A real options game approach to health technology assessment

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Abstract

Current economic evaluations do not explicitly acknowledge that there are multiple decision points throughout the lifecycle of new health technologies which, in the presence of uncertainty and irreversible consequences of those decisions, influence value. Real options analysis (ROA) has been proposed to overcome these limitations. However, applications to date all assumed that decisions influencing the arrival of information are made by the same actors making the decisions on adoption.

The aim of this thesis is to explicitly incorporate into health technology assessment (HTA) the impact of uncertainty on decision making about new health technologies in the presence of irreversibilities. I present a series of analyses comparing "traditional" economic evaluation methods to applications of ROA using the case study of drug-eluting stents (DES).

The conventional application of ROA allowed for flexibility in decisions incorporating all economic consequences of changing decisions. Over and above uncertainty surrounding the current estimate of value, three major components contributing to the economic value of the new technology were assumed to also change over time. This type of analysis can be used to determine the optimal initial decision allowing for changes in decisions and the optimal timing for review. However, it assumes that new information will always be revealed, regardless of the original decision on adoption. To reflect the combined impact of coverage, pricing and research decisions in HTA and therefore to make information arrival endogenous, a more complex approach is suggested: a Real Options Game (ROG) combining ROA with a game theoretical approach. In the ROG the HTA body and the manufacturer are assumed to play a sequential, incomplete information game, where the manufacturer has control over the arrival of information. The manufacturer decides whether to submit evidence, reduce price and conduct more research, while the HTA body decides on adoption. The DES analysis modelled a series of decision points between 2005 and 2010, with decisions not depending on hindsight, but allowing for predicted changes in value, incorporating a drift in information and responses by the other party. Payoffs were estimated for both players using a probabilistic Markov model. Optimal strategies incorporating the impact of earlier decisions on research were determined.

HTA is a dynamic and interactive process, therefore results of the ROA analyses sometimes suggested a different course of action compared to traditional analyses. The best decision may depend on predictions of how other parties will react, as well as likely evolution of the evidence base and the costs of decision reversal.

List of abbreviations

ACD	Appraisal consultation document
AWR	Approval with research
BMS	Bare metal stent
CABG	Coronary artery bypass graft
CTC	The Cardiothoracic Centre, Liverpool
DES	Drug-eluting stent
EME	Efficiency and Mechanism Evaluation Programme
EVCI	Expected value of complete information
EVPI	Expected value of perfect information
EVPPI	Expected value of partial perfect information
EVSI	Expected value of sample information
FAD	Final appraisal determination
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
INB	Incremental net benefit
MSDA	Multi-stage decision analysis
NB	Net benefit
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NME	New medical entity
NPV	Net present value
OIR	Only in research
PCI	Percutaneous coronary intervention
PPO	Preferred provider organisation
PSA	Probabilistic sensitivity analysis
PTCA	Percutaneous transluminal coronary angioplasty
QALY	Quality-adjusted life year
R&D	Research and development
ROA	Real-options analysis
ROG	Real-option game
RRR	Relative risk reduction
STA	Single technology assessment
TVR	Target vessel revascularisation

UK United Kingdom

VBA Visual Basic for Applications

VoI Value of information

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"The action which follows upon an opinion depends as much upon the amount of confidence in that opinion as it does upon the favourableness of the opinion itself" (Knight 1921)

1 Introduction

1.1 The need for economic evaluations in health care

Economic analysis relies on the understanding that resources are limited but potential uses of those resources are unbounded. Since resources that are used to produce health care such as human resources, capital and materials are limited, and since until the whole population of the world does not live forever in perfect health our want for health care is seemingly unbound, health care is to be defined as an economic good.

According to mainstream economic theory, when particular conditions are met, the distribution and production of economic goods is best left to individuals/firms pursuing their own goals. Most economic goods meet the conditions, however, health care differs from other economic goods in a number of ways, most of which have been documented by Arrow in 1963 (Arrow 1963). Therefore the health care 'market' differs from the competitive market as described in economic theory and individual patients' demands and competition between health care providers does not ensure that the market equilibrium reached in a free market for health care will be optimal. This has lead to the creation of varied health care systems where the decisions about provision and consumption of services are determined (at least partially) outside the scope of free markets.

Since the distribution of goods cannot be determined by the markets, decision making has been delegated to collective decision making agents (public or private insurance agencies or government bodies) and mechanisms put in place that ensure the correct use of resources and appropriate distribution of goods and services, however appropriate may be defined. Therefore, decision making in health care is a realm of social policy. Goods need to be assessed by the rules of social choice, and economic evaluation is an aid in the assessment step of this process. Economic evaluation is the *"comparative analysis of alternative courses of action in terms of both their costs and consequences"*.(Drummond and others 2005) The evaluation may be undertaken by a broad set of analytical approaches used to describe and compare (incrementally) the benefits and costs of competing uses of resources.(Morris, Devlin,

and Parkin 2007) It is not intended here to provide a summary of all possible approaches to the valuation of benefits and costs and how these should be compared. Regardless of which approach one adopts to valuing benefits and costs, once benefits and costs have been valued, the decision on economic grounds can be reached following a set of rules (although the decision may be altered due to consideration of other factors not included in the economic analysis). The analytical framework for decision-making in health care is to provide explicit, rational considerations to help maximise some set of objectives (health, social utility function, individual welfare) within a constrained budget.

In order for economic evaluations to provide sound assessment, and therefore to be a useful tool for decision making, they must satisfy a set of criteria. The most accepted criteria that specify the minimum requirements for an evaluation were developed by Drummond and colleagues as summarised in Table 1-1.(Drummond and others 2005) Later guidelines provide more detail, but the dimensions for the assessment criteria remained very similar.(Philips et al. 2006; Caro et al. 2012; Roberts et al. 2012; Briggs et al. 2012; Siebert et al. 2012; Eddy et al. 2012) Over and above these general criteria, particular criteria relating to the specific clinical context should also be adopted to assess the quality of the evaluation within a specific indication.

Table 1-1 Criteria to assess economic evaluations

Criteria
• Viewpoint: The research question must be well-defined and the scope of the investigation specified in advance; • The evaluation should take into consideration all relevant comparators; • The consequences of each alternative has to be established in a valid and reliable way, i.e. information from all potential sources should be encompassed, sources should be identified in a systematic manner, and the validity of the data needs to be established; • Both costs and benefits need to be valued credibly; • The economic evaluation should incorporate time preference (i.e. discounting); • The additional costs and benefits of the alternatives need to be compared to each other; • Uncertainty in the estimates of the outcomes has to be assessed.

A sound economic evaluation may be undertaken in a number of ways; however, almost all evaluations have to rely on some form of modelling to satisfy all the criteria outlined above.(Buxton et al. 1997) Models have many advantages, and they provide a framework within which information from disparate sources can be brought together consistently. (Briggs,

Claxton, and Sculpher 2006) In this thesis there is one aspect of economic evaluation through the use of modelling that I want to focus on: uncertainty.

1.2 The role of uncertainty

1.2.1 Classification of uncertainty

In his pivotal book published in 1921 Knight laid down the foundations for our current understanding of uncertainty.(Knight 1921) He complained that the term 'risk' is used very loosely in everyday speech as well as in economic discussions. In current economic evaluations the same can be said about the term 'uncertainty'. Knight provided a distinction between risk and uncertainty. According to his definition risk is a measurable uncertainty, it is a known random or stochastic process where all possible outcomes are known and where the likelihood of each outcome is known with certainty. Knightian uncertainty refers to an unmeasurable, non-quantitative form of process, where the distribution of the outcome is not known.

According to Knight, the probability of events in the case of risks can be determined in two ways. One can either deduce the probabilities mathematically - a priori probability- or empirically evaluate frequencies from historical instances – statistical probability. Determining that the probability of a perfect dice landing on any particular face is 1 in 6 is an a priori probability calculation. However, if one would suspect that the dice is loaded, therefore the probabilities cannot be determined a priori, one could calculate the statistical probability, i.e. the frequency of landing on a particular face by carrying out a large number of throws. A priori and statistical probabilities have also been classified as "objective" probabilities.(Carnap 1971)

However, Knight argued that in everyday decision making there is often no valid basis of any kind for classifying instances and therefore to derive any form of objective probability.(Knight 1921) Still, decisions are being made in situations which are in a high degree unique on what Knight termed as "estimates" based on one's past experiences and the confidence in one's ability to make correct decisions. A similar subjective theory of probability was also formulated by Ramsey, (Ramsey 1931) and later more extensively by de Finetti. (de Finetti 1937) The concept of subjective probabilities emphasises that uncertainty depends not only on patterns of information, but on the opinions of individual people.(Savage 1962) However, the use of the adjective "subjective" is questionable and has led to misinterpretations of the theory. Subjective probability is not something "*fetched out of the sky on a whim*". (Jeffrey 2004) To aid clarity, the term "personal" probability was introduced by Savage.(Savage 1954) In his pivotal work, Carnap defined personal probability as the probability assigned to a

proposition or event *H* by a person *X*, in other words, the degree of belief of *X* in *H*.(Carnap 1950; Carnap 1971) That is, using the Knightian definitions, it is the estimate of a specific individual of the probabilities associated with a highly unique situation. Subjective probability "*is what your actual judgement should be, in view of your information to date and of your sense of other people's information, even if you do not regard it as a judgement that everyone must share…*" (Jeffrey 2004)

In summary, there are three types of uncertainty. The first type is uncertainty that can theoretically be resolved if one were to know all defining characteristics and laws of interaction or if one had enough resources to observe all instances instead of limited samples, i.e. risks or uncertainty with objective probabilities. Secondly, uncertainty that one doesn't have empirical data on, but still can make judgements about based on past experience or expertise, i.e. uncertainty that nevertheless can be characterised with personal probability. Bayesian statistics combines these two types of uncertainties in the analysis by looking at how evidence (objective probabilities) change the intrinsically subjective (personal) prior probabilities. The last type of uncertainty is the truly unknown, uncertainty caused by unanticipated, fortuitous events, the *vis major*.

1.2.2 Uncertainty in economic evaluations

Economic evaluation methods described in this thesis are capable of incorporating the first two types of uncertainty: uncertainty that can be quantified either by objective or subjective probabilities. However, analytical methods have limited use in dealing with the truly unknown. Although it is important to keep this distinction in mind, the terms uncertainty and risk will be used interchangeably in the thesis, but will always refer to the first two types, i.e. quantifiable uncertainty.

1.2.2.1 Sources of uncertainty

Briggs and colleagues have developed a taxonomy for uncertainty in economic evaluations alongside clinical trials. (Briggs, Sculpher, and Buxton 1994) They distinguished between methodological disagreement between studies that hinders cross-study comparison of results that have employed different methods; sampling variation; uncertainty surrounding the extrapolation from intermediate clinical outcomes to long term health outcomes; with the question of whether the results of the study can be generalised to other settings adding the last layer of uncertainty. Manning and colleagues developed a classification for economic evaluations relying on modelling. (Manning, Fryback, and Weinstein 1996) They discussed the uncertainty surrounding key parameters of the model ('parameter uncertainty'), including the

uncertainty about the appropriate rate of inflation in the medical field or the discount rates, the transferability of efficacy parameters of clinical trials to real world effectiveness, as well as sampling variation. 'Model uncertainty' on the other hand encompassed uncertainty about the correct method to combine model parameters ('model structure uncertainty') and uncertainty related to the reproducibility of the analysis itself, i.e. would a different analyst conceive, structure and parameterise the model in the same way ('model process uncertainty'). Briggs also distinguished between methodological uncertainty, parameter uncertainty, modelling uncertainty (including structure and process uncertainty), and uncertainty around generalisability/transferability of results in economic evaluations applying modelling methods. (Briggs 2001) The difference between the systems of Manning and colleagues and Briggs is that in Briggs parameter uncertainty relates only to sampling variation, while questions about the appropriate discount rates and time horizon to use are grouped under methodological uncertainty.

Methodological uncertainty refers to the availability of different approaches to value resources and health outcomes, the inclusion of and level of time-preference in the evaluations, and selecting the perspective and time horizon of the evaluations.

Parameter uncertainty stems from variability and heterogeneity between patients. Individual patients will differ from each other in e.g. their response to treatment and how their quality of life is affected by the disease or the treatment itself even if their baseline characteristics are identical. This type of random uncertainty has been termed variability, and can be reduced by gathering more information. (Briggs, Claxton, and Sculpher 2006) However, if the differences between patients can be explained by differences in patient characteristics, one talks about heterogeneity. Heterogeneity will not disappear with more knowledge and larger sample sizes, but can be reduced through stratification. Patient level variability and patient heterogeneity also lead to uncertainty over population level parameters.

Structural uncertainty relates to the fact that there are often a number of credible structural assumptions that can be made to characterise the underlying natural disease process or the impact of treatment.

Uncertainty stemming from different sources should be assessed in different ways. Table 1-2 provides the recommendations found in the literature.

Table 1-2 Methods to assess uncertainty by source

Source	Method	Reference
Methodological uncertainty	Standardisation, reference case	(Gold and others 1996; National Institute for Health and Clinical Excellence June 2008)
Variability	Probabilistic analysis	(Briggs 2001, 172-214)
Heterogeneity	Subgroup analysis	(Briggs 2001, 172-214)
Structural uncertainty	Scenario analysis; model averaging; model selection based on prediction performance	(Bojke et al. 2006)
Generalisability / transferability	Deterministic sensitivity analysis	(Briggs 2001)

1.2.2.2 Uncertainty leading to decision uncertainty

All these types of uncertainties result in a distribution of possible cost-effectiveness ratios.(Briggs, Claxton, and Sculpher 2006) If the distribution straddles the cost-effectiveness threshold, i.e. there is a higher than zero percent chance that the new technology is not cost-effective, then the uncertainty in the evaluation also leads to decision uncertainty.(Claxton et al. 2005) However, a decision has to be made. The assessment of the implications of decision uncertainty is an essential part of the decision-making process about new health technologies. (Claxton et al. 2005)

1.3 Decision making under conditions of uncertainty

Decision analysis had been defined as a systematic approach to individual decision making under uncertainty (Raiffa 1968) It provides a formal, transparent, and orderly approach to assist the decision maker in identifying the preferred course of action from competing alternatives.

The foundations of decision analysis are provided by a set of axioms developed by von Neumann and Morgenstern, and Savage.(von Neumann and Morgenstern 1944; Savage 1954) These axioms[1] imply that the attractiveness of alternatives should depend on:

[1] To construct a utility function over uncertain outcomes (gambles), people's preferences should be complete, transitive, continuous, monotone and independent of irrelevant alternatives. Von Neumann and Morgenstern proved that, as long as all the preference axioms hold, then a utility function exists, and it satisfies the expected utility property (for a gamble g with outcomes $\{a_1, a_2,...,a_n\}$, with effective probabilities $p_1, p_2,...,p_n$ respectively, $u(g) = p_1u(a_1) + p_2u(a_2) + ... + p_nu(a_n)$ where $u(a_i)$ is the decision-maker's utility from outcome a_i)

- The likelihoods of the possible consequences of each alternative and
- The preferences of the decision makers for those consequences.

The technical implications are that expected utility of the each alternative can be calculated and that alternatives with higher expected utilities should be preferred.(Keeney 1982)

On a societal level the Arrow-Lind Theorem states that, under certain assumptions[2], the social cost of risks tends to zero as the population tends to infinity, therefore projects can be evaluated on the basis of expected net benefit alone.(Arrow and Lind 1970) When applied to decisions about adoption of new health technologies this means that health technologies should be selected for reimbursement within a health care system based on their mean net benefit (NB) irrespective of the distribution surrounding the mean. (Claxton 1999) The above described notion is sometimes termed the ”irrelevance of inference”, that is the irrelevance of whether the difference between the health technologies can be regarded as statistically significant or to fall outside the Bayesian range of equivalence. The decision process is then simplified to answering two separate questions:

- Should the technology under consideration be reimbursed?
- Should further research be undertaken to reduce uncertainty?

In Claxton’s original framework, decision uncertainty only plays a role in answering the second question, although one still needs to characterise uncertainty to correctly estimate the expected net benefit if the model is non-linear and to assess the value of collecting more information.

However, an audit of the UK’s National Institute for Health and Care Excellence’s (NICE) practices regarding sensitivity analyses in health technology assessments reported that “*Some Committee members expressed the view that where uncertainty is greater, the decision should tend towards a negative*”.(Andronis, Barton, and Bryan 2009) Are decision makers simply irrational, or are there factors missing from the irrelevance of inference argument?

Later reviews and critiques of irrelevance of inference did not question the irrelevance of arbitrary statistical inference, but emphasised that the reimbursement decision needs to be taken simultaneously with the decision whether additional research is to be

[2] The conditions are that 1) the government funds all costs initially and only when the benefits are being distributed should it attempt to recover costs through taxation; 2) the return of the project must be independent of individual income; and 3) the returns must be spread over a reasonably large number of individuals.

undertaken.(Sculpher and Claxton 2005a) The decision on reimbursement also alters future research possibilities as dissemination of the new technology will decrease the number of patients available to participate in research and also raises ethical questions about whether it is acceptable to randomly withdraw reimbursed technologies from patients.(Chalkidou et al. 2008) Reimbursing new cost-effective technologies when it is efficient to require additional evidence raises questions on the reversibility of decisions. (Sculpher and Claxton 2005a; Chalkidou et al. 2008; Palmer and Smith 2000)

Decision makers are not irrational, but the "irrelevance of inference" decision-making framework implicitly assumes that switching between health technologies can be undertaken at no cost, that is decisions are completely reversible and there are no initial investments that would later become sunk costs if the technology is to be withdrawn. If there are irreversibilities associated with a decision, then uncertainty starts to matter. Over and above the economic costs of switching between health technologies, political, ethical, and social pressures also often make it difficult for healthcare payers to reverse coverage decisions. Decision-makers may well be justified in being cautious about implementing new technologies with promising but uncertain benefits, if their decisions cannot be easily or costlessly reversed if they later turn out to have been wrong.

In the UK, decision makers at NICE often consider the date when guidance will be reviewed, and do recognise the need to assess the cost associated with a possible change in the decision about the technology (the consequences of irreversibility) and the impact on ongoing research of issuing guidance.(Claxton et al. 2005; Claxton et al. 2012; National Institute for Health and Care Excellence April 2013) However, the consideration is done implicitly by the Appraisal Committee (if at all) and not explicitly in the economic evaluation itself.

Real options analysis (ROA) has been proposed as a way to acknowledge and quantify the importance of uncertainty and irreversibility in Health Technology Assessment (HTA).(Palmer and Smith 2000) Generally, a real option is defined as the right, but not the obligation to take an action in the future. (Amram and Kulatilaka 1999) As will be explained in Chapter 0, ROA has its roots in financial theory, and it allows for the explicit incorporation of flexibility (e.g. in terms of timing, adjustments to scope in response to changes in the value of the investment and abandonment of investments) into the structure of the decision. ROA integrates the uncertainty and irreversibility associated with a technology into a unifying theory of economic evaluation. The advantage of ROA is in incorporating multiple decision-points during the lifetime of the technology and explicitly taking into account the cost associated with delaying

or changing the decision; therefore making it possible not only to indicate the magnitude of certain types of uncertainty, but also to quantify its impact on the economic evaluation.

There are three characteristics of decisions that must all hold for real options to exist: (Palmer and Smith 2000)

1) there must be uncertainty about the future state of the world;
2) the investment must entail an irreversible commitment of resources; and
3) there must be discretion as to the timing of the investment.

Although many have recognised the importance of acknowledging uncertainty, the flexibility in timing of decisions and the consequences of irreversibility, (Bridges 2004; Claxton et al. 2005; Miller 2005; McCabe, Claxton, and O'Hagan 2008) ROA has not been adopted in a systematic way.(Meltzer and Smith 2011) Recently, Forster and Pertile have shown that when adoption, treatment and research decisions are viewed as a single economic project, the evaluation should account for the expected costs and benefits of additional research; the flexibility and irreversibility of the actions; and the dynamic nature of the decision process.(Forster and Pertile 2013) We know that adoption decisions can fundamentally alter future research possibilities by raising ethical concerns for patients randomised not to receive an approved technology, as well as changing the incentives for manufacturers to conduct new studies. (Chalkidou et al. 2008) Forster and Pertile assumed that new information in later periods will definitely resolve uncertainty. But in real life whether, how and when new information will arrive is not independent of the adoption decision.

1.4 Aim and objectives of the thesis

My aim with this thesis is to explore the feasibility of using ROA in HTA to explicitly incorporate the impact of uncertainty on decision making about new health technologies in the presence of irreversibilities. I will compare economic evaluation methods that deal with uncertainty differently and show what questions could be answered with the use of ROA that are currently left to the implicit consideration of decision makers.

ROA has been applied to HTA before in a few instances.(Palmer and Smith 2000; Eckermann and Willan 2008b; Attema, Lugner, and Feenstra 2010; Grutters et al. 2011; Favato et al. 2013), but methodological assumptions in the current thesis differ from previous works applied to HTA in the following three main areas:

- Modelling information arrival for separate components that contribute to the value of the new technology;
- Including not just uncertainty in the current estimate of the value of the technology (static uncertainty, as in the option value calculations based on the expected value of sample information in the works of Eckermann and Willan (Eckermann and Willan 2008b; Eckermann and Willan 2008a; Willan and Eckermann 2012a; Eckermann and Willan 2013)), but also trends in information over time (dynamic uncertainty);
- Explicitly modelling interactions between actors.

Past methodological works on ROA in HTA suggest that the value of the technology under evaluation should follow a predetermined stochastic process.(Palmer and Smith 2000; Driffield 2003) That is, the NB should evolve over time in a partially random fashion. This approach had been used extensively in financial markets and there is a vast literature offering solutions to the optimisation process. However, such stochastic processes may not reflect the characteristics of value in health care properly and therefore may be difficult to interpret in the context of economic evaluations of new health technologies.(Eckermann and Willan 2008b) Furthermore, in the case of new health technologies there is no historical data that would enable estimation of the trend and/or volatility of change in value. However, possible changes in the components of NB could be predicted with more certainty. Therefore one novelty in the application of ROA to HTA that I suggest in this thesis is to model change in the components that generate value in health care rather than trying to model change in value directly. By modelling change in the components of NB, it becomes possible to draw the process that NB follows over time empirically.

Eckermann and Willan through a series of publications have also developed an approach that estimates the option value of delaying the adoption decision on a new health technology. They focused on reducing uncertainty, and show that it would be optimal to undertake further research if the expected value of information from such research exceeds the expected opportunity costs.(Eckermann and Willan 2007; Eckermann and Willan 2008a; Eckermann and Willan 2008b; Willan 2008; Eckermann and Willan 2009; Eckermann, Karnon, and Willan 2010; Willan and Eckermann 2012a; Willan and Eckermann 2012b; Eckermann and Willan 2013) For promising technologies for which current evidence suggest an expected positive but uncertain incremental net benefit (INB), there are then three options: adopt with no trial (i.e. adopt the technology on the basis of current evidence, with no additional evidence required), delay and trial (i.e. delay the adoption decision and undertake a trial to provide further evidence), and adopt and trial (i.e. adopt while undertaking a trial). Repeating the analysis from the payer's

and then from the manufacturer's perspective, their framework can also be used to establish the (globally) optimal research design and maximum price of the intervention acceptable to the payers, and the optimal research design and minimum price acceptable to the manufacturer.(Willan and Eckermann 2012b) However, the framework's underlying assumption is that there exists a true INB that remains constant through time and each new trial is expected to improve the estimate of this true INB (expected value of perfect information is expected to reduce when evidence is updated with new information) (Eckermann and Willan 2007) and reduce the expected per patient opportunity loss(Willan and Eckermann 2012b) (even though INBs calculated from individual trials may vary, they are all viewed as samples from an underlying distribution(Willan and Eckermann 2012a)). Their works represent uncertainty that remains the same through time (static uncertainty).

However, the empirical evidence on estimates of effectiveness measures cumulated over time does not confirm the existence of a true underlying value to which our estimates would oscillate towards with ever decreasing uncertainty. Although the evidence is limited, the studies that do exist show a trend in effectiveness over time.(Ioannidis 2005; Gehr, Weiss, and Porzsolt 2006) These findings suggest an evolution of knowledge, rather than a random variation around an underlying, unknown true value. The findings suggest an uncertainty that that evolves through time (dynamic uncertainty). Herein lays the one of the main differences of the methods proposed in this thesis compared to the methods developed by Eckermann and Willan. Representing dynamic uncertainty requires different methods from representing static uncertainty, and cannot be captured by expected value of information calculations. Therefore in this thesis I will assume that the mean (the best) estimate of effectiveness follows a stochastic process with a trend over time to incorporate the decision makers' expectation for the evolution of knowledge. As a consequence of this assumption, I also propose in the thesis that rather than evaluating the expected value of perfect information (EVPI), we should be focusing on the expected value of complete information (EVCI) which in addition to having perfect information about the current value of the new health technology also incorporates knowledge about how that value is going to change in the future.

The application of ROA that has been seen in the literature a few times allows for describing the dynamic nature of the decision process with flexibility in decisions as well as incorporating all economic consequence of changing decisions. (Palmer and Smith 2000; Attema, Lugner, and Feenstra 2010; Grutters et al. 2011; Favato et al. 2013) This evaluation method helps us uncover the value of waiting for more information. Over and above determining the optimal

initial decision allowing for changes in decisions, I will also show how this method could be used to determine the optimal timing for review.

To the best of my knowledge, all previous applications of ROA to date assumed that arrival of information on the health technology under evaluation in the future is independent from the initial decision to be made about its adoption. Even in the framework of Eckermann and Willan, both the payers and the manufacturer are assumed to optimalise within their own jurisdiction, determining their optimal trial size and price without considering the constraints of the other party. There is no strategic interaction between the payer and the manufacturer during the joint decision on adoption and the need for further research. I propose a novel, more complex approach to incorporate strategic interaction and make information arrival endogenous. Combining ROA with a game theoretical approach would allow us to connect the decisions about adoption and further research providing the new information about the technology in the future even if the decisions about these questions are made by different actors; while at the same time keeping the advantages of ROA in evaluating the adoption decision in a dynamic environment.

The objectives of the thesis are to compare three economic evaluation methods to assess the feasibility of using ROA:

- A traditional economic evaluation including probabilistic evaluation, EVPI and EVPI for parameters calculation to serve as the control;
- A "simple" ROA in which simplicity refers not to the methods, but to the simplifying assumption that information arrival is independent of previous decisions - the analysis will introduce expectations for how components of the value of the health technologies are expected to change; and a
- A real option game combining elements of ROA with game theory to model strategic interactions in which decisions have to be made in consideration of how the other players might react to internalise information arrival.

In all of the analyses the decision makers will be assumed to be rational, maximising a pre-specified objective function. I will argue that the best course of action, defined as the series of decisions leading to the highest benefit according to the decision maker's objective function, suggested by ROA may be different from the one suggested by traditional analyses depending on the expected change in evidence base and the costs of decision reversal.

1.5 Structure of thesis

Chapter 0 starts with a critique of the current static approach to economic evaluation and shows how the assumptions necessary for the traditional economic evaluation methods to apply only in selected situations. An evaluation encompassing the full life-cycle of the new technology will be needed if there is either no flexibility in the decision but there is known variation between the relative costs and effects between patient cohorts, or if there is flexibility in the timing of the decision with some decisions leading to irreversible consequences, i.e. if real options exist. I argue that knowledge about the new technologies accumulates over time and that there are likely to be systematic drifts in knowledge, therefore the (estimated) value of the technologies also changes as may the decisions about their use. Therefore incorporating the impact of this flexibility into the economic evaluation of new technologies is necessary to better understand the true value of these technologies.

Chapter 0 provides an introduction to the underlying concept of financial and real options. ROA is a relatively new field and terminology varies, so a working definition to be used throughout this thesis is provided. The section also includes a review of methods to characterise uncertainty in ROA and then, given the chosen characterisation method for uncertainty, methods to determine the value of the new technology incorporating the impact of that uncertainty (i.e. a review of solution methods). The chapter ends with a review of game theoretical methods that will enable me to incorporate strategic interactions between actors involved in bringing new health technologies to the market into the economic evaluation.

Chapter 0 presents a review of the literature showing how ROA has been previously applied in relation to health technologies. I show that although advocates of ROA have recognised the importance of irreversibilities and incorporating multiple decision points along the line in the development and assessment of new health technologies, minimal consideration has been given to the fact that those multiple decisions are made by multiple decision makers and the studies did not represent the strategic interactions between the decision makers.

Chapter 0 describes the modelling framework. Although the methods described in this thesis could easily be extended to more complex situations, for the purposes of this thesis a simpler framework was chosen within which the principles of the analyses can be presented. A detailed description of the assumptions made in the analyses is provided and a short overview of the technology chosen as a case study: the assessment of drug-eluting coronary artery stents (DES).

Chapter 0 describes the development of an economic model which allowed the calculation of the treatment costs and health benefits for patients receiving DES versus those patients receiving current standard care (bare metal stents – BMS). Stochastic model evaluation enabled the quantification of parameter uncertainty around the cost effectiveness of DES. Separate EVPI and expected value of perfect information for parameters (EVPPI) calculations were then also carried out to answer the questions whether further research is warranted and what type of information would be most useful to reduce uncertainty around future decisions.

Chapter 0 describes a naive application of ROA allowing for flexibility in decisions incorporating all economic consequence of changing decisions. The analysis introduces expectations for how key components of the value of the health technologies are expected to change and determines the optimal initial decision allowing for changes in decisions as well as the optimal timing for review from the decision maker's perspective.

To make information arrival endogenous a further extension is suggested in Chapter 0, combining ROA with a game theoretical approach. Two agents (the payer and the manufacturer of the new technology) are assumed to play a sequential, incomplete information game, where the manufacturer has control over the arrival of information. The manufacturer's steps include decisions to submit, reducing the effective price, conducting more research, while the payer decides if and when to accept. This model allows the determination of optimal strategies incorporating the impact of earlier decisions on research, including the optimal time to submit for review from the manufacturer's perspective.

Chapter 0 presents the discussion of the analyses and the conclusions of the thesis. ROA methods and underlying assumptions are discussed and areas for future research are identified. The innovative features within the thesis are highlighted. I argue that a real options game approach could feasibly contribute to our current understanding about the value of new health technologies.

2 Assumptions of current economic evaluations

2.1 Introduction

This chapter examines in more detail the methods applied in the majority of economic analyses that are currently undertaken and their underlying assumptions. I will explain how the current evaluations use a static approach. Although it has been recognized that decision making about new health technologies is a dynamic process, the methods of many economic evaluations informing these decisions do not represent the policy choices accurately and therefore cannot properly inform these decisions when there are significant consequences of the decisions that cannot be reversed if the decision later turns out to be wrong. Economic evaluations, where relevant, should be extended to cover multiple cohorts and to include real options (incorporate the impact of flexibility and irreversibility in the timing of the decisions).

2.2 Current static approach to economic evaluation

Decision-making about the acceptance of new health technologies is in effect a constrained optimisation problem over the lifetime (T) of the new technology. Let N_t denote the number of patients eligible to start treatment in any given year. Then $\sum_{t=1}^{T} N_t$ gives the effective population, the maximum number of patients that may be treated over the lifetime of the new technology.

The reimbursement body needs to decide what proportion of patients (s_t) from the effective population should benefit from the use of the new technology. In many cases this means trying to the find the patient subgroup for which it is worth funding the new technology. Uncertainty around the value of the new technology may stem from parameter uncertainty and patient heterogeneity. Heterogeneity refers to true differences in outcomes between patients, which can be explained by differences in patient characteristics. Pharmacoeconomic guidelines recognise the importance of acknowledging patient heterogeneity, but there is a lack of consensus on how to deal with heterogeneity.(Grutters et al. 2013; Ramaekers, Joore, and Grutters 2013) Performing the evaluation separately for each patient strata (Coyle, Buxton, and O'Brien 2003; Briggs, Claxton, and Sculpher 2006; Espinosa et al. 2014) or separating parameter uncertainty and heterogeneity via the use of nested Monte Carlo simulations have both been suggested.(Koerkamp et al. 2010; Vemer, Goossens, and Rutten-van Molken 2014) Essentially both methods require that evaluation and decision making are

separated for identified patient subgroups. For simplicity, the models in this thesis will disregard patient heterogeneity. Therefore in case of rejection of the new technology s_t would be 0%, while full acceptance of the technology with no restrictions would mean that s_t may reach 100%.

The main question that the reimbursement body needs to decide is whether and when should current practice (*i=0*) be replaced by the new intervention (*i=1*). However, the vast majority of economic evaluations performed to this date that are aimed to help decision makers do not answer this question.

2.2.1 The simplified objective function

Current economic evaluations calculate the expected effects (E_1 and E_0) and the expected costs (C_1 and C_0) of the new and the old technologies per patient over the time when the new technology is expected to have an impact on either the costs or the health benefits of this patient. Let *H* denote this time horizon which captures the impact of the health technologies under evaluation within the lifetime of the cohort of patients evaluated. Note that both E_{it} and C_{it} (*i=0,1*) represent expectations of stochastic variables for patients receiving treatment *i* in time period *t*. Also, to allow comparisons between costs and health benefits occurring in different time periods, both *E* and *C* should be present values (discounted values) of the streams of costs and benefits occurring over *H*. The evaluation is undertaken for a single cohort of patients assuming that they all either receive the new technology (*s=100%*) or that they all receive the old technology (*s=0%*). If λ denotes society's maximum willingness to pay for health benefits (the threshold), the decision then becomes to choose either the new or the old technology (by setting *s* to be 100% or 0%) so that expected net monetary benefit for these patients is maximised as shown in Equation 1:

Equation 1

$$\max_s NB = s(\lambda \sum_{h=1}^{H} E_{1h} - \sum_{h=1}^{H} C_{1h}) + (1-s)(\lambda \sum_{h=1}^{H} E_{0h} - \sum_{h=1}^{H} C_{0h})$$

2.2.2 Value of information

Once the decision has been made based on Equation 1, value of information (VoI) analysis provides an analytical framework which can be used to establish the value of acquiring additional information to inform a decision problem.(Claxton 1999; Claxton and Sculpher 2006)

If we denote the uncertain parameters in the model with *Θ*, then from Equation 1 above the optimal decision with current information is to choose the intervention that generated the maximum expected net benefit ($max_i E_\Theta NB[i,\Theta]$). With perfect information (for a particular

value of Θ), the decision maker could select the intervention that maximises the known net benefits ($max_i NB[i,\Theta]$). However, the true values of Θ are unknown, so the expected value of a decision taken with perfect information is found by averaging the net benefits of these optimum choices under perfect information over the distribution of Θ ($E_\Theta max_i NB[i,\Theta]$). The expected value of perfect information (EVPI) for an individual patient is the difference between the expected value of the decision made with perfect information and the decision made on the basis of current information:

$$EVPI = E_\Theta max_i NB[i,\Theta] - max_i E_\Theta NB[i,\Theta]$$

The EVPI for the population is usually calculated using an estimate of incidence (I) over the lifetime of the technology (T) and a discount rate (r) as:

$$Population\ EVPI = \sum_{t=1}^{T} \frac{I_t}{(1+r)^t} EVPI$$

The population level EVPI provides an upper limit to the cost of further research. Further research is only worthwhile, if its costs are below the population EVPI.

2.2.3 Critique of the static approach to economic evaluation

The starting point of traditional economic evaluations is a single decision point. The course of action is decided at the beginning of the evaluation and is assumed to be followed through to the end of the evaluation's time horizon (H). However, analysing technologies at a single point in time only leads to the correct decision if the adoption decision can be fully and costlessly reversed and if there is no flexibility in the timing of the decision.(Forster and Pertile 2013) In these cases, the decision on adoption of the technology and the decision on conducting further research are independent. That is, "irrelevance of inference" (Claxton 1999) only holds if no real options exist. If real options do exists, there are multiple interrelated decision points throughout the lifetime of the technology, and the dynamic impact of the decisions made at different time points should not be ignored in the evaluation.

Furthermore, the static approach to economic evaluation also assumes that the patient cohort evaluated is representative of all patients who may receive the technologies during the lifetime of the new technology. Even in the value of information calculations, the EVPI for the patients receiving the treatments at different time points is assumed to be the same, the single cohort for which the EVPI was calculated is thought to be representative of all patient cohorts.

These interrelated simplifying assumptions (no real options exist and the evaluated cohort is representative of all cohorts) are discussed in more detail below.

2.2.3.1 No real options - the assumption of a single decision point

If there is no flexibility in the timing of the decision and the decisions can be fully reversed at no additional cost, assuming a single decision point in the evaluation is appropriate. However, these conditions are not always met.

At an individual patient level, some technologies are truly irreversible. For individual patients a decision whether or not to undergo a surgical procedure may be irreversible if the impact of the procedure cannot be undone at a later date, or if the operation will become impossible if the patient's condition deteriorates. However, the impact of other health technologies can be reversible for individual patients; the effect may wane or stop once treatment ceases.

At the population level, decisions about the adoption of new health technologies are almost always reversible. After a change in the decision, new patients can receive another treatment. But the change in decision may not be easy or costless. Facilities or new protocols developed for the new technology will need to be changed and rewritten if the decision is reversed, not to mention other political implications associated with reversing a decision. These costs may be substantial and they may impede reversibility. Although decision makers may consider the possibility to change the decision later in view of new evidence, this possibility and the costs associated with reversing the decision are not incorporated explicitly into the economic evaluations at all.

2.2.3.2 The assumption about the representativeness of a single cohort

Most economic evaluations calculate outcomes for a single cohort - only the prevalent cohort or only the next incident cohort - of patients. That is, of the effective population ($\sum_{t=1}^{T} N_t$) only N_1 is modelled. This may mean that current evaluations do not capture all future patient-related benefits and costs within the lifetime of the health technology.

Hoyle and Anderson show through the use of algebraic expression the special situations when modelling only the first cohort is sufficient.(Hoyle and Anderson 2010) They prove that the ICER of the first incident cohort and therefore the decision made about the acceptance of the new health technology only equals the ICERs for all future incident cohorts within the lifetime of the technology if the discount rates for costs and benefits are equal. Although most countries recommend the same discount rate for costs and benefits, discounting the health effects at a lower rate than costs is a valid method of taking into account of the increase in the future value of health and is recommended by the UK Department of Health.(Gravelle and Smith 2000; Department of Health 2004; Claxton et al. 2011a) What is more important for the current discussion is that they also point out that the length of time a patient cohort may

benefit from the new technology may depend on the type of technology and where we are in the lifecycle of the technology itself. If there is evidence that different patient cohorts in time will have a different treatment experience, they should be stratified according to time of treatment and analysed separately; all patients cannot be assumed to be the same as the initial cohort.

