other methods, which are described below.

A method which has been recently proposed involves ranking projects in the portfolio by the value of their return-on-investment (ROI) (Sharpe et al.,1998). The first stage of this method involves identifying the investment alternatives for each project. The second stage involves determining the expected value and ROI for each project alternative. The final stage of the method involves identifying the project alternative which yields the highest ROI and ranking the projects based on these values. The highest-ranking project is then selected.

In contrast, because of the characteristic of the problem involved in portfolio management, a number of other methods use a multi-dimensional approach within an operational research framework to select R&D projects (Cook et al., 1982; Martel et al., 1988; Bard, 1990; Stewart, 1991). In addition, the theory of option pricing (Black et al., 1973) has recently emerged from the financial field and used in R&D project selection (Nichols, 1994) as well as to improve decision making about the sequence and timing

of strategic investments (Luehrman, 1998). Another method based on the examination of five key criteria - commercial value, probability of success, cost, strategic fit, and time – has also been proposed (Baker, 1998).

2.1. Monte-Carlo simulation

Most business decisions that are made within companies are based on incomplete knowledge about how the future will evolve primarily because of the increasingly complex and uncertain environment in which these companies operate. Factors such as the globalisation of business and new technologies have been the main contributors. For example, when a company decides to launch a new product, there are risks involved because of uncertainties about the product's market potential, competing technologies that may be available in the future, development costs and the price at which the product will command in the market place.

To reduce the magnitude of the uncertainties, risk analysis is often used as a tool to guide the decision-maker into taking calculated risks. Risk analysis can be used to:

- Test the sensitivity of the outcome such as rate-of-return to the main assumptions used in the analysis;
- Identify the main uncertainty drivers such as those that have a significant effect on the outcome;
- Calculate the worst- and best-case scenarios associated with the outcome so that contingency plans can be created;
- Consider and evaluate alternative methods to manage and reduce risks.

Two techniques that are often used in risk analysis are sensitivity and scenario analysis. Examples of the application of these techniques are in the examination of how sensitive an airline's profit is to the capacity utilisation of aircraft and hours flown (Pitman Publishing, 1997), and in the evaluation of capital investments (Hertz, 1979). However, the main disadvantage associated with these techniques is that only a range of possible outcomes is presented and not the likelihood of achieving each possible outcome. For example, in the examination of an airline's profit, these techniques often present only a range of possible profit levels and not give the likelihood of achieving each particular level. Further, the analyst has discretion as to which variables and the range over which these can be varied in the sensitivity analysis, and therefore creating the potential for selection bias. In addition, interpretation of a sensitivity analysis is essentially arbitrary because there is no guidance as to what degree of variation in the results is acceptable as robust, and one-way sensitivity analysis carries a risk that interactions between parameters may not be captured.