2.2.3.2.1 Treatment duration, the length of time the technology impacts a patient and the lifetime of the technology

The lifetime of the technology (*T*) is a separate concept from treatment duration (*D*) and the length of time individual patients' outcomes are influenced by the health technology (*H*) as well as from the lifetime of the patients using the health technology (*L*). Treatment duration (*D*) is determined by the type of the technology. Surgical procedures usually last a few hours with a few days or weeks of recovery, antibiotics require a fixed course of treatment (e.g. 5-7-14 days), oncology treatments may be given for a fixed number of cycles, while medication for chronic disease may be given indefinitely. The time individual patients' outcomes are influenced by the treatment (*H*) will always be larger or equal to *D*. The difference between *H* and *D* is also treatment specific. The effect of contraceptives may disappear in the next menstrual cycle after their use is stopped, and the blood pressure of a patient forgetting to take their medication for hypertension will be elevated straight away. On the other hand, 5 years of treatment with pravastatin was associated with a significant reduction in coronary events for a subsequent 10 years in men with hypercholesterolemia who did not have a history of myocardial infarction (Ford et al. 2007), and hip replacement increases the mobility and function, therefore the quality of life of patients sometimes for more than a decade after the actual operation.(Sexton et al. 2010) *H* will always be shorter or equal to the lifetime of the patient using the technology.

$D \leq H \leq L$

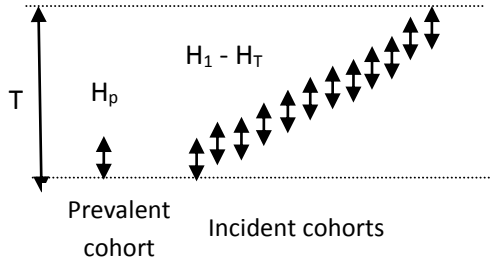
The lifetime of the technology on the other hand is determined by speed of research and development in the disease area of the technology. It will depend on how quickly the now innovative technology will be replaced by an even newer, more efficacious technology. The relationship between *D, H* and *T* determines whether it is acceptable to model only a single cohort.

D and *H* might be small as shown in Figure 2-1, for example in the case of treatments for acute infections. In these cases the costs and benefits experienced by future patients may be similar to those of the modelled cohort and there may be very little difference between the prevalent

and the incident cohort. Even the very last cohort treated with the technology in question will receive the treatment for the same length of time. That is, if H_p denotes the time the new technology impacts the prevalent patients' outcomes, while H_t with $t=1,2, \ldots, T$ denotes the times the new technology impacts the outcomes of incident patients receiving the treatment in period t, these Hs will be constant:

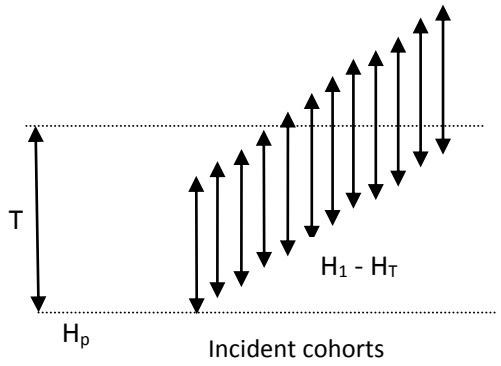
$H_p=H_1=H_2= \ldots = H_T$

Figure 2-1 Relationship between T and H in short acute treatments



However, if H in the initial cohort is large, then H for the future cohorts will depend on the type of the condition and the type of the technology. H is large in the case of chronic conditions, such as treatment for hypertension or diabetes. It is also large in the case of hip replacement or most implanted medical devices. However, the implanted hip or the implanted coronary arterial stent will not be removed and replaced just because a newer version is available. In these cases the patients who have been successfully treated with the old technology from the prevalent cohort will not receive the new technology at all ($H_p=0$). For all incident cohorts H will remain constant and the effect and costs associated with its use will also be similar across all incident cohorts ($H_1=H_2=\ldots=H_T$), and H will stretch into time periods beyond T. This is illustrated in Figure 2-2.

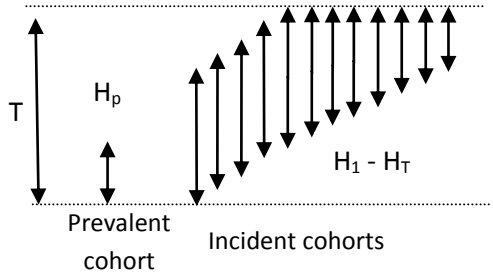
Figure 2-2 Relationship between T and H in long not replaceable treatments



Patients taking oral medication for hypertension or diabetes however may be switched over to the new medication as soon as it becomes available. This poses problems for the calculation

of costs and effects on both ends of the lifetime of the technology (see Figure 2-3). The prevalent cohort has been receiving treatment for their condition for some time already, their baseline characteristics, the severity of their disease may be different from the characteristics and severity of patients who are newly diagnosed. Therefore the length of treatment (*D*), associated costs and the health benefits that might be achieved in the prevalent cohort may be different from those in the incident cohorts. Another issue presents at the end of the lifetime of the new technology. This technology is likely to be just as easily replaced by an even newer technology, therefore incident cohorts starting their treatment late in the lifetime of the technology will not receive the treatment for as long as the initial cohorts. D_t when t is large will be shorter than D_t when t is small. This raises the question, how much of the benefits and costs associated with the treatment under evaluation should be attributed to the late incident cohorts. One needs to determine how much further *H* should be modelled after *T*.

Figure 2-3 Relationship between T and H in long, replaceable treatments



Hoyle and Anderson point out that the ICERs will differ widely according to which cohorts were actually included in the analysis.(Hoyle and Anderson 2010) We may also add that recommendations may differ according to what assumptions were made regarding the difference between the new technology's impact in the prevalent versus the incident cohorts due to differences in patient characteristics (if these are taken into account) and about the impact of shorter treatment times either in the prevalent cohort or in incident cohorts staring treatment close to the end of the product lifecycle.

The issues around heterogeneity, including the differences in the length of time treatment is received (*D*) between cohorts has prompted O'Mahony and colleagues to agree that all patient cohorts should be included in the analyses, but also to recommend not aggregating estimates over multiple cohorts.(O'Mahony et al. 2013) They argued that cost-effectiveness analyses should inform policy makers of heterogeneity in cost-effectiveness. Reporting cost-effectiveness on aggregate across all patient cohorts masks this heterogeneity due to differences in *H* and does not facilitate separate decisions for specific cohorts. Their argument is valid, however ethically it may not be acceptable to differentiate between patients upfront

according only to the time when they receive treatment. If the population is otherwise homogenous, the differences between patient cohorts over time according to their length of *H* (and, more importantly, the differences between patient cohorts due to the impact of earlier decisions on the information we have on the new technology), should be acknowledged in a single combined analysis that takes into account the dynamic effects of the decision too.

2.2.4 Conclusions

Decision making about new health technologies is a dynamic process. Thinking about this process has been extended by a number of writers, moving beyond the "irrelevance of inference" argument.(Claxton 1999) Basing current decisions only on current evidence and not worrying about changing decisions in the future has been shown to apply to only a subset of situations.(Forster and Pertile 2013) In all other cases irrecoverable costs and impacts on information arrival should be taken into account.(Claxton et al. 2012) But the methods of economic evaluations informing these decisions have not followed the same evolution. Current economic evaluations still largely employ static, single decision-point methods, assuming that the modelled cohort remains constant in terms of treatment experience. Since the decisions about the adoption of new health technologies concern a changing flow of patients over time where there is some freedom over the timing of the adoption decisions, the decisions themselves may influence the arrival of future information and the decisions may only be changed with new information becoming available at a cost, methods of traditional economic evaluations do not represent the policy choices accurately and therefore cannot properly inform these decisions. Economic evaluations should be extended to cover multiple cohorts and to incorporate the impact of flexibility and irreversibility in the timing of the decisions. Sections 2.3 and 2.4 will discuss the implications of relaxing these simplifying assumptions further.

2.3 Relaxing the single cohort assumption

Equation 1 presented the simplified decision rule we use today to determine acceptance of new health technologies. This next section discusses how the decision rule needs to be amended if one wants to relax the simplifying assumptions. If the length of time that patients use the new technology or patients' characteristics are expected to change over time, instead of modelling a single cohort, technologies should be evaluated based on the impact of all patient cohorts that are expected to be affected by the introduction of the new technology to be able to understand the true effect of the new technology (Hoyle and Anderson 2010; O'Mahony et al. 2013). For the manufacturer of the technology it is also very important to understand potential sales (determined by the numbers of patients available and the length of

time they are expected to use the new technology) and therefore potential profits to be gained over the complete lifespan of the technology. The evaluation may be done separately for each patient strata or in a combined analysis. In a traditional economic evaluation both provide valuable insight. However, the differences between the stratified and combined approaches become important if we are also to relax the assumptions about the inflexibility of the timing of the decision in later sections on this chapter. But even in a single decision situation it is paramount to understand how many patients would be affected at each time-point within the lifecycle of the new technology.

2.3.1 Whose costs and benefits?

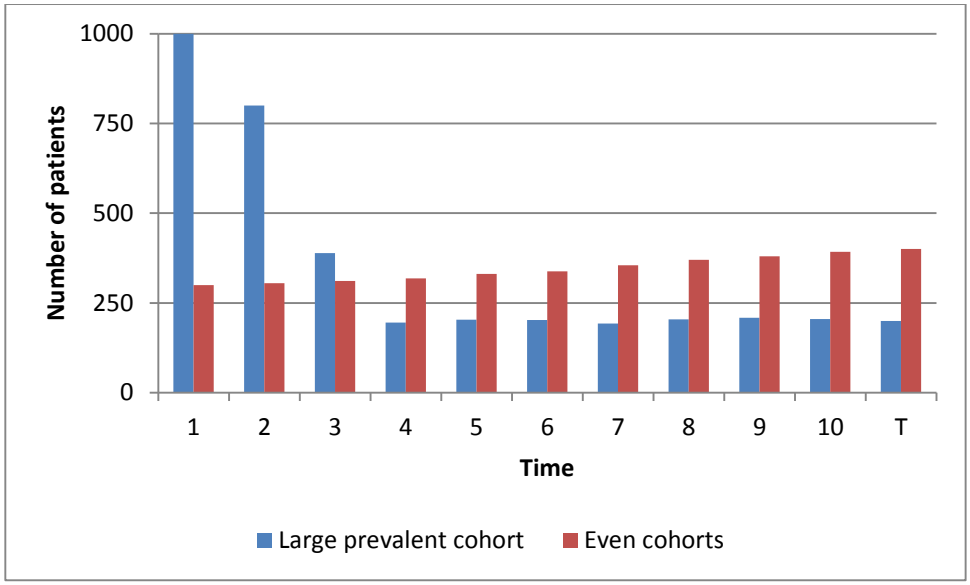
The numbers of patients affected by the new technology are in fact the product of two factors: the size of the patient cohorts requiring some form of treatment and the uptake of the new technology, that is, the proportion of patients actually using the new technology (which was indicated as *s* in Equation 1). In real life, *s* is rarely a binary, all or nothing type variable due to variability in payer, patient and/or clinician choice.

2.3.1.1 The size of patient cohorts requiring treatment

The size of the patient cohorts requiring treatment over the lifetime of the new technology will be determined by the epidemiology of the underlying disease, its prevalence and incidence, the length of the window of time within the disease when treatment is appropriate and the characteristics of the new technology. The numbers will vary according to whether the disease presents as an acute event or whether it is a chronic condition. They will also vary according to whether the new technology needs to be implemented only once or for a short period of time, or whether it requires continuous use through the treatment window.

Figure 2-4 shows two typical scenarios. The number of patients requiring treatment over the lifecycle of this hypothetical treatment is exactly the same (3,800 patients in total over eleven years). However, the distribution of patients over time is different: in one scenario patient numbers are large in the first few periods, and then numbers dwindle. In the other scenario patient numbers remain relatively stable with a slight increasing trend over time.

Figure 2-4 Scenarios for change in number of patients over time



The number of patients requiring treatment will be relatively stable over time in the case of acute diseases, for example the number of cases of appendicitis is expected to be relatively constant per annum. Chronic conditions may also produce even cohorts if continuous treatment is required. For example, the number of patients requiring treatment for hypertension is expected to be stable (or slightly increasing), since treatment is required for the whole lifetime of the patients once diagnosed. Another case is technologies that are to be used only once in fields where older treatments have already existed. The prevalent cohort has already received the old treatment, therefore the numbers of patients will be determined by the incidence of the disease. Most medical devices would fall under this category.

However, if the new short-use technology provides a solution where no treatment has been available before, a different picture emerges. Patient numbers requiring treatment are expected to be large at the beginning, as the prevalent cohort requires treatment, but then patient numbers will decrease to incorporate only the incident cases.

2.3.1.2 The proportion of patients using the new technology

The speed of uptake will also depend on a number of factors. Models usually assume that the diffusion curve, i.e. the curve depicting the proportion of people using a new technology over time is an 'S' shaped curve.(Geroski 2000; Meade and Islam 2006) Diffusion rates first rise and then fall over time leading to slow uptake in the early periods, then adoption speeds up followed by a period of slow approach to satiation. The diffusion curve is therefore convex in the beginning then concave after an inflection point. There are a number of models available

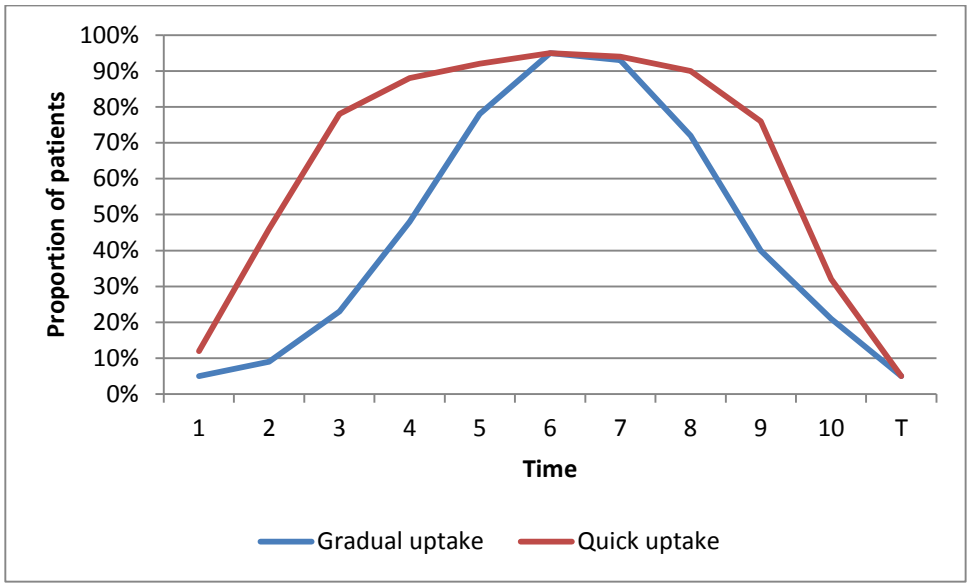
to explain the S shape of the curve. In one classification, epidemic models assume that information about the new technology spreads in a similar fashion to communicable diseases, where initial users need to accumulate experience with the new technology first, then pass on this knowledge to non-users, and these epidemic models rely on the type of information diffusion and characteristics of the populations using the new technology to specify the shape of the diffusion curve; probit models use individual choice based models in which differences between individuals impact on when they adopt the technology; density dependent models use the concepts of legitimation and competition to explain differences in the adoption decisions; while another way to think about technology diffusion is as a model of choice between technologies based on the phenomena of information cascades.(Geroski 2000) Another review categorised models in two dimensions: whether they treat the arrival and value of a new technology as certain or uncertain and whether they include the possibility of strategic interaction in the market of the new technology.(Hoppe 2002) However, empirical research does not always support the 'S' shape. Recently Comin and Mestieri analysed the diffusion of 104 technologies from over 150 countries over the last 200 years, and showed that in 53% of the technology-country cases the diffusion curve had a concave shape once the intensity of use is also taken into account.(Comin and Mestieri 2014)

In the field of health care, the proportion of patients using the new technology (*s*) will also depend on the characteristics of the technology, that is, whether it is possible to replace the old technology with the newer one right after adoption of the new technology (in which case *s* may reach 100% early on). For example patients requiring treatment for acute health events may be prescribed new tablets rather than the old ones straight away. In other cases, mostly in chronic diseases, patients already successfully treated using the old technology will not be required to switch to the new one. Therefore the new technology will only reach incident cases initially with *s* increasing only gradually as prevalent patients fail on their old treatments and are switched to the new one. This is characteristic of many medical devices where a well-functioning device will not be replaced just because a newer device becomes available. Similarly, patients responding well to older treatment regimens in oncology or many other chronic diseases will finish their current treatment course before moving onto the new technology.

Similarly, the decline in the number of patients at the end of the lifecycle of the new technology may take different forms, again depending on the method the treatment can be replaced with the even newer one and the speed of uptake of this newer technology. Ex ante, there is no information about the even newer technology to be developed in the future, but

generally we expect the curves to be symmetrical with the even newer treatment replacing the now new technology in the future in a similar fashion as the new replaced the old technology. Figure 2-5 depicts two different scenarios. In the 'gradual uptake' scenario the curve follows an 'S' shape starting convex and then becoming concave, while in the scenario I termed 'quick uptake' the curve has a concave shape. There is very little evidence on what the diffusion curve actually looks like for medical technologies. (Conti 2012; Serra-Sastre 2012)

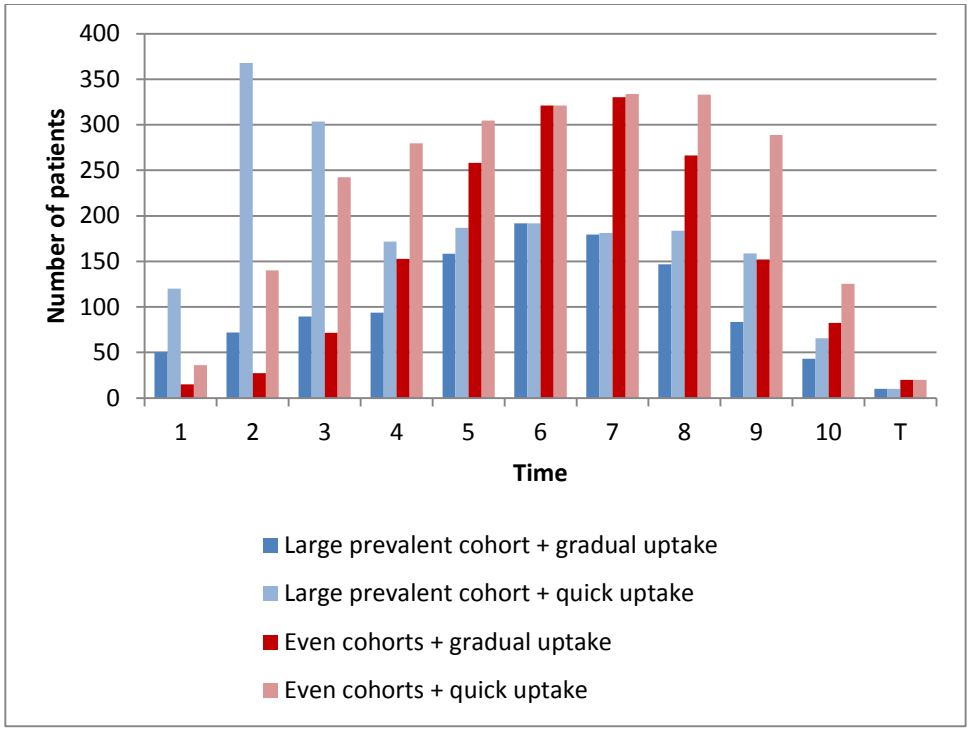
Figure 2-5 Scenarios for uptake of new technology over time



2.3.1.3 Patient numbers using the new technology

Combining the scenarios for patient numbers and speed of uptake illustrates how, in this very simple example, the actual numbers of patients using the technology may be very different over time according to the characteristics of the underlying condition and of the technology itself (see Figure 2-6). Naturally, some combinations are likely to be more common than others, e.g. chronic conditions requiring long-term treatment are likely to be associated with a gradual uptake of new treatments. Nonetheless, the number and composition of patients using the new technology will be specific to the condition and the technology, and therefore should not be omitted from the lifecycle evaluation of the new technology.

Figure 2-6 Combinations of patient number and uptake scenarios



The next section presents how Equation 1 could be extended to incorporate information on the numbers of patients and uptake of the technology to incorporate all potential patient cohorts over the lifetime of the new technology.

2.3.2 The objective function for the technology life-cycle

A more comprehensive objective function for the HTA body would be to maximise the net benefit for the entire patient population that may benefit from the new treatment over the lifetime of the new technology. It needs to incorporate a notion of the number of patients requiring treatment at each period and the proportion of patients actually using each treatment alternative. The objective function at a given maximum willingness to pay (λ) for health benefits then becomes:

Equation 2

$$\max_{s_t} NB = \sum_{t=1}^{T} N_t \left[s_t \left(\lambda \sum_{h=1}^{H_t} E_{1th} - \sum_{h=1}^{H_t} C_{1th} \right) + (1 - s_t) \left(\lambda \sum_{h=1}^{H_t} E_{0th} - \sum_{h=1}^{H_t} C_{0th} \right) \right]$$

where N_t denotes the number of patients eligible to start treatment in a given year, s_t the proportion of patients using the new technology, E_{ith} represents the expected present value of the benefits of the treatment i and C_{ith} the costs of treatment i for patients starting treatment in period t, currently in their h^{th} period after initiation of the treatment.

Within this framework, both expected effects and expected costs of the technologies have the suffix *t*, therefore may change over time and with the characteristics of the patient populations eligible for treatment at any given time point. Also, the length of time the technologies exert an impact on benefits and costs (*H*) also depends on where we are in terms of the lifecycle of the technologies. This enables us to incorporate the different types of interactions between the type of the technology, *T* and *H* as described in Section 2.2.3.2.1.

Equation 2 still assumes patients starting treatment in any given period are similar enough to warrant treating them as a single patient cohort. Possible heterogeneity between patients and how to handle this with subgroup analysis or stratified analysis has been described in a number of studies and methodological guidelines.(Grutters et al. 2013) The lessons from this thesis hold in the case where there is significant heterogeneity between patients, but then similarly to previous recommendations, analyses need to be carried out separately for all identified patient stratum. For the purposes of this thesis, patients are assumed to be homogenous within each cohort N_t, but there may be differences between cohorts across time, due to changing patient characteristics, differences in the duration of treatment (*D*) and the length of time the treatment impacts patients' outcomes (*H*).

2.3.3 Conclusions

Since the potential benefits and costs of treatments might change over time simply because the length of time that patients use the technologies might change (in addition to the fact that characteristics of patients may change), it is important to incorporate all potential patient cohorts into the economic evaluations of new health technologies aiming to inform HTA bodies in their optimisation problem. The traditional framework should only be used if all underlying assumptions about the representativeness of the modelled patient cohort are acceptable. Otherwise at least a stratified analysis according to time of treatment should be conducted if it is possible to formulate different recommendations for different cohorts. An evaluation encompassing the full life-cycle of the new technology will be needed if there is either no flexibility in the decision but there is known variation between the relative costs and effects between patient cohorts, (Hoyle and Anderson 2010) or if there is flexibility in the timing of the decision with some decisions leading to irreversible consequences, i.e. if real options exist.

The next sections will describe how current calculations could be further extended to relax the assumption about the single decision point to introduce flexibility around the timing of the decisions and the explicit consideration of irreversibilities to enable economic evaluations to better reflect the objective function of the reimbursement body.

2.4 Arrival of new information

As shown in the previous section, traditional analyses are static answering the adoption question at a specific point in time and assuming that the decision about the adoption of the new health technology can be fully and costlessly reversed if conditions change. However, most HTA bodies do have some freedom in determining which technologies should be evaluated in a given time period; that is, they have flexibility over the timing of their decisions. Furthermore, decisions about health technologies have implications for further research, therefore they can influence if and when new information about the technology becomes available.(Chalkidou et al. 2008) Therefore there may be irreversible consequences of adoption decisions even if the new technology itself does not require capital investments e.g. new facilities or staff training. Decisions may and should be changed at later time points if the original decision turns out to be wrong in light of new evidence. But these changes are not costless and are not independent from the original decision. This section describes how real options analyses may be applied to lift the assumptions about inflexibility in timing and independency of decisions.

2.4.1 Expected change in value

ROA is an evaluation method that explicitly allows for flexibility in the timing or changing of decisions (Amram and Kulatilaka 1999). More detail will be provided in Chapter 0, but the advantage of ROA is in incorporating multiple decision-points during the evaluation period and explicitly taking into account the cost associated with later changing the decision. To be able to do this, this type of analysis requires additional information on how the value of the technology/investment is expected to change in the future.

The key difficulty in the practical application of ROA lies in how to predict future change in the expected value of healthcare technologies. Past applications of ROA in HTA suggest that the NB of the technology under evaluation should follow a predetermined stochastic process. (Palmer and Smith 2000; Driffield 2003) That is, the NB should evolve over time in a partially random fashion. This approach had been used extensively in financial markets and there is a vast literature offering solutions to the optimisation process. However, such stochastic processes may not properly reflect the characteristics of value in health care and therefore may be difficult to interpret in the context of economic evaluations of new health technologies.(Eckermann and Willan 2008b) The next section provides a few examples to explain why the evaluation of health technologies may be different from the evaluation of financial instruments.

2.4.1.1 Value in health

The main difference between financial options and real options relates to the conception of value. The "value" of the financial instruments underlying financial options is their price. With the assumption of efficient markets, the price of a financial instrument always incorporates all available information. Therefore the price changes according to immediate supply and demand as well as according to any new information about the state of the actual physical asset to which the financial instrument is linked (e.g. the company or economy in general) as well as according to any shift in expectations about the state of the world in the future. Price can be readily observed with certainty, at little or no cost, and nowadays in real time.

In contrast, the value of real technologies and investments cannot always be continuously observed, and furthermore it may be a construct that is not truly observable. There are a number of factors that make the definition and estimation of future value particularly difficult for real investments in general and healthcare investments in particular.

There is no clear agreement on what constitutes value in health care.(Culyer 1989; Birch and Donaldson 2003; Brouwer et al. 2008; Coast 2009)

The benefits and costs of a new health technology are also not directly observable. Most of the impact will take place in the future, therefore it needs to be predicted using modelling techniques and building on multiple sources of evidence. Therefore the estimated benefits and costs are subject to different types of uncertainty. Some of the uncertainties are quantifiable (e.g. parameter uncertainty), but others (such as structural uncertainties) are more difficult to quantify.

Even prices might be difficult to observe due to imperfections in the healthcare market. List prices for drugs are available, but it is not known what individual discounts have been negotiated. The situation is worse for medical devices where even the determination of the actual price of the device can be hindered by the confidential nature of individual negotiations and contracts between the manufacturers and purchasers.

2.4.1.2 Factors driving changes in value

In the case of new technologies, there are no historical data that would enable estimation of the trend and/or volatility of change in value. We do not observe the necessary information on the change in value of new technologies to be able to determine the parameters for such a process. There are only a few instances where economic evaluations have been undertaken repeatedly over time, and even then it is hard to determine whether the differences in the

estimated value are caused by differences in structural assumptions or by new evidence. However, possible changes in the components of NB could be predicted with more certainty.

Historical information on prices of pharmaceuticals and costs of some other health care resources are readily available, and one can investigate the observed long-term price changes and build expectations about the future price changes of new technologies (see e.g. the study by Hoyle regarding expected change in the price of pharmaceuticals (Hoyle 2008))

Predicting changes in our knowledge about effectiveness is more difficult, however one at least usually knows when the next big trials are likely to report or when the decision-making body is expected to undertake the next assessment. There may often be 'learning effects' that cause drift of effectiveness and costs over time. Also there is some evidence about a negative trend in the effectiveness of new technologies over time.(Ioannidis 2005; Gehr, Weiss, and Porzsolt 2006) This finding may be a result of publication bias (e.g. in the timing of publication for negative trials) or changes in patient populations within trials over time, rather than any real change in effectiveness over time. Nonetheless, whether there are common patterns through the life-cycle of new technologies is an empirical question. How "far" can one go in trying to find common patterns in terms of time, type of technology and indication should be examined. Since in most cases HTAs concern new technologies, we need to know whether using historical observations is acceptable, for example on changes in effectiveness from older drugs in the same indication. Can parameters for predicting the price change of a new medical device be estimated based on observed price changes of other medical devices in the same indication? Or even any medical device in general?

Thus the net benefit of a health technology from a payer perspective cannot be measured. NB is a construct and is not easily estimated. It is always surrounded by uncertainty, and can only be updated intermittently as new information arrives.

2.4.2 The impact of the adoption decision on further information arrival

Over and above the characteristics of value development, health care is also different from financial markets in the field of information arrival. There are many individual actors on financial markets, therefore the flow of information is independent of investors. Actions of individual decision-makers do not prevent future transactions by other actors; that is, they cannot prevent the arrival of new information. In the case of health technologies, an adoption decision may fundamentally alter future research possibilities by raising ethical concerns regarding access to care in patients randomised not to receive the adopted new technology, as well as changing the incentives of manufacturers of the product to conduct new studies.

(Chalkidou et al. 2008, 1642-1653) As noted by Walker and colleagues, some HTA bodies may have a remit to order research to be undertaken, while others can only wait for that information to be provided by others.(Walker et al. 2012) The questions of whether and how and when new information will arrive on the technology under evaluation are not independent from the decision about the adoption of the technology. Simple ROA undertaken on behalf of the decision-making body may tell us the value of waiting for more information. However, in real life that information may never see the light of day.

2.4.3 Conclusions

Incorporating the impact of flexibility into the economic evaluation of new technologies is necessary to better understand the true value of these technologies. Knowledge about the new technologies accumulates over time, therefore the value of the technologies also changes as may the decisions about their use. However, earlier decisions may have irreversible impacts on arrival of information about the technology. Furthermore, the introduction of some technologies may have other costs associated with it that cannot be recovered if the decision is later reversed. The advantage of ROA methods lies in the explicit consideration of the irreversible components of the decision and the consequences of changing decisions later. However, in health care previous decisions about the adoption of new technologies may jeopardise the arrival of new information on the new technologies, therefore this interdependence also needs to be incorporated into the analyses.

2.5 Conclusions

Most traditional economic evaluations involve the quantification of costs and benefits of the new health technology and the costs and benefits of the old health technology for a single cohort of patients over the period in which the new technology is expected to influence outcomes. This approach implies a static view of the world assuming a single decision-point and that the modelled cohort remains constant in terms of treatment experience. This traditional framework should only be used if the decisions can be fully and costlessly reversed and if the modelled patient cohort can be assumed to be representative of all patients who will use the new technology. Economic evaluations should be extended to cover multiple cohorts and to incorporate the impact of flexibility and irreversibility in the decisions.

3 Real options and games in relation to health technologies

3.1 Introduction

In the previous chapter I argued that economic evaluations should be extended to cover multiple cohorts and to include real options to take account of the impact of flexibility and irreversibility in the decisions. The concept of real options is closely linked to financial options. Therefore section 3.2 will review the basic features of financial options. The concept of options has been applied to value options about real life investments too. However, there is no agreement between researchers about what constitutes a real option. Section 3.3 begins with a short list of the different definitions of real options in the literature; then a working definition of real options to be used in this thesis is developed. Even with a single definition, there exist a number of different kinds of real options, so the chapter continues with a classification of real options. ROA is a collective term for a number of different methods, so a short overview of methods to the evaluation of real options then follows.

ROA was developed to aid a single decision maker. However, there are a number of actors involved in bringing a new health technology to market: the developer of the technology, the developer of competing technologies, and the purchaser(s) of the new technology who may also want to commission an assessment of the value of the technology from an HTA body. The decisions of each of these actors may have a profound impact on the value of the new technology, therefore the strategic interactions between these actors should not be ignored in the evaluation of the technology. To enable this type of analysis, standard ROA needs to be extended and paired with game theory. So this chapter closes (section 3.4) with a brief discussion of game theory and a description of the concept of real option games, which approach will be used to model the HTA of a new technology in Chapter 8 later.

3.2 The basic concepts behind financial options

A financial option on a stock is the right to trade the stock at a specified price at or until a specified time-point. (Hull 2005) Options are financial instruments allowing the investor to manage their risks in the future.

Options are classified by character and type.(Perlitz, Peske, and Schrank 1999, 255-269) "Character" refers to the kind of trade action that may be performed. Options giving the owner the right to buy a stock are call options, while options giving the owner the right to sell

a stock are called put options. Besides these basic options, there also exist compound options. Compound options are options on options; that is, the exercise payoff of a compound option involves the value of another option. In finance, compound options are usually used in the currency markets. The first option gives the right to trade a second option, which will then give the right to buy or sell the currency at a fixed exchange rate. In valuing real life projects, compound options are useful for staged business projects that may or may not be abandoned at later time points.

The type of option relates to the timing of the trade. Options are only valid for a specific time-period, and the time to expiration is usually denoted by T. If the trade may only take place at the time point of expiration, one talks about a European option. In American options the trade (the buying or selling) may take place at any time-point up until expiration. In the usual notation, C and P denote the value of an American call and put option respectively, while c and p denote the value of a European call and put option respectively.(Hull 2005)

The value of the option is determined by a number of factors:

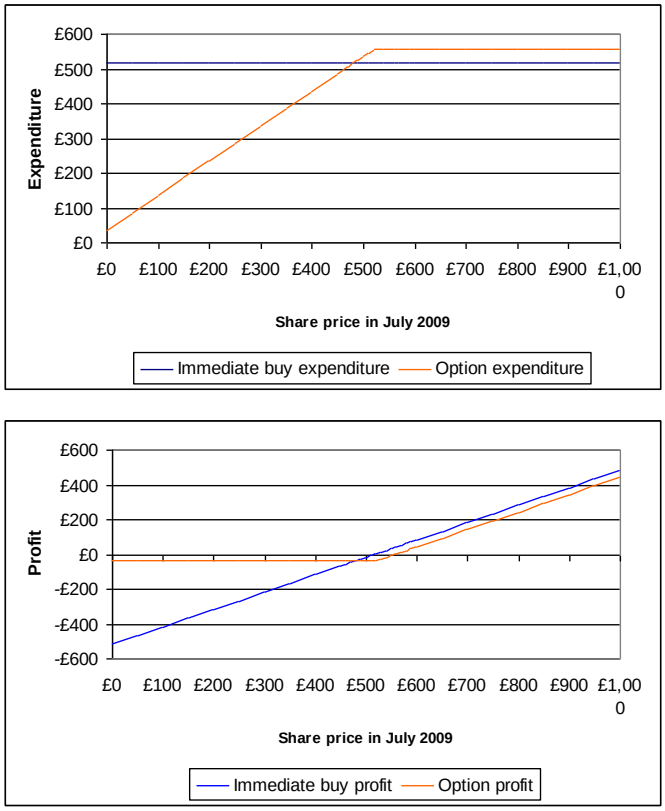
- *K*: the strike price, i.e. the pre-specified price at which the underlying stock may be traded;
- *T*: the time to expiration;
- S_0: the spot price, which is the current (t_0) price of the underlying stock;
- δ: the volatility of the underlying stock price, which is a measure for variation of the price of the stock over time[3].

Call options will only be exercised if the price of the stock at time *T* is higher than the strike price. In these cases, the owner realises a profit of the difference between the stock spot price and the strike price (minus the price the owner had to pay for the option). If the spot price is lower than the strike price, the owner has no obligation to exercise the option, and the option will expire with the owner of the option preferring to buy the stock at the spot price. Put options follow the same logic in the opposite direction. The owner of the option will only want to exercise the option, sell the stock at the strike price, if the spot price at time *T* is lower than the strike price. The owner's gain is then the difference between the strike price and the stock price net of costs. If the stock can be sold at a higher price on the market than the strike price, the owner will let the put option expire without exercising it. Formally, the intrinsic value of an option at any time point is: $max(S_t-K, 0)$ for a call option and $max(K-S_t,0)$ for a put option.

[3] The annualized volatility, σ, is the standard deviation of the instrument's yearly rate of return.

As an example, the shares of United Utilities were traded at £517 on 23 February 2009 at the London Stock Exchange. Assume that we had needed to own this share in July 2009. We could have bought the share at £517 in February and kept it until July. If share prices had gone up between February and July, we would then have made a profit. However, if the share price had fallen, we would have made a loss, as we could have bought the share at a lower price in July. Our profit in July after having purchased the share in February would have been a linear function of the July share price. In this situation, we would have faced the potential of great losses or great gains, as shown by the blue line in Figure 3-1. Suppose that the option to buy the share for a strike price of £520 in July 2009 was traded for £37 in February 2009. We could have bought the option in February, and waited to see how the stock price changed. If it was below £520 in July, we could then have bought the share on the stock market, and left the option to expire, incurring only the loss of £37. If the July price was above £520 however, we would have exercised the option, and provided the price was above £557 (£520+£37) we would have realised a profit. Thus options limit the amount of losses encountered without limiting the magnitude of profits (except for the price of the option itself). The main objective of options (and most financial derivatives) is to reduce the risk to investors stemming from the volatility of prices. In fact, the vertical distance between the two profit functions in Figure 3-1 if the share price is high, is exactly £37, the cost of the option. One can think of this as an insurance fee to protect against the losses that one might have incurred had the share-price fallen. As with any insurance, the price of the option is directly linked to the expected degree of uncertainty.

Figure 3-1 The impact of options on expenditure and profit



Researchers early in the 1900s understood that models that described the random movement of particles suspended in a fluid (a liquid or a gas) resulting from their collision with quick atoms or molecules in the fluid (stochastic diffusion models) could also be used to describe the movement of stock prices. However, solving these differential equations to derive market prices for the options was a challenge. (Kogut and Kulatilaka 2004) The breakthrough idea by Black and Scholes (Black and Scholes 1973) and Merton (Merton 1973) was that the cash-flow of the option could be reconstructed by short selling the stock (selling a stock that is not currently owned by the trader) and investing the money. In other words, one can create a riskless portfolio by combining the option and the share transaction, a portfolio that will generate the same cash-flow regardless of stock price changes. Once risk was eliminated, the equations could be solved and the value of the option calculated. In fact there are more ways than one to arrive at the solution and these methods will be presented in section 3.3.2.4 below.

3.3 Real options

3.3.1 Background and definitions

Generally, a real option is defined as the right, but not the obligation to take an action in the future. (Amram and Kulatilaka 1999) Black and Scholes already noted in their ground-laying article on financial options, that the firm could also be valued by treating the right of the bondholders as a call in the value of the firm. (Black and Scholes 1973) At the time of expiration, the bondholders are paid by the firm from the firm's funds, in effect they will own the firm's value. They also have the option to own the firm at the time of their choosing until expiration, since they may decide to sell their bond before expiration. The exercise price of this option equals the then current face value of the bond. It was then Myers who suggested that this approach could be applied more broadly in the valuation of corporate investments. (Myers 1977) McDonald and Siegel offered technical innovations in the application of option valuation to investments that do not have a corresponding financial market, (McDonald and Siegel 1986) and these were subsequently generalised by Cox, Ingersoll and Ross.(Cox, Ingersoll, and Ross 1985) One of the earliest applications of real options was to the pricing of oil prospects, by Paddock, Siegel, and Smith.(Paddock, Siegel, and Smith 1988) The last three decades have seen a huge academic interest in, and high expectations for ROA. However, there is still no consensus on what constitutes a real option and how the concept could be used.