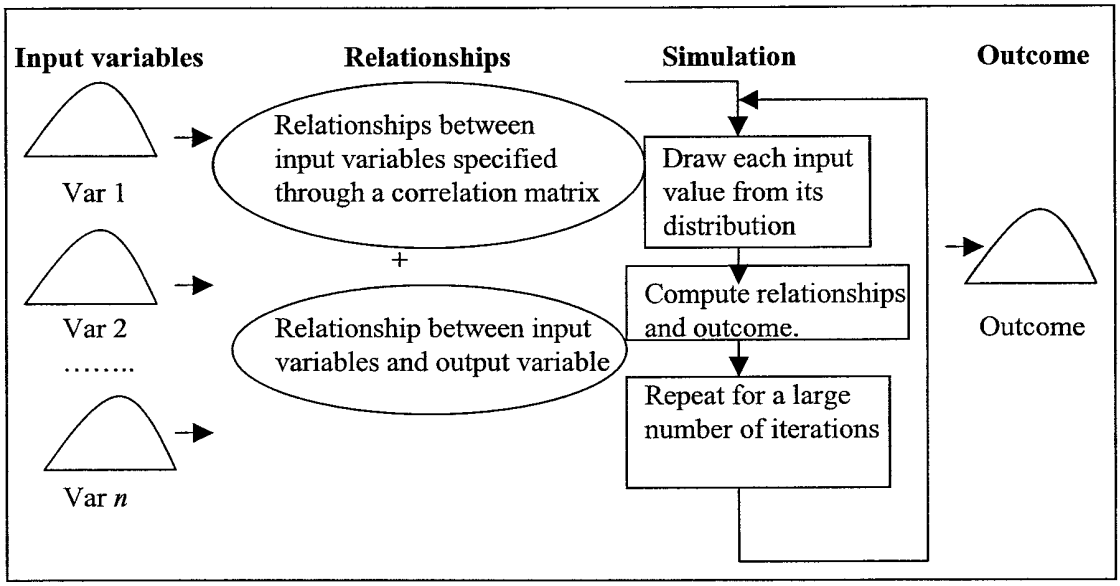

Figure 1. A schematic representation of the Monte-Carlo simulation technique.

Monte-Carlo simulation overcomes these disadvantages and an overview of the technique is illustrated in Figure 1. There are four stages involved. Firstly, all input and output variables are specified. For example, in the examination of an airline's profit, input variables would typically be number of hours flown, ticket price, and capacity of flights flown. The output variable would be annual profit.

The second stage involves specifying probability distributions to represent uncertainty or variation in these input variables. The parameters used to define the probability distributions, such as the mean and standard deviation, may be obtained from either analyses of historical data, managerial judgements, expert opinion, or can be derived using estimates of expected and 95% lower/upper boundary values (see Appendix).

The third stage involves specifying the relationship between input variables using, for example, a correlation matrix as well as the relationship between input variables and the output variable.

The fourth stage involves running the simulation. For each input variable, a value is selected from its own probability distribution using Monte-Carlo simulation. Values from all input variables are then used in the computation of the output variable value through the input-output relationship. This procedure is repeated a large number of times.

The result is a probability distribution for the output variable presenting the probability of achieving not only the expected value but also a range of other values. In the above example, the distribution of annual profit would give the range of profit levels as well as the expected profit. It would also allow the decision-maker to examine the main uncertainty drivers causing the variation in profit and possible combinations of input variables that can potentially lead to catastrophic consequences. As a consequence, contingency plans can be created to reduce the variation and uncertainties in annual profit levels.

2.2 Pearson Index

In contrast to selecting projects by considering the likelihood of different outcomes, other methods have been proposed based on ranking projects in an order of preference. Amongst these, the Pearson Index (Pearson, 1972) is considered to be the simplest to use and interpret. With this method, an index is calculated for each project and the highest-ranking project is the most attractive and should be selected for further development. The index is expressed as a ratio of expected net present value - the difference between discounted reward and sum of discounted costs weighted appropriately by conditional success probabilities at each development stage - to expected cost. Mathematically, it is expressed as

$$D = \frac{r\,p_1\,p_2 \ldots p_n - \left(c_1 + c_2\,p_1 + \ldots + c_n\,p_1 \ldots p_{n-1}\right)}{c_1 + c_2\,p_1 + \ldots + c_n\,p_1 \ldots p_{n-1}}$$

where c_i is the discounted cost of development at stage i of the project ($i=1,2,..,n$), p_i is the conditional probability of success at stage i given that the project has survived stage $i-1$, and r is the potential reward if the project is successful.

	Project		
	A	**B**	**C**
Cost at stage 1	6	6	2
Cost at stage 2	4	4	4
Cost at stage 3	2	2	6
Overall cost	12	12	12
Probability of success at stage 1	0.8	0.3	0.8
Probability of success at stage 2	0.5	0.5	0.5
Probability of success at stage 3	0.3	0.8	0.3
Overall probability of success	0.12	0.12	0.12
Overall reward	30	30	30
Pearson index (D)	**-0.64**	**-0.52**	**-0.526**

Table 1. An example illustrating the application of the Pearson Index to three hypothetical projects.

To illustrate this method, we will use a hypothetical example as presented in Table 1. All three projects A, B and C have identical reward, overall cost, and overall probability of success throughout the three stages of development. The method will discriminate between the three projects as follows. If the discounted cost at each stage of the project, overall reward and overall probability of success are identical for two projects but, if one project is more likely to fail at the early stages, then this project is to be preferred. This is illustrated by the characteristics of project B compared to A whereby project B is the preferred project based on a higher index value. Further, if the conditional probability of success at each stage of development, overall reward and overall cost are identical for two projects, but higher costs are to be incurred in the later stages of a project, then this particular project is the more favourable. This is illustrated by the characteristics of project C compared to A whereby project C is preferred.

There are, however, weaknesses associated with this method. Firstly, the index does not capture the 'option value' of projects which is increasingly considered to be an important factor (Dixit et al., 1994; Senn, 1996). Secondly, it is not entirely certain as to how the conditional success probability and cost at each stage of development should be estimated. Both Bayesian and Frequentist approaches have, however, been suggested as possible methods to estimate these parameters (Senn, 1998). Other relevant issues associated with the method, such as the value of information concerning the conditional success probability at each stage of the project and time penalties, have also been discussed (Senn, 1996).

3. Application of Portfolio Management Techniques

3.1. The Pharmaceutical Industry

In the current economic climate, pharmaceutical companies are under increasing pressure to bring to market a minimum of five innovative products a year. The market for pharmaceuticals is now global and all countries are imposing their own version of cost containment. The US market is moving more towards a managed care environment, while simultaneously the regulatory environment worldwide is becoming more complex and more stringent. As a result, pharmaceutical companies are facing difficulties in maintaining existing industry-average growth rates of 10% while expected expenditure on R&D is likely to fall because of the increasing use of financial straight-jackets by pharmaceutical companies to contain costs. To complicate the picture further, companies are re-engineering and changing the internal structures of R&D to achieve short-term improvements, despite the fact that R&D investment decisions should be long-term as they will affect business performance and the state of health care for 10-20 years or more.

Because of the substantial costs involved in bringing a drug to market, pharmaceutical companies have to determine, at the very early stages of development, which compounds are to be pursued along the R&D path and which are to be discontinued. These decisions are becoming ever increasingly pivotal as the advent of new research techniques such as high throughput screening and genomics have opened up an entirely new and diverse range of opportunities so that the R&D pipeline is bulging at the input end. Thus the challenge for R&D departments is not the desperate search for dwindling opportunities, but the need to focus their efforts and resources on those opportunities which have the highest chance of being translated into worthwhile cost-effective, efficacious and safe products. In other words, companies have to manage their drug portfolios efficiently and need to balance the demands along a number of strategic dimensions (*e.g.* stability under different scenarios, balance across therapeutic areas, stages in the development pipeline) given the company's technical and commercial resources, in order to maximise the return on research and to invest in building the technical base. To assist pharmaceutical senior executives in achieving their strategic goals, we propose the following method based on a combination of the Pearson index and Monte-Carlo simulation.

With this method, instead of assuming the overall reward, as well as cost and conditional success probability at each development stage of the project as fixed, it is more appropriate to assume that each of these parameters are estimated with a degree of uncertainty which can be represented by 95% upper boundary estimate. This boundary estimate along with the expected value are used in the derivation of probability distributions from which values are drawn at random (see Appendix).

The procedure involved is as follows:

1. a) For each project, select the overall reward, cost and conditional success probability at each development stage of the project at random from their respective probability distributions using MC simulation.
   b) Calculate the Pearson index.
   c) Repeat steps (a) and (b) a large number of times to arrive at a probability distribution for the Pearson index.
2. Repeat step (1) for each project.

In practice, we would suggest step (1) be initially performed for at least 100 iterations. The number of iterations should then be doubled, and the shapes of the resulting probability distributions as well as their mean and standard deviation compared. This should be repeated with the number of iterations doubled each time until the shape of the probability distribution, as well as its mean and standard deviation converge.

For each project, the probability distribution presents the likelihood of observing its expected Pearson index value as well as the range of these values. This information allows the decision-maker to assess the viability of selecting a particular project for development based on its expected Pearson index value, in light of uncertainties in conditional success probabilities, overall reward and cost estimates. In addition, the information allows the decision-maker to determine which of the input variables contribute significantly to the variation in the Pearson index values, and subsequently can then be examined in greater detail.