Most authors agree that net present value (NPV) type valuation processes that rely on discounted cash flow calculations have a serious limitation. Future investment decisions are assumed to be fixed at the outset, and any type of managerial or technological flexibility is ignored. In such valuations of corporate investments, risk is incorporated only as an adjustment to the discount rate, requiring higher returns from projects that are deemed more risky. However, using a single risk adjusted discount rate implies a very arbitrary assumption about the risk associated with future cash flow estimates, namely that such risks increase geometrically with time. (Chow and McNamee 1991) In decision making in health care, discount rates are not even adjusted for risk. Claxton and colleagues argue that the discount rate should be chosen according to whether the social objective is to maximise discounted health outcomes or the present consumption value of health; whether the budget for health care is fixed; and that it should also depend on the expected growth in the cost-effectiveness threshold and the expected growth in the consumption value of health.(Claxton et al. 2011a) But regardless of whether the discount rates are adjusted or not adjusted for risk, there is no

allowance for deferral, nor is there allowance for changing the decision as new information is uncovered.

The real options framework moves away from evaluation of single "now or never" type decisions. The central view of ROA is that uncertainty creates opportunities. (Amram and Kulatilaka 1999) It allows for the explicit incorporation of flexibility (e.g. in terms of timing, adjustments to scope, or abandonment in response to changes in the value of the investment) into the structure of the decision. Similarly to financial options, real options can be thought of as insurance against losses, allowing the decision maker to change the decisions if they later turn out to be wrong in the light of new information. However, the terminology of real options has not crystallised yet, and McGrath and colleagues identified four different but overlapping concepts in the literature. (McGrath, Ferrier, and Mendelow 2004, 86-101) Although the authors do not acknowledge it, it seems that the four concepts are presented in a rank order with growing abstraction from the concept and definition of financial options.

The first set of papers defines option value as a component of the total value of the firm. In the case of start-up companies, industries with lots of research and development activities, as well as in fields which require little physical material for production, such as internet companies, there is usually a gap between the fundamental value of the firm (the sum of the value of its assets and projected future cash-flows) and the total market valuation of the firm. The difference is thought to be explained by the option value of any growth opportunity or a chance for future investment/expansion/change in scope that stems from the firm's current resources and capabilities.

The second set of papers aims to value specific investment proposals with option-like properties. These papers present investments with uncertain pay-offs, such as research and development proposals, drilling for oil or developing real estate. McGrath, Ferrier, and Mendelow observed that many investments in innovations would be foregone if they were evaluated using a traditional NPV technique, ignoring the potential options of the development process.(McGrath, Ferrier, and Mendelow 2004) In these cases, option value may stem from the preservation of choices or from the flexibility to change decisions. These papers argue that there is value in preserving flexibility and deferring decisions to a later date, or the ability to change decisions at a later date when more information becomes available, rather than committing to a single course of action at the outset.

The third approach to defining options focuses on the choices that managers might make, as opposed to a simple evaluation of the resource itself. Amram and Kulatilaka define the

following as real options: the option to wait to invest, the option to expand capacity (growth options), flexibility options, the option to abandon projects (exit options), and learning options. (Amram and Kulatilaka 1999) Similarly, Perlitz and collegues distinguish six different kinds of real options (Perlitz, Peske, and Schrank 1999):

- The option to defer an investment project;
- The "time-to-build" option, staging investments as a series of outlays creates the option to abandon the enterprise midstream. Each stage can be viewed as an option on the value of subsequent stages and valued as compound options (options on options);
- The option to abandon an investment project;
- The option to contract, expand or temporarily shut down an investment;
- In the development of products, the option to switch inputs (what materials the product is made of or what powers the production line) or outputs (what is the end product);
- The growth option of a firm to increase its market value.

The possibilities are almost endless, since one can always *"initiate, abandon, expand, contract, wait, slow down, speed up, switch, sell, or sequence a project"*. (Williams and Hammes 2007)

The last set of papers uses option reasoning as a heuristic for strategy. In other words, real options provide a way of thinking about the economics of strategic investments. Option reasoning in this sense sees investment choices as a chain of events, focusing on path-dependency and tries to replace the separate evaluation of individual projects without accounting for the firm's historical steps, current circumstances and future strategy.

It is clear that as Borison has put it "*There is a great deal of agreement about the appeal of the underlying concepts*" (Borison 2005). However, the actual application of real options analysis has not been canonised. In this thesis I will take a general view of real options closely related to the third set of papers identified by McGrath et al. (McGrath, Ferrier, and Mendelow 2004). Real options are choices that are present in situations in which actors consider partly irreversible investments under uncertainty, where the uncertainty endures over a period of time and initial decisions are subsequently revisited.

3.3.2 Valuation of real options

I defined real options to be (sequential or potentially repeated) choices under uncertainty. In this environment, the choice is both ex ante and ex post, simultaneously.(Kogut and Kulatilaka

2004) Actors decide what to do based on current information. They may also perform actions (e.g. make new decisions) in the future, ex post to a realization of (a chain of) events. However, the actor's choice is also based on the future; the action is already predicated on the basis of expectations.

Traditional evaluation techniques focus on what would be the optimal choice based on current information. The extra layer in ROA lies in the description and consideration of expectations. ROA requires a description of risks, expectations on how value might change in the future and what actions may be taken in response to these changes. Therefore Amram and Kulatilaka suggest dividing the valuation into three distinct steps (Amram and Kulatilaka 1999):

- Identifying and defining real options
- Establishing the mathematical representation of uncertainty
- Choosing the solution method.

3.3.2.1 Identifying and defining real options

The first step in the evaluation process is to define what constitutes the option(s). Similarly to financial options, one needs to know the basic character and type of option. The character of the real option will be defined by the choices available to the decision maker. Answers to questions such as "can the decision be deferred?", or "can the project be stopped?", or more generally "what flexibility does the decision maker have in terms of the timing and scoping of the project?", will determine the character of the real option(s) to be evaluated. One also needs to define the time period over which the real option exists: the time to expiration has to be determined. One must also know the type of the option. If the flexibility to perform the action in question is available at any time point until expiration (like in an American financial option) the analysis will require a different structure compared to a situation when actions can only be undertaken at specific time points (like in a European financial option).

One also needs to determine the consequences of the actions (analogous to the strike price) and whether any investments need to be made in order to enable the performance of certain future actions (i.e. do the real options themselves have a price higher than zero).

Similarly to all types of economic models, an important consideration is how time is handled in the analysis. ROA methods can be broadly classified into continuous and discrete according to the paradigm used to represent the evolution in time of the model's input variables (e.g. project value, option exercise price, etc).(Perlitz, Peske, and Schrank 1999)

3.3.2.2 Establishing the mathematical representation of the uncertainty

The second step in ROA involves determining the sources of uncertainty. In financial options, the only source of uncertainty is the price of the underlying asset. We know the current spot price, but we only have an expectation about future prices. In real options models there may be more than one source of uncertainty. Real life projects may depend on a number of inputs whose prices may vary over time. If the option concerns a development of a product, there is technical uncertainty whether a suitable product can be devised in time. There may also be variations in the market, making the success of the finished product uncertain too. A combination of all these uncertainties can be thought of as parallel to uncertainty surrounding future asset prices in financial options. Furthermore, besides the uncertainties relating to the future prices or technical and economic success, real options very often consider assets that are not traded. Therefore there is usually no certain estimate of the current value of the asset either. This type of uncertainty is missing from financial options, because the spot price there is always observable.

Once the sources of uncertainty are identified, one needs to determine the nature of the uncertainty. The main distinguishing factor is the relationship of uncertainty with time. Representing uncertainty that remains the same through time (static uncertainty) requires different methods from representing uncertainty that evolves through time (dynamic uncertainty). This differentiation is one of the main differences of the methods proposed in this thesis compared to the methods developed by Eckerman and Willan (see e.g. (Eckermann and Willan 2008b). Eckermann and Willan assume that the value of new health technologies is subject to static uncertainty, whereas I believe that it is subject to dynamic uncertainty too.

3.3.2.2.1 Static uncertainty: probability distributions and chance nodes

Static uncertainty is present in traditional economic evaluations. This relates to either the fact that the decision maker does not have complete information about the input parameters and/or the fact that occurrence of events may be random. These types of uncertainties should be represented by assigning probability distributions to input parameters and building chance nodes into the model to include random occurrences of events in the same way as in traditional economic evaluations. In contrast, dynamic uncertainty can be represented by shifting the probability distributions over time.

3.3.2.2.2 Dynamic processes in time

If the expectation is that value might change in the future, one needs methods that describe the evolution of value through time. The description must correspond to how time is generally

handled throughout the evaluation, therefore one can distinguish discrete and continuous processes. Within both types, it is also important to determine how the value is expected to change.

3.3.2.2.2.1 Continuous time processes

Within continuous processes, Dixit and Pindyck differentiate between the diffusion process, the jump process and the mean-reverting process.(Dixit and Pindyck 1994)

In a diffusion process, the values move through time without sudden jumps up or down. These processes are also called Brownian motion or pedesis and they were first used to describe the random motion of particles suspended in a liquid or gas fluid. The particles' trajectories are random, because they are continuously subjected to random displacements due to collisions with atoms and molecules.

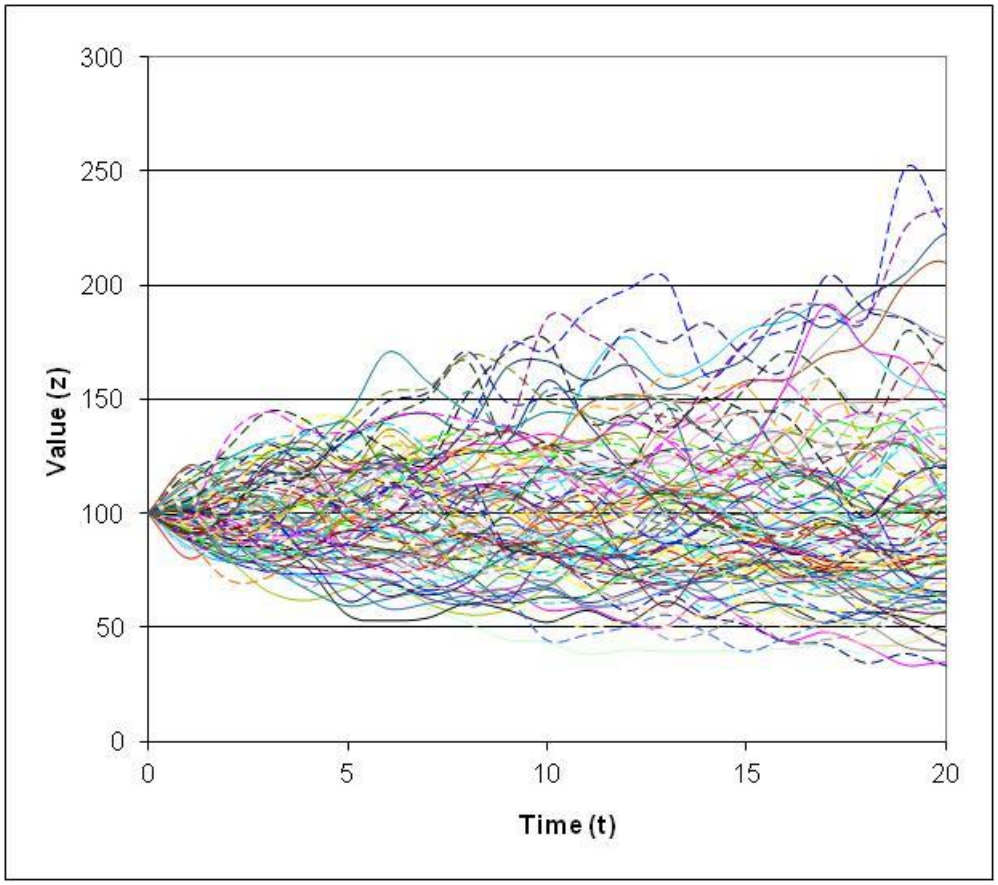
The most common stochastic process is a Wiener process. In this simple process, changes over a given time period are normally distributed and the increments are independent: a change in any time period depends only on the current value. Formally, *z*, the value of interest follows a Wiener process if

1. $\delta z = \varepsilon\sqrt{\delta t}$, where ε is a random variable following a standard normal distribution and *t* is time, and

2. values of δz for any two time intervals are independent.

So a change in the value of *z* in a long period of time (*z(T)-z(0)*) has a mean of 0 and a variance of *T*. Figure 3-2 shows one hundred predictions using a simple Wiener process for changes in value over 20 days where the starting value was 100, and the expected annual change was 0 with a standard deviation of 10%. As seen from the figure, each realisation provides a possible pathway for the value.

Figure 3-2 Hundred realisations of a Wiener process



The stochastic process can be made more complex by relaxing one or more of the Wiener process assumptions. If the process also includes a trend, it becomes a generalised Wiener process, also called a Wiener process with a drift (Hull 2005):

$$dx = a * dt + b * dz$$

where *a* and *b* are constants, so the first part of the equation (*a*dt*) describes the drift rate per unit of time, while the second part of the equation introduces a random noise through the Wiener process. In a small time interval *δt*, the change in the value of *x (δx)* can be written as:

$$\delta x = a\delta t + b\varepsilon\sqrt{\delta t}, \text{ where } \varepsilon \sim \Phi(0,1).$$

Therefore the change will also be normally distributed with the following properties:

$$\delta x \sim N(a\delta t, b\sqrt{\delta t})$$

Ito processes allow for the trend and variance of the process to be dependent on current state and time:

$$dx = a(x,t) * dt + b(x,t) * dz$$

Sudden jumps can also be introduced into the process, for example to represent shocks to the system. In this case the movements may become discontinuous and are usually described by a Poisson distribution. The magnitude of the jumps may be fixed or they may be stochastic, depending on the requirements of the model.

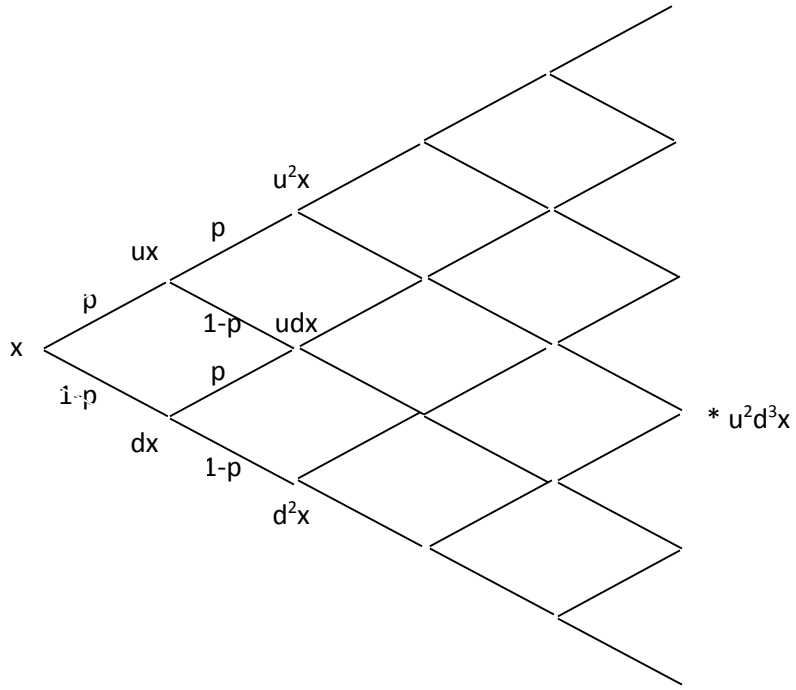
As shown in Figure 3-2, stochastic processes simulated through Brownian motion tend to move far away from their starting point.(Perlitz, Peske, and Schrank 1999) It is also possible to make the incremental changes in the process depend on previous values and compensate for moves which take the process too far away from its starting point. These types of processes are called mean-reverting processes.

3.3.2.2.2.2 Discrete time lattices

The discrete time equivalents of stochastic processes can be represented by lattices (trees branching out from the current value and representing the possible future values of the asset at certain time points). In these methods the period of interest is divided into small intervals. Within each interval the value of interest is assumed to change slightly to reflect risk. Each node in the lattice represents a possible price of the underlying asset at a given point in time where the value follows a discrete time random walk. Most often, the value may increase or decrease by a given amount (creating a binomial lattice) or increase, stay the same or decrease (creating a trinomial lattice).

A typical binomial lattice is shown in Figure 3-3. Although it is not a necessary condition for the generation of the lattices, if the increase/decrease is assumed to be constant or proportional to the value, then the lattice recombines at later time-points, i.e. the investment will have the same value in time period two if its value increased in period one and then decreased in period two or if its value decreased first and then increased. In Figure 3-3 the value of interest (x) is assumed to increase by $u\%$ with probability p and decrease by $d\%$ with probability $1-p$.

Figure 3-3 Recombining binomial lattice



The figure also displays the close relationship between discrete time and continuous stochastic processes, with the realisations of the Wiener process (see Figure 3-2) showing the same fan shape as the binomial lattice (see Figure 3-3). In fact, binomial trees tend toward the Black-Scholes equation which uses a Wiener process to model asset price movements in the continuous limit.(Casault, Groen, and Linton 2014)

3.3.2.2.2.3 A critique of the traditional Gaussian approach for biotechnology

All dynamic processes described until now assume that uncertainty can be modelled as Geometric Brownian motion. This has been shown to be true for financial assets, but Casault and colleagues warn that the assumption of normality may not be appropriate to model the value of projects in biotechnology research.(Casault, Groen, and Linton 2014) The authors argued that new information about the status of research and development projects does not arrive continuously with equal probability to increase or decrease the value of the underlying product, which would result in normal random walk dynamics. In reality, decision makers only make adjustment when new information with strategic impact is available or at set project intervals. Casault et al. claim there is currently little research into techniques that accurately account for the sudden large fluctuation events in value that occur frequently in biotechnology R&D. Due to the discrete nature of the arrival of new project information and its drastic impact on the value of the resulting product, these types of assets are not only characterized by high-risk and high-reward, but also rapid changes. A failure to meet regulatory hurdles or unforeseen negative efficacy results in critical tests can lead to a rapid decrease of value, while

the recognition of an unanticipated use of a molecule can lead to a rapid increase in value. These rapid changes would be almost impossible to characterise with the above-described processes. Casault and colleagues show that the stock market price behaviour of biotechnology firms is not Gaussian due to its thick tails (extreme low and extreme high values are more likely to occur than would be expected in a normal distribution) as well as asymmetry (the distribution is skewed, with values that are the same distance above or below the mean not having the same probability). The authors suggest the use of Cauchy distributions to describe risks in the return profile to be expected from investments in R&D activities in biotechnology firms. Cauchy distributions are power law distributions, that is, they specify the relationship between two quantities, where a relative change in one quantity results in a proportional relative change in the other quantity. For example, the standard Cauchy distribution is the distribution of a random variable that is the ratio of two independent standard normal variables.

3.3.2.3 Choosing the solution method

The last step in the process of evaluating real options is to choose the solution method. There are many to choose from. Kogut and Kulatilaka called real option pricing "part and parcel of a tool bag of techniques".(Kogut and Kulatilaka 2004) However, not all tools are fit for all purposes.

Borison provided a framework for choosing a valuation method for real options.(Borison 2005) The choice depends on answers to the following questions:

- Applicability: what does the calculated real option value represent, and when is it appropriate to use this calculation?
- Assumptions: when applied appropriately, what are the notable assumptions underlying the approach, and what is the evidence regarding the validity of these assumptions?
- Mechanics: provided the assumptions are valid, what steps are involved in applying the approach, and what are the associated difficulties?

Potential solution techniques are reviewed briefly below.

3.3.2.4 Solution methods

3.3.2.4.1 Analytical solutions

If uncertainty is described by a continuous time diffusion process, partial differential equations may be employed to find an analytical solution in some circumstances. However, their

applicability may be restricted by the underlying assumptions that were necessary to arrive at a closed form solution. The most famous closed form analytical solution is the Black-Scholes option pricing equation.(Black and Scholes 1973)

The Black-Scholes equation's underlying assumptions are the following (Hull 2005):

- The stock price is assumed to follow a Wiener process, with both the mean return (μ) and volatility (σ) assumed to be constant over time;
- Short selling, selling of financial assets that one does not yet own, is permitted;
- There are no transaction costs or taxes, and no indivisibilities (i.e. one is able to trade portions of assets too, no matter how small, such as 1/5th of a stock);
- No dividends are paid until the expiration date;
- There are no arbitrage opportunities: this law states that if two assets have exactly the same payoffs in every state of nature, they must have the same value to prevent people making money with no investment. If one of the assets would have a lower value, we could short sell the asset with the higher value, from that money buy the asset with the lower value, pay the pay-offs of the short sold asset from the pay-offs of the bought asset (since they always have the same pay-offs) and pocket the difference in prices;
- Trading is continuous;
- The risk-free rate of interest (*r*) is constant and the same for all maturities (length of investment), that is r is the same for all time periods.

The stock price follows a Wiener process, therefore:

$$dS = \mu S dt + \sigma \mathrm{Sdz}$$

If *f* is the price of the derivative contingent on *S*, then from Ito's lemma we know that changes in the value of the derivative can be expressed as:

$$df = \left(\frac{\partial f}{\partial S}\mu S + \frac{\partial f}{\partial t} + \frac{1}{2}\frac{\partial^2 f}{\partial S^2}\sigma^2 S^2\right)dt + \frac{\partial f}{\partial S}\sigma S dz$$

If one creates a portfolio by short selling the derivative and buying *∂f/∂S* part of a share, then the value of the portfolio (*Π*) would be:

$$\Pi = -f + \frac{\partial f}{\partial S}S$$

Then a change in the value of the portfolio in a small period of time is

$$\delta\Pi = -\left(\left(\frac{\partial f}{\partial S}\mu S + \frac{\partial f}{\partial t} + \frac{1}{2}\frac{\partial^2 f}{\partial S^2}\sigma^2 S^2\right)\delta t + \frac{\partial f}{\partial S}\sigma S\delta z\right) + \frac{\partial f}{\partial S}(\mu S\delta t + \sigma S\delta z)$$

$$= (-\frac{\partial f}{\partial t} - \frac{1}{2}\frac{\partial^2 f}{\partial S^2}\sigma^2 S^2)\delta t$$

The equation does not involve δz, therefore the portfolio is riskless during time δt, so in the absence of arbitrage opportunities it has to make the same return as other risk-free assets:

$$\delta\Pi = r\Pi\delta t$$

By substituting the formulas for Π and $\delta\Pi$ one arrives at the Black-Scholes-Merton differential equation:

$$rf = \frac{\partial f}{\partial t} + rS\frac{\partial f}{\partial S} + \frac{1}{2}\sigma^2 S^2\frac{\partial^2 f}{\partial S^2}$$

The particular solutions depend on the boundary conditions. Since the differential equation is independent of risk preferences, any set of preferences may be used when evaluating *f*. The Black-Scholes solution assumed that investors are risk neutral (therefore $\mu=r$).[4]

Although the Black-Scholes solution has very restrictive assumptions, analytical solutions can be extended to account for features of real assets.(Amram and Kulatilaka 1999) Solutions are available for underlying assets that have leakages in value; that is, where the owner of just the call option on the asset may not receive some form of pay-off that would be paid to the owner of the asset. For example, if the adoption of a new health technology is delayed, the additional health benefits that could be achieved with the new technology between now and the delayed time of adoption can be thought of as leakage. Analytical solutions are also available for situations where value follows a log-normal diffusion process with random jumps (a jump-diffusion process).

3.3.2.4.2 Numerical procedures

Binomial and trinomial lattices may be solved by numerical procedures. The lattices are folded back, assuming that only the optimal decision was taken at every time point.

Taking the recombining binomial lattice shown in Figure 3-3 as an example, the values at the end of the lattice can be determined by deciding with certainty if the option needs to be exercised or not. If there are a total of *N* movements in the lattice, the intrinsic value of the

[4] The solution for a call option is $c=S_0N(d_1)-Ke^{-rT}N(d^2)$, where $d_1=(ln(S_0/K)+(r+\sigma^2/2)T)/(\sigma\sqrt{T})$, $d_2=(ln(S_0/K)+(r-\sigma^2/2)T)/(\sigma\sqrt{T})-d_1-\sigma\sqrt{T}$, and $N(x)$ is the cumulative probability distribution for the standard normal distribution.

option at each end node which can be reached with a number (*j)* of up movements and a number (*N-j)* of down movements is:

$$f_{N,j}=max(K-S_0u^jd^{N-j},0)$$

Then rolling back the tree, the value at each previous node *i* (with $0\leq i\leq N$ and $0\leq j\leq i$) can be determined until the starting point of the lattice is reached:

$$f_{i,j}=e^{-r\delta t}[pf_{i+1,j+1}+(1-p)*f_{i+1,j}].$$

3.3.2.4.3 Decision analysis

Decision analysis, a systematic approach to decision making under conditions of imperfect knowledge applying probability theory to calculate the optimal strategy from among a series of alternative strategies, is already used in HTA. That some form of economic modelling is needed to assess the impact of new health technologies has been accepted as an unavoidable fact of life.(Buxton et al. 1997) However, in the conventional use of decision analysis in HTA, we estimate the net present value (NPV) of a flow of health consequences and costs resulting from a one-off decision to use a particular technology rather than some comparator(s).(Drummond and others 2005) These traditional NPV methods assume that the decision remains fixed. For ROA, this approach needs to be extended to introduce flexibility over the current decision as well as to incorporate future decisions. This very simply means that instead of the single decision node as in traditional models, ROA requires the inclusion of multiple decision nodes along the line. Therefore the method becomes a multi-stage decision analytic (MSDA) approach. The method is also sometimes referred to as the expected net present value (ENPV) method in the literature. (Kellogg and Charnes 2000; Pandey 2003; Willigers and Hansen 2008) However, this label is confusing, because traditional single decision models have the same aim: to calculate expected NPV. The differentiating factor is rather in the number of decision nodes incorporated. MSDA has decision nodes in the middle of the decision trees too, allowing later decisions to be contingent on, or changed according to, how uncertainty is settled.

This approach can be applied at an individual level or at a population level. To illustrate, let us assume that a new drug is about to be reimbursed, but that there is uncertainty around the responder rate. Treating one patient costs £43,400 more than the comparator, and provides 2 QALYs more for responding patients but only 0.5 QALYs more for non-responders. There are 5,000 eligible patients. The current estimate of the proportion of responders is 70%. A traditional NPV decision tree is shown in Figure 3-4A.

Figure 3-4 Comparison of traditional decision tree with MSDA

Figure A: NPV

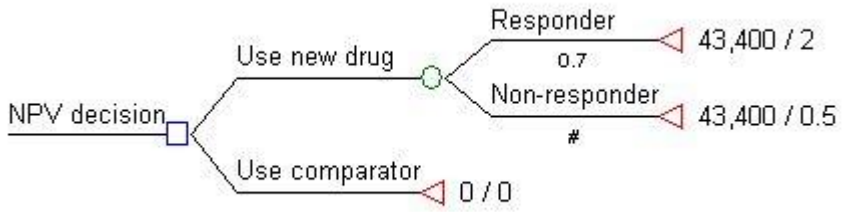
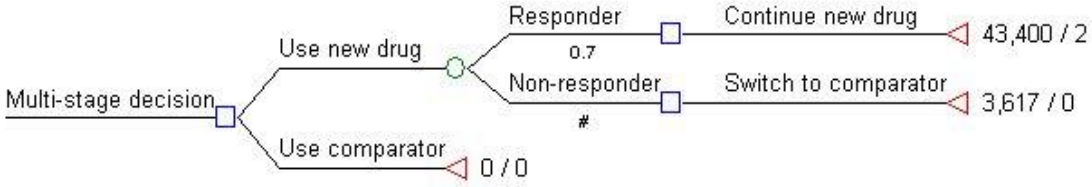


Figure B: MSDA



Disregarding discounting (for simplicity), the incremental cost-effectiveness ratio (ICER) of the new drug is £28,000/QALY and the estimated budget impact is £217 million. However, if response may be determined after one month, the decision could be changed then, allowing only responding patients to continue treatment. The MSDA decision tree incorporating additional decision nodes after response status was revealed and applying the stopping rule is shown in Figure 3-4 B. If information about response is accurate and free, then the ICER falls to £22,475/QALY gained and the budget impact is reduced to a little above £157 million.

Many current economic evaluations already follow MSDA methods at the individual patient level when incorporating, for example, stopping rules, maybe not even realising that in effect they are adding in the real option of abandonment. MSDA methods at the population level are not often applied. They could be useful in budget impact models for example, to incorporate the impact of possible later decisions on changes in the indication or dosing, etc. Published examples of the MSDA approach will be discussed in more detail in the next chapter (in Chapter 4). Application of the method on both the individual and population levels requires a clear definition of when and how decisions may be changed.

In the presence of uncertainty, pathways and corresponding pay-offs are simulated and the decision analytic models are evaluated probabilistically, in the same way as in the probabilistic evaluation of medical decision models to assess parameter uncertainty. The mechanics

involve sampling random values for all model parameters, then calculating pay-offs.(Hull 2005) These two steps are repeated a large number of times to generate a distribution for the pay-offs and to calculate the expected pay-off. Datar and Mathews showed that if the probability distribution of the project is generated with a Monte-Carlo simulation, then the real option value can be understood as the probability-weighted average of the payoff distribution.(Datar and Mathews 2004) They also showed that under the same conditions, the simulation method is algebraically equivalent to the Black-Scholes formula.

The advantage of the simulation method is that the inputs required for its application are similar to those required in traditional NPV analysis, health economists are already familiar with simulation methods for probabilistic evaluation of medical decision models. Simulations may handle complicated decision rules, complex pay-offs and more than one source of uncertainty.(Hull 2005) The simulation method is robust when the underlying distributions are not Gaussian, and can handle jump diffusion processes too (when a diffusion process is combined with a jump process).(Datar and Mathews 2004) Furthermore, if the decision or pay-off depends not only on the value at a particular time point but also on the path to that point, a solution can only be found with the simulation method.(Amram and Kulatilaka 1999)

Once the expected pay-offs are determined, decision models are also solved by rolling back the tree, similarly to lattices.

3.3.2.4.4 Dynamic programming

If the decisions taken at different time-points are of the same nature, one may use dynamic programming to solve the optimisation problem.(Dixit and Pindyck 1994) Dynamic programming relies on Bellman's Principle: given the choice of the initial strategy, the optimal strategy in the next period is the one that would be chosen if the entire analysis were to begin in the next period.(Amram and Kulatilaka 1999) Therefore in the solution, the sequence of similar decisions is broken down into two components: the immediate decision and a value function that incorporates the consequences of all subsequent decisions. Stochastic programming is a related method aiming to find a robust strategic initial decision followed by rolling contingency plans which respond to different future outcomes.(Birge and Louveaux 1997; Shapiro, Dentcheva, and Ruszczynski 2009)

3.3.2.4.5 Classification of solution methods

The above described solution methods differ in their underlying assumptions and applicability. Borison differentiated between five different approaches according to the assumptions used and the sources of data feeding the models:(Borison 2005)

- The Classic Approach (No arbitrage, Market data): assumes that a portfolio of traded investments can be constructed to replicate the returns of the real option, and the option can be valued based on standard no arbitrage arguments (same as financial options)
- The Subjective Approach (No arbitrage, Subjective data): In place of the explicit identification of a replicating portfolio, this approach uses entirely subjective estimates of inputs, but at the same time relies on the same standard no arbitrage arguments as the Classic Approach
- The Marketed Asset Disclaimer Approach (Equilibrium based, Subjective data): This approach states that the present value of the cash flows of a project without flexibility (that is the NPV) is the best estimate of the market value of the project.(Copeland and Antikarov 2001)
- The Revised Classic Approach (Two investment types): the classic approach to real options analysis should be used when investments are dominated by market-priced or public risks, and dynamic programming/decision analysis should be used when investments are dominated by corporate-specific or private risks.
- The Integrated Approach (Two risk types): Use financial option pricing methods to value risks that can be hedged by trading existing securities and decision analysis procedures to value risks that cannot be hedged by trading.

Although Borison's classification is complete, it is important to highlight that in general, the uniqueness and complexity of the assets or projects evaluated by ROA makes it impossible to find a twin security or a tracking portfolio that would replicate the returns of the original project. Markets for these assets and projects are also either non-existent or far from being efficient, therefore one cannot rely on the no arbitrage assumption. The use of financial option pricing techniques will not be appropriate in most real option evaluations.

3.3.3 Limits to the use of real options

As Kogut and Kulatilaka warned: *"The knowledge of assumptions and subtleties is more critical in the periphery than in the core of a theory".*(Kogut and Kulatilaka 2004) Understanding the limitations of ROA approaches is of utmost importance if ROA is to be applied to the rather atypical environment of HTA.

As noted earlier, there is usually no efficient market for the assets or projects evaluated in HTA, so one cannot rely on no arbitrage arguments to derive value. This is why most ROA

studies rely on the market asset disclaimer assumption to determine value.(Zapata and Reklaitis 2010) This assumption states that the present value of the cash flows of a project without flexibility is the best estimate of the market value.(Copeland and Antikarov 2001) In effect it means that the risk of the project with the flexibility is deemed to be the same as the risk of the project without flexibility. Therefore the same discount rates may be used in both cases, so the present value of the pay-offs for corresponding branches from the two projects will be the same.

Due to the lack of efficient markets and tracking portfolios in real option contexts such as HTA, there is also no historical information on how uncertainty has evolved over time. Therefore the expectations regarding the evolution of future risks are either based on very limited data or are completely subjective.(Amram and Kulatilaka 1999)

Although ROA had been shown to provide a better estimate of value for single assets or projects, ROA does not easily capture project interactions.(Zapata and Reklaitis 2010) If a firm makes multiple investments that draw upon a pool of resources, it may create unforeseen resource shortages and delays. However, it may also create learning spill-overs and the developer may be able to take advantage of economies of scope.(Vassolo, Anand, and Folta 2004) As a result, when there are multiple real options present that interact with one another, their individual values may be non-additive.(McGrath 1997)

ROA was developed to better capture the economic (meaning monetary) value of investments. However, there may be other aspects that drive decisions regarding real assets. This is especially true for new health technologies. For example the National Institute for Health and Care Excellence (NICE) states that economic value is just one of the factors it considers when considering new technologies.(National Institute for Health and Clinical Excellence 2008) However, ROA can be extended to incorporate other measures of value. Zhao and Chen recognised that treating new technologies as only economic investments fails to consider the thrill and fulfilment of developing science itself (Zhao and Chen 2009): a scientific discovery not only attempts to use existing science but also to advance scientific knowledge and capture the value of the knowledge it creates. Therefore they created a ROA using a model for an optimal stopping rule to drug discovery, but based on scientific quality rather than financial returns.

3.3.4 Conclusions

Traditional valuation processes have a serious limitation. Future investment decisions are assumed to be fixed at the outset, and any type of flexibility is ignored. In this section real

options were defined as choices that are present in situations in which actors consider (at least partly) irreversible investments under uncertainty, and where initial decisions are subsequently revisited. ROA provides a set of techniques to explicitly incorporate these possible changes in decisions in the light of new information.

The extra layer in ROA compared to traditional decision analysis is the description of expectations regarding new information. ROA requires the formulation of how value might change in the future and what actions may be taken in response to these changes. Therefore ROA requires the following steps: identifying and defining what constitutes the real options; establishing the mathematical representation of uncertainty and choosing the solution method.

3.4 Interactions between actors in health care

3.4.1 The need for simultaneous decisions

It has been argued, that questions on adoption, treatment and further research should be taken simultaneously.(Sculpher and Claxton 2005b; McKenna and Claxton 2011; Forster and Pertile 2013) Furthermore, they should be taken while keeping in mind the dynamic nature of the decision process.(Forster and Pertile 2013) However, in many cases decisions regarding adoption of a new technology into the health care system, offering the new technology to individual patients and conducting further research about the new technology may be made by different agents.

3.4.2 Strategic interactions

There is empirical evidence that competitive effects have the greatest influence on the likelihood of a pharmaceutical company taking out an option, surpassing even the impact of the scope of the opportunity and the extent of prior experience of the company in the field.(McGrath and Nerkar 2004) McGrath and Nerkar examined patterns of R&D patenting for all participants in the U.S. pharmaceutical industry over a period of 17 years (from 1979 to 1995), and looked at the propensity of a firm to take out a new option (operationalised as the instantaneous probability or hazard rate of taking out a second patent in a patent subclass that is new to the firm). They found that in the early stage of a new technological arena, the more competitors that take out options, the greater will be the incentive for additional firms to take out options. A research field is found more attractive if competitors have also found the field attractive. The authors argue that as players enter, all of them benefit from the net investment into the area and the concomitant reduction in technical uncertainty that this produces. As the area matures, however, continued investment will only be attractive for

those firms who perceive that they will be in a good position to exercise their options. For the rest, allowing their options to expire (or trading them with one of the more advantaged firms) makes more sense, leading to a downturned U shape for the relationship between the number of options taken out and the number of competitors.

Over and above the impact of competition, which influences the likelihood of developing the new health technology in the first place, there is interaction between the purchasers and providers of the new health technologies. In many countries with national health service type health care provision a single purchaser negotiates with the single provider of the new health technology. In effect the situation is a bilateral monopoly, with ample of room for interaction and negotiations between the actors in the assessment of the technology. Furthermore, the actors deciding on the adoption of new technologies and conducting further research may be different too. As noted by Walker and colleagues, some HTA bodies may have a remit to order research to be undertaken while others can only wait for that information to be provided by others.(Walker et al. 2012) However, the decision on reimbursement alters future research possibilities as dissemination of the new technology will decrease the number of patients available to participate in research and also raises ethical questions about whether it is acceptable to randomly withdraw reimbursed technologies from patients. (Chalkidou et al. 2008) Whether and how and when new information will arrive on the technology under evaluation is not independent from the decision about the adoption of the technology. If the decision maker on the adoption of the technology is different from the decision maker on further research, there is a strategic interaction between the two actors. These types of interaction cannot be captured by ROA alone.

3.4.3 Real option games

In recent years, a growing number of papers in the real option literature have incorporated game theoretic concepts to take account of strategic interactions between actors.(Azevedo and Paxson 2010) Game theory aims to provide an abstract framework for modelling situations involving interdependent choices. It relies on the notion that players in a game have expectations about how the other players think, and in making their decisions about exercising their options, players do take into account what they think the other player's reaction will be to their own actions.

3.4.3.1 Background on game theory

Game theory provides analytical tools designed to help us understand the phenomena that we observe when decision makers interact. It is therefore the perfect tool to understand the

impact of exercising one's options on other decision makers and their actions. Unless otherwise indicated, this section relies on formulations and definitions provided in the pivotal textbook on game theory written by Osborne and Rubinstein.(Osborne and Rubinstein 1994)

The major assumptions that underlie game theory are that:

- Decision makers pursue well defined exogenous objectives, i.e. they are rational;
- Decision makers take into account their knowledge or expectations of other decision makers' behaviour, i.e. they reason strategically.

In game theory, the basic entity is a player. A player may be an individual or a group of individuals making decisions. One of the main characteristics of games is the number of players they include (usually denoted by *N*). A game is a description of strategic interaction including the actions that the players can take and the players' interests. The game has to describe who moves when, what the players know when they move and what they can do.(Mas-Colell and Whinston 1995) Note that the game itself does not specify the actions that the players do take. To find out what the players will do, we also need to know the outcome of each possible set of actions and the players' preferences. A solution on the other hand is a systematic description of the outcomes that emerge in the game; that is, a systematic description of the actions the players will take if they follow their interests (preferences).

3.4.3.1.1 Types of games

Games may be classified according to how the players' plans of action are devised. A strategic game is a model of a situation in which each player chooses his plan of action once and for all. These types of games are also called games in normal form (von Neumann and Morgenstern 1944), or simultaneous-move games.(Mas-Colell and Whinston 1995) The players' decisions are made simultaneously, so that players have no information about the plan of action chosen by any other player. However, simultaneous does not necessarily mean that the actions are taken at the same point in time. The only thing that matters is that the players make their decisions independently, with no player having information about the choice(s) of any other player before making his own decision.

Extensive games on the other hand specify the possible order of events and actions and each player can consider and reconsider his plan of action whenever he has to make a decision.(Osborne and Rubinstein 1994) These types of games are also called sequential or dynamic games.(Mas-Colell and Whinston 1995) Since decisions and moves are spread across time, sequential games are better suited to model the process of bringing a new health technology to market and HTA.

Games may also be differentiated according to the level of information that players have about each others' moves. A game is one of perfect information if all players know the moves previously made by all other players. Only sequential games can be games of perfect information because players in simultaneous games by definition do not know the actions of the other players. In games with imperfect information players may not be fully aware about what the other players have been doing in parts of the game.

In game theory, the concept of perfect information is separate from the concept of complete information. Complete information requires that every player know the actions and payoffs available to the other players but not necessarily the actions taken. So perfectness relates to what other players have done (the history of the game), while completeness relates to knowing the potential actions and their associated outcomes (the structure of the game). Games of incomplete information, however, can be reduced to games of imperfect information to arrive at a solution.(Leyton-Brown and Shoham 2008) This transformation will be described in more detail in section 3.4.3.2.2.3, because this is the method that will be implemented in Chapter 0.

3.4.3.1.2 Rational decision making in games

The fundamental assumption of game theory is that each decision maker is rational in the sense that they are aware of their alternatives, form expectations about any unknowns, have clear preferences and choose their actions deliberately after some process of optimisation.(Osborne and Rubinstein 1994) Formally this rational behaviour is described by the following elements:

- A set *A* of actions from which the decision maker makes a choice - in real option games one of the actions will be to exercise the option;
- A set *C* of possible consequences of these actions;
- A consequence function *g: A → C* that associates a consequence with each action;
- A preference relation on the set *C* which is compete, transitive and reflexive;

In many games the decision maker's preferences are specified by a payoff function (also called a utility function (*U*)) so that *x* will be preferred to *y* if and only if *U(x) ≥ U(y)*. The values of such a function are referred to as payoffs.

Given any set B ⊆ A of actions that are feasible in some particular case, a rational decision maker will choose the optimal action by solving the problem:

$$max_{a \in B} U(g(a))$$

Similarly to modelling decision making under uncertainty in traditional settings, most of game theory also uses the theories of von Neumann and Morgenstern (1944) and of Savage (1972). So if the consequence function is stochastic, meaning that for each $a \in A$ the consequence g(a) is a lottery (a probability distribution) on C, then the decision maker is assumed to maximise the expected value of a von Neumann-Morgenstern utility function.(Osborne and Rubinstein 1994)

3.4.3.2 Game solutions

3.4.3.2.1 Simultaneous-move games

The most commonly used solution concept in game theory is that of the Nash equilibrium.(Osborne and Rubinstein 1994) In a Nash equilibrium, each player holds the correct expectation about the other players' behaviour and acts rationally. Formally a profile $a^* \in A$ of actions is a Nash equilibrium if for every player $i \in N$ (a^*_{-i}, a^*_i) is preferred to (a^*_{-i}, a_i) for all $a_i \in A_i$. That is, no player has an action that would be preferred to that generated by a_i^*, given that other players have all chosen their equilibrium actions. Even more simply, it is not worth deviating from the strategy given the expected actions of other players.

Not all games have a Nash equilibrium and some games may have more than one.

3.4.3.2.2 Sequential games

Over and above the elements required for normal form games, a full description of sequential games also need the following:

- A set *H,* which describes the sequence of actions. Each member of *H* is a history, a possible pathway in the game, while each component of a history is an action taken by a player;
- A function *P* that assigns to each nonterminal history (i.e. each decision node within the game) a member of *N*. In other words, *P* is the player function assigning a player to each decision, *P(h)* being the player who takes an action after the history *h*.

After any nonterminal history *h,* player *P(h)* chooses an action from the set

$$A(h) = \{a: (h, a) \in H\}$$

A strategy of a player is a plan that specifies the action chosen by the player for every history after which it is his turn to move. In effect, a strategy is a contingency plan: what will my actions be if the other players did this or that.

3.4.3.2.2.1 Sequential games with perfect information

In sequential games the concept of Nash equilibrium on its own is not enough to rule out non-credible strategies. Therefore in most solutions a stronger concept, that of sequential rationality is used. Sequential games with perfect information can be partitioned into subgames. A subgame is a part of the complete game (a branch), which starts at a decision node that is not the first node. Sequential rationality requires that the strategy be optimal in every subgame. In other words a player's strategy should specify the optimal action at every decision point in the game.(Mas-Colell and Whinston 1995) The concept is strongly related to the Bellman principle used in backward induction (e.g. in the rolling back of lattices and decision trees and dynamic programming (see Section 3.3.2.4)) which states that the optimal strategy in the next period is the one that would be chosen if the entire analysis were to begin the next period. Formally, a subgame perfect equilibrium is a strategy profile s^* for which for any history h the strategy profile $s^*|h$ is a Nash equilibrium of the subgame.

3.4.3.2.2.2 Sequential games with imperfect information

Unfortunately, sequential games with imperfect information (i.e. where the players do not know the full history leading up to their decision point) may not have subgames at all. If players do not know the history, then they are not aware of their exact position within the game: they do not know which decision node they are at. If we do not know where the decision node is, we cannot cut off the branch starting from it, and cannot create and analyse a subgame. Histories that are indistinguishable to player *i* form a so called information set ($\hat{I}$), which is a collection of decision nodes among which the player knows he is at one, but cannot tell at which one exactly. On graphical representations of games, decision nodes belonging to the same information set are usually connected with a dotted line. In these games, strategies can only be formed on information sets and a 'pure strategy' is a function that assigns an action to each information set.

A natural application of sequential rationality to extensive games with imperfect information leads to the requirement that each player's strategy be optimal at each of his information sets. However, optimality cannot be determined without the use of outside information. Therefore solutions of games with imperfect information also require a description of players' beliefs about the history that occurred. A system of beliefs (β) is a specification of probability $\beta(x)\epsilon[0,1]$ for each decision node *x* such that

$$\sum_{x\in\hat{I}}\beta(x) = 1$$

for all information set $\hat{I}$ in the game. That is, a belief system attaches a probability to each decision node, the probability that the player is at that particular decision node within the information set. It also enables us to calculate an expected (probability weighted) pay-off associated with each action available at the information set.

The solution using the notion of sequential equilibrium then states that the strategy is optimal if for each information set of each player *i* the strategy of player *i* is a best response to the other players' strategies, given player *i*'s beliefs at that information set.

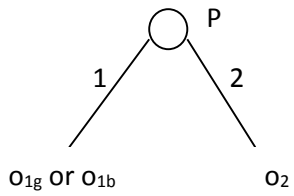
3.4.3.2.2.3 Sequential games with incomplete information

Information is complete if players have knowledge about all the actions available as well as associated payoffs in a game. In real life decision making, including decision making in HTA, information will never be complete. Decisions have to be made under conditions of uncertainty and in HTA there will always remain some uncertainty about the true value of a new health technology. Since the adoption decision focuses on trying to adopt only those technologies that provide additional value (and for now it is irrelevant how that value is measured), if true value is uncertain, the payoffs associated with either adoption or rejection of the technology will be uncertain too. Games in HTA will always be games of incomplete information.

Games of incomplete information, however, can be reduced to games of imperfect information to arrive at a solution.(Leyton-Brown and Shoham 2008) The transformation introduces an extra player, "nature", into the game. Nature is a player who has no strategic interests in the outcome. In effect, nature's role is to act as a random number generator to represent uncertainty in payoffs in a form of imperfect information game.

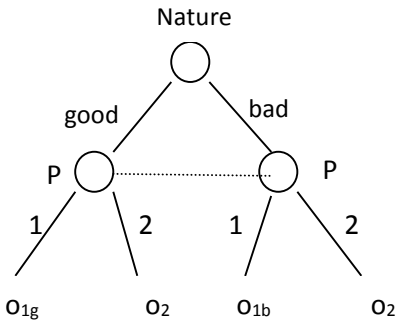
In a simple example, let us assume that the player (P) has two actions at a certain decision point: action 1 and action 2. However, the payoffs associated with one of the actions are uncertain with action 1 leading to outcome o_{1g} if the state of the world is good and outcome o_{1b} if the state of the world is bad (see Figure 3-5).

Figure 3-5 Example of game with incomplete information



If there is no clear dominance in the game, that is if payoffs from action 2 are not clearly preferred to payoffs from action 1 regardless of the state of the world, or vice versa, the game above may be transformed into a game with imperfect information and solved using the notion of sequential equilibrium as described above. The transformation is presented in Figure 3-6. Now the player has complete information (he knows the outcomes after each action), but he has imperfect information (he does not know what nature's decision was and does not know which decision node he is at) and therefore his two decision nodes belong to the same information set. If we can associate a belief system with the player (e.g. he may believe that the probability of world being in a good state is *p*, while the probability of the world being in the bad state is *1-p*), the game may be solved using sequential equilibrium so that the player must chose action 1 if $p*o_{1g}+(1-p)*o_{1b}$ is preferred to o_2.

Figure 3-6 Transformation into a game with imperfect information



This transformation of an incomplete information situation into a game with imperfect information will be applied in the evaluation presented in Chapter 0.

3.4.4 Real option games in the literature

The first paper in real options literature to consider interactions between firms was authored by Smets.(Smets 2003) Since then real option games have been applied to investment decisions in competitive markets many times and Azavedo and Paxson offer comprehensive

reviews.(Azevedo and Paxson 2010; Azevedo and Paxson 2014) The standard real option game model concerns competing firms wanting to invest, where the value of the investment is treated as a state variable that follows a known process, the investment problem is studied in isolation as if it is the only asset on the firm's balance sheet (i.e., the game is played on a single project); and there are usually two players, that is two firms holding the option to invest.

3.5 Conclusions

This chapter provided an overview of the concepts behind financial and real options and game theory.

Financial options limit the magnitude of losses encountered. The main objective of options (and most financial derivatives) is to reduce the risk of the investors stemming from the volatility of prices. Real options have the same aim. Instead of assuming future decisions are fixed, real options methods explicitly incorporate managerial and technological flexibility. Option value in real settings stems from the fact that we do not have to live with the consequences of bad decisions forever. Decisions can and should be changed, actions should be amended if they are proved erroneous in the light of new evidence.

Real option methods allow for the explicit incorporation of flexibility in terms of timing, the changes in the value of investment and abandonment of investments into the structure of the decision. There is no gold standard methodology and the choice should always depend on the kind of real option included in the analysis, on what type of uncertainty surrounds the current decision and our expectations regarding the future. The assumptions underlying financial option pricing techniques will rarely hold for the case of real options. Therefore decision analytic techniques and/or dynamic programming is preferable. Simulation techniques have been shown to be especially flexible and are able to incorporate most challenges that real life assets and projects may pose.

Although it has been shown that decisions on adoption, treatment and further research should be evaluated as a single economic project, very few studies have recognised that these decisions may not fall into the jurisdiction of the same decision maker. If there are separate decision makers deciding these important aspects, then real option analysis needs to be extended to include strategic interactions. Pairing ROA with game theory provides a way to incorporate the interdependency between different decision makers in an HTA situation. Since the HTA process involves a number of decisions, the decision makers have the chance to reconsider their actions after observing what others have done, and decisions about new

health technologies are always made under conditions of uncertainty, a real option game in HTA should be a sequential game with incomplete information.

4 Health technologies and real options in the literature

4.1 Introduction

In this chapter I present a review of studies that have applied ROA in the field of health or health care. Since my aim was to assess the feasibility of routinely applying ROA methods to the evaluation of health technologies, I appraised previous studies according to whose perspective they were conducted from, and the type of real options analysed. I also wanted to understand how previous studies have characterised uncertainty over time, as health care differs from financial markets fundamentally. For routine use of a method it is important to have sufficient information, so I also investigated what data sources have been used to estimate model parameters that are not currently needed for traditional economic evaluations.

4.2 The literature on real options in health care

4.2.1 The search strategy

To identify articles dealing with real options in the field of health care, I searched the Scopus database. Scopus is the largest abstract and citation database of peer-reviewed literature (scientific journals, books and conference proceedings).

I performed a narrow search to identify articles that presented ROA in the context of economic evaluation of health technologies on 18 September 2014. The aim was to identify articles that specifically identified their evaluation technique as ROA either as “real option analysis” or as “real option” in the context of an “evaluation”. In addition, the studies had to focus on economic impact and value of health technologies. The search algorithm and number of hits are shown in Table 4-1. The search terms were applied to either the article title, abstract or among the keywords, as it was hypothesised that if a study employed a novel technique such as ROA, this would be mentioned in a prominent place.

Table 4-1 Narrow search algorithm

Search	Search Algorithm	Hits
1	"real option" AND (analysis OR evaluation)	1,873
2	cost OR economic OR budget OR expenditure OR "resource utilization" OR "resource utilisation" OR "resource use" OR "health care utilization" OR "health care utilisation" OR "health care use" OR "economic evaluation" OR "cost benefit" OR "cost effectiveness" OR "cost utility" OR "cost minimisation" OR "cost minimization" OR "pharmaceutical economics" OR pharmacoeconomics	2,575,962
3	health OR "health care" OR "health technology" OR drug OR pharmaceutical OR medical OR "medical device" OR "medical devices"	10,321,403
4: 1&2&3		51
5	Type: Conference Review	7
6: 4 NOT 5		44

I reviewed abstracts of the 44 hits. A further 15 articles were excluded, because they did not consider evaluation of human health technologies (four articles were on environmental economics; three articles each on electronic system health management and disaster planning; two studies described treatment patterns or attitudes toward treatments that patients or physicians would never choose, and hence could not be considered "real" options; and one article each on functional foods, vehicle product lines and a theoretical paper on health capital accumulation). Therefore, the narrow search identified 29 relevant studies.

ROA is a relatively new field and it is certainly new in HTA. There is no consensus about terminology and it was likely that the narrow search missed studies that did perform ROA, but maybe labelled the analysis differently (e.g. included the terms "calculation of option value" or "evaluation of flexibility" instead of "real option analysis"). So I augmented the narrow search with a broad search. For the broad search, terms were defined more loosely allowing for "option value" as well in the context of health, the publications had to be in English, but they were not required to specify that an economic evaluation was conducted. To allow for a broader scope I looked for any mention of the search terms in the article text too (see Table 4-2).

Studies were to be included in the literature review if they met all of the following criteria:

- Concerns a health technology: pharmaceutical, medical device, diagnostic/screening test, or a procedure;
- An economic evaluation of the health technology or of the company producing the health technology is undertaken;

- The description of the evaluation method acknowledges ROA;
- English-language report available.

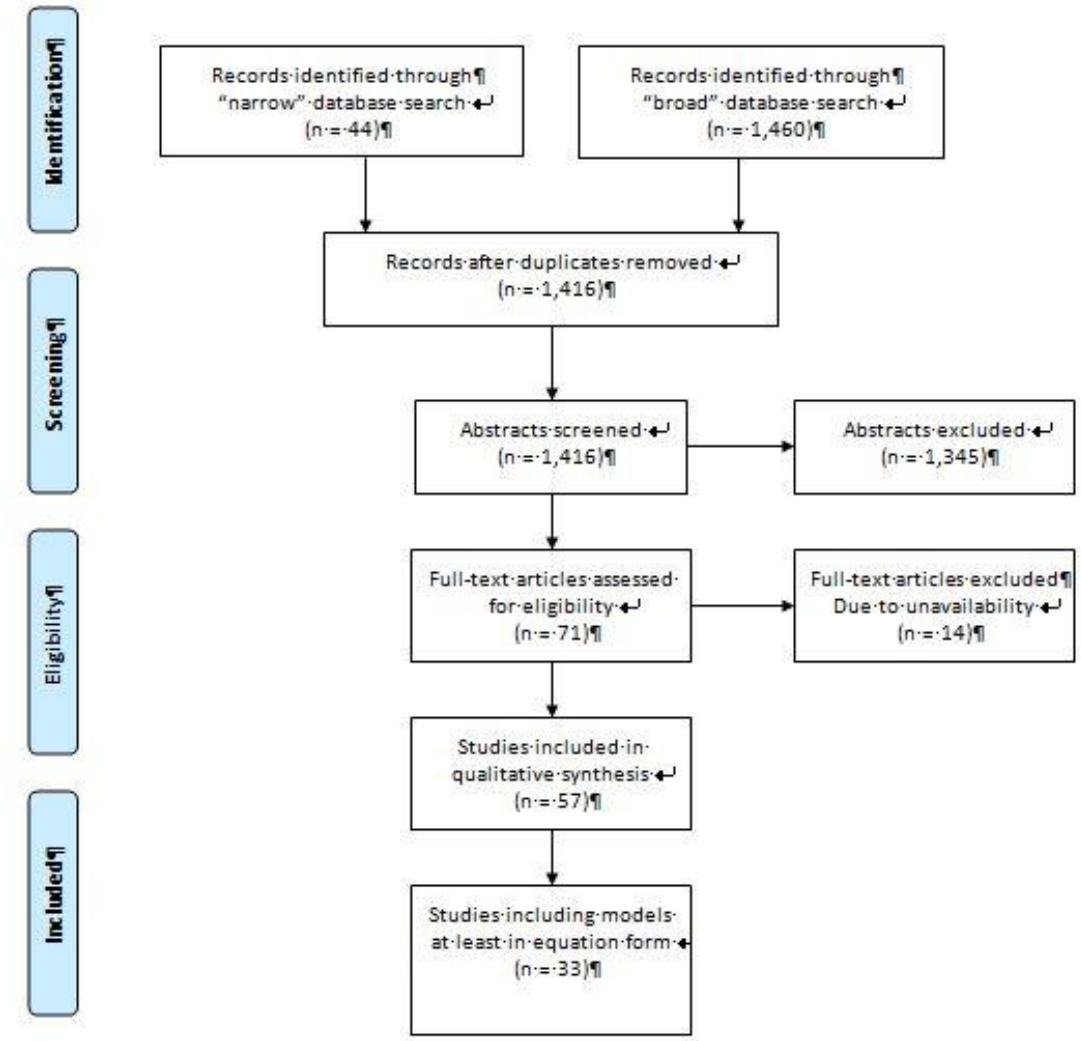
Table 4-2 Broad search algorithm

Search	Search Algorithm	Hits
1	ALL ("real option" OR "real options" OR ”option value”) AND ALL (health OR healthcare OR pharmaceutical OR drug OR medical)	2,554
2	1 AND LANGUAGE , "English"	2,502
3	2 AND(EXCLUDE (SRCTYPE , "p") OR EXCLUDE (SRCTYPE , "d") Excluding conference proceedings and trade publications	2,287
4	Excluding subject areas of: engineering; computer science; environmental science; mathematics; agricultural and biological sciences; biochemistry, genetics, molecule biology; chemical engineering; energy; arts and humanities; earth and planetary sciences; chemistry; materials science; physics and astronomy; veterinary	1,460

I reviewed the abstracts of the 1,460 studies for relevance, and included 42 additional articles that were not captured by the narrow search.

Of the 71 articles of interest, I was able to obtain the copies for 57 articles. These 57 articles were reviewed to examine the range of real options methods that have been applied in the field of health care. Some publications provided theoretical background to the use of ROA or only mentioned ROA as a potential area for further research highlighting possible advantages or areas of concern regarding its application to HTA. These informed my understanding of ROA, but did not provide guidance on the actual application of the method to HTA. Therefore only studies which included an economic model at least in an equation form were selected for detailed discussion in this chapter. The process of article identification and selection is illustrated in Figure 4-1.

Figure 4-1 Article identification and selection



When during my research it became apparent that I would like combine real options methods with game theory, the literature search was further extended. I carried out a separate search on 4 August 2014 to identify studies in the field of health care which specifically identify their method to describe the interaction between decision makers as a combination of ROA and game theory. The search terms are described in Table 4-3.

Table 4-3 Real option game search algorithm

Search	Search Algorithm	Hits
1	TITLE-ABS-KEY ("real option" OR "real options" OR "option value") AND TITLE-ABS-KEY (health OR healthcare OR "health care" OR pharmaceutical OR drug OR medical)	205
2	TITLE-ABS-KEY (game OR "game theory" OR "real option game")	161,241
3	1 AND 2	3

Unfortunately the three identified studies were only available in an abstract format.

4.2.2 Review criteria

When reviewing the articles containing a model at least in an equation form, information was extracted on the following characteristics:

- Perspective: what was the setting of the study? Who was the decision maker that evaluated the option(s)?
- Data: Where was data obtained from?
- Characteristics of the option(s) included
- Risk characterisation method
- Solution method

4.3 Findings from the literature

Results from studies which reported a model (at least in equation form) were included and are reported in Table 4-4. 40 evaluations were identified in 33 publications.

4.3.1 Level of application

The scope of the identified studies demonstrates that the ROA approach can be applied at all levels where economic evaluations are currently undertaken (see Figure 4-2). The majority of the studies concerned the value of developing new health technologies from the perspective of the manufacturer, but studies were also performed from a societal or payer perspective, from the view-point of a local health care organisation (e.g. a hospital) and of a single patient or physician making individual treatment decisions.

Figure 4-2 ROA studies by perspective

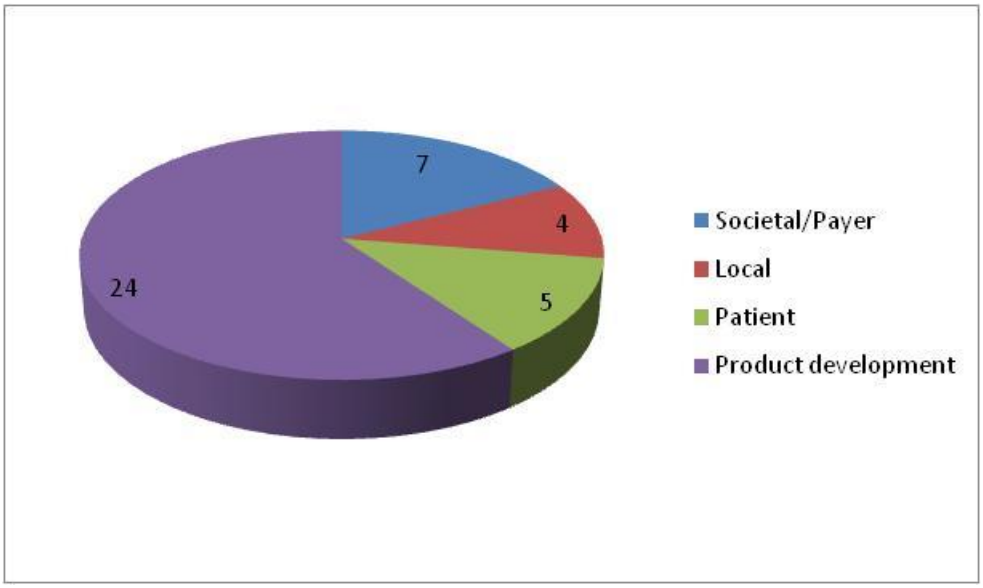


Table 4-4 Real options models in the field of HTA in the literature

Source	Technology	Data source	Option	Risk characterization method		Solution method
Payer/Societal level						
(Palmer and Smith 2000)	Hypothetical new health technology	Equations only	Defer decision	Stochastic process	Value of new technology follows Wiener process with drift	Dynamic programming
(Driffield 2003)	Hypothetical new technology	Illustrative data	Compound option to approve and then abandon	Stochastic process	Expected benefit of treatment follows Wiener process with drift	Iterative procedure to converge on solution to a PDE
(Driffield 2003)	Hypothetical new drug	Illustrative data	Defer decision	Stochastic process	Expected benefit of treatment follows Wiener process with drift with additional Poisson jumps	Numerical methods to find solution for PDE
(Attema, Lugner, and Feenstra 2010)	Stockpiling antiviral drugs as a precautionary measure against possible influenza pandemic	Empirical data	Delay investment in antiviral drugs	Stochastic process	The hazard rate of an influenza outbrake follows a Wiener process	Analytical solution through Bellman equation (backward induction in continuous time)
(Grutters et al. 2011)	Proton therapy compared to stereotactic body radiotherapy in inoperable stage I NSCLC	Actual data	Adopt without further research vs adopt and undertake trial vs delay adoption and undertake trial	Probability distributions	Monte Carlo simulation of all inputs and EVSI calculations	EVSI simulations (Monte Carlo)
(Favato et al. 2013)	HPV vaccination	Actual data	Stop or alter vaccination strategy	Fuzzy pay offs	NPV of vaccination strategy is a triangular fuzzy number	Analytical solution
(Forster and Pertile 2013)	Drug-eluting stents	Actual data	Delay adoption	Probability distribution	Incremental net benefit of DES has a distribution	Analytical solution

Source	Technology	Data source	Option	Risk characterization method		Solution method
Local healthcare organisation level						
(Pertile 2007)	PET-scanner	Equations+ illustrative data	Defer investment and change scope of investment	Stochastic process	Number of scans follows a Wiener process with drift	Dynamic programming
(Levaggi and Moretto 2008)	Hypothetical investment to improve quality	Equations only	Defer investment in new technology	Probability distributions	Random productivity shock to health generation in period 2 due to patient characteristics or input prices	Analytical solution through backward induction
(Pertile 2009a)	PET-scanner	Actual data	Timing and size of project (PET scanner only, fully equipped PET) and possible expansion of project	Probability distributions	Number of patients and scans needed are time-dependent; costs and tracers sold are uncertain, and number of scanners follows a Poisson distribution	Simulation (Monte Carlo)
(Levaggi, Moretto, and Pertile 2012)	PET-scanner	Illustrative data	Set timing of investment and number of patients scanned	Stochastic process	Effectiveness follows Brownian motion, while arrival of new technology making PET obsolete follows a jump process	Analytical solution
Patient perspective						
(Driffield 2003; Driffield and Smith 2007)	Treatment of abdominal aortic aneurysm	Illustrative data	Defer treatment	Stochastic process	Trinomial tree for monetary benefit of treatment	Numerical procedure (folding back the tree)
(Driffield 2003)	Life-support for comatose patients	Illustrative data	Abandonment option	Stochastic process	Expected benefit from life support follows Wiener process with drift	Dynamic programming
(Shechter, Alagoz, and Roberts 2010)	HIV therapy	Actual data	Optimal time to initiate therapy: Irreversible treatment now vs wait for new better treatment	n/a	Provides results for different combinations of new treatment improvement, length of trial and probability of trial success	Analytical solution through Bellman equation (backward induction)

Source	Technology	Data source	Option	Risk characterization method		Solution method
(Sengupta and Kreier 2011)	Choice between health care providers (PPO vs HMO)	Actual data	Option of going out of network available in a PPO, plus the option to switch plans	Stochastic process	Health follows a combined Brownian motion with downward drift and Poisson jump process (serious illness shock)	Dynamic programming
(Meyer and Rees 2012)	Watchful waiting	Equations only	Timing of medical intervention as an optimal stopping problem	Stochastic process	Patient's development follows a geometric Brownian motion process (plus Poisson jump process for sudden discontinuous deterioration)	Analytical solution
Developer perspective						
(Ottoo 1998)	New biotechnology	Illustrative data	Growth opportunities	Stochastic processes	Both value of investment in new biotechnology and capital costs follow correlated Wiener processes with drift	Analytical solution (Black-Scholes analogue)
(Perlitz, Peske, and Schrank 1999)	New drug development	Illustrative data	Compound options to continue development	Stochastic process	Project value follows a geometric Brownian motion process	Analytical solution (Black-Scholes analogue)
(Kellogg and Charnes 2000)	New medical entity (NME)	Actual data	Abandon development at each phase	MSDA with chance nodes	Decision tree with expected cash flows generated by the new drug	Numerical procedure (folding back the tree)
(Kellogg and Charnes 2000)	New medical entity (NME)	Actual data	Abandon development at each phase, plus compound call option on second NME	Stochastic process	Binomial tree for value of new drug	Numerical procedure (folding back the tree)

Source	Technology	Data source	Option	Risk characterization method		Solution method
(Loch and Bode-Greuel 2001)	CNS-selective T-type calcium channel modulators in sleep disorders or epilepsy	Actual data	Abandon development and growth options to different indications (head trauma, dementia and "unknown" indication)	MSDA with chance nodes	Decision tree with expected and simulated cash flows generated by the new drug	Numerical procedure (folding back the tree)
(Loch and Bode-Greuel 2001)	Serotonin receptor modification for stroke	Actual data	Abandon development and growth options to different indication	MSDA with chance nodes	Decision tree with expected and simulated cash flows generated by the new drug	Numerical procedure (folding back the tree)
(Loch and Bode-Greuel 2001)	L-type calcium channel supression for dementia	Actual data	Abandon development	MSDA with chance nodes	Decision tree with expected and simulated cash flows generated by the new drug	Numerical procedure (folding back the tree)
(Benninga and Tolkowsky 2002)	New drug development	Illustrative data	Abandon development	MSDA with chance nodes	Decision tree (binomial tree) for cash flows generated by new drug	Numerical procedure (folding back the tree)
(Rosati 2002)	New drug development	Illustrative data	Gather information on competitor or acquire competitor	MSDA with chance nodes	Decision tree with expected profits	Numerical procedure (folding back the tree)
(Burman and Senn 2003)	New drug development	Equations only	Stop drug development after a trial	Probability distributions	Commercial value has normal prior distribution, and is updated with new observations from trial	Dynamic programming (backward induction)
(Pandey 2003)	New drug development	Illustrative data	Abandon development	MSDA with chance nodes	Decision tree with expected cash flows generated by the new drug	Numerical procedure

Source	Technology	Data source	Option	Risk characterization method		Solution method
(Schwartz 2004)	New drug development	Actual data (sector averages)	Abandon development	Stochastic processes	Cost of completion and net cash flow of new drug both follow Wiener processes with Poisson jump process for catastrophic events	Analytical solution to PDE if new drug is valued after completion; Simulation if valued before completion
(Cassimon et al. 2004)	New drug development	Actual data (sector averages)	6-fold compound option to develop drug in stages	Stochastic process	Value of the new drug follows Wiener process with drift	Analytical solution to PDE (extension of Black-Scholes formula)
(Bode-Greuel and Greuel 2005)	New drug development	Illustrative data	Abandon development	MSDA with chance nodes	Decision tree with expected cash flows generated by the new drug	Numerical procedure (folding back the tree)
(Johal, Oliver, and Williams 2008)	New medical device	Illustrative data	Abandon development	Binomial tree	Decision tree with expected cash flows generated by the new medical device	Numerical procedure (folding back the tree)
(Willigers and Hansen 2008)	New drug development	Illustrative data	Abandon development	MSDA with chance nodes	Decision tree with expected cash flows generated by new drug	Numerical procedure (folding back the tree)
(Willigers and Hansen 2008)	New drug development	Illustrative data	Abandon development	Stochastic process	Binomial tree for price of new drug	Numerical procedure (folding back the tree)
(Willigers and Hansen 2008)	New drug development	Illustrative data, actual data for stochastic processes	Abandon development	Stochastic processes	Ornstein-Uhlenbeck process (mean-reverting) for cash flows generated by new drug, separate Wiener processes for cost of completion and Poisson jumps for external failure by development phase	Simulation (least-squares Monte Carlo)

Source	Technology	Data source	Option	Risk characterization method		Solution method
(Girling et al. 2010)	Tissue-engineered bladder	Actual data	Abandon development	MSDA with chance nodes	Shows impact of different levels of uncertainty around disutility of cystoplasty (and illustratively around production and marketing costs)	Analytical solution
(Cook et al. 2011)	Path-dependency in oncology drug development	Equations only	Incremental development leading to option of break-through development	Binomial tree	Binomial tree	n/a
(Pennings and Sereno 2011)	New drug development starting from Phase III	Illustrative data	Compound call options (to enter into Phase 3 then to launch)	Stochastic process	Future cash-flows follow a mixed jump-diffusion process : log-nromal jump diffusion process with constant Poisson jumps to model complete ruin	Analytical solution
(Erbas and Memis 2012)	New product development	Actual data (interviews)	Phase I R&D project potentially leading to Phase 2 project	Binomial tree	Binomial tree for sale expectations	Numerical procedure (folding back the tree)
(Hoe and Diltz 2012)	New drug development	Illustrative data	Abandon development	Stochastic process	Sales follow geometric Brownian motion; development costs follow a controlled diffusion process; Required (stochastic) development time for each phase is revealed when the expected capital cost process hits zero; Poisson jumps for catastrophic events	Simulation and backward induction
(Fujiwara 2013)	New product development	Illustrative data	Rainbow sequential compound option	Binomial tree	Binomial tree for value of new product	Numerical procedure (folding back the tree)

4.3.1.1 Societal perspective

At societal or healthcare payer level, the timing of reimbursement decisions is crucial. It was Palmer and Smith who first highlighted the importance of the capability to defer decisions to wait for new information (Palmer and Smith 2000). Driffield (Driffield 2003) evaluated a similar option to defer the decision on a hypothetical new drug. Driffield also presented a model in which the evaluation of a hypothetical new technology was characterised as having a compound option (i.e. an option whose exercise entitles the owner to another option): the first step being the option to approve a new technology, the approval then creating the option to later abandon the technology. These early, mainly theoretical works in the 2000s were followed by more applied HTA studies after 2010. Attema and colleagues looked at the value from a public health perspective of stockpiling antiviral drugs as a precautionary measure against a possible influenza pandemic.(Attema, Lugner, and Feenstra 2010) In their study, the source of uncertainty was the timing of an influenza outbreak, and they compared stockpiling of drugs now with the option of delaying this investment. Favato and colleagues compared the value of vaccinating one, two or more birth cohorts against HPV.(Favato et al. 2013) However, as opposed to a traditional evaluation where the vaccination strategies would be assumed to continue as planned, their evaluations included the option to stop or alter the vaccination strategy in the light of new information.

Forster and Pertile revisited the question of delaying decisions on the adoption of new technologies until uncertainty is resolved.(Forster and Pertile 2013) They were able to present analytical solutions for a two-period framework under the restrictive assumption that all uncertainty is completely eliminated by the second period. They claimed that they viewed adoption, treatment and research decisions as a single economic project, however, the example that they used took the responsibility to eliminate uncertainty out of the hands of the decision maker and assumed that research would be carried out regardless of what decision was made about the adoption. This is a very important assumption, and the implications will be discussed further in section 3.4 below.

The study by Grutters et al. (Grutters et al. 2011) followed the methods propagated by Eckermann and Willan.(Eckermann and Willan 2008b) Eckermann and Willan argued that decision makers generally face joint research and reimbursement decisions. Therefore they are faced with the options to either adopt the new technology without any future research (AN: adopt and no trial), adopt the technology but ensure that a trial is conducted (AT: adopt and trial); or delay the adoption and wait for the results of the trial (DT: delay and trial). They showed that for irreversible decisions AT is always dominated by AN, and the option value of

delay, the incremental value of DT compared to AN, equals the EVSI of the trial minus the expected benefit forgone while waiting for the new information and the costs of conducting the trial. For decisions which are reversible, but at a cost, the optimal choice is also related to the cost of reversal. In this situation, AT becomes a viable option, and the EVSI for the AT option will be directly related to the costs of reversal. If the cost of reversal is zero, then the EVSI for the AT option equals the EVSI for the DT option. However, as the costs of reversal increase, the EVSI for the AT option will decrease. Therefore the optimal choice between AN, AT and DT depends on the EVSI with DT, the EVSI with AT (and therefore the costs of reversal), the benefits foregone with delay and the costs of the trial. This approach relying on EVSI assumes that there is no evolution of effectiveness, or other parameters, over time. Using this framework, Grutters and colleagues compared proton therapy with stereotactic body radiotherapy in inoperable stage I non-small cell lung cancer. They showed that in the Netherlands, adopt and trial was found to be the preferred option, with an optimal sample size of 200 patients. However, doubling the costs of the trial would make immediate adoption with no trial optimal, while if the costs of reversal were doubled, the delay and trial option was optimal.

Dreyfuss and Roberts critiqued the Grutters paper regarding the source of efficacy data used to calculate the benefits associated with the treatment options as coming from a too small and unreliable trial.(Dreyfuss and Roberts Jr. 2011) However, they applauded the use of the technique. They argued that ROA will be the most useful when there is a reasonable chance that the treatment modality is superior, but additional information would be helpful. They also highlighted the fact that the same dilemma about the worth of waiting for more information is present when considering accelerated approval mechanisms for new technologies and ROA could be fruitfully applied there too.

Willan and Eckermann also applied their approach from a dual perspective.(Willan and Eckermann 2012b) The suggested value of information calculations may be carried out by both the payer and the company to determine the maximum price acceptable to the payer and the minimum price acceptable to the company. However, the authors envisaged separate calculations, with both the payer and the company optimising within their own jurisdiction to find price boundaries within which price negotiations may take place.

4.3.1.2 Local perspective

At local provider or commissioner level, ROA may help in evaluating timing, scope and/or phasing of investments. Pertile (Pertile 2009b; Pertile 2007) used ROA to evaluate whether a hospital should invest in a new PET scanner. The options evaluated related to the timing of the

investment, and the scope of the project. Hospitals may purchase the scanner but still buy the tracer from another site. Alternatively, with a higher capital outlay, the tracer can be produced on the same site where the scan is provided. The two studies differed in how they handled uncertainty and in the perspective of the analysis. The 2007 publication focused solely on a single hospital's optimisation problem, treating the number of patients to be scanned as an exogenous variable which follows a geometric Brownian motion. The 2009 publication extended the analysis, and looked at an optimisation problem based on the principles of community health needs assessment, therefore numbers of scans needed were calculated within the model based on the catchment area of the hospital, the need for scans and the number of scanners available at each time period. Pertile found that the best strategy for Verona University Hospital in the Veneto Region would have been to invest in a full PET facility (scanner and tracer production) only after four years.(Pertile 2009b)

Levaggi and Moretto used ROA to examine a hospital's decision to invest in new technology to improve quality of care (Levaggi and Moretto 2008). Their study is unique in expanding the perspective of the study to incorporate not just the hospital, but also the purchaser, therefore pairing ROA with optimising contracts under informational asymmetry. The method allows for differential information between the actors, but optimises the contract from the viewpoint of the purchaser only, therefore falls one step short of the game theoretical approach examined later in this thesis. The framework was later applied to PET scanners, showing that if the purchaser included both a variable (a per patient) and a lump-sum component in the reimbursement for providing a new health technology, then efficiency could be ensured both in the timing of adoption (dynamic efficiency) and the intensity of the use of the technology (static efficiency).(Levaggi, Moretto, and Pertile 2012) If the reimbursement included only a per patient component, a trade-off may emerge between dynamic and static efficiency.