In practice, there are a number of specific variants on the conditional success probabilities, overall reward and cost which different pharmaceutical companies would adopt (see Table 2). In addition, other factors such as the clinical value of the product, the degree to which the final product fits the company's strategic aims, and the timescale over which the product can be delivered to market and their variants should be considered for incorporation into our proposed technique.

Factor	Variants
Reward	Peak year sales, expected value, net present value, internal rate of return, return on investment, market value, economic value added.
Conditional probability of success	Regulatory demands (NDA, product license application, or other regulatory submission), legal considerations, responses of competitors and changes in market share, probabilities of passing through stages I to III, political pressures.
Cost	Research cost, cost to registration, cost to market launch, head count loss, overhead loaded cost, templated cost, actual forecast cost, capital costs.
Clinical value	Clinical feasibility, safety, efficacy, pharmacokinetics and other benefits over existing medicines
Strategic fit	Long-term growth and development of the company, individual therapeutic/disease area goals, uniqueness of the concept or risk of medicine.
Time	Patent life remaining at the time of a medicine's launch, time to develop and to reach market.

Table 2. Factors and their variants for incorporation into the simulation.

The simulation model may be extended to evaluate compounds that are not just investigational, but also those which are marketed, a combination of marketed and investigational or may focus on a subset of these groups. Further, it is insufficient to focus solely on projects as the lowest common denominator. Each indication, dosage form, route of administration, and dosing regimen should be evaluated.

3.2. Health Care Policymakers

In the past three decades, global expenditure on healthcare has increased at an unprecedented rate, as a direct consequence of changes in the medical marketplace and political, social, demographic, and economic environments in countries worldwide. Numerous interacting factors have contributed to increased health care costs including prolonged life-expectancy, technological progress of medical technologies, and enhanced expectations of patients on the quality of healthcare. Healthcare expenditure in the OECD countries has risen steadily to an average of 8% of GDP per capita in the nineties, from around 7% of GDP in the eighties and 5% in the seventies (OECD, 1996). However the demand for health care in the future is unlikely to waiver and many countries are faced with economic pressures as they struggle to constrain the growth of expenditures for medical care. In these circumstances, policymakers are faced with two options: either limiting access to healthcare services or achieving a better use of limited healthcare funds.

The purpose of economic evaluation, or economic appraisal, of healthcare technologies is to compare the relative value of two or more alternatives in terms of their costs and consequences in the pursuit of creating better health and/or longer life (Drummond et al.,1997). Costs are the monetary values of resource inputs required to produce a health

outcome and consequences are the monetary and non-monetary outcomes of applying a particular intervention.

Cost-effectiveness analysis is one such type of economic evaluation, where the health outcome benefits of treatment regimens are measured in natural units, such as years of life saved, symptom-free days or cases detected. In the evaluation of the cost-effectiveness of two treatment regimens, the population incremental cost-effectiveness ratio (ICER) is estimated from patient cost and effectiveness data and is used to determine which is the cost-effective treatment regimen.

Because of uncertainty in cost and effectiveness estimates, however, sensitivity analysis is often conducted to examine the implication of this uncertainty on the sample estimate of the population ICER. In particular, sensitivity analysis has been widely advocated for assessing the problems of data uncertainty in economic appraisals of healthcare programmes in guidelines belonging to several jurisdictions that require the provision of economic data for reimbursement (Commonwealth of Australia, 1990; Ontario Ministry of Health 1991). However, there are major limitations with sensitivity analysis such as variable selection bias and the non-examination of interactions between variables. Consequently, the $(1-\alpha)100\%$ confidence interval has been adopted as the standard technique, where α is often set at 0.05, to represent uncertainty around the ICER estimate.

Many methods have been proposed to estimate the confidence interval including confidence boxes, confidence ellipses, the Taylor series expansion, Fieller's theorem, and non-parametric bootstrapping (Willan et al.,1996; Chaudhary et al.,1996). Of these, non-parametric bootstrapping has been suggested as the preferred method and an in-depth discussion of the method is given by Briggs and colleagues (Briggs et al.,1997).