4.3.1.3 Patient perspective

ROA also provides an explicit technique to find the optimal timing of medical intervention at an individual patient level.

Driffield and Smith (Driffield and Smith 2007) used ROA to evaluate the watchful waiting option (deferring treatment) for abdominal aortic aneurysm, while Driffield (Driffield 2003) used a similar approach for the opposite question, to determine how long life support should be provided for comatose patients: when life support should be abandoned.

Meyer and Rees provided the theoretical framework for the above watchful waiting dilemma.(Meyer and Rees 2012) The options in watchfully waiting involve monitoring a

patient's health state over time and deciding whether to undertake a medical intervention, or to postpone it and continue observing the patient. The authors considered the timing of medical interventions as an optimal stopping problem, with the development of the patient's health state in the absence of intervention following a stochastic process. The value of options grows with uncertainty and not surprisingly Meyer and Rees also found that in most cases an increase in the degree of uncertainty over the patient's development makes waiting more attractive.

The above three studies took into consideration existing treatment options. Shechter et al. on the other hand addressed a topic not considered in previous models of patient treatment: the possible downstream availability of improved treatment options coming out of the medical research and development (R&D) pipeline.(Shechter, Alagoz, and Roberts 2010) In their model, a patient may prefer to wait and take the chance that an improved therapy comes to market rather than choose an irreversible treatment option that has serious quality of life ramifications and would render future treatment discoveries meaningless for that patient. Their Markov decision process model was used to define the optimal time to initiate HIV treatment and incorporated uncertainty around the development of new therapies and their effects.

Sengupta and Kreier applied ROA to a different question of interest to individual patients.(Sengupta and Kreier 2011) Their study was based in the US, and their focus was an individual's choice between a Preferred Provider Organization (PPO) and a Health Maintenance Organization (HMO) under uncertainty regarding future health. The authors modelled health as a stochastic process whose fluctuations arise from three sources: 1) health evolves over time with a downward drift over the lifespan; 2) health is also subject to small, mean zero random fluctuations which represent minor, short-term illnesses with full recovery; and 3) there exists a small possibility every period of a serious illness resulting in a large, discrete fall in health (a jump). The model evaluated the two health plan choices taking into account the embedded flexibility to receive coverage for out-of-network care if the PPO health plan is chosen plus the option to switch between plans. They also found that greater uncertainty increases option value, that is, in their model potentially greater health problems increase the value of the option to go out of network for the PPO enrollee.

4.3.1.4 Product development perspective

It is no surprise that a large number of studies were found concerning the development process of new health technologies from the developing company's point of view. New health technology development can be viewed as a typical investment decision, and techniques used

in other fields are more readily applicable. Furthermore, the natural phases in the development process, moving from identification of a potential new medical entity to a pre-clinical phase and then through the well-defined and regulated clinical development process before the launch of a new technology, readily offer themselves to be interpreted as a series of stop/go decisions (abandonment options at the end of each phase). Ten of the identified studies fell within this category.(Kellogg and Charnes 2000; Loch and Bode-Greuel 2001; Benninga and Tolkowsky 2002; Pandey 2003; Schwartz 2004; Bode-Greuel and Greuel 2005; Johal, Oliver, and Williams 2008; Willigers and Hansen 2008; Girling et al. 2010; Hoe and Diltz 2012) In these models, the development process may be abandoned at the end of each phase if the new technology fails to meet the necessary criteria for a successful launch.

The development phases all build on the information gathered in and the success of the previous phases. Therefore another common interpretation of the development process is to view it as a series of compound call options.(Perlitz, Peske, and Schrank 1999; Cassimon et al. 2004; Pennings and Sereno 2011; Fujiwara 2013). As noted earlier, compound options are options on options: that is, the exercise payoff of a compound option involves the value of another option. In the health technology development process this means that the successful completion of a development phase (exercising the call option on the development phase) gives the right to the developer to enter into the next phase of the development (the call option on the next phase).

The notion of one successful development leading to another development is also captured in other forms. Cook described path-dependency in oncology, stressing that innovation builds on itself and an incremental development may lead to the option of a break-through development.(Cook et al. 2011) He argued that ignoring the value of the second option will undervalue the first incremental technology and could potentially reduce oncology R&D. Erbas and Memis also included in their evaluation of a Phase I R&D project its potential to lead to a Phase II project.(Erbas and Memis 2012) These are both compound options, even though the authors have not labelled them as such.

Studies conducted at the very early stages of the development process may not even be able to specify what the indication of the new technology should be, or what development phases it must go through. For example Ottoo used ROA to value new biotechnology firms, which have limited assets and no cash-flow yet, therefore their value must stem from potential growth opportunities.(Ottoo 1998) In the model, a biotechnology firm gains access to productive technology by completing basic R&D projects before its competitors, thereby procuring patent protection to obtain access to monopoly rents. The growth option is

exercised by incurring the manufacturing and marketing expenses, both of which are unknown a priori. General growth options may also be used to value the potential of new health technologies to be used in new, currently unspecified indications.(Loch and Bode-Greuel 2001)

The above approaches may also be combined. Kellog and Charnes used abandonment options to model the development of a first new medical entity (NME).(Kellogg and Charnes 2000) However, their model also included the potential of the first NME leading to the discovery of a second NME in the form of a compound call option on the second NME. Loch and Bode-Greuel in their analysis of a central nervous system-selective T-type calcium channel modulator included a separate development path with abandonment options in two indications (sleep disorders and epilepsy), but combined the above with growth options to other indications as well, such as pursuing an indication for head trauma, dementia or even a yet unspecified indication.(Loch and Bode-Greuel 2001)

Two studies did not fit any of the above categories.(Rosati 2002; Burman and Senn 2003) The model developed by Burman and Senn did not follow the usual development phases, but propagated more frequent examination of the success of new drugs in development.(Burman and Senn 2003) Their first model included a series of dichotomous trials, meaning that the new drug is either successful or fails in these trials. The drug has to be successful in each trial for the development to continue. Failure anywhere in the chain of trials implies that the drug must be abandoned. The assumption of dichotomous evaluation of the success of clinical trials was then later relaxed, and replaced with the prior distribution for the market value of the new drug being updated whenever more information was obtained from a new trial so that a single failed trial did not necessarily lead to the abandonment of the whole development. Rosati on the other hand considered a completely different type of option.(Rosati 2002) She examined the implications of having a competitor in the field, and the options to gather information on the potential threat posed by the competitor or, in a separate model, to actually acquire the competitor to eliminate the risk.

4.3.2 Sources of data

The novelty of ROA is also displayed in the lack of real-world evaluations in the field. The majority of models identified relied on equations only, or used hypothetical numerical examples to illustrate their reasoning. Table 4-5 shows the break-down by study perspective.

Table 4-5 Use of real data by perspective of study

Perspective	Number of studies	Number with real data	Real data %
Societal/Payer	7	4	57%
Local	4	1	25%
Patient	5	2	40%
Product development	24	8.5*	35%
Total	40	15.5	39%

* The third model by Willigers and Hansen uses real world data for the stochastic processes, but illustrative data for all other model parameters, therefore it was given a 0.5 weight.

The identified ROA models in Table 4-4 are ordered by publication date within categories. With the exception of product development studies, a clear time trend can be observed. Earlier studies describe the concept; provide the equations that could be used to derive a solution; and maybe illustrate the approach with a numerical example. Later studies were more likely to present the results from real world analyses.

4.3.3 Risk characterisation methods

The focal point of ROA is that uncertainty creates opportunities.(Amram and Kulatilaka 1999) It is therefore an important consideration in ROA how future changes in value (risk) should be described in the model and how these risks should be evaluated. Except for two studies which compared ROA methods (Kellogg and Charnes 2000; Willigers and Hansen 2008), very few evaluations mentioned the possibility of describing risk and future changes differently. None provided arguments for the selection of specific valuation or risk characterisation methods.

The study by Kellog and Charnes compared an MSDA approach, where the decision tree allowed for the abandonment of the development of an NME after each phase and used the expected cash flows generated by the new drug as payoffs, with an approach describing the value of the new drug over time using a binomial lattice.(Kellogg and Charnes 2000) They did not find significant differences between the risk characterisation methods in terms of the option value predicted. They did find, however, that the value predicted differed significantly from the actual value observed on the financial markets after phase I at the time. They assumed that the new NME would behave like the industrial average, and this worked well when little was known about the drug. As projects move into phase II and later, more drug-specific assumptions about time to launch, market size and probability of success reflected the observed value more accurately.

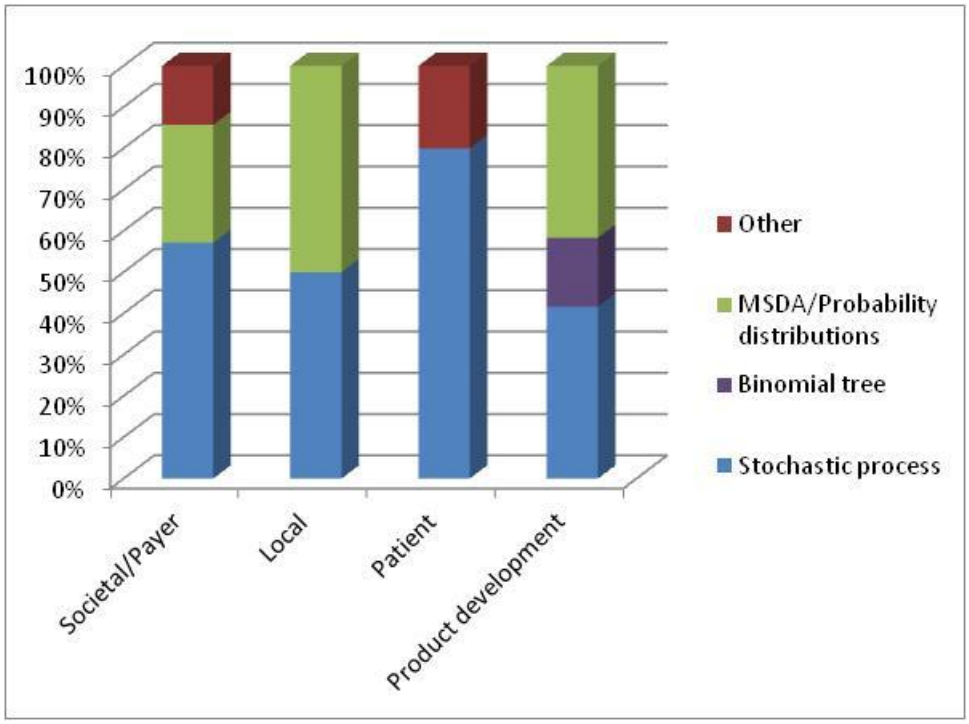
Willigers and Hansen also compared an MSDA and a binomial tree.(Willigers and Hansen 2008) They also included a third risk characterisation option: modelling components of the value of

the new drug using continuous time stochastic processes. In their example, the cash-flows generated by the new drug were assumed to follow a mean-reverting process, the cost of completion followed a Wiener process as well as including Poisson jumps to represent external failure for each development phase. The model was solved using simulation (least squares Monte Carlo method). As opposed to Kellog and Charnes, they did find differences between the methods, with the stochastic process simulation method providing consistently higher values than either the MSDA or the binomial tree method. However, the difference in results can be explained by differences in what was included in the methods. The simulation method was the only one that modelled uncertainty in the development time too and an immediate response to bad outcomes. Higher levels of uncertainty and full managerial flexibility always lead to higher option value. The authors did not examine the predictions of the more flexible methods if they were restricted only to the options depicted by the less flexible methods.

Table 4-6 Use of risk characterisation methods in the identified ROA models

Perspective	Stochastic process	Binomial tree	MSDA / Probability distributions	Other
Societal/Payer	4	0	2	1
Local	2	0	2	0
Patient	4	0	0	1
Product development	10	4	10	0
Total	20	4	14	2

Figure 4-3 Use of risk characterisation methods by perspective



As shown in Table 4-6, most studies used either a stochastic process or probability distributions to describe uncertainty. Stochastic processes have the built in ability to model the trajectory of future changes in value. The choice of the specific stochastic process reflects the special nature of information arrival regarding health technologies. As opposed to financial markets, the flow of information on new health technologies is not continuous.(Casault, Groen, and Linton 2014) New information is revealed in discrete steps each time a trial reports. The results of each trial may have a drastic impact on the value of the technology, resulting in rapid changes. Most authors in the identified studies recognised this feature of health technology development, and 12 of the 20 studies using stochastic processes incorporated a jump process to model these sudden information influxes. All 14 studies using probability distributions also acknowledged the importance of discontinuities and sudden changes in value in health. Three studies did this explicitly. Levaggi and Moreto (2008) allowed for a random productivity shock to health generation in their model.(Levaggi and Moretto 2008) Burman and Senn (Burman and Senn 2003) and Grutters (Grutters et al. 2011) explicitly incorporated the impact of new trial(s) reporting in their model. The former study applied a Bayesian approach, where the prior normal distribution for the commercial value of a new drug was updated with new observations from the finishing trials, while the latter study relied on EVSI of future trials in its evaluation. Details were provided above in sections 4.3.1.4 and 4.3.1.1, respectively. The other studies used the structure of the MSDA models to represent time points where new information was expected to be revealed.

4.3.4 Real option games in the literature

In the field of health and health technologies only three studies have been identified that apply a real options game approach.(Fujiwara 2010; Nigro et al. 2013; Fujiwara 2014) Based on the available abstracts, they all focus on the biotechnology industry, modelling the decisions of whether and when to ally with a pharmaceutical company to develop a new product. Although strategic interactions are also present in decisions made regarding health technologies in other circumstances too, real option games have never been applied before outside the product development perspective.

4.4 Conclusions

In this chapter I discussed how real options have been applied to the field of evaluation of health technologies. There is a close relationship between ROA and value of information approaches, however, only papers which formally described their methods as ROA were included in the review. Therefore there may be other potentially relevant value of information studies that were not considered here.

The literature search has identified applications of ROA relating to many differing aspects of health technology evaluation. Not surprisingly, the majority of studies concerned the development of new health technologies (pharmaceuticals and medical devices) from an industry perspective, since this field is the closest to traditional investment decisions in corporate finance. Studies from a societal or payer perspective focused on the timing of adoption decisions in relationship to the body of evidence that is available and that is expected to be available in later time periods. A similar issue, which has been often explored with ROA, is the optimal timing of medical interventions at an individual patient level. At local provider or commissioner level, ROA may also help in evaluating scope and/or phasing of investments, besides, of course, the same question about the timing of investments.

Most studies used either a stochastic process or probability distributions to describe uncertainty. The choice of the specific stochastic process was rarely discussed, although the choice of the method should be justified. The choices did reflect the special nature of information arrival regarding health technologies, with many studies applying jump processes to model the sudden changes in value characteristic of health technologies due to the lumpy arrival of information when new trials report. Studies relying on probability distributions either modelled information shocks explicitly, or used the structure of the MSDA models to represent time points where new information was expected to be revealed.

The literature demonstrates that the ROA approach can be applied at all levels where economic evaluations are currently undertaken. The majority of the studies concerned the value of developing new health technologies, but studies were also performed from a societal or third party payer perspective, from the view-point of a local health care provider and of a single patient or physician making individual treatment decisions. Very little was found on the choice between risk characterisation methods. The only two studies that did make comparisons between methods suggest that the assumptions made should be as specific to be technology under evaluation as possible, with model structures assuming more or quicker interventions in reaction to changes in information leading to higher values.

Due to the lack of efficient markets for health technologies, information is only revealed through research efforts: some actor has to conduct (at a cost) clinical trials or other type of studies to find new information. Information has public good characteristics, since the new research may benefit other parties at no extra costs, so this has implications for the interactions between actors. Although it has been shown that decisions on adoption, treatment and further research should be evaluated as a single economic project, very few studies have recognised that these decisions may not fall into the jurisdiction of the same decision maker. Only three studies have applied a real options game approach and all of them concerned the interaction of a large pharmaceutical company wanting to acquire a biotechnology firm with an innovative product. No previous studies have been identified that would apply a real options game approach to model the strategic relationship between the developer of a new health technology and the payer for the health technology deciding over the adoption of the technology. The remainder of the thesis will focus on an economic evaluation of a new health technology from a dual perspective, both a societal/payer and an industry perspective. The findings from the literature have informed the methods of the economic evaluation presented in a number of ways:

- Helping to identify the type of options available to either payers or the manufacturers of the new health technology;
- Demonstrating the acceptability of stochastic processes to represent the evolution of uncertainty around the value of health technologies, even though the processes would not be continuously observable in this field;
- Showing that, although using information from similar technologies (or even industry-wide averages) can be informative, estimates of the expected trend and expected variability over time should be technology-specific;

- Providing examples of how ROA has been combined with game theory in relation to more traditional investment decisions in health care.

The succeeding chapters will present different methods of evaluation, examining and comparing the assumptions underlying each type of evaluation and the conclusions that can be drawn from them. A traditional economic evaluation of a new health technology (presented in Chapter 0) will be compared to a simple ROA including the option to review and change decisions regarding adoption at later dates (presented in Chapter 0). However, these calculations omit the impact of the decisions on later decisions and on carrying out further research, and they also neglect the strategic interactions between parties in HTA situations,. Therefore Chapter 0 will present the first application of a real options game approach to HTA to internalise the process of information arrival.

5 The Case Studies – Background and Key Assumptions

5.1 Introduction

Previous chapters have provided an introduction to the concept of real options analysis and game theory as well as an overview of how these concepts have been used previously in the field of health care. In this chapter the underpinnings and the background for the three case studies which will be described in detail in the next three chapters are provided.

5.2 Key assumptions

The development and introduction of new health technologies in reality usually involves multiple manufacturers of competing technologies; multiple healthcare commissioners; and multiple international markets that all look to each other and are connected by mechanisms such as reference pricing. For the purposes of this thesis a simpler framework was chosen within which the principles of the analyses can be presented. It is important to emphasise that these simplifying assumptions have been adopted for convenience in this initial analysis, and that the methods can be extended to reflect more complex situations when necessary. I discuss the limitations of the simple framework and propose a series of possible extensions in the final, Discussion Chapter (Chapter 9).

5.2.1 A single setting

A single country is considered, or a single, well-defined patient population. The current framework does not include any geographical or interpersonal external effects: no consideration is given to how the decision in this single setting might influence decisions in other settings. "Intertemporal" effects, the impact of earlier decisions on information arrival in later periods, will be considered in the third model presented in Chapter 0.

5.2.2 A single payer

Health care systems differ widely, and therefore the number and level of actors involved in the decisions about adoption of new health technologies also differs substantially. Decisions can be made at a national level by a single decision-making body, or they can be made at a more local level, in which case the number of decision-makers will increase. The bodies assessing new health technologies may also be separate from the payers. Some HTA bodies only give recommendations which the payers may choose to ignore, while the recommendations of

other HTA bodies become mandatory. In this thesis, I consider a single payer who has direct impact on the use of health technologies within its jurisdiction.

Payers also differ in their range of authority. Walker and colleagues have developed a framework for coverage decisions.(Walker et al. 2012) They considered six key situations according to a positive or negative answer to three questions regarding the purchaser's authority:

1. Whether a purchaser can delay a decision or reverse it in the future in the face of new information;
2. Whether the purchaser has some influence over the effective price of the technology; and
3. Whether the purchaser can ensure further research is conducted if necessary.

As I noted in the Introduction, Palmer and Smith have identified three characteristics of investment decisions that must all hold to generate value from flexibility over the timing of decisions.(Palmer and Smith 2000) The third of these was that there must be discretion as to the timing of the investment. Thus, ROA will only be helpful for payers who can answer "yes" to the first of Walker and colleagues' questions. I therefore consider a payer with some flexibility in the timing of its decisions or the ability to review those decisions at a later date. I have also assumed that the decision-making body in this example is similar to NICE such that it has no influence over the price of the technology and cannot ensure further research is conducted.

5.2.3 Single technology by a single manufacturer

I also assume that the new technology under evaluation is truly innovative in the sense that there will be no similar technologies entering in the near future. Therefore the modelling framework includes a single new technology developed by a single manufacturer replacing a single old health technology. The impact of other new technologies or competitors to the manufacturer are not included directly, although the framework does include a notion of market share and the lifetime of the new technology, which indirectly includes the effect of other, even newer technologies entering the market.

5.2.4 Independence of treatable population

I have assumed the treatable population to be independent from the population participating in further research. This is an acceptable assumption for large patient populations, where trials do not become too lengthy due to the lack patients available to participate, and the

impact of treating patients in research situations is negligible on future sales. This assumption, as with the other assumptions listed in this chapter, can be relaxed when they are considered unrealistic for a particular application.

5.2.5 No patient heterogeneity

As stated in Chapter 2, for the purposes of the current analyses I assume that explainable variability between patients is not an issue, i.e. that there are no subgroups in the population in which the economic value of the new technology might be different, or rather that any such subgroups have been separated out and dealt with in parallel analyses. Since there is no need to (further) stratify patients the decision becomes restricted to a simple yes or no (in our notation *s* may either equal 100% or 0%).

5.2.6 Objective functions

The payer was assumed to maximise the net monetary benefits for its population over the lifetime of the new technology (as described in Equation 2 in Chapter 2 above) using a societal willingness to pay for health benefits of £20,000, while the manufacturer was assumed to maximise profits over the technology lifetime. Since, at the time of analyses, most costs related to research and development of the new technology are already sunk, profits of the manufacturer were influenced only by the volume of sales and price of the new technology, production costs and the cost of any new research that may be required.

Naturally, other objective functions may be possible too. According to the behavioural theory of the firm, the manufacturer may just want to hit a sales target or achieve at least some minimum level of profit without necessarily maximising its value.(Cyert and March 1992; Argota and Greve 2007) As discussed in Chapter 2, what constitutes value in health care, therefore what should the payer focus on has also been the topic of debate for long time. Any objective function is feasible as long as its components can be calculated with the disease model.

5.2.7 Available information

In real life, the payer (or its HTA body) and the manufacturer may have different understandings and interpretations of the available evidence, or one may have privileged access to some evidence. However, for the purposes of my analyses in this thesis I assumed that the payer and manufacturer share a common knowledge set about the value of the new technology and a common set of assumptions about how that value might change. In other words, the same model with the same inputs and assumptions was used for the evaluations undertaken from both the payer's and the manufacturer's perspective. Estimates of future

change in value were determined using an ex ante approach, i.e. they were all based on information that was available at the time of the original decision.

Future research may extend the analyses to relax these assumptions.

5.3 The case study

5.3.1 Drug-eluting stents

Percutaneous coronary intervention is a nonsurgical technique for treating obstructive coronary artery disease. Its aim is to open narrowed or blocked coronary arteries. Stenting is now the standard of care for coronary intervention, but patients can still be at risk of restenosis, the proliferation of smooth muscle cells that would decrease arterial lumen space again following bare metal stenting, leading to need for a repeat procedure. Drug eluting stents were a breakthrough in reducing the incidence of restenosis in coronary arteries due to the controlled release of antiproliferative agents, thereby reducing the need to repeat coronary interventions.(Jenkins, Prendergast, and Thomas 2002; Fattori and Piva 2003)

NICE issued guidance in 2003 (National Institute for Clinical Excellence 2003) and 2008 (National Institute for Health and Clinical Excellence July 2008) limiting the use of DES in the NHS to lesions longer than 15 mm and arteries with a 3 mm calibre. In the later guidance they also specified that the price differential between DES and BMS can be no greater than £300. However, work for the 2008 determination began in 2005 with initial negative determinations, many appeals, and requests to collect and submit more information and to re-run analyses with new information. Finally, the initial suggested decision not to adopt DES was reversed. The assessment of DES seemed a good candidate to test ROA methods.

The setting was chosen to be England and Wales corresponding to the jurisdiction of NICE. To illustrate the applicability of ROA methods to future HTAs, the time of the first evidence submissions in 2005 was chosen as the time-point for my analyses, and I only used information that was available at that time. It is important to understand that, although I will be simulating the arrival of information and changes in cost-effectiveness over the period from the start of the review in 2005 to the final determination in 2008, the calculations are conducted ex ante, using only 2005 information.

5.3.2 The objective

The objective of the research was to determine what decision could have been made on the adoption of DES in 2005, using each of the following three methods: “traditional” economic analyses, simple ROA, and a real option game (ROG); and to compare the impact of the

decisions stemming from each method from both the payer's and the manufacturer's perspective.

5.3.3 Overview of the case study models

Traditional economic evaluation requires the quantification of costs and benefits of the new health technology and the costs and benefits of the old health technology for a single cohort of patients over the period in which the new technology is expected to influence outcomes. Chapter 0 describes the development of an economic model to estimate treatment costs and health benefits for patients receiving the new health technology versus those patients receiving current standard care. Stochastic model evaluation enabled the quantification of parameter uncertainty around the cost effectiveness of DES. Separate EVPI and EVPPI calculations were then also carried out to answer the questions whether further research is warranted and what type of information would be most useful to reduce uncertainty around future decisions.

Two ROA models are then presented in Chapters 7 and 8. In these models, selected input parameters in the economic model were allowed to follow a stochastic process, rather than attempting to model the net benefit of the new intervention directly as a stochastic process. The inputs were selected based on the sensitivity of the model as determined in the traditional economic analyses in Chapter 6, my expectations of how the parameters might change over time and availability of evidence.

Chapter 0 describes an application of ROA following financial traditions allowing for flexibility in decisions incorporating the economic consequence of changing decisions. The analysis determined the optimal initial decision, allowing for possible future changes in decisions and expectations of information arrival. The model also estimates the optimal timing for review from the decision maker's perspective. However, this simple ROA model assumes that information arrival is exogenous, and new information will always be revealed regardless of the previous decision(s) about adoption.

To make information arrival endogenous in situations where decisions over approval and further research are made by different parties, a novel approach is suggested in Chapter 0, combining ROA with game theory. Two agents (the payer and the manufacturer of the new technology) were assumed to play a sequential, incomplete information game, where the manufacturer had control over the arrival of information. The manufacturer's steps included decisions to submit, reduce the effective price and conduct more research, while the payer decided whether or not to accept the new technology. This model allowed me to determine

the optimal strategies incorporating the impact of earlier decisions on research, including the optimal time to submit for review from the manufacturer's perspective.

6 Traditional economic evaluation of drug-eluting stents

6.1 The original models used in the appraisal

The second NICE appraisal of coronary artery stents took over three years to complete, with the final scope for the proposed review published on 11 January 2005 and the final appraisal determination (FAD) published on 1 February 2008. During this time the economic model used to assess the value of drug-eluting stents (DES) changed considerably.

The initial (pre-2005) scope for the appraisal included comparisons of coronary artery bypass grafting (CABG) vs DES and bare-metal stents (BMS) as well as a comparison of DES versus BMS. Therefore the initial model developed by the economic review group accommodated both comparisons.(Hill et al. 2004) However, unfortunately the model is not reported in enough detail to allow its replication. Since for patients normally requiring a CABG there was a clear survival advantage for CABG over both DES and BMS, so that CABG was always superior, much of the complexity needed to model consequences of CABG was later dropped and the economic review group developed a simplified version of the initial model, as described in detail by Bagust and colleagues.(Bagust et al. 2006) This model was the basis on which the final determination in 2008 was made. (personal communication from prof. Bagust) I have therefore chosen the simplified Bagust model to represent the common view on data and the impact of DES at the beginning of my evaluation period in 2005.

6.1.1 The Bagust model

The initial Hill et al. HTA model assumed no difference between BMS and DES in mortality and occurrence of stroke and AMIs, as the difference between the drugs did not reach statistical significance in the trials. The simplified Bagust model did not even consider these events. The narrowing of the vessel diameter and therefore the need for a repeat procedure is signaled by the reccurrence of angina, with a successful repeat procedure alleviating the symptoms of angina again. The benefits of DES were assumed to be confined to a lower rate of repeated procedures (TVRs – target vessel revascularisation procedures).(Bagust et al. 2006) Since the patients suffer from recurrent severe angina while waiting for a repeat intervention (the Bagust model assumed 15 weeks of waiting time for repeat stent insertion) on a population level the lower rate of repeat procedures results in reduction in time spent with angina Furthermore, the time horizon of the Bagust model was one year only, as most repeat

interventions were expected to occur within this time period. So, using the notation from Chapter 2, *D* is a very short period for stents (a few days), while *H* was assumed to be one year.

Model inputs and consequently model results were reported for 42 different subgroups of patients. The subgroups were defined according to the following characteristics:

- Elective or non-elective percutaneouse coronary intervention (PCI)
- Number of risk-factors present
    - From none to three of four risk factors present from calcification, angulation >45 degrees, restenotic lesion, triple-vessel disease in the case of elective patients
    - From none to two risk factors present from vessel diameter < 2 mm and prior CABG in the case of non-elective patients
    - Type of drug-eluting stent (sirolimus-eluting stent or paclitaxel-eluting stent)
- Number of stents used in the index procedure

The model assessed the incremental cost-utility of DES compared to BMS by comparing the net additional cost (the extra cost for each DES used, less any savings in treatment costs) to the loss of utility avoided as a result of the fewer reinterventions expected from the use of DES. The incremental cost-effectiveness ratio (ICER) of DES compared to BMS was calculated by dividing the incremental cost of DES per repeat intervention avoided by the incremental benefit achievable with DES per repeat intervention avoided (see Table 6-1).

Table 6-1 Calculation algorithm used in Bagust model

Component	Calculation algorithm
Incremental cost per repeat intervention avoided	(DES price premium*Average number of stents per patient) / (Risk of 2nd procedure* DES relative risk reduction); Minus average cost of re-referral and investigation per patient with recurrent symptoms; Minus average cost per patient undergoing repeat revascularisation procedure; Minus average cost per patient of additional post-revascularisation follow-up care
Incremental benefit per repeat intervention avoided	QALY loss per year with severe angina*Average time spent with symptoms(in weeks) / 52 Plus average QALYs lost per patient recovering from repeat procedure

The results ranged from DES being dominant in some high risk subgroups to ICERs of almost £600,000/QALY gained, with most ICERs above £100,000/QALY gained. Bagust and colleagues initially concluded that DES are not cost-effective compared to BMS except for a very small minority of patients.(Bagust et al. 2006)

6.2 Methods

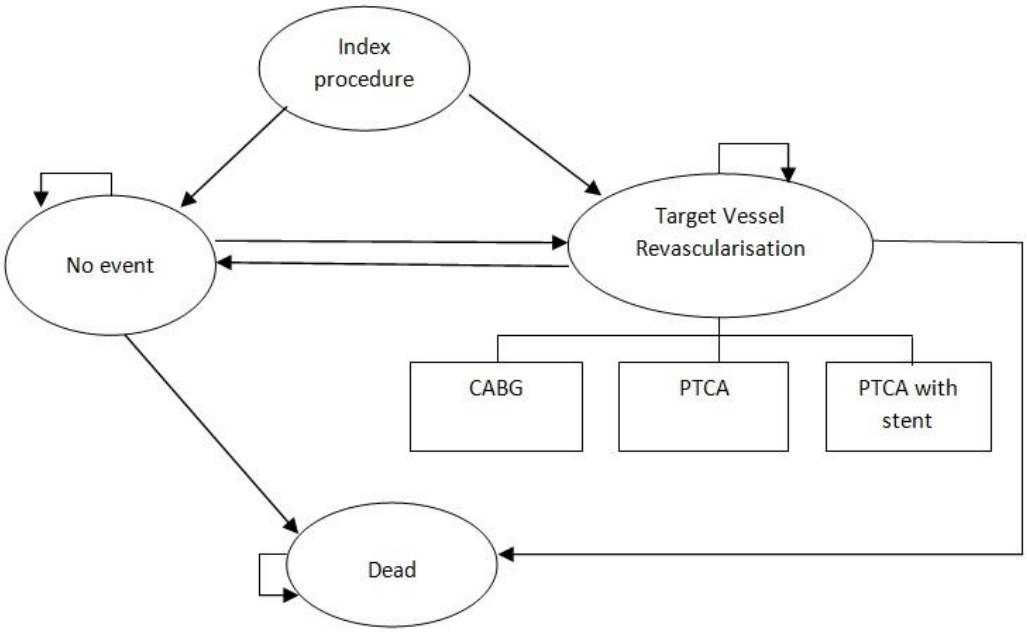
6.2.1 Model structure

The Markov model submitted by the manufacturer of the zotarolimus-eluting stent in 2005 was developed by me. A version of the model tracking repeat procedures (TVRs), acute myocardial infarction and late stent thrombosis was published in 2009.(Remak et al. 2010) This model was adapted here to predict the number of TVRs needed in the one year following the index operation to be in line with the assumptions used in the Bagust model that informed the assessment process between 2005 and 2008.

My Markov model was developed in Microsoft Excel® to assess the cost-effectiveness of DES compared to BMS in a UK setting in 2005. The target population consisted of patients with coronary artery disease with *de novo* native coronary artery lesions. The perspective taken was that of the UK NHS with only direct medical costs included. The lifetime of coronary artery stents is about four to five years (personal communication from Medtronic), therefore DES in use in 2005 were assumed to be replaced by even newer stents by 2010.

The model structure is shown in Figure 6-1 . The model structure is identical for the two model arms: in one, eligible patients receive a drug-eluting stent, while in the other, patients receive a bare metal stent during the index procedure. The model tracks the need for TVRs and mortality in monthly cycles. A patient undergoing a TVR may need a repeat PCI. The repeat procedure can be a percutaneous coronary angioplasty (PTCA) with stent, a PTCA without stenting or a CABG. It was assumed that patients undergoing repeat intervention with stenting would receive the same type of stent as in the index procedure.

Figure 6-1 Model structure



The 42 patient groups identified in the original assessment were very much disputed in the discussions during the technology assessment process.(National Institute for Health and Clinical Excellence February 2006) My aim here is to showcase the applicability of the real options approach rather than to conduct a detailed analysis of DES, therefore the model that I used in the analyses presented in this and the following two chapters considered the pooled overall population instead of numerous subgroups. Naturally, if there is evidence of heterogeneity in the patient population, the subgroups should be handled separately in real life analyses.

I calculated the impact of the technologies on population health and on the manufacturer's profit in all three analyses presented in this thesis (Chapters 6-8) using a top-down approach. Firstly, the number of patients requiring a PCI procedure until 2010 was estimated. In line with the original budget impact calculations by NICE, a fixed proportion of these patients was assumed to be eligible for stenting. Of those eligible for their initial stenting, again only a fixed proportion was assumed to actually receive DES according to the market share predictions of manufacturers.

6.2.2 Model inputs

Only data and assumptions from the Bagust model were used to reflect the thinking around DES at the time of the 2005 assessment.(Bagust et al. 2006) Model parameters are shown in Table 6-4.

6.2.2.1 *Estimation of effectiveness*

Since NICE considered all DES to be similar and evaluated them as a single entity, I have also pooled all available evidence on DES regardless of the specific type of drug eluted in a meta-analysis assuming fixed effects. In 2005, the following clinical trials were available: three trials reported on the paclitaxel-eluting stent (TAXUS I(Grube et al. 2003), TAXUS II(Colombo et al. 2003) and TAXUS IV (Stone et al. 2004)); two trials reported on sirolimus-eluting stent (RAVEL (Morice et al. 2002) and SIRIUS (Holmes Jr. et al. 2004)); and one trial reported on zotarolimus-eluting stent (ENDEAVOR II (Fajadet et al. 2006)). I reviewed the trial publications and extracted information on numbers of patients in each treatment arm and the number of observed TVRs at one year.

Table 6-2 Target vessel revascularisation rates in clinical trials of DES available in 2005

		BMS			DES			Date
Drug	Trial	n	TVR	TVRr (%)	n	TVR	TVRr (%)	
Paclitaxel	TAXUS I	30	4	13.3%	30	1	3.3%	Nov 2002
	TAXUS II	132	21	15.9%	129	13	10.1%	Aug 2003
	TAXUS IV	652	111	17.1%	662	47	7.1%	Apr 2004
Paclitaxel pooled		814	136	16.8%	821	61	7.4%	
Sirolimus	RAVEL	118	28	23.7%	120	1	0.8%	Jun 2002
	SIRIUS	525	140	26.7%	533	45	8.4%	Feb 2004
Sirolimus pooled		643	168	26.1%	653	46	7.0%	
Zotarilomus	Endeavor II	599	94	15.7%	598	47	7.8%	Sept 2005
Total pooled		2,056	398	**19.4%**	2,072	154	**7.4%**	

Legend: TVR – target vessel revascularisations; TVRr – target vessel revascularisation rate (TVRr=TVR/n)

A similar meta-analysis was undertaken by the technology assessment group for paclitaxel- and sirolimus-eluting stents.(Bagust et al. 2006) Their results were similar to those shown here, but not entirely the same. The discrepancy is likely due to differences in dealing with reporting mistakes in the studies presenting the results of the clinical trials.[5]

Monthly transition probabilities were estimated assuming that the event rates are constant between assessment time-points. The 12- month cumulative probabilities for TVR and death

[5] For example, results of TAXUS-IV were reported ambiguously.(Stone et al. 2004) The sum of target lesion revascularisations (TLR) and non-target lesion TVRs should equal the total number of TVRs. However, Stone et al. reported 4.4% TLR, 2.9% non-target lesion TVR, but 7.1% TVR (≠ 4.4%+2.9%) for paclitaxel, so there may be slight differences between meta-analyses depending on which TVR rate was extracted from the study.

were converted to monthly cycle probabilities using the usual formulas [Miller & Homan, 1994]:

$$r_{12} = -\ln(1-p_{12}),\ r_{cycle} = \frac{r_{12}}{12}, \text{ and } p_{cycle} = 1-\exp(-r_{cycle}),$$

where *p* and *r* stand for probability and rate, respectively.

The relative risk reduction was also calculated according to its definition as

$$RRR = \frac{TVRr_{DES} - TVRr_{BMS}}{TVRr_{BMS}} = -0.616 \text{ (-0.542—0.678)}$$

6.2.2.2 Resource use

The original model provided results by number of stents used, but the mean utilisation of stents was not reported for the risk groups. Therefore I assumed that the average number of stents in the index procedure is the same as that reported for repeat procedures. The mean number of stents used was 1.87, with a 95% confidence interval of 1.62-2.15 stents. (Bagust et al. 2006) The asymmetry in the confidence interval suggested a skewed distribution, therefore uncertainty around the number of stents used was represented using a lognormal distribution with the above-mentioned 95% confidence intervals.

Similarly to both the initial HTA model and the Bagust model, I assumed that during repeated stenting procedures, the same type of stent would be used as in the index procedure. Recurrence of symptoms was associated with visits to a cardiologist and an angiography. The type of repeat revascularisation was determined based on an audit of the Liverpool Cardiothoracic Centre (CTC) also performed by Bagust and colleagues.(Bagust et al. 2006) Clinical follow-up after a CABG or PTCA with or without stenting consisted of visits to a cardiologist and cardiac surgery.

6.2.2.3 Costs

Unit costs were taken directly from the original model which adjusted the NHS Reference Costs for 2004-05 and the NHS Tariff Costs (2004-05).(Department of Health) The Bagust model did not vary costs in the probabilistic analyses. However, there could be considerable uncertainty in costs, especially in the cost of the stents themselves, therefore in my model I included variability around cost parameters.

The Bagust model combined and adjusted cost codes for scope (i.e. to ensure consistency between data sources with respect to what type and level of resource use is included in the

cost calculations) from at least two different sources.(Bagust et al. 2006) Unfortunately, the process was not described in enough detail for replication, therefore uncertainty around the reported procedure costs was estimated separately. The NHS Reference Costs provided the number of cases for the year, the estimated mean cost and the interquartile range. This set of information however is not enough to calculate the variance around the mean estimate, therefore the standard deviation was imputed from the mean and the 25th percentile assuming a gamma distribution, and then the standard error of the mean calculated by definition from the imputed standard deviation and the number of cases reported. On average (weighted by the number of cases) the standard errors were 0.61% of the means and this value was used to characterise uncertainty around all cost parameters in the model with the exception of the stent prices. Due to the individual negotiations between hospital trusts and manufacturers, variability in stent prices is likely to be larger than variability in other costs. However, the negotiated prices are confidential, so in the absence of other information it was assumed that the SE of the stent cost parameters would be a magnitude larger at 10% of the mean.

6.2.2.4 Utility values

Since the assumption was that DES and BMS differ only in the number of repeat revascularisations needed, the original NICE model only took account of the disutility associated with recurrent symptoms while waiting for a repeat intervention and with further interventions. For my model I calculated utilities relative to a baseline asymptomatic coronary heart disease value (0.86) based on EQ-5D measurement in the Arterial Revascularization Therapies Study(Serruys et al. 2001), and then applied the disutilities associated with angina symptoms before procedures and disutilities associated with the procedures and subsequent recovery reported by Bagust et al. (Bagust et al. 2006).

6.2.2.5 Calculation of impact

I used the number of finished consultant episodes for PTCAs (HRG E15) for the six years prior to 2005 to predict the expected annual increase in the number of patients requiring a PCI (see Table 6-3). The average annual increase in the number of patients requiring PTCA was estimated to be 16.83% (SD 3.57%).

Since the Bagust model concerned only cost-effectiveness, I followed the assumptions in the earlier Hill et al model as far as possible in the calculation of population health impact and manufacturer profits over the lifetime of DES. Therefore 88% of patients presenting for a PTCA were assumed to receive stents (based on the proportion of patients with single- or two-vessel disease as reported by the CTC Audit used in the initial model).(Hill et al. 2004) Even if

approved, DES were expected to reach only 20% (SD 5%) of the population receiving stents (personal communication from Medtronic), the remaining patients still receive BMS. Using the notation from Chapter 2 I assumed that '*s*' would equal 20%. The original budget impact calculations on behalf of NICE also assumed that 25-30% of stented patients would receive DES.(Hill et al. 2004) For simplicity, it was also assumed that DES will take 20% of the market share immediately after a positive adoption decision, that is, there would be an immediate jump in the uptake from 0% to 20% at the time of decision, if the decision was positive.

Table 6-3 Annual increase in PCI cases

Year	Elective	Non-elective	Total	Annual increase
1999	9,924	7,503	17,427	-
2000	10,467	9,732	20,199	15.91%
2001	11,697	10,889	22,586	11.82%
2002	14,402	12,571	26,973	19.42%
2003	15,547	15,733	31,280	15.97%
2004	18,973	18,882	37,855	21.02%

From the viewpoint of the manufacturer, production costs of a stent were assumed to be 25% (SD 2.5%) of its price.(personal communication from Medtronic) The costs associated with research and development of the newer stents are, at this stage, sunk costs, and so were not included in the calculations. It was also revealed to me that in the case of stents, the costs associated with gaining approval for the new technology, producing the necessary documentation for technology assessments and the costs of marketing were all negligible compared to production costs and were therefore assumed to be zero.(personal communication from Medtronic)

6.2.2.6 Discounting

No discounting was applied within the cost-effectiveness model as the time horizon was only one year. However, for comparability across patient cohorts requiring treatment in different years all impact costs and effects were discounted to the base-year of 2005 using an annual discount rate of 3.5% for both monetary and health outcomes.

Table 6-4 Model parameters

Item	Mean	SE or CI	Distribution	Source	Comment
EFFECTIVENESS					
BMS TVR at one year	19.4%	0.87%	Beta	Meta-analysis of trials	See Table 6-2
RRR with DES	61.6%	54.2% - 67.8%	Beta	Meta-analysis of trials	See Table 6-2
RESOURCE USE					
Index procedure					
Number of stents used (DES or BMS)	1.87	1.62-2.15	Lognormal	Bagust et al., 2006	From CTC audit, after elective PTCA
Repeat procedures					
Angiography	1	n/a	Not varied	Bagust et al., 2006	Assumption
Cardiology visits	2.1	1.94-2.26	Uniform*	Bagust et al., 2006	From CTC audit, before elective PTCA
Type of TVR					
PTCA	36.6%	28.9%-45.0%	Beta	Bagust et al., 2006	From CTC audit, after elective PTCA, linked to other PCIs
PTCA with stent	54.5%	46.0%-62-7%	Beta	Bagust et al., 2006	From CTC audit, after elective PTCA, linked to other PCIs
CABG	8.9%	5.1%-15.2%	Beta	Bagust et al., 2006	From CTC audit, after elective PTCA, linked to other PCIs
Number of stents used	1.87	1.62-2.15	Lognormal	Bagust et al., 2006	From CTC audit, after elective PTCA
Follow-up after PTCA w or w/o stent and CABG					
Cardiology visits	2.18	1.72-2.64	Uniform*	Bagust et al., 2006	From CTC audit, after elective PTCA
Cardiac surgery visits	0.81	0.42-1.20	Uniform*	Bagust et al., 2006	From CTC audit, after elective PTCA

COSTS					
Procedures					
PTCA	£3,190	£19.46	Normal	Bagust et al., 2006	NHS APC Spell Costs 2005/05 E15 deflated to 2003/04 prices
CABG	£7,750	£47.28	Normal	Bagust et al., 2006	NHS APC Spell Costs 2005/05 E04 deflated to 2003/04 prices
Driver stent	£370	£37.00	Gamma	Bagust et al., 2006	Market average
Endeavor stent	£870	£87.00	Gamma	Bagust et al., 2006	BMS plus price list differential of £500
Recurrence of symptoms					
Angiogram	£372	£2.27	Normal	Bagust et al., 2006	NHS Reference costs 2003 E02op
Cardiology visit	£93	£0.57	Normal	Bagust et al., 2006	NHS Tariff Costs 2004/5 E15op deflated to 2003/04 prices
Follow-up					
Cardiology visit - first	£130	£0.80	Normal	Bagust et al., 2006	NHS Tariff Costs 2004/5 E15op deflated to 2003/04 prices
Cardiology visit - subsequent	£93	£0.57	Normal	Bagust et al., 2006	NHS Tariff Costs 2004/5 E16op deflated to 2003/04 prices
Cardiac surgery visit - first	£214	£1.31	Normal	Bagust et al., 2006	NHS Reference costs 2004 Spec 170 adjusted by Tariff Costs
Cardiac surgery visit - subsequent	£172	£1.05	Normal	Bagust et al., 2006	Cardiology ratios
UTILITIES					
QALY weights					
No event	0.86	0.15	Beta	ARTS	EQ-5D
QALY losses					
Annual QALYs lost to angina	0.135	0.122-0.148	Beta	Bagust et al., 2006	From ARTS & SoS trials
QALYs lost per PTCA	0.0056	0.005-0.006	Beta	Bagust et al., 2006	From ARTS & SoS trials
QALYs lost per CABG	0.033	0.031-0.035	Beta	Bagust et al., 2006	From ARTS & SoS trials

* For these parameters uniform distribution in the interval between the 95% confidence interval was achieved using Excel's BETAINV function, setting $\alpha=\beta=1$ and the distribution lower and upper bounds to equal the specified confidence interval.

6.2.3 Analyses

In the base-case deterministic analysis, the expected total costs and QALYs for the DES and BMS, as well as the ICER, were calculated using the model structure described above and the means of the parameters. One way sensitivity analysis was performed on all model parameters using the 95% confidence intervals of the parameters as ranges. The impacts of the 15 most influential variables on the Incremental Net Benefit (INB) of DES versus BMS were plotted, assuming a threshold of £20,000/QALY.

To test the impact of parameter uncertainty, a probabilistic analysis was also undertaken. Key model parameters were assigned a distribution. Simultaneous random sampling from these distributions was used to estimate the ICER and the population health impact and manufacturer profits over the lifetime of the DES technology (between 2005 and 2010). The distribution types and parameters associated with model variables are shown in Table 6-4. The simulation was repeated 1,000 times. Results of the probabilistic sensitivity analysis were plotted on the cost-effectiveness plane and were used to calculate cost-effectiveness acceptability curves.

To check the face validity of the reconstructed model, the subgroup-specific analyses carried out with the original Bagust model were replicated, and the results of the two models were compared.

Since value of information analyses have become more commonplace since 2005, I also calculated the Expected Value of Perfect Information (EVPI) and the Expected Value of Partial Perfect Information (EVPPI) for parameter groups. The parameter groups considered were:

- Effectiveness parameters (BMS TVR and DES RRR)
- Resource use parameters
- Cost parameters
- Utilities

The evolution of cardiac stents is very quick, so the life-time of the product (*T*) was taken to be 5 years based on communication from Medtronic. Since the number of PTCAs has been increasing steadily in the years before 2005 (from about 17,500 patients in 1998-1999 to almost 38,000 patients 2003-2004) (NHS Reference Costs, 1998-99 to 2003-04 – see Table 6-3 for more detail), and was predicted to continue to rise at a similar rate, the effective population treated per annum was assumed to be 50,000 in the value of information calculations.

6.3 Traditional model results

6.3.1 Comparability to Bagust model

To check the face-validity of the reconstructed model, I replicated the risk group analyses reported for the Bagust model.(Bagust et al. 2006) Table 6-5 shows the results published by Bagust and colleagues for elective patients using a paclitaxel DES (for 12 risk groups of the 42 in the study). My model produced entirely different results. I believe there might have been either a calculation or a reporting mistake around RRR in the Bagust model used by NICE. Matching all other inputs, but using 1-RRR, my model predicted ICERs that were very close to those reported by Bagust et al., despite the differences in modelling approach (see Table 6-6). However, using 1-RRR in my analyses would fail to replicate the TVRs observed in the clinical trials: resulting in a TVR for DES at one year of almost 13% instead of the 7.4% expected based on the meta-analyses of all clinical trials. Unfortunately the original Bagust paper only reported the ICERs and not the cost or QALY predictions, therefore it is hard to pin-point where the mistake might have been, but ICER results of the current model with 1-RRR seem to follow the original predictions nicely.

Table 6-5 Incremental cost-effectiveness ratios by Bagust et al. for paclitaxel DES (elective patients)

Paclitaxel DES No. Used	Elective patient risk groups			
	No risk factors	1 risk factor	2 risk factors	3 or 4 risk factors
1	£205,800	£113,000	£22,700	-£7,700
2	£481,900	£296,300	£115,700	£55,000
3	£758,100	£479,600	£208,700	£117,700

Table 6-6 Incremental cost-effectiveness ratios of current traditional model for paclitaxel DES (elective patients) with 1-RRR

Paclitaxel DES No. Used	Elective patient risk groups			
	No risk factors	1 risk factor	2 risk factors	3 or 4 risk factors
1	£206,350	£114,058	£22,608	-£8,139
2	£471,690	£287,223	£104,670	£43,535
3	£737,031	£460,387	£186,733	£95,209

6.3.2 Deterministic results

Model predictions for the clinical outcomes (TVRs) were comparable to the meta-analysis results. The model predicted TVRs for7.7% and 19.6% of the population treated with DES and BMS respectively, compared to the meta-analysis results of 7.4% and 19.4% as reported in Table 6-2.

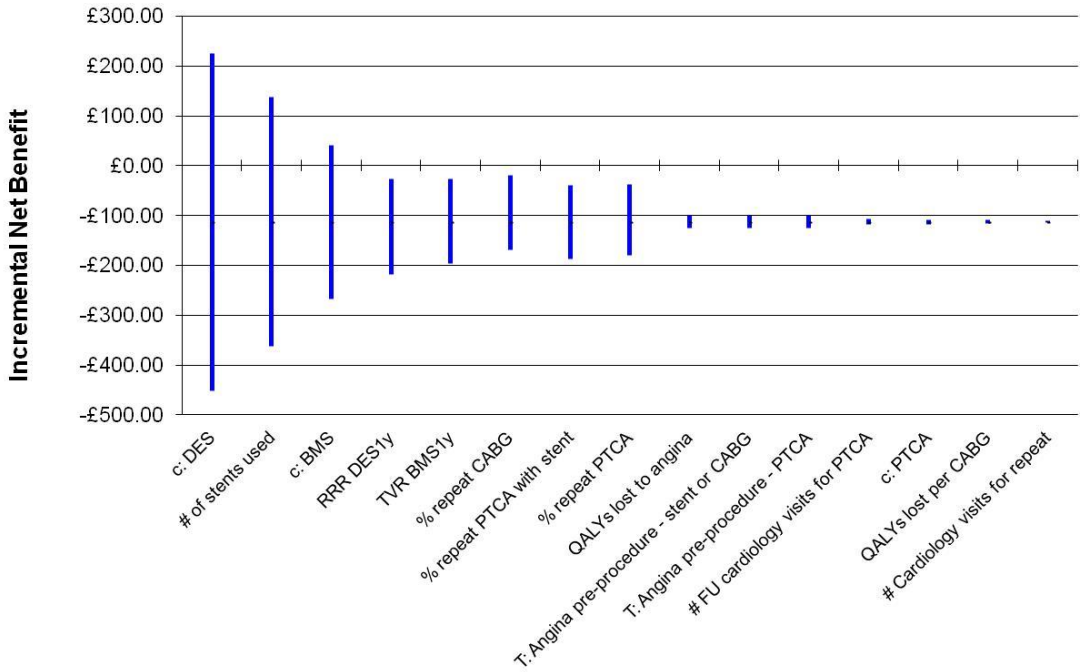
Base-case deterministic results are shown in Table 6-7. Although the price premium of DES was £500, the incremental cost of treatment with DES was only £310 due to the reduced need for revascularisations. DES were also associated with small positive incremental QALY gains, and therefore had an incremental cost-effectiveness ratio of £31,464.

Table 6-7 Base-case model results

	DES	BMS	Incremental
Costs	£5,652	£5,342	£310
QALYs	0.8386	0.8287	0.0099
ICER			£31,464

As expected, stent prices and the number of stents used had the most impact on the results (see Figure 6-2), followed by revascularisation rates and the distribution of repeat procedures. The model was very robust to changes in all other model parameters.

Figure 6-2 One-way sensitivity analyses for the traditional model



Note: INB was calculated at a threshold of £20,000/QALY
Legend: c: cost of; T: length of time with; FU: follow-up

6.3.3 Results of the probabilistic analyses

Results of the probabilistic analyses were in line with the deterministic findings. As shown in Figure 6-3 differences between the two types of stents were relatively small in terms of QALY gains, therefore even small changes in costs caused a large variation in the cost-effectiveness

of DES compared to BMS. With a base-case ICER above £30,000/QALY DES could not be considered cost-effective. However, there was considerable uncertainty as DES still had a 39% probability of being cost-effective at a threshold of £20,000/QALY (see Figure 6-4).

Figure 6-3 Probabilistic analysis results on the cost-effectiveness plane

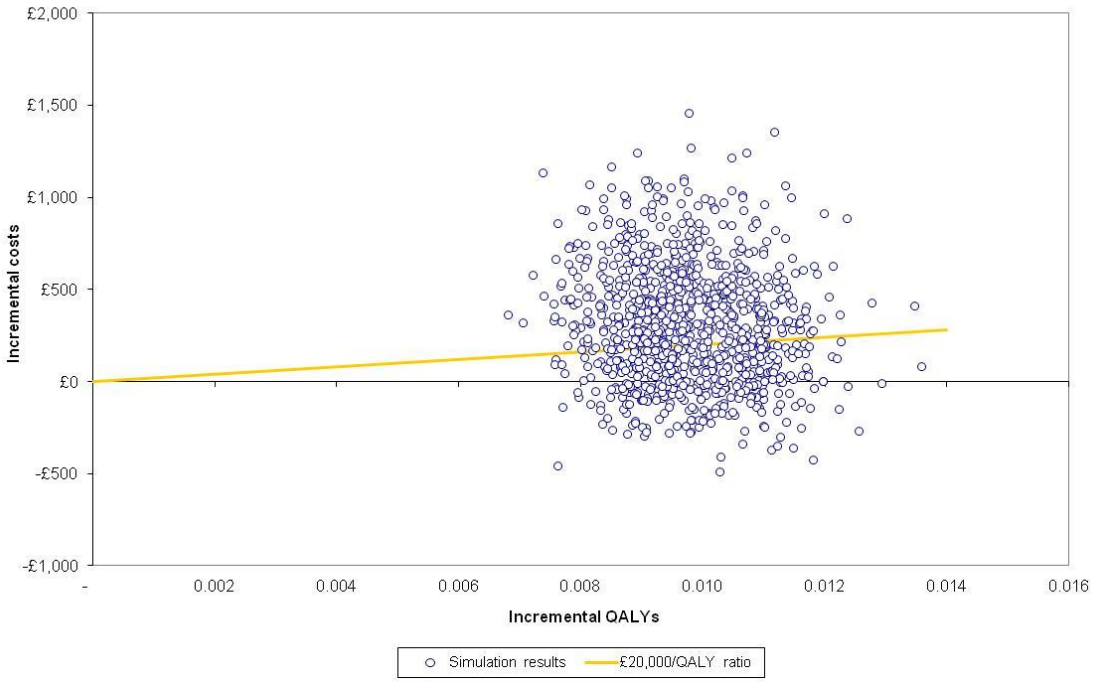
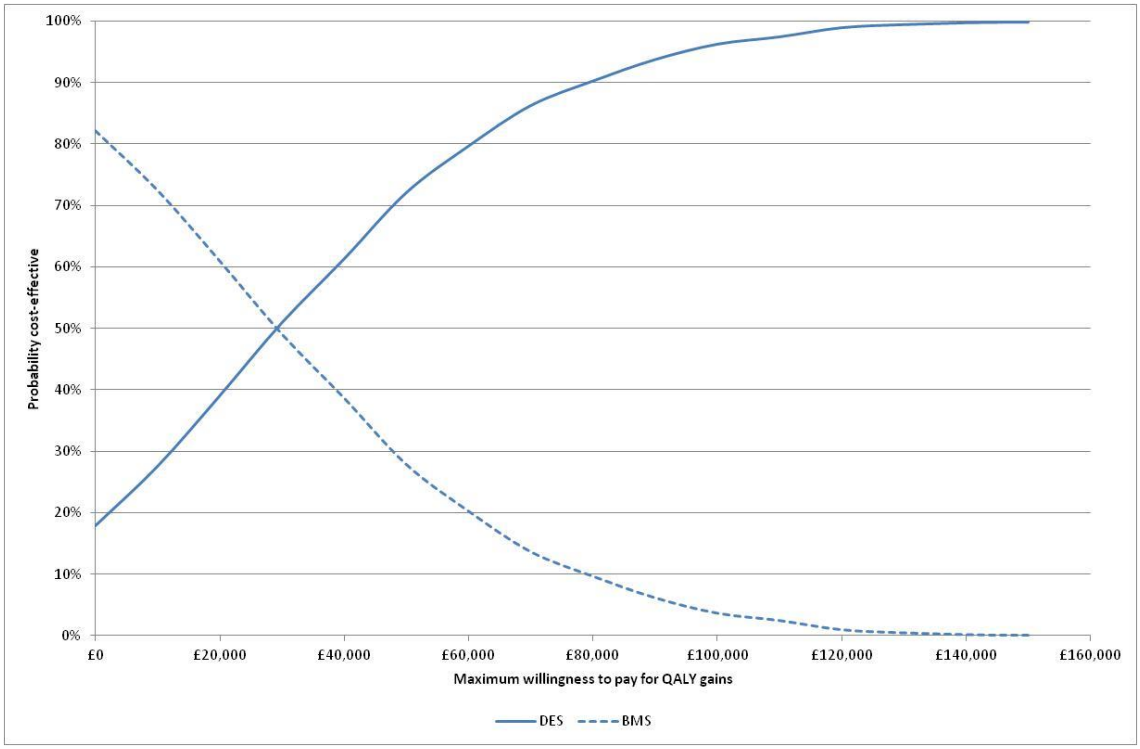


Figure 6-4 Cost-effectiveness acceptability curve of DES compared to BMS



6.3.4 Value of information analyses

The population level EVPI was almost £18 million at a threshold of £20,000/QALY (see Figure 6-5). The EVPPI calculations showed (see Figure 6-6) that we could gain most by conducting further research around resource use (which included the number of stents used in the procedures and the distribution of the type of interventions needed during revascularisation) and costs (which included the price of the stents).

Figure 6-5 Population level EVPI at different thresholds

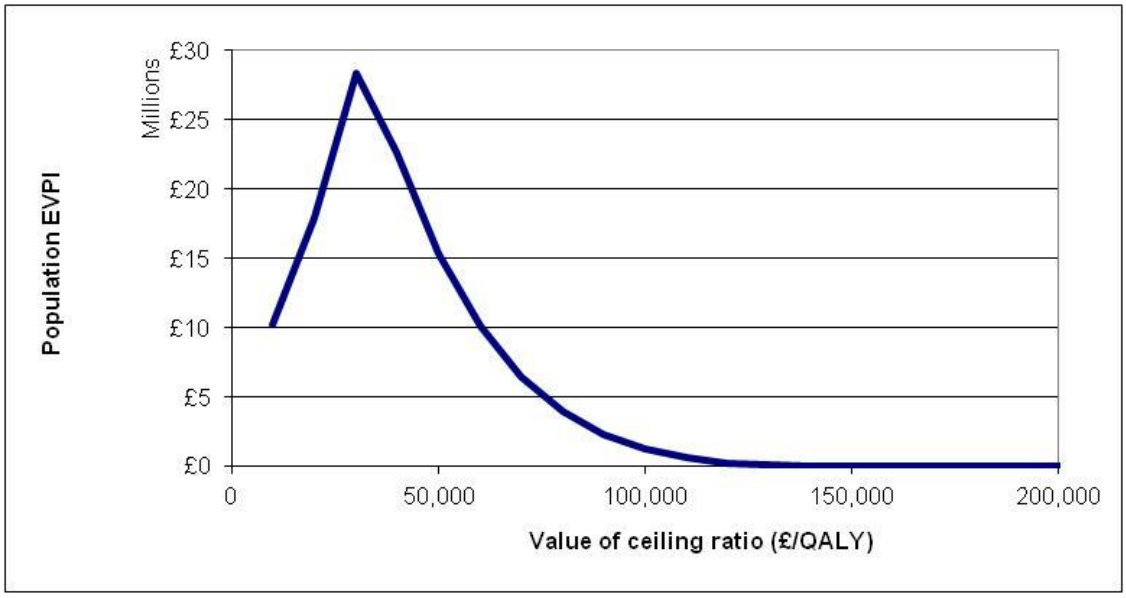
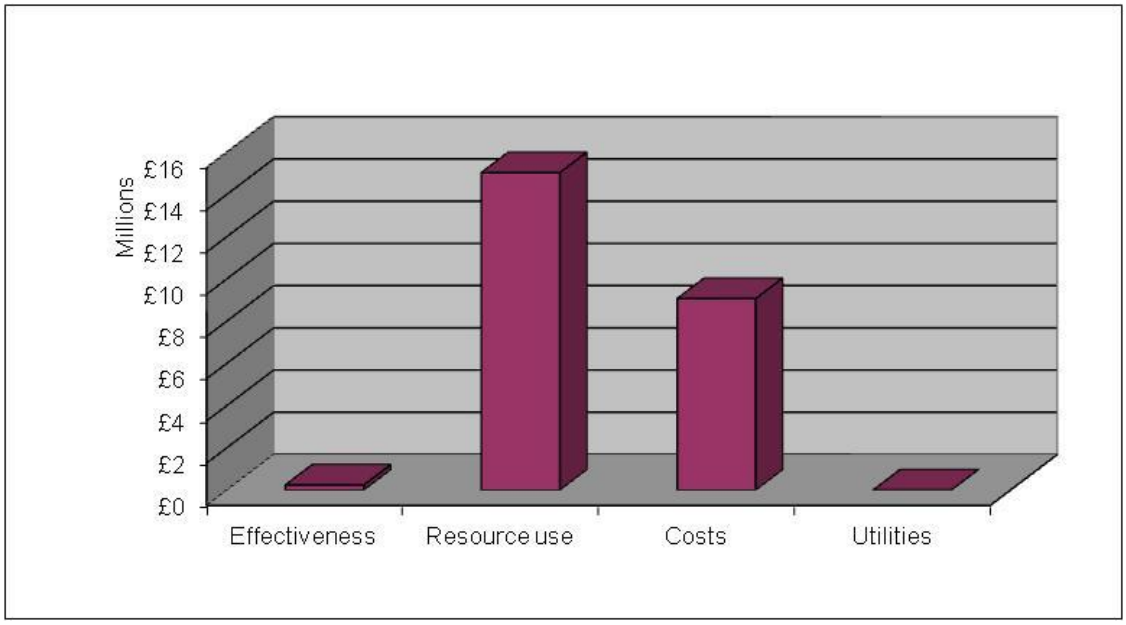


Figure 6-6 Population level EVPPI for parameter groups



6.3.5 Impact on a population level

Since the treatment is not reversible for individual patients, and the same discount rates were used for costs and effects, it the calculation of population level impact all patients within the lifetime of DES were taken to be the same as the cohort in the base case analysis. Costs and effects and the ICER for the cohort in the analysis are the same for all cohorts. Table 6-8 shows the estimated numbers of patients over the lifetime of DES who would have been affected in the UK.

Table 6-8 Estimated size of affected patient population in the UK

Year	Total number of patients using stents	Number of patients using DES if approved
2006	45,467	9,093
2007	53,117	10,623
2008	62,055	12,411
2009	72,497	14,499
2010	84,696	16,939

Based on these calculations, at the population level the introduction of DES would result in a gain of more than 600 QALYs over five years (see Table 6-9), even though only about a fifth of the eligible population was assumed to actually receive DES. Given that DES were not estimated to be cost-effective, this health gain would have been achieved at an unacceptably high price, and the introduction of DES would have been predicted to result in a loss of net benefit (using a £20,000/QALY threshold) as shown in Table 6-10. Furthermore, the expected profit of the manufacturer is zero, because, based on this analysis, DES would not be recommended.

Table 6-9 Population level QALY gains (2006 value)

Year	DES accepted	DES rejected	Difference
2006	37,770	37,680	90
2007	44,125	44,021	105
2008	51,550	51,428	122
2009	60,225	60,082	143
2010	70,359	70,192	167
Total	**264,029**	**263,403**	**626**

Table 6-10 Population level net benefit (£ - 2006 value)

Year	NB with DES accepted	NB with DES rejected	INB of DES
2006	509,693,062	510,720,277	-1,027,215
2007	595,459,058	596,659,123	-1,200,065
2008	695,656,890	697,058,890	-1,402,000
2009	812,715,000	814,352,914	-1,637,914
2010	949,470,466	951,383,991	-1,913,525
Total	**3,562,994,476**	**3,570,175,195**	**-7,180,719**

Based on these traditional analyses, DES should not be recommended and the manufacturer should have abandoned its development. However, there is considerable uncertainty over these predictions. 40.6% of the simulations resulted in a positive incremental net benefit (see Figure 6-7 for the whole distribution), but there was a very wide range from a loss of £110 million to a gain of £60 million. If approved, the manufacturer could expect profits of above £72 million, but again with the range extending to almost £250 million (Figure 6-8).

Figure 6-7 Distribution of predicted population-level INB

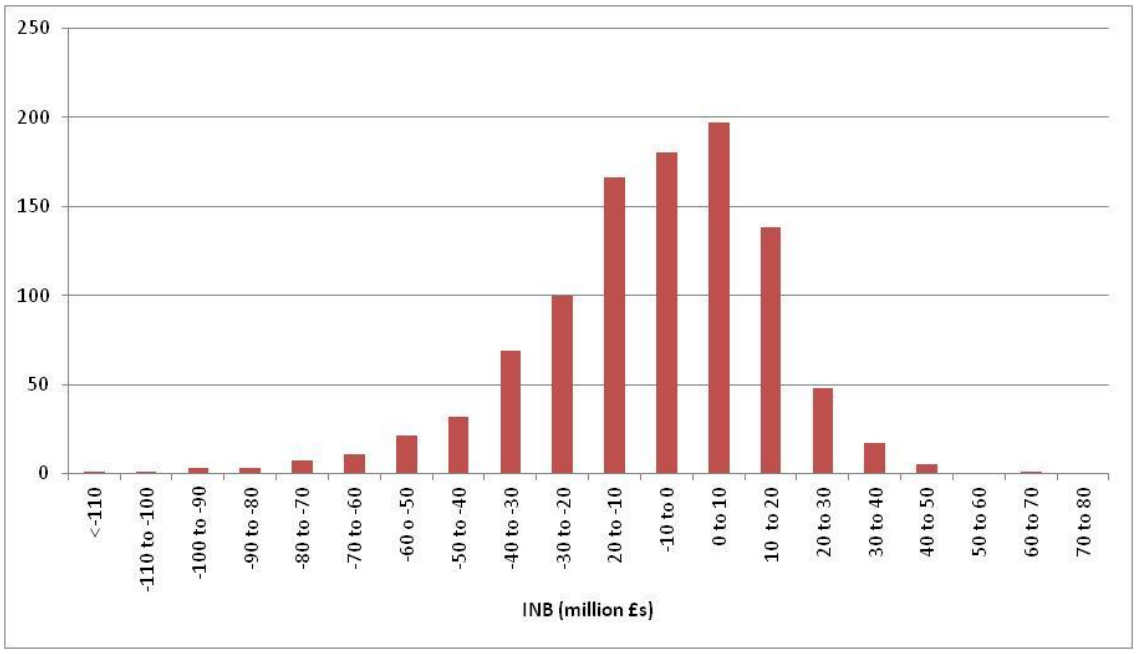
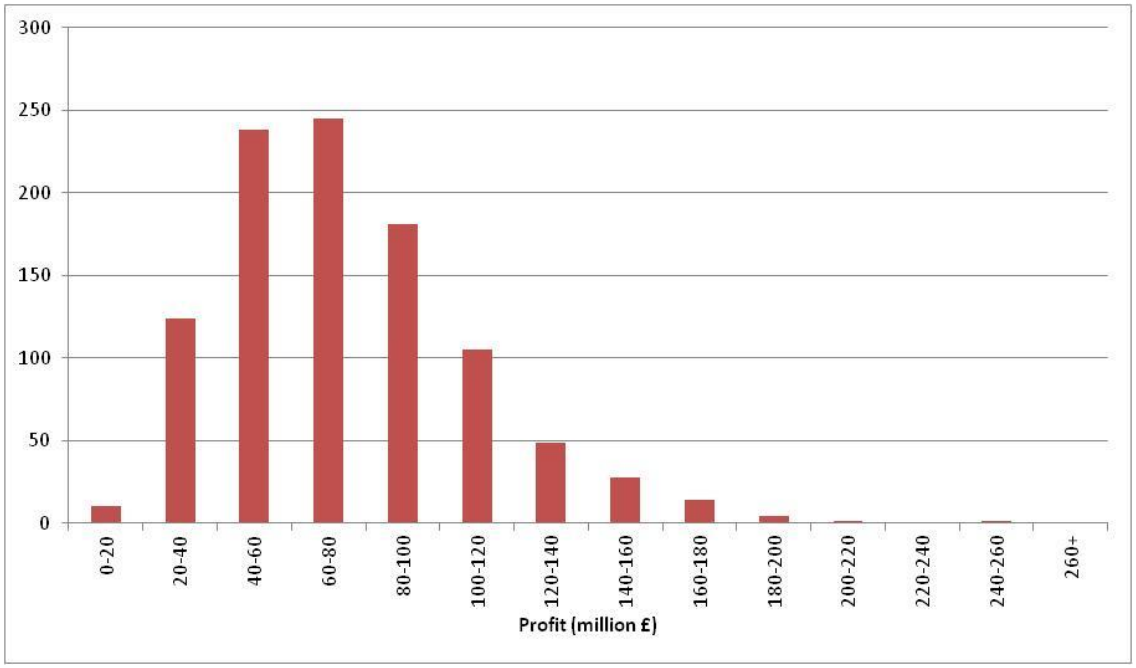


Figure 6-8 Distribution of predicted manufacturer profit conditional upon acceptance



6.4 Discussion

The traditional analysis presented in this chapter described the development of an economic model which allowed the estimation of the treatment costs and health benefits for patients receiving DES, the new health technology, compared with those patients receiving BMS, the then current standard care. Stochastic model evaluation enabled the quantification of parameter uncertainty around the cost effectiveness of DES, revealing considerable uncertainty. EVPI and EVPPI calculations were also conducted, and suggested that future research was warranted, especially around the main cost and resource use parameters.

In Chapter 2, *H* denoted the timeframe which captures the impact of the health technologies under evaluation within the lifetime of the cohort of patients evaluated. The model presented in this chapter used a model time-frame of one-year, assuming that differences between the impact of stents on the patients' health outcomes would be negligible after this time. However, this assumption was already disputed at the time of the original assessment, with two of the ten published economic evaluations using longer time horizons (Liverpool Reviews and Implementation Group August 2007) as well as all of the models submitted by the manufacturers. Later reports of clinical trials also confirmed that the reduction in the need for revascularisations with DES is maintained even after one year. Nonetheless, compared to the five-year life-cycle of the product (*T*), the time horizon of impact (*H*) of even one year is relatively large. But DES are not immediately replaceable, i.e. stents still in working order will

not be replaced just because a newer version becomes available, therefore although the cost-effectiveness of DES might have changed with longer time horizons, the approach to the evaluation would have remained the same. The fact that DESs are not replaceable and the modelling choice of annual cohorts mean in practice that the assumptions about the representativeness of a single cohort hold in our model. Therefore the impact for individual patients remained constant, model parameters were not altered over time in the calculation of population level impact outcomes.

Cohort size on the other hand was constantly increasing, as predicted based on past trends, which had an impact on INB, EVPI and EVPPI estimates. What was not known at the time, however, was that extrapolation of past trends seriously underestimated the actual numbers of patients treated with DES.(Ludman 2012) There was a shift in clinical practice after the introduction of DES including a new patient group. While previously the majority of patients undergoing cardiac stenting were chronic angina patients, with time the focus shifted to acute AMI patients increasing the patient numbers enormously. However, these types of shifts in practice are not predictable from data.

The analyses presented here showcased a common situation where at the time of evaluation there remain high levels of uncertainty. It has been shown that in the UK there is a lower probability of acceptance by NICE at a given ICER if there is more uncertainty.(Devlin and Parkin 2004) However, current economic evaluation methods do not differentiate between cases where the expected ICER is the same, but levels of uncertainty around that ICER differ. Value of information calculations only address the question of whether more evidence collection would be worthwhile. Chapters 7 and 8 will present a real-options approach where levels of uncertainty and how the value of the technology is expected to change are integral to the analysis. I will show that in contrast to the traditional methods presented in this chapter, ROA may provide different answers regarding approval of new technologies when there are different levels of uncertainty around the cost-effectiveness results.

7 Simple real options approach to evaluation of drug-eluting stents

Traditional analyses, like the one presented in the previous chapter, can indicate whether a new technology is expected to be worth the expenditure and whether more research is likely to be worthwhile. However, they give no guidance on whether or how to take account of uncertainty around the expected cost-effectiveness in the presence of some flexibility over the timing of decisions or the ability to review decisions at a later date, and at least some irreversible costs or consequences of the current decision . This chapter provides an applied example of a simple real options analysis, which may help to answer some of the questions left open by traditional economic evaluations.

7.1 Methods

7.1.1 Underlying assumptions

In this example I am using the general modelling framework and simplifying assumptions defined in Chapter 5, and (unless otherwise stated) the assumptions and parameter estimates used for the DES model described in Chapter 6.

7.1.1.1 Assumptions regarding information

ROA requires an estimation of how value will evolve over time. Predicting future changes in value is not a simple task. The term 'simple' in the title of this chapter refers to two specific simplifying assumptions that I made for this analysis:

1) Arrival of information about the change in value will be independent from the current decision about adoption. This means that (worthwhile) new research will always be carried out, even if the current decision is to accept the new technology;
2) The change in value will be observable, meaning that the results of any new research will always be published and/or submitted to the decision-making body during reviews.

These assumptions will be lifted in Chapter 8 where manufacturers' decisions over whether to carry our further research and whether to provide the payer with the results of the new research will be integrated into the model itself.

7.1.1.2 Assumptions regarding change in value

As discussed in Section 2.4.1, there are many reasons why the perceived value of new technologies might change over time, including learning effects, publication bias, or a change in the severity or type of patients using the technology. However, such changes have not been documented in any systematic way. We have very little information on whether there are common trends in the evolution of the overall value of new healthcare technologies; therefore the level of analyses was taken one step down. Instead of predicting future changes in the incremental net benefit associated with the new technology, I allowed the three most important components of the value to change:

- The effectiveness of the comparator: measured by the TVR rate for BMS;
- The relative effectiveness of the new technology: measured by the RRR in TVR achievable with DES compared with BMS;
- The additional price of DES compared to BMS.