The bootstrap method is based on sampling, with replacement, the cost and effectiveness data pairs for each patient in each treatment group. However, it is well appreciated that, for example, unit costs in multicentre/multinational studies can vary considerably not only between countries, but within countries (Drummond et al., 1992). This variability in unit costs can be represented in the form of a 95% upper boundary estimate. We therefore propose that this information, when it is available, should be incorporated into the bootstrap method to represent the cost variability at the patient level.

An outline of our proposed technique is as follows. We assume that a comparison is to be conducted using patient cost and effectiveness data from the treatment and control groups. Further, for each unit cost, there exists a 95% upper boundary estimate which is used together with the expected unit cost estimate to derive its log-normal distribution. Details of the derivation of the central moments of the log-normal distribution for unit costs are given in Appendix. The steps involved are as follows:

1. Select each unit cost at random from its own logistic normal distribution using MC simulation.
2. Compute the total cost (c_i) for each patient i in each group by taking the sum of products of the respective unit costs (c_{ij}) and the quantity of resources used (q_j). This is expressed as $c_i = \sum_j \left(c_{ij}\, q_j\right)$.
3. Repeat steps (1) and (2) a large number of times, each time selecting each unit cost from its own distribution and computing the total cost, to arrive at the total cost probability distribution for patient i. The expected value obtained from this distribution is used to represent the cost for that patient and is denoted as c_i^{MC}.
4. Apply the bootstrap technique as outlined by Briggs and colleagues using the cost/effect data pairs (c_i^{MC}, e_i) for patients in each group to arrive at the bootstrap estimate of the population ICER and its standard error.
5. The (1-α)100% confidence interval is then computed to represent the uncertainty around the estimate of the population ICER using the bias corrected and accelerated percentile method as recommended by Briggs and colleagues.

The advantage with this method is that variability at the unit cost level is incorporated into patient total cost. The bootstrap method can then be applied to patient cost and effect data taking into account uncertainty in the estimate of the magnitude of the difference in mean cost and effectiveness, as well as the correlation between the numerator and denominator of the ICER ratio.

4. Conclusions

It has been demonstrated in this paper that portfolio management techniques can be used to support the decision-maker in making the optimal decision in R&D project selection and allocating scarce health care resources. These techniques are an aid to decision-making, and are not a decision-provider, which is an enormously mistaken expectation of portfolio management systems. Through adopting an approach that is simple and transparent, portfolio management has the potential to develop into a highly useful decision-support tool that should be repeated on an ongoing basis and must be repeatable.

The techniques presented here are underpinned by the assumption that there exists a (95% upper) boundary estimate for the conditional success probabilities, reward and costs. Further, it is assumed that uncertainty in these parameters can be represented by the logistic-normal and log-normal distributions, and that these distributions are independent. These assumptions are examined below.

With regard to the 95% upper boundary estimate, there is a case to be made that this is a subjective estimate and therefore may question whether the methods presented in this paper is valid. We would argue, however, that subjective probability estimates do not generally invalidate methods that use them (Doubilet et al., 1985). To improve the accuracy of the boundary estimate, we suggest the use of a Delphi-panel of experts to arrive at a consensus estimate (Evans, 1997).

With regard to the distributional assumption, we suggest the exploration of the suitability of the logistic- and log-normal distributions suggested in this paper as well as other parametric families of distributions. In our follow-up papers, the techniques presented in this paper will be empirically tested using trial data to determine the most appropriate distribution.

With regard to the independence assumption, this assumption would be met in the R&D project selection case because conditional success probabilities, costs as well as overall reward between projects are likely to be independent. However, unit costs used in the bootstrap calculation of the confidence interval for the population ICER estimate are likely to be correlated. The relationship between unit costs and its impact on the results will be investigated in our follow-up papers.

In addition to the areas mentioned above which will be investigated in our follow-up papers, we will also investigate and examine the significance and impact of a project's 'option value' and other factors summarised in Table 2 on its expected Pearson index.