There are a number of potential stochastic processes that I could use to model the future change in the above model parameters (see Section 3.3.2.2.2). No studies have yet examined which of the candidate processes would be more suitable to model future changes in either of the effectiveness parameters. However, Hoyle has observed that the relative price for chemicals in the British National Formulary can be usually well described by assuming a constant rate of decline each year.(Hoyle 2008) Naturally, one will expect random variation around this decline. Therefore, for simplicity and in the absence of any other information, I assumed that all three dynamic parameters (x) would follow a Wiener process with a drift over time (t):(Hull 2005)

$$dx_t = \alpha dt + \sigma dz$$

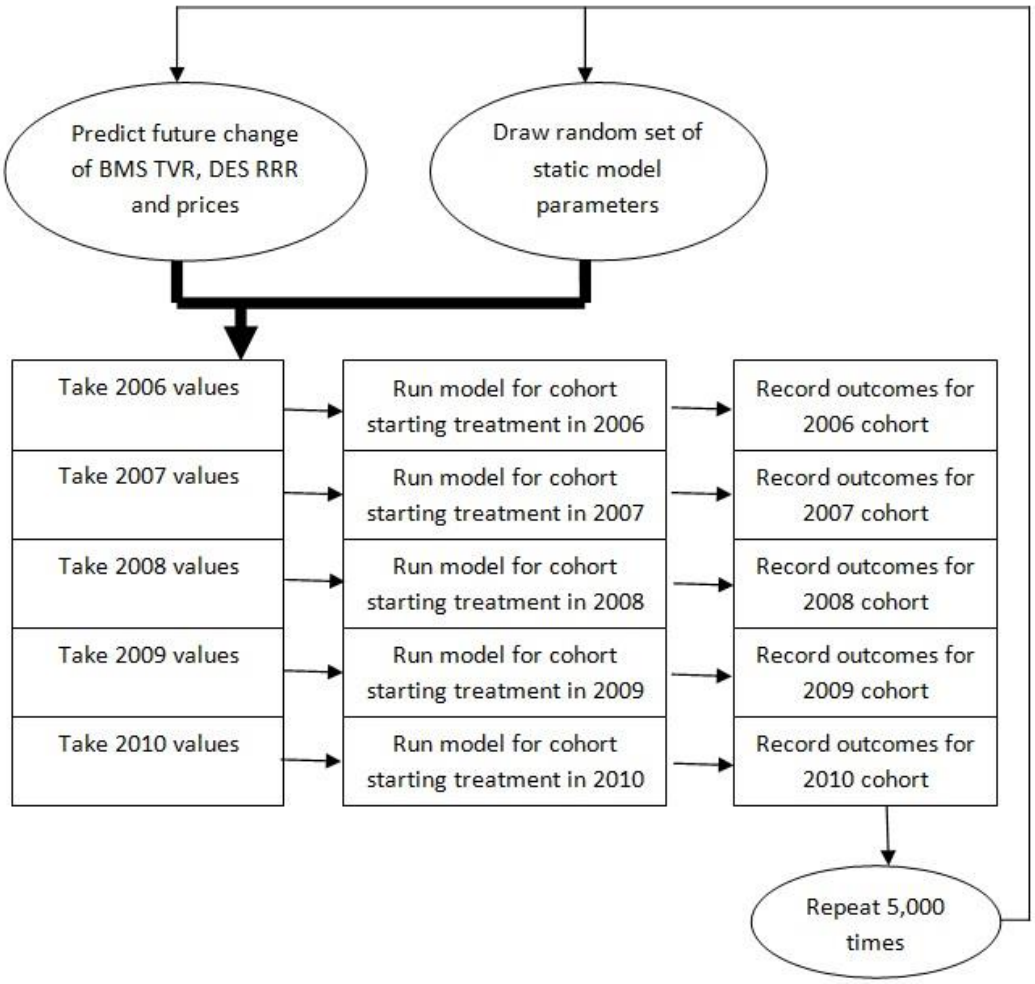
where α is the expected change, i.e. the trend, σ the volatility and z the Wiener process. The Wiener process (also called Brownian motion) is the most common stochastic process. As explained in Chapter 3, in a Wiener process changes over a given time period are normally distributed, and the increments are independent (a change in any time period depends only on the current value). The Wiener process with drift can be calibrated so that the drift parameter ensures a constant rate of change each year, while the Wiener process components introduce a random variation around this trend.

7.1.2 Calculation algorithm

Real option calculations can be performed using an existing traditional economic model. The traditional economic model estimates the overall value (NB) of the technologies under evaluation for a cohort of patients starting treatment at a specific time point. In ROA there are a number of decision points in the future, so the model needs to be rerun with the time-specific parameters as many times as there are decision points in the evaluation.

Predicting future change in one or more of the model parameters adds another layer to the current uncertainty about the true value of the parameters. Therefore as shown in Figure 7-1, I drew one set from the (static) random parameters in the model and one realisation of how the future might unfold for each dynamic parameter (by a random draw from a standard normal distribution for the Wiener process, dz) in annual intervals between 2006 and 2010 in parallel at each iteration. In this formulation dynamic uncertainty is in addition to current static uncertainty, but no hierarchy between the two types of uncertainties was assumed. The model was re-evaluated with the changed parameters and the population outcomes re-calculated for each year. Due to the high levels of uncertainty (parameter uncertainty plus uncertainty around future changes) 5,000 iterations were undertaken to obtain stable estimates of the model outputs. The code was programmed with Visual Basic within Excel, and the annotated code is provided in Appendix I.

Figure 7-1 Calculation algorithm



Results then need to be accumulated for each year. As an illustration, Table 7-1 depicts the case of a model where the relevant time horizon, the length of time over which health outcomes and costs differ between the treatments (*H*), is three years, while the lifetime (*T*) of the new technology is 5 years. For example, health outcomes and costs for the year 2008 would comprise the third year outcomes for patients starting treatment in 2006, the second year outcomes for patients starting treatment in 2007 and the first year outcomes for the cohort starting treatment in 2008. Whether outcomes for 2011 and 2012 need to be taken into account depend on the characteristics of the technology under evaluation as discussed in Section 2.2.3.2.1. In our case study of DES, the traditional evaluation has limited *H* to one year, therefore only the results presented in bold in Table 7-1 were included in the analyses.

Table 7-1 Patient cohorts across time

Start in	Year 2006	2007	2008	2009	2010	2011	2012
2006	**Year 1 outcome$_{2006}$**	Year 2 outcome$_{2006}$	Year 3 outcome$_{2006}$				
2007		**Year 1 outcome$_{2007}$**	Year 2 outcome$_{2007}$	Year 3 outcome$_{2007}$			
2008			**Year 1 outcome$_{2008}$**	Year 2 outcome$_{2008}$	Year 3 outcome$_{2008}$		
2009				**Year 1 outcome$_{2009}$**	Year 2 outcome$_{2009}$	Year 3 outcome$_{2009}$	
2010					**Year 1 outcome$_{2010}$**	Year 2 outcome$_{2010}$	Year 3 outcome$_{2010}$

The above calculations were undertaken for both treatment arms, and the population impact (total INB) and potential manufacturer profit associated with either accepting or rejecting DES were calculated for each year according to the population size and market share predictions described in Chapter 6.

7.1.3 Model inputs

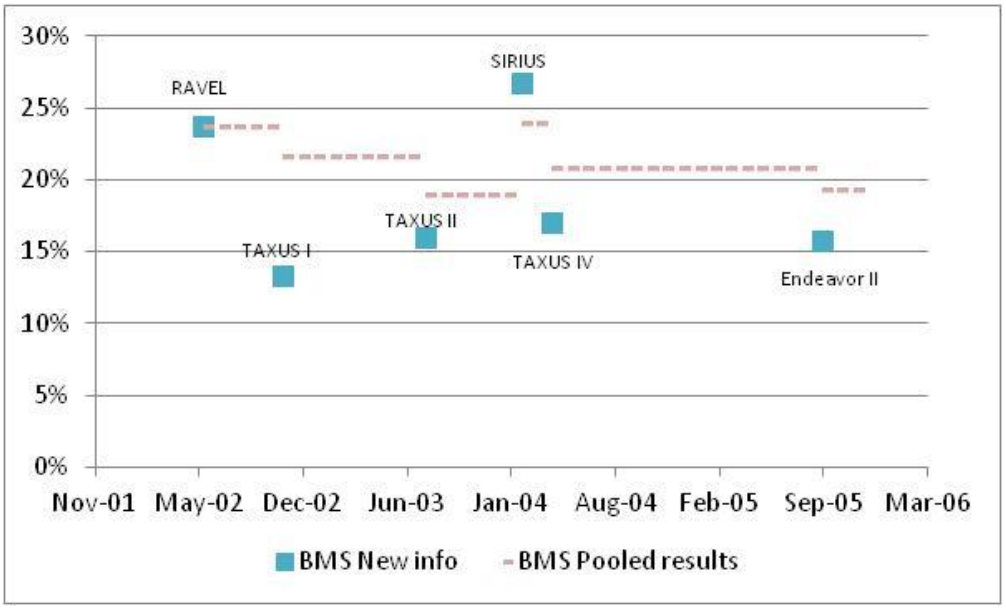
7.1.3.1 Estimation of stochastic process parameters

The parameters for the two processes governing the effectiveness of the treatments were estimated based on the evolution of knowledge about stents up till 2005. A cumulative meta-analysis was performed, adding information at each time that a new trial was reported to estimate parameter values at monthly intervals. This time series of historical cumulative knowledge was then used to estimate parameters for the Wiener processes, which were then used to predict further evolution of the effectiveness evidence between 2005 and 2010.

The trend variables (α) were calculated by fitting a linear trend in Excel, while volatility (σ) was calculated, by definition, as the standard deviation of the continuously compounded return r (i.e. in our case, the change in knowledge) such that $TVR_{t+1}=TVR_t * e^r$.

Figure 7-2 Evolution of effectiveness parameters over time

a) Probability of TVR over 12 months with BMS



b) RRR of 12 month TVR probability with DES versus BMS

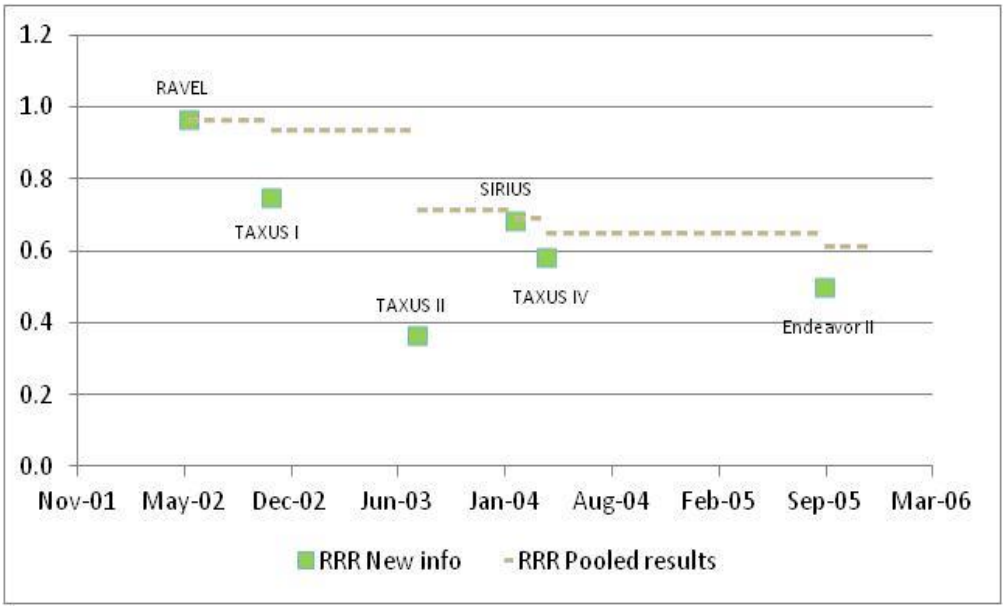


Figure 7-2 shows the changes in the knowledge about the TVR probability and RRR up to the time of the analysis (2005). A negative trend in the estimated RRR can be observed, DES also appeared to be less effective over time, similarly to the findings of Ioannidis and Gehr and colleagues.(Ioannidis 2005; Gehr, Weiss, and Porzsolt 2006)

In the absence of any other information (at the time of the 2005 decision), prices of the two stents were assumed to follow a similar trend to pharmaceuticals as shown by Hoyle and colleagues, decreasing by 3.8% (SD 2.5%) annually.(Hoyle 2008)

The estimated effectiveness and cost parameters are reported in Table 7-2.

Table 7-2 Stochastic process parameters

Variable	T	α	σ
BMS TVR	Months	-0.00061	0.05151
DES RRR	Months	-0.00913	0.04385
Price	Years	-0.038	0.025

100 realisations of the predicted relative prices the decision maker is expected to face are shown in Figure 7-3. Note that in this simplified ROA case study the decision maker was assumed to have no influence over the price of the technology. The predictions are in line with what Hoyle has observed, with most predictions falling by a factor of between 0.7and 0.9 after five years. His observations about the actual relative price decrease for chemical entities for the BNF section 'Hypertension and Heart Failure' are reproduced in Figure 7-4.

Figure 7-3 100 realisations for predicted stent prices

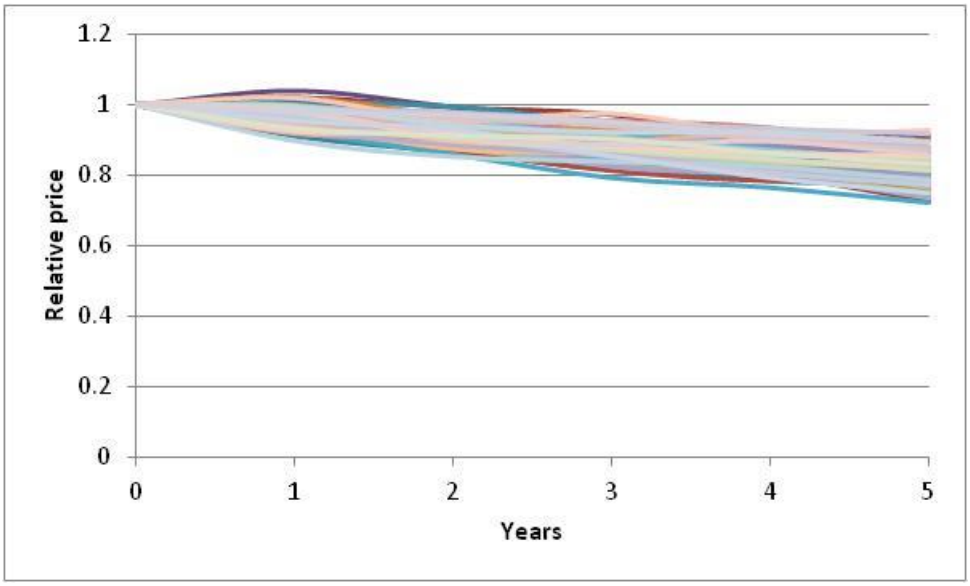


Figure 7-4 Reproduction of Figure 2 from (Hoyle 2008, 589-602)

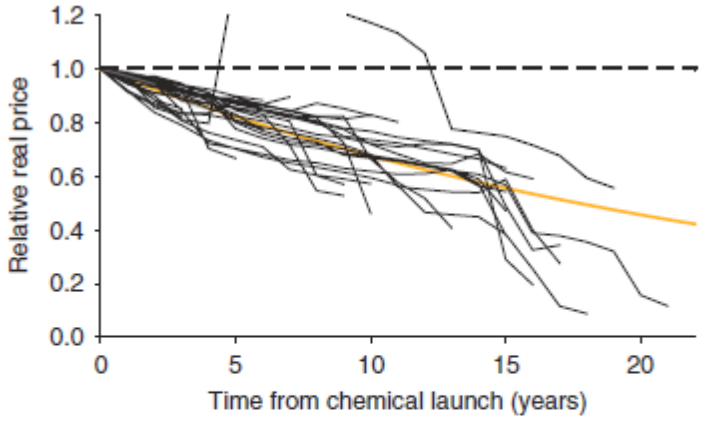
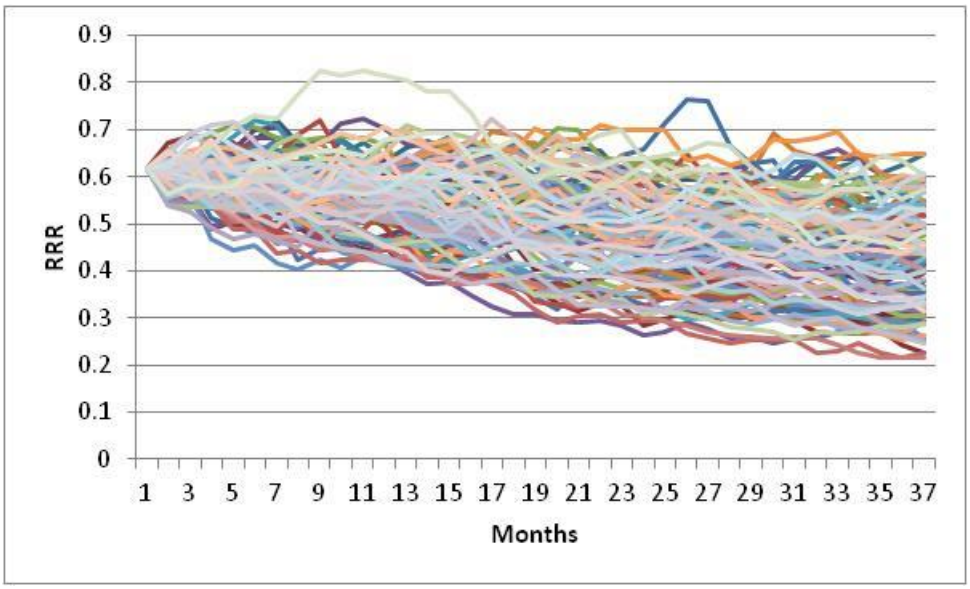


Fig. 2. Relative real price since chemical launch for the *British National Formulary* (BNF) section 'Hypertension and Heart Failure'. Each line corresponds to a different BNF chemical. The current assumption in cost-effectiveness models of no change in real price is shown by the dotted line. The model best fit is shown by the coloured line.

However, stochastic processes always have a fan-like shape with individual predictions deviating more and more from the trend the further into the future one ventures. This is also apparent in the prediction of future changes to the RRR of DES (shown up until 3 years in Figure 7-5).

Figure 7-5 100 realisations for predicted DES RRR

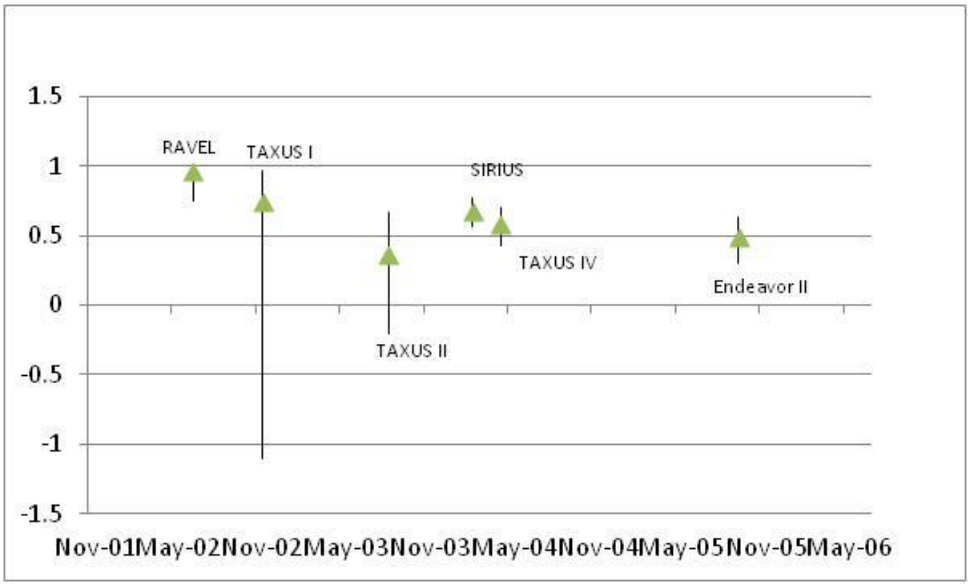


The increase in uncertainty may seem counterintuitive, given that in real life the accumulation of knowledge, the inclusion of more and more trials in a meta-analysis, is associated with a decrease in uncertainty around the pooled point estimate (see Figure 7-6). However, the

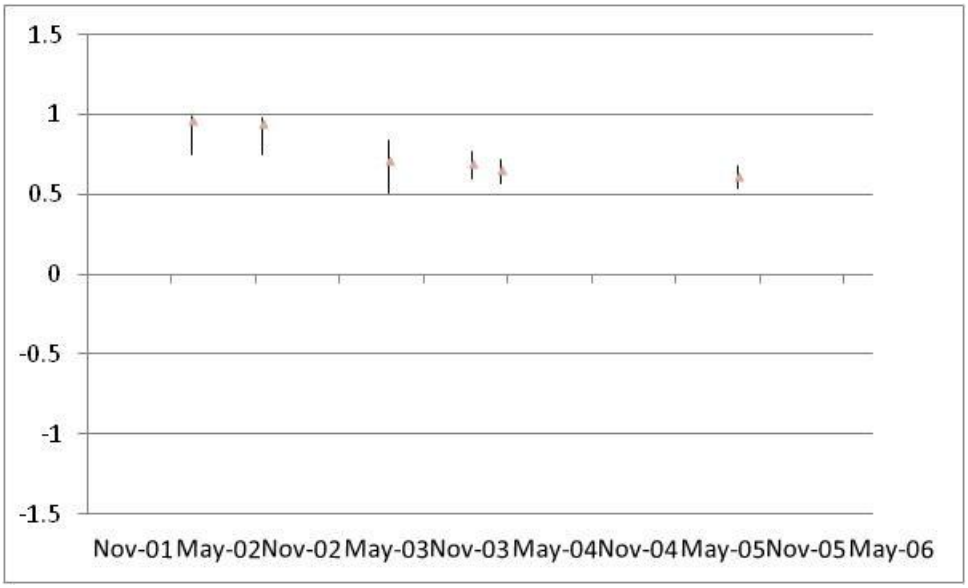
thinking behind these cumulative meta-analyses is that with time we can converge on a one true point estimate, whereas the thinking behind ROA is that the point estimate itself will vary with time and for the purposes of this analysis we need to predict where that point estimate may lie in the future. Figure 7-6 does show that the point estimates after adding each new trial did vary quite a lot, changing from 0.965 to 0.616 over the course of just over two years, therefore taking 0.616 as the starting point the predicted range from about 0.2 to 0.65 where the point estimate may lie three years into the future does not seem unrealistic.

Figure 7-6 Change in uncertainty around DES RRR over time

a) Uncertainty in individual trial estimates



b) Uncertainty in cumulatively pooled estimates



7.1.3.2 The cost of reviews and changes in decisions

ROA should explicitly incorporate all costs associated with future decision points. In this case study, this meant quantifying the costs of undertaking a review of evidence and the costs of changing a prior decision.

No studies were found quantifying the cost of NICE technology appraisals. Their 2012-2013 annual report shows a spending of £8.7 million for the Centre for Health Technology Evaluation.(National Institute for Health and Clinical Excellence 2013) The annual report encompasses the period from 1 April 2012 to 31 March 2013. I reviewed the NICE website to identify the number of evaluations undertaken in this year (see Table 7-3). During this period, 65 assessments were undertaken. This implies that undertaking one review costs, on average, around £134,000. Furthermore, the Technology Assessment Groups (TAGs) and Evidence Review Groups (ERGs) are remunerated by the National Institute for Health Research. Their guidance states that "we would expect a short report to cost approximately £60k".(National Institute for Health Research 2014) Therefore I estimated the cost of a review to be £193,846 (£8.7 million / 65 + £60,000). This is a conservative estimate of costs to the healthcare system, as it does not account for costs to NHS commentators or the opportunity cost of committee member's time. I therefore tested the impact of assuming higher costs for the review process in sensitivity analysis.

Table 7-3 Number of assessments undertaken by NICE April 2012-March 2013

Type of assessment	Quantity
Centre for Health Technology Evaluation	
Technology appraisal	28
Medical technology guidance	4
Diagnostic guidance	4
Interventional procedure guidance	29
Total for Centre	65
Centre for Clinical Practice	
Clinical guideline	19
Public health guideline	5
Total for Centre	24
Overall total	**89**

Using DES rather than BMS requires no extra training or capital investment, therefore in this case study I assumed that the cost of changing the decision would relate only to the costs of disseminating the outcome of the review. The annual spending of NICE's Communications Directorate was £1.9 million.(National Institute for Health and Clinical Excellence 2013) In addition to the 65 evaluations mentioned above, 24 guidelines developed by other Centres were also publicised on the NICE website (see Table 7-3). So the average cost of changing the decision around stents was estimated to be £21,348 (£1.9 million / 89). Again, the true cost to the NHS of changing a decision is likely to be much greater than this, as commissioners and providers will incur costs to implement guidance, so I tested a range of assumptions about the cost of a future decision change in sensitivity analysis.

7.1.4 Analyses

The decision maker (the payer or their agent, the HTA body) is faced with a number of options when evaluating new health technologies:

- No buy strategy: It may reject the use of DES altogether based on current evidence;
- A call option (i.e.no buy with a buy option): it may reject the use of DES for now, but reserve the right to accept DES if and when changes in the evidence indicate that DES are cost-effective compared to BMS;
- A put option (i.e. buy with a sell option): it may accept DES now based on its expectation that DES will be shown to be cost-effective in the future, however reserving the right to withdraw its recommendation if the expectation is not fulfilled;
- Buy strategy: it may accept DES now based on its expectation that DES will be shown to be cost-effective.

Note that real life strategies are usually a mixture of these pure options. Even if a new a technology is recommended, the technology may be re-evaluated at a later date. Similarly, a rejection does preclude a review of the evaluation. NICE in the UK may also recommend that the new technology is to be used only in research (OIR), which would be a conditional call option, while an accept with research (AWR) recommendation would be a conditional put option.

Claxton and colleagues provided an algorithm to choose between these different type of recommendations (accept, AWR, OIR, or reject) depending on answers to questions such as "Is the technology cost-effective?", "Are there irreversible costs?", "Is more research worthwhile?", "Is further research possible with approval?", "Will uncertainty be resolved with time? ", and "Are the benefits of research greater than its costs?".(Claxton et al. 2012) Traditional analyses answer the questions on cost-effectiveness and whether more research is

worthwhile. The simple ROA analyses also answers the question on irreversible costs, the costs of re-assessment and assumes that new information will definitely be revealed with time. The choice between these strategies then depends on expectations regarding how quickly and by how much the value of DES might change, and what it will cost to undertake further assessments to uncover that change in value.

As noted earlier, in this simple ROA new information is assumed to flow in continuously and independently of the previous decisions. Therefore, the decision maker also has control over the timing of its reviews. If the change in value is expected to be slow and/or the cost of carrying out a review is high, longer review times may be appropriate. On the other hand, if the change in value is expected to be quick and/or carrying out a review is does not put too much of a burden on resources, then shorter review times should be recommended.

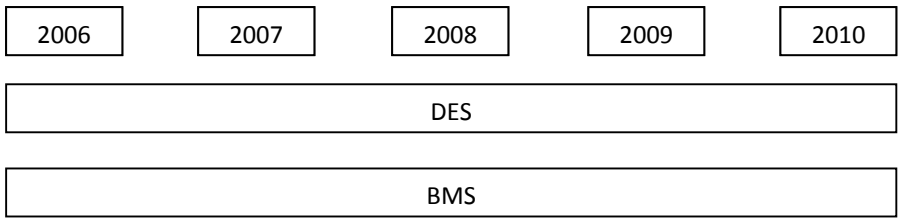
Taking the above considerations into account, I compared the expected total population outcomes for the following ten potential strategies facing the decision maker:

- Reject DES with no further review
- Reject DES now, but review the decision every year;
- Reject DES now, but review the decision every two years;
- Reject DES now, but review the decision on the third year;
- Reject DES now, but review the decision on the fourth year;
- Accept DES with no further review
- Accept DES now, but review the decision every year;
- Accept DES now, but review the decision every two years;
- Accept DES now, but review the decision on the third year;
- Accept DES now, but review the decision on the fourth year;

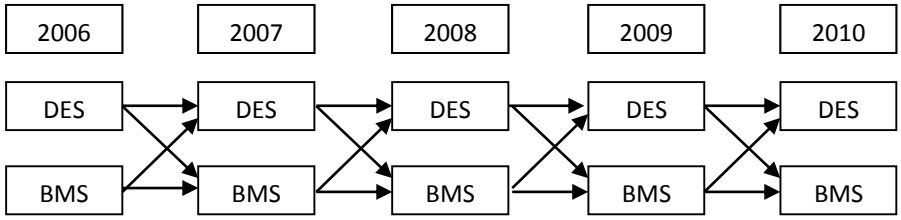
Figure 7-7 shows the resulting potential decision pathways according to the timing of the reviews.

Figure 7-7 Decision pathways according review times

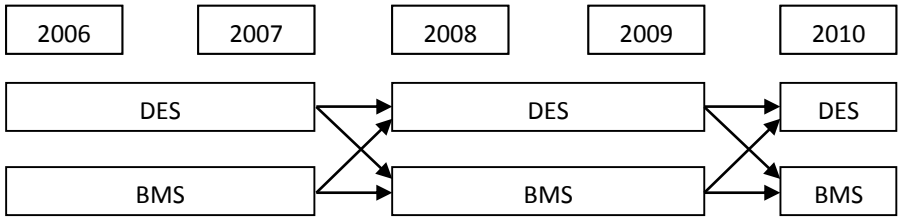
a) No reviews



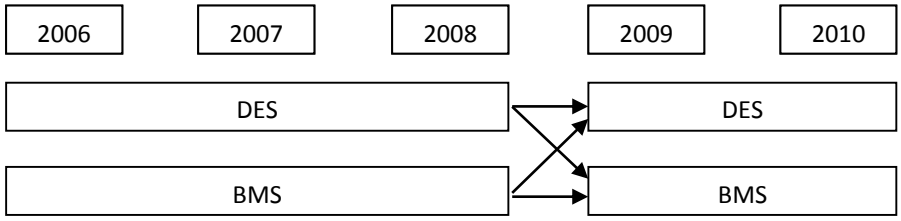
b) Annual reviews



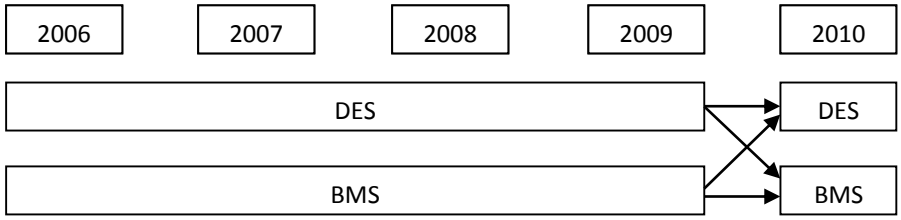
c) Biennial reviews



d) Review in 3 years



e) Review in 4 years



The analyses were undertaken from a NICE perspective. The model generated the population net monetary benefit (at a £20,000 per QALY threshold) that would occur each year if DES

were accepted or rejected. It was then determined for each of the 5,000 iterations and for each of the strategies when a change (or in some cases multiple changes) in decisions would yield a greater NB. For each iteration, I could therefore predict the optimal decision path from the potential paths depicted in Figure 7-7. For each strategy, the population health gain measured in QALYs, the population net monetary benefit associated with the treatment, the cost of reviews and implementation if need be, and the manufacturer's profits were then calculated based on the optimal decision paths for each iteration. The resulting outcomes were averaged across iterations to calculate the expected outcomes associated with each strategy.

Sensitivity analyses were carried out around the cost of reviews and the cost of changing of the decisions. The influence of population size was also tested in sensitivity analyses, but with the number of iterations reduced to 100 to achieve a reasonable runtime.

7.2 Simple real options model results

7.2.1 Determining the optimal strategy

Table 7-4 shows the predicted population level net benefit for each year within the lifetime of DES if DES were to be accepted or rejected. Based on the projected changes in the components of the value of DES, one expects DES to be shown to be cost-effective by 2008. However, due to the uncertainty surrounding these estimates this does not necessarily mean that the best option is to simply review the evidence in three years' time.

Table 7-4 Population level expected net benefits with simple ROA (means of 5,000 iterations)

Year	NB with DES accepted	NB with DES rejected	INB of DES
2006	510,700,122	511,709,680	-1,009,552
2007	580,246,653	580,391,222	-144,569
2008	659,380,749	658,630,920	749,829
2009	750,937,755	749,098,194	1,839,561
2010	855,408,405	852,282,058	3,126,347
Total	**3,356,673,682**	**3,352,112,074**	**4,561,608**

Population level outcomes associated with each strategy are presented in Table 7-5. Rejecting DES with no further consideration of the question led to the lowest results regardless of which outcome one examines. The calculations suggest that based on the current (2005) levels of uncertainty and expectations of how the three main dynamic parameters in the model would change over the time horizon, rejecting DES now, but reassessing them every year would lead to the highest attainable NBs, despite the burden of annual reviews.

Table 7-5 Population outcomes by strategy in simple ROA

Reject DES	No review	Review every year	Review every 2 years	Review in 3 years	Review in 4 years
Average no. of decision changes	n/a	0.96	0.75	0.59	0.62
Total QALY gain	245,929	246,308	246,240	246,161	246,062
Total manufacturer profit*	£0	£27.6	£22.0	£15.9	£8.7
Total NB*‡	**£3.352.1**	**£3,361,9**	**£3,360.9**	**£3,359.2**	**£3,356.3**
NB of treatment*	£3,352.1	£3,362.6	£3,361.3	£3,359.3	£3,356.5
Cost of reviews and changes	£0	731,249	364,605	186,133	180,449
Difference in total NB compared to no review*		**£9.78**	**£8.80**	**£7.04**	**£4.22**
Accept DES	No review	Review every year	Review every 2 years	Review in 3 years	Review in 4 years
Average no. of decision changes	n/a	1.05	0.68	0.41	0.38
Total QALY gain	246,580	246,397	246,437	246,486	246,537
Total manufacturer profit*	£61.8	£38.0	£43.7	£49.8	£56.1
Total NB*‡	**£3,356.7**	**£3,360.9**	**£3.359.8**	**£3,358.8**	**£3,357.8**
NB of treatment*	£3,356.7	£3,361.6	£3,360.1	£3,358.9	£3,357.9
Cost of reviews and changes	£0	732,973	363,090	182,798	176,006
Difference in total NB compared to no review*		**£4.20**	**£3.08**	**£2.08**	**£1.09**

* In £ million

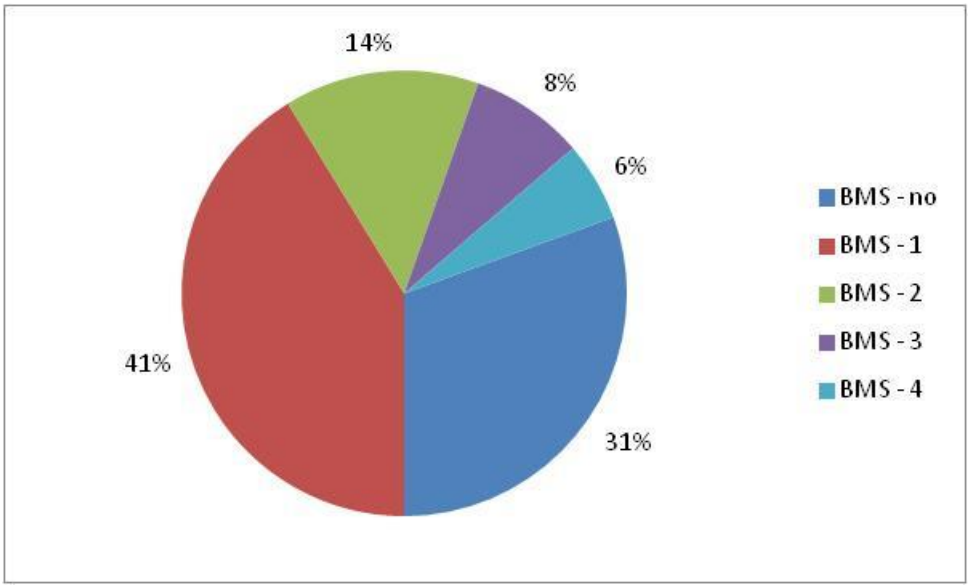
‡ Calculated as NB of treatment NB – Cost of reviews and changes

Being aware of the results of the traditional economic evaluation, it is not surprising that accepting DES with no further review results in the highest population QALY gains, and of course, would mean highest profits for the manufacturer. Although traditional evaluation showed rejection of DES (with no review) to be superior to acceptance of DES (with no review), here acceptance results in a positive INB compared to rejection. The difference is explained by the way outcomes for future cohorts are predicted in the two types of analyses. The traditional economic evaluation used all information that was available in 2005, but assumed for the calculation of population benefit that all model parameters would remain constant over time, i.e. there would be no change in value of the technologies under evaluation. A traditional analysis conducted in 2008, using all available evidence at that time would probably have found DES to be cost-effective. ROA on the other hand incorporates expected change, using all the information available at 2005 as the starting point, but forecasting changes in model inputs at the time of the reviews. The advantage of the simple ROA approach over traditional analysis is that it gives an estimate of when the decision should be reviewed.

It is also clear from the results that more frequent reviews are associated with changing the decisions more often, and therefore higher review and implementation costs. The average number of predicted changes is reported in Table 7-5, but the average masks the fact that in some iterations the decision had to be changed 3 or even 4 times over the course of five years.

As in a cost-effectiveness acceptability curve, it is possible to determine the proportion of iterations in which each strategy was optimal. As shown in Figure 7-8, rejecting DES with annual reviews was optimal in the highest proportion of iterations at the threshold of £20,000/QALY. The put options, accepting DES now despite the current evidence and reviewing this decision later, were never optimal. However, the costs of changing a decision were relatively low in this case study compared to the population level net benefits. Put options are more favourable when these costs are higher. The next section presents the sensitivity analyses, including those around the cost of decision changes.

Figure 7-8 Proportion of time each strategy was optimal



Legend: BMS – no: reject DES now with no further review; BMS -1: reject DES now with review every year; BMS – 2: reject DES now with review every two years; BMS – 3: reject DES now with a review after three years; BMS – 4: reject DES now with a review after four years

7.2.2 Sensitivity analyses

7.2.2.1 Impact of changes in the costs of reviews and decision changes

One expects the optimal review time to increase as the cost of reviews and decision changes increases. This effect is clearly demonstrated in Table 7-6, where biennial instead of annual reviews become optimal when the cost of changing the decisions reached £1 million or the cost of conducting the review reached about £6 million. At even higher costs, changing decisions become too burdensome, and it is more efficient to simply accept DES with no further review, based on the expectation that it will be shown to be cost-effective in time, even though it is not cost-effective at the time of the analysis.