In summary, we have presented the methodological foundation upon which decision-makers can answer the following questions:

R&D project selection:

1. Which project should be selected for development based on its expected Pearson index value given uncertainty in estimates of the conditional success probability and cost at each stage of development, and overall reward?
2. What is the degree of certainty that the selected project is the optimal one?

Health care resource allocation:

1. What are the $(1-\alpha)100\%$ bootstrap confidence limits around the population ICER estimate given uncertainty in unit cost estimates?

Risk and uncertainty are undoubtedly inherent in the commitment of present resources to future expectations. Without the correct methodology to deal with risk and uncertainty, any important choice that leads to uncertain outcomes is uninformed. When the methodology is properly applied and understood, the decision-maker - whether it be a pharmaceutical business executive, government policy-maker, scientist or legislator - would be better equipped to decide why one course of action might be more desirable than another.

Within the spirit of the HESG, this is very much work in progress and is being prepared for likely submission to a business/management journal.

Suggestions and comments are welcomed on:

1. *The usefulness of portfolio management techniques for healthcare resource allocation problems.*
2. *The distributional assumptions (logistic- and log-normal distributions) suggested in this paper as well as other parametric families of distributions.*

3. *The usefulness of Frequentist versus Bayesian approaches to estimate conditional success probabilities and development costs associated with the Pearson index technique.*

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Appendix: Derivation of probability distributions

In this section, we present the methodology for deriving the mean and standard deviation of the distribution for success probabilities, overall cost and reward, as well as unit costs from which MC simulation can be used to draw values at random. For the derivation of the distribution of success probabilities, we adapt the method as proposed by Doubilet and colleagues for deriving the mean and standard deviation of the distribution for a random variable X taking a range of $(0,1)$. For overall cost, reward and unit costs, we derive the mean and standard deviation of the distribution for a random variable X with a range of (a,b), where $b>a\geq 0$.

A.1 Success Probabilities

To derive the mean and standard deviation, we assume there exists an expected estimate (m) and a 95% upper (l) boundary estimate of the success probability. We further assume that the random variable $X\in(0,1)$ representing the success probability follows a logistic-normal distribution. In other words, $\log\left(\frac{X}{1-X}\right)$ follows a Normal distribution with mean μ and standard deviation σ. The mean and standard deviation of the distribution of $\log\left(\frac{X}{1-X}\right)$ are then defined as follows:

1. If $m\notin(0.5, 0.025, 0.975)$ then $\mu=\frac{B-E\sqrt{B^2-M^2+M^2E^2}}{\left(1-E^2\right)}$ where $M=\text{logit}(m), B=\text{logit}(l), E=1.96/\Phi^{-1}(m), \text{logit}(X)=\log\left(\frac{X}{1-X}\right)$ and $\Phi^{-1}(\cdot)$ is the inverse of the Normal distribution function.

2. If m=0.5, μ=0.
3. If m=0.025 or 0.975, $\mu=\left(M^2+B^2\right)/2B$.
4. $\sigma=|\mu-B|/1.96$.

In general, the mean and standard deviation are always defined when m is greater than 0.025 and less than 0.975. A detailed derivation of these formulae as well as a discussion of the limitations of these results are given by the authors. If the boundary estimate is a 95% lower one, the mean and standard deviation can be derived in a similar fashion.

A.2 Cost at each development stage, Overall Reward and Unit Costs

To derive the mean and standard deviation of the distribution for the cost at each development stage, overall reward and unit costs, we assume that the expected value (c) can be represented by the median rather than the mean, and that there exists a 95% upper limit estimate (u). We further assume that a random variable X, which is used to represent these parameters, follows a log-normal distribution. In other words, log (X) follows a Normal distribution with mean μ and standard deviation σ. Then the mean

(and median) of the distribution of $\log(X)$ is $\log(c)$ and the standard deviation is $(\log(u)-\log(c))/1.96$. These central moments define the distribution from which MC simulation can be applied to draw values of log (X) at random. Once a value of log (X) is drawn from its distribution, this is exponentiated to give the corresponding value of X, ensuring that the resulting MC samples for the cost at each stage of development, overall reward, and unit costs are positive. The mean and standard deviation can be derived in a similar fashion for a 95% lower limit estimate.