Table 7-6 Two-way sensitivity analysis around cost of reviews and change

Cost of reviews	Cost of change											
	£0	£20,000	£50,000	£100,000	£500,000	£1,000,000	£2,000,000	£3,000,000	£4,000,000	£5,000,000	£6,000,000	£7,000,000
£0	BMS - 1	BMS - 1	BMS - 1	BMS - 1	BMS - 1	BMS - 2	BMS - 2	DES - no	DES - no	DES - no	DES - no	DES - no
£200,000	BMS - 1	**BMS - 1**	BMS - 1	BMS - 1	BMS - 1	BMS - 2	BMS - 2	DES - no	DES - no	DES - no	DES - no	DES - no
£500,000	BMS - 1	BMS - 1	BMS - 1	BMS - 1	BMS - 1	BMS - 2	BMS - 2	DES - no	DES - no	DES - no	DES - no	DES - no
£1,000,000	BMS - 1	BMS - 1	BMS - 1	BMS - 1	BMS - 1	BMS - 2	BMS - 3	DES - no	DES - no	DES - no	DES - no	DES - no
£2,000,000	BMS - 1	BMS - 1	BMS - 1	BMS - 1	BMS - 2	BMS - 2	DES - no	DES - no	DES - no	DES - no	DES - no	DES - no
£3,000,000	BMS - 1	BMS - 1	BMS - 1	BMS - 1	BMS - 2	BMS - 2	DES - no	DES - no	DES - no	DES - no	DES - no	DES - no
£4,000,000	BMS - 1	BMS - 1	BMS - 1	BMS - 1	BMS - 2	BMS - 2	DES - no	DES - no	DES - no	DES - no	DES - no	DES - no
£5,000,000	BMS - 1	BMS - 1	BMS - 1	BMS - 1	BMS - 2	DES - no	DES - no	DES - no	DES - no	DES - no	DES - no	DES - no
£6,000,000	BMS - 1	BMS - 1	BMS - 2	BMS - 2	DES - no	DES - no	DES - no	DES - no	DES - no	DES - no	DES - no	DES - no
£7,000,000	DES - no	DES - no	DES - no	DES - no	DES - no	DES - no	DES - no	DES - no	DES - no	DES - no	DES - no	DES - no

Legend: BMS -1: reject DES now with review every year; BMS – 2: reject DES now with review every two years; BMS – 3: reject DES now with a review after three years; DES – no: accept DES now with no further reviews

7.2.2.2 *Impact of population size*

The size of the population to be treated over the lifetime of the new technology influences the magnitude of net benefits to be gained by changing decisions. With a fixed INB per patient, more benefit can be gained by changing decisions that turn out to be wrong in light of new evidence with larger populations. Therefore, compared to the potential gains with large populations, conducting reviews and changing decisions are relatively cheap. The smaller the population, the more expensive reviews are in relative terms.

This effect was tested in the model by changing (increasing and decreasing) the size of the patient population by the same fixed proportion for each of the five years within the model time horizon. The optimal time to review the original decision increased to two years once the population fell to the quarter of its original size (about 15,000 patients treated per year). With a further decrease to below 5% of the original population size (about 3,000 patients treated per year) conducting further reviews is no longer worthwhile. However, in contrast to what a traditional analysis would suggest (i.e. rejecting DES), the optimal strategy at this very small population size is to accept DES straight away based on the expectation that new information will later prove its cost-effectiveness.

Table 7-7 Impact of population size on optimal strategy

Population size compared to original size	Optimal strategy
1%	DES - no
5%	DES - no
10%	BMS - 2
20%	BMS - 2
25%	BMS - 2
50%	BMS - 1
100%	BMS - 1
150%	BMS - 1
200%	BMS - 1
500%	BMS - 1
1000%	BMS - 1

7.3 Discussion

This chapter explored the feasibility of using real options analyses in HTA. The simple application used here may help to determine the optimal first decision and optimal review times, balancing the costs of undertaking the reviews and the consequences of having to

change decisions. It showed that given the high levels of uncertainty surrounding the value of DES and the relatively small estimated cost to review and (if necessary) to change decisions compared to the gains achievable in a large population, more frequent assessments resulted in better outcomes for the payer. Our case study suggested that in the case of DES versus BMS, the optimal solution would have been to review the evidence annually. Despite the ROA method's advances over traditional analyses in explicitly incorporating future decisions points and changes in the decisions, there remain considerable limitations.

It has been noted by Ades and Sutton that calculations like these are meaningless unless the assessment of uncertainty is accurate.(Ades and Sutton 2006) The remark holds especially true for predicting change in value. The task is made more difficult given that predicting such changes requires estimation of parameters that are currently not routinely measured or estimated and no consensus exists on the best methods to calculate them. For example, I estimated the cost of changing practice as only the cost to disseminate the information by NICE. However, in other disease areas it may be necessary to retrain staff, assign dedicated staff or dedicated areas within the facilities to perform tasks associated with the new technology, and/or the purchase or selling of specialist equipment may be also required.

Results were also sensitive to the assumed population size. It has been suggested that the population size over time and the expected lifespan of the new technology, as well as the variability in these quantities could be estimated by analysing trends in the volumes of sales of similar technologies in the past. (Hoyle 2010) I used this approach in this case study. As in population level value of information calculations, I assumed the lifespan of the technology to be constant, although it could become a stochastic parameter in future studies. The value itself was based on personal communication from the manufacturer of one of the DES rather than on any specific analysis of the lifetime of past medical devices.

The most challenging aspects of the analyses presented here are the methods and parameters for predicting future changes with new information. The use of stochastic processes is borrowed from financial economics. (Eckermann and Willan 2008b) These processes assume an immediate and continuous updating with new information, which is at odds with how research is conducted and information is revealed in health care. The lumpy arrival of information may suggest the use of a different type of stochastic process, e.g. a mean-reverting process with possible Poisson jumps to depict the impact of a new trial reporting. Expected value of sample information calculations (McKenna and Claxton 2011) or clinical trial

simulations (Caro and Ishak 2010) may provide methods that fit the framework of health technology assessment better.

The analyses assumed no other implications to the decision-maker of changing decisions than the monetary costs associated with disseminating the new recommendation. There were iterations in the simulation that required a change in the recommendation every time a new review was carried out. It is a concern that decision-makers would be unwilling to change their decisions too frequently to preserve their reputations even if the changes would benefit society as a whole. Currently decision makers such as NICE are thought to provide the definitive verdict about the cost-effectiveness and acceptability of health technologies. Applying this type of simple ROA in real life would require a change in attitude from the decision makers and a change in how their decisions are viewed by the public and other health care decision makers, or an estimate of what is the monetary value such decision makers place on their "reputation". The application of the method is currently hindered by the lack of a price tag on the non-economic aspects of issuing guidance about new health technologies.

Furthermore, adoption of technologies alters research possibilities.(Chalkidou, Hoy, and Littlejohns 2007) Although the simple application of ROA may give some insight into the relationship between current uncertainty, how that uncertainty is expected to unfold, the benefits achievable with the "correct" decision and the costs of assessment and decision change, it is fundamentally flawed. The simple approach omits the impact of the decisions on later decisions, that is, it fails to acknowledge that information arrival is endogenous and the role of strategic interactions between multiple decision makers. The next chapter will describe a new approach which incorporates aspects of ROA with game theory to internalise the process of information arrival.

8 Evaluation of drug-eluting stents within a real options game

8.1 Introduction

In the previous two chapters I presented two methods of analysis for new health technologies. The traditional analysis ideally incorporates all information that is currently available regarding the new technology, but gives no guidance on how uncertainty around the expected cost-effectiveness should influence decisions in situations where there is some real option value. The "simple" real options approach helped to determine the optimal initial decision incorporating; expectations around future change in value of the new technology; flexibility in the timing and reversal of decisions; and economic consequences of delay or changing decisions. The "simple" ROA can also give some guidance on when the decisions should be reviewed.

However, these calculations omit the impact of decisions on later decisions, on other parties' actions and on prospects for further research. In this chapter, I describe a new approach which incorporates aspects of ROA with game theory to internalise the process of information arrival and reflect strategic interactions between decision makers. As described in Chapter 3, two agents (the payer and the manufacturer of the new technology) will be considered. These agents are assumed to play a sequential, incomplete information game, where the manufacturer has control over the arrival of information. This type of analysis enables us to explicitly incorporate the impact of earlier decisions on research and to account for other players' reactions.

8.2 Methods

8.2.1 Underlying assumptions

Similarly to previous chapters, I am using the general modelling framework and simplifying assumptions defined in Chapter 5, and (unless otherwise stated) the assumptions and parameter estimates used for the DES model described in Chapters 6 and 7.

8.2.1.1 Assumptions regarding information

This analysis lifts some of the simplifying assumptions made in the previous chapter. In particular, I integrate the manufacturer's decisions over whether to carry out further research

and if so whether to provide the decision-maker with the results of the new research into the model. Therefore the assumptions regarding information arrival change to the following:

3) Arrival of information about the change in value depends on the financial incentives of the manufacturer to carry out further research. The achievable financial gains for the manufacturer are determined by: the population size, when and how the decision maker decides to adopt the new technology and the costs of carrying out the research. Therefore the arrival of information is dependent on previous decisions. If the original decision was to reject the new technology, there may be situations when the manufacturer decides against new research. Similarly, once the technology has been adopted, the incentive to provide new information is lost;
4) The change in value is not always observable for the payer, as the manufacturer decides whether or not to resubmit the updated evidence.

8.2.1.2 Assumptions regarding change in value

The assumptions regarding the stochastic processes driving the change in value of DES have not changed from the previous chapter. The TVR rate for BMS, the RRR in TVR achievable with DES and stent prices are still assumed to follow Wiener processes with drift with the parameters calculated in Section 7.1.3.1. As previously noted, the stochastic processes characterising evolution of the dynamic model parameters could easily be changed, for example to include jumps or to simulate trial outcomes more directly or to incorporate only static uncertainty, if this was thought to be appropriate.

Additional assumptions related to the symmetry of knowledge between the decision maker and the manufacturer are also required: I assumed that both parties share the same beliefs regarding:

- the value of the technology at the time of the initial assessment (i.e. they agree on the inputs, structure, assumptions and results of the traditional analyses), although they do not necessarily have the same information later on if the manufacturer conducts a trial but decides not to share the results, and
- how that value is expected to change. That is, they both use all available evidence at the start of the evaluation and the same assumptions about the stochastic processes to predict changes in the components of value of DES.

In other words, they share the same belief system about the initial probability distribution of the INB and about how that distribution is expected to change over time (see section 8.2.2.4 below for more detail).

In reality, the two players may have different understandings and interpretations of available evidence. They might also have privileged access to some evidence. Future studies could easily relax these assumptions as this would only require one additional calculation of how the other player values the technology at each decision time point. The calculation process is described in detail in Section 8.2.3 below.

8.2.2 Game structure

The three most basic elements that characterise a game are the players, their strategies and the pay-offs.(Osborne and Rubinstein 1994) In this model I have described the decision-making situation as a two-player, sequential, incomplete information game based on the processes of NICE's STA.

8.2.2.1 Players and information sets

The development and introduction of new health technologies involves multiple players. There may be multiple manufacturers of competing technologies. The number of decision makers is determined by the setting, and it is not uncommon to have multiple healthcare commissioners. However, in this case study I demonstrate the use of a real options game with only two players. The two players are:

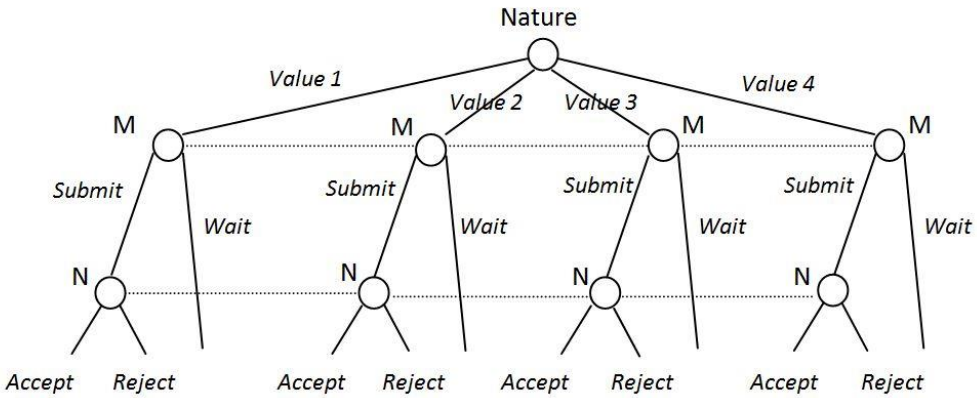
- a payer, whose advisory HTA body is similar in its remit to NICE, i.e. there is a funding directive that requires health care commissioners to comply with recommendations in a NICE technology appraisal within three months of its publication, but it does not have the jurisdiction to negotiate on price;
- and the manufacturer of the DES.

Players with different characteristics, such as an HTA body that also negotiates prices, may also be used. Players with different characteristics would have different sets of possible moves and strategies, and therefore the structure of the game would change too. I chose the simpler framework with an HTA body that only decides on adoption to demonstrate the use of the real option game approach. Inclusion of other players such as competing manufacturers is also possible. It would again make the game structure more complex, by requiring additional assumptions about the relationships between the players' information sets and the number of possible strategies would increase, but would not fundamentally change how the game is

solved. Therefore the method is illustrated here with the simpler two-player frame-work, but the extension of the approach with more options for the decision maker and additional players will be discussed in Chapter 9.

Since we do not know the true value of DES relative to BMS, we only have an estimate of the distribution of its INB, the game is an 'incomplete information' game. As discussed in Section 3.4.3.2.2.3, games with incomplete information can be transformed into games with imperfect information and are traditionally described as if there were three players in the game.(Leyton-Brown and Shoham 2008) The game involves the two 'real' players, and a third player called 'Nature'. In the usual formulation, Nature makes a random first move at the beginning of the game, deciding the true value of the technology in that particular game. In our case, Nature may choose any value from the continuous distribution of the INB for DES versus BMS, but for illustrative purposes Nature's move with only four possible distinct outcomes is depicted in Figure 8-1. The two real players have imperfect information, because they cannot observe Nature's move. The players know the likelihood of ending up at each node at the time of the decision, but neither NICE (decision points marked by N), nor the manufacturer (decision nodes marked by M) know exactly which node they are at. These undistinguishable nodes belong to the same 'information set' for the two real players throughout the game (by convention they are connected by a dotted line on Figure 8-1).

Figure 8-1 Nature's move in an incomplete information game



The information sets (i.e. what the players know about their position at each step in the game) are also influenced by whether one envisages the game as being simultaneous or sequential. In simultaneous games the moves do not necessarily have to be made at the same time, but the players cannot observe which strategy the other player has chosen, so it is as if they have

made the decision at the same time. In the HTA setting this is not the case; the actions of the players are clearly visible to the other players. HTA bodies let the manufacturer, and in most cases the whole public, know about their decision on the adoption of the new technology. On the other side, manufacturers also cannot keep the fact that they have submitted evidence on their new technology a secret. The conduct of clinical research is also governed by strict laws, and manufacturers are expected to register clinical trials. However, reporting of the results of all trials is not (yet) compulsory, and so is not necessarily expected in the game. As described below in section 8.2.2.2, the manufacturer may decide not to publish or to submit results of a negative trial for a second assessment. Nevertheless, everyone will know if new information was submitted. Therefore the game presented here is sequential in its nature; the steps of the players follow one another, with both players able to observe the moves of the other party. In a future extension of the game, it may become necessary to include simultaneous segments or more imperfections into the game. For example, if a competing manufacturer were to be added, the competitors might not be able to observe one another's moves, and some moves may have to be made at the same time.

8.2.2.2 Strategies

The steps that the players can take are also very much dependent on the setting. In my example model, I took the processes of NICE's STA as a basis, with the manufacturer deciding the timing of evidence submission, whether to offer decreases in the price and whether to conduct more research. The payer relying on a NICE-type HTA body only the takes the evidence that is provided to it by the manufacturer, it does not conduct research of its own, and decides whether to accept the technology and recommend its use.

As a first step, the manufacturer may decide to submit for a review now (i.e. in 2005), or to delay the NICE assessment to wait for more information.

Since the models presented in this thesis also assumed that there is no patient heterogeneity, if the evidence is submitted now, NICE can only decide whether to accept the technology or to reject it. If patient heterogeneity is present, the accept/reject decision would have to be made separately for each indication or for each patient subgroup, or equivalently, the model may be run with a mixed cohort with the adoption decision comprising criteria defining which patients should be offered the new technology. NICE also has the remit to recommend that the new technology be used as part of a research programme ("only in research" or "approval with research").(Claxton et al. 2012) However, these recommendations make up only 2% of STA

recommendations, and were not included in the current model.(Longworth et al. 2013) The model can easily be extended to include these options too.

After the first review, the manufacturer may decide to introduce a patient access scheme (PAS). There are many different types of PAS in the UK, based on individual negotiations between the manufacturer and the Department of Health (DoH), ranging from simple discounts to complex rules dependent on monitoring: for example, some patients may be treated free of charge, based on their response status or duration of treatment. As noted above, in this thesis I assume a homogenous patient group. If no further stratification is possible, the PAS could not relate to restricting access to some subgroups of patients. Therefore the end effect of any PAS in this setting will be that it reduces the effective price of the technology for the funding party. Instead of modelling many different types of PAS, I therefore allow for a fixed direct reduction to the price of DES if a PAS is offered. Other, more specific formulations, or ones that are linked to a predefined trigger could be included in future analyses.

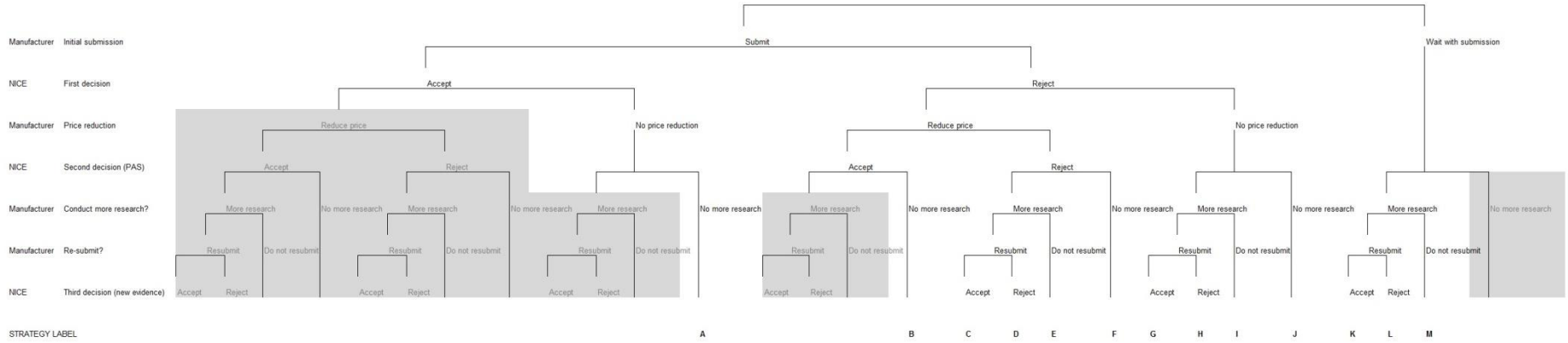
I assumed that if a PAS is offered, it always will be sufficient to be approved by the DoH. The technology under the PAS will then be reviewed by NICE again under the new agreed price (second assessment). Again, this simplifying assumption could be relaxed to reflect the price negotiation process.

If the initial decision made by the manufacturer was to wait, or if the technology was rejected by NICE (with or without a PAS), the manufacturer would have to decide whether to conduct more research, and then, whether it should submit the resulting evidence to NICE.

Finally, NICE conducts the third review and decides on acceptance.

The complete extensive form game for a single move of Nature is shown in Figure 8-2.

Figure 8-2 The complete extensive form game for one move of Nature



Note: Sections in grey are dominated and were excluded from the game.

However, some of the moves will be surely dominated in this two-player game. For example, it is unlikely that the manufacturer would offer a price reduction after the technology has been already accepted by NICE. Not conducting research after deciding not to submit evidence at the beginning of the game is also dominated in this simplified single setting game, although in reality this might be a good option if the manufacturer wants to avoid a negative recommendation from NICE to preserve sales in other markets. Excluding the options that we know will never be chosen results in the decision flow-diagram shown in Figure 8-3. Following the algorithm, 13 distinct strategies can be drawn. These are reported in Table 8-1.

Figure 8-3 Decision algorithm

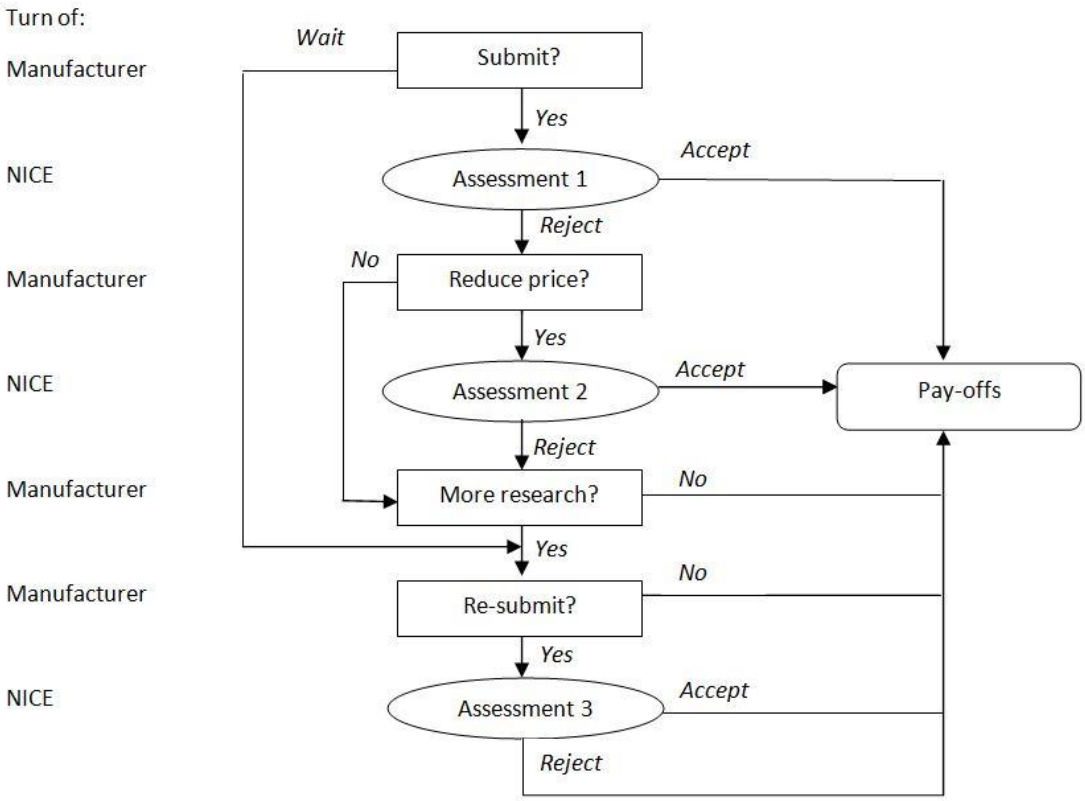


Table 8-1 Real option game strategies

Strategy	A	B	C	D	E	F	G	H	I	J	K	L	M
Initial submission	Submit	Submit	Submit	Submit	Submit	Submit	Submit	Submit	Submit	Submit	Wait	Wait	Wait
Decision 1	Accept	Reject	Reject	Reject	Reject	Reject	Reject	Reject	Reject	Reject	n/a	n/a	n/a
Price reduction	No	Yes	Yes	Yes	Yes	Yes	No	No	No	No	n/a	n/a	n/a
Decision 2	n/a	Accept	Reject	Reject	Reject	Reject	n/a	n/a	n/a	n/a	n/a	n/a	n/a
More research?	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Re-submit?	n/a	n/a	Yes	Yes	No	n/a	Yes	Yes	No	n/a	Yes	Yes	No
Decision 3	n/a	n/a	Accept	Reject	n/a	n/a	Accept	Reject	n/a	n/a	Accept	Reject	n/a
Strategy group	**1**	**2**	**3**	**3**	**3**	**2**	**4**	**4**	**4**	**1**	**5**	**5**	**5**
Effectiveness information at	Jan 2005	Jan 2005	Jan 2008	Jan 2008	Jan 2008	Jan 2005	Jan 2008	Jan 2008	Jan 2008	Jan 2005	Mar 2007	Mar 2007	Mar 2007
Price	Original	Reduced	Reduced	Reduced	Reduced	Reduced	Original	Original	Original	Original	Original	Original	Original
DES available from	Mar 2006	Mar 2006	Apr 2009	n/a	n/a	n/a	Apr 2009	n/a	n/a	n/a	May 2008	n/a	n/a

Naturally, other formulations of the game are possible too. The simple decision whether to offer a fixed reduction in the effective price may be replaced by a multi-choice decision looking at a range of possible price reductions and trying to identify the optimal magnitude of effective price reduction to be offered in the PAS. Similarly, the question whether to conduct a fixed type of research with a fixed sample size and expected cost and a fixed timeline may be extended too. The manufacturer may have different research options. An 'average' randomised clinical trial is included in the current game, however the manufacturer may have ways to expedite the research, for example by committing more funds towards it in the hope of recouping those expenditures by gaining faster acceptance.

Furthermore, the expectation that prices will generally decrease over time may mean that some of the strategies that were deemed to be dominated may be viable after all. For example, the current game excluded the strategy of delaying submission now, but then not conducting further research. Since DES cannot be considered cost-effective given current evidence, if no further research is conducted, then all other things equal, they will not be considered cost-effective at the time of resubmission. Therefore because the combined effect of the changes in the dynamic parameters predict improved cost-effectiveness for DES over time with new information, it is always better to conduct more research to reveal this improvement and gain approval compared to no profits. However, in real life the technology could be introduced in multiple markets, then if the technology's lifetime is long enough to permit the wait, it may become a viable strategy to just wait in this setting until the price decreases enough to make the new technology cost-effective without the need for further evidence on its effectiveness.

Part of this structural uncertainty has been tested as part of the sensitivity analyses which will be described in detail in section 8.2.5, while other tests can be carried out in future studies.

8.2.2.3 Player pay-offs

Similarly to the previous two analyses, the decision maker was assumed to care about the population level incremental net benefits associated with the new technology over the lifetime of the technology, while the manufacturer's pay-offs were formulated in terms of profits over the same time horizon.

Using the stochastic processes as in the simple ROA example in the previous chapter, the future values of the dynamic parameters were forecast between 2005 and 2010. Each of the 13 strategies is associated with different timing as to when and what type (price or effectiveness) information will be revealed. Information about the cost-effectiveness of DES is

revealed at different time-points according to the previous decisions of the manufacturer and NICE.

In the game, decision times are internal to the game itself. Undertaking evaluations or conducting new research all take time. In strategies A, B, F and J new information is not revealed at all. For these strategies, the pay-offs for the lifetime of DES were calculated using all originally available information in 2005, just like in the traditional analyses. For all other strategies, it was first determined when the new information would be available, and for each probabilistic iteration a set of forecast values for the dynamic parameters at that time was sampled from the stochastic processes (alongside values for the static parameters) and used to calculate the population level pay-offs.

Similarly, in the strategies including a PAS (strategies B – F), the INB of DES and manufacturer profits were all calculated with the reduced price.

The players were assumed to be rational, integrating the information that is expected to arrive in the relevant strategies as shown in Table 8-1 right from the beginning of the game. This means that for example in strategy K the manufacturer decides not to immediately submit information to NICE, but rather wait until more research is conducted. However, the population outcomes with BMS between the start of the model and the time of the delayed submission were calculated with the stochastic process parameters predicted for the time of the resubmission.

8.2.2.4 Beliefs of the players

Naturally, the best response in a situation depends on the belief system of each player. The players' belief systems were assumed to be based on the distribution of INB according to current knowledge about the value of DES and a common set of assumptions about how that value might change. That is, the probability that nature chose a certain evolution of value for DES was determined by the distribution of INB (to determine the starting point for the value path) and the stochastic processes for the effectiveness and price parameters (to determine the actual path of value change).

8.2.2.4.1 Knowing the pay-offs

To make this an imperfect information game, the players also had to know each other's maximand. I assume that the decision maker is trying to maximise the net benefit of the population during the life time of the new technology and that the manufacturer is trying to maximise profits, although other objective functions (see Section 5.2.6) can also be easily

incorporated. The only requirement here is that the players need to be aware what is being valued and how it is being valued by the other player.
The players are also assumed to be risk neutral. They are interested in the expected net benefits and expected profits achievable with each strategy and do not care about the uncertainty associated with the pure strategies' pay-offs.

8.2.2.4.2 Symmetry in information

This game also assumed that the beliefs of both players about the distribution of INB and therefore the distribution of profit were the same and based on current knowledge about the value of DES and a common set of assumptions about how that value might change. Naturally, in reality they may have different understandings and interpretations of available evidence, or privileged access to some evidence. Different beliefs about the distribution of INB would not change the game structure, but they could affect the pay-offs each player attributes to each strategy.

8.2.2.4.3 Expectation of acceptance

In the setting of the case study, NICE rejects the use of an absolute threshold for judging the level of acceptability of a technology.(Rawlins and Culyer 2004) It argues that as the Incremental Cost-Effectiveness Ratio (ICER) increases the likelihood of rejection increases. That is, in our case the decision maker takes into account other factors too, over and above the economic value of the new technology, when deciding whether to accept it. These other factors, however, are not necessarily quantified in the economic analysis.

For the solution of the game, the players need an expectation of NICE's decision at each of the three possible assessments. Dakin and colleagues have examined and modelled the factors influencing NICE's recommendations for or against use of health technologies.(Dakin et al. 2013) Although NICE emphasises that cost-effectiveness is not the only consideration in health technology appraisals, cost-effectiveness alone correctly predicted 82% of the decisions. The best-fit model included 18 variables and classified 84.67% of NICE decisions correctly, which is only a small improvement over the ICER only model. Furthermore, although the odds ratios for the coefficients were reported for three of the five models, the constants in the equations were not, so I could not replicate the prediction equations with multiple parameters. The study did report the ICERs where the models predicted the probability of acceptance to be 25%, 50% and 75%. Using these numbers, I back-calculated the prediction equation for the ICER only model (the ICERs were rounded to thousands according to the study report) from

three equations (one for each probability of acceptance) with just two unknowns (the constant and the coefficient):

$$Logit\ (p) = ln\ [p/(1-p)] = constant + coefficient * ICER$$

The p and ICER pairs reported by Dakin and colleagues, as well as the calculated constant and coefficient are shown in Table 8-2.

Table 8-2 The calculation of the ICER only model from (Dakin et al. 2013)

Results reported at p	ICER
25%	£60,377
50%	£43,949
75%	£27,548
The calculated parameters	
Constant	3.02118
Coefficient	-0.06866

Both players were assumed to use the above equation to predict the probability of acceptance at each assessment and evaluate strategies on the expected outcomes, i.e. weighting the pay-offs of individual reject/accept strategy pairs using this probability. The equation above was developed for technologies that are both more costly and more effective compared to the old technology, technologies that fall in the north-east quadrant of the cost-effectiveness plane. For situations where DES dominates BMS, where the calculated ICER would be negative, we used an ICER of £0/QALY to calculate the probability of acceptance. If BMS were shown to be dominant, 1 minus the probability of acceptance if dominated was used, while for situations where DES were less costly and also less effective, the above equation provides the probability of rejection.

Other formulations are possible here as well. Players may simply assume that everything below a certain cost-effectiveness threshold will be accepted. Or the prediction equation could be made more complex. If the equations from Dakin and colleagues were available, the model could take into account other factors influencing the acceptability of technologies, such as the number of reported randomised controlled trials, the number of patients in the trials, whether the new technology is the only treatment in a disease area, whether the patients are children, the type of appraisal, the type of the disease itself and uncertainty in the reported ICERs.(Dakin et al. 2013)

Note that although NICE is thought to generally accept technologies with an ICER under £20,000/QALY and needing special circumstances to accept technologies with an ICER above £30,000/QALY (Rawlins and Culyer 2004), Dakin and colleagues found that the probability of rejection only exceeds the probability of acceptance when the ICER increases above £44,000/QALY.(Dakin et al. 2013) This finding is at odds with the calculation of NBs in the model, because NBs were calculated using a £20,000/QALY threshold. To test the impact of these contradictory assumptions, two further sets of analyses were also performed. Firstly, the uncertainty around acceptance was removed from the game, and technologies with ICERs below £20,000/QALY were assumed to be accepted with certainty, while those above this threshold were assumed to be rejected. Secondly, the game pay-offs were recalculated using the ICER value, where the probability of acceptance was reported to be 50% (£43,949/QALY), as the threshold. The issue relating to the uncertainty around the probability of acceptance will be discussed in more detail in the next Chapter.

8.2.2.4.4 Constant beliefs across information sets

In the case study it was assumed that the belief systems about nature's move do not change between information sets. That is, although the information set for the manufacturer if the new technology has been rejected in the first assessment is different from the information set if the technology has been rejected at the second assessment with a PAS, this knowledge is assumed not to influence the belief system about the original distribution of INB. In this example players do not adjust their assessment of the probability of each action in Nature's initial move at any decision throughout the game. Note, however, that the probability of acceptance does change across information sets.

8.2.3 Calculation algorithm

Due to the sequential nature of the game described above, the real option game calculations could be performed in Excel building on the traditional economic model. In the game, the length of each process (i.e. the time it takes to carry out an assessment or the time it takes to carry out more research) is assumed to be fixed, therefore decision times as well as if and when new information will be revealed are all determined by the chosen strategy.

The traditional economic model had to be rerun with parameters specific to the time-point when new information is revealed, the time-points when decisions are changed and the pricing arrangements agreed during the strategy to estimate population level outcomes. These dates for the base-case are reported in Table 8-1.

The 13 strategies can be classified into five categories according to the factors influencing the value calculated in the traditional model (the time when new information is revealed and the presence of a PAS):

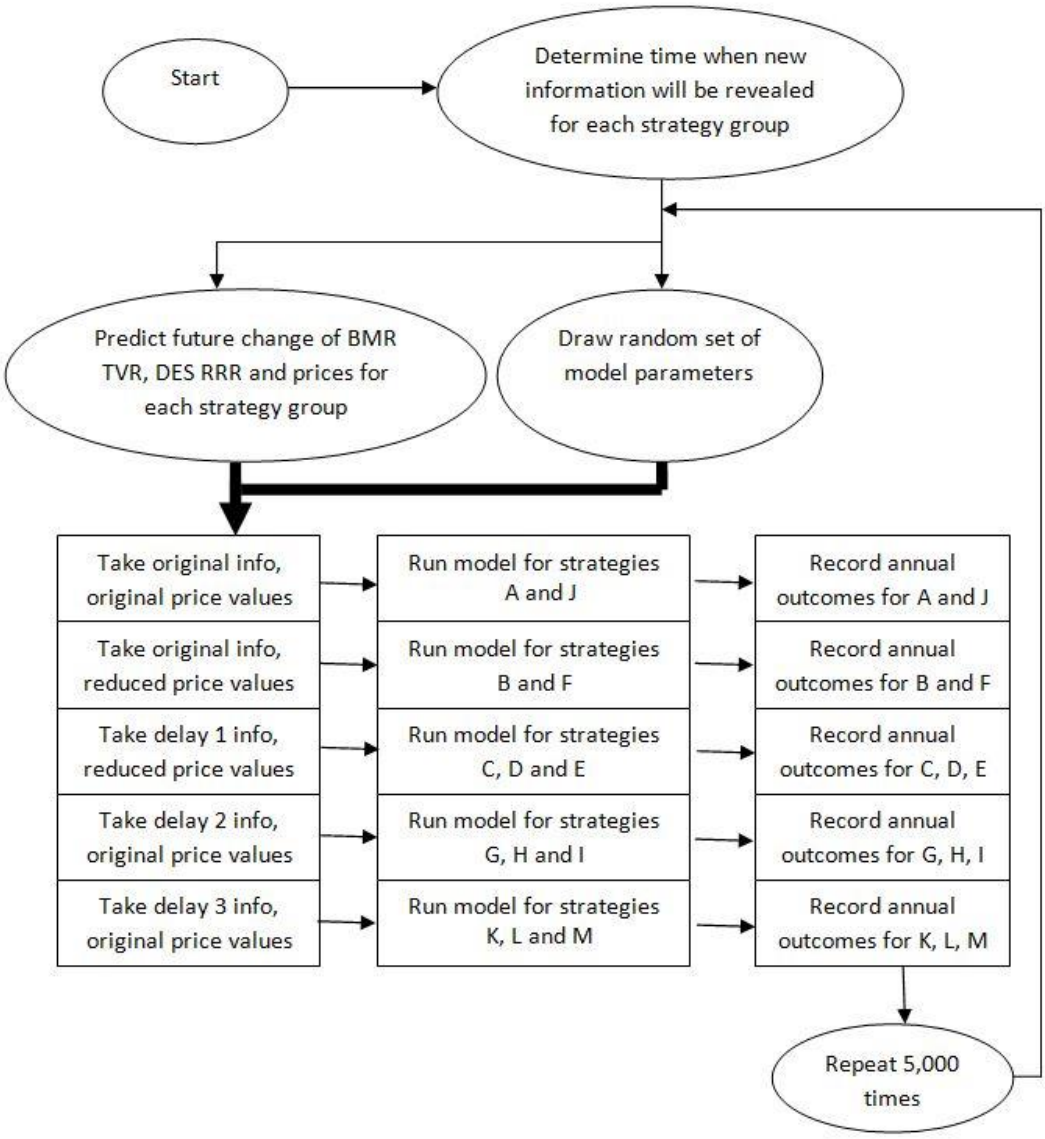
1. Strategy A and J: no new information and no price reduction;
2. Strategy B, F: no new information with price reduction;
3. Strategy C, D, and E: new information after delay due to original assessment, second assessment with PAS and conduct of research (delay 1) with price reduction;
4. Strategy G, H and I: new information after delay due original assessment and conduct of research (delay 2) and no price reduction;
5. Strategy K, L and M: new information after delay due to conduct of research only (delay 3) with no price reduction.

As in the simple ROA presented in the previous chapter, predicting future change adds another layer to the uncertainty about the true value of the parameters. Therefore as shown in Figure 7-1, for each probabilistic iteration of the model I drew one set of values for the static parameters in the model (as in the traditional probabilistic evaluation of a model) and one realisation of what the parameters following stochastic processes might look like at the time that new information is revealed for each of the five strategy groups. Note, that these 'realisations' are a priori predictions made at the original decision point (Jan 2005), not revised predictions if and when new information is revealed. The durations of each possible length of delay (delay 1, 2 and 3) are determined by assumptions about the appraisal process, the time to agree any PAS and the time to conduct any further research (see Section 8.2.4.1 below).

It is important to note that in order to truly represent nature's move the strategies had to be evaluated in parallel, drawing from a common set of parameters representing static parameter uncertainty and the same realisation of the stochastic processes at each iteration. Allowing the static probabilistic model parameters or the dynamic parameters following stochastic processes to be drawn separately for each strategy (within a given iteration) would introduce unnecessary noise into the model. For each iteration, the model was run with the same sets of static/dynamic parameters for both policy options (if DES were or were not to be recommended for use) and the population outcomes were saved for each year. Results were then accumulated for each year, for each strategy, taking values from the without-DES scenarios until the dates when DES would be recommended, and taking values from the with-DES scenarios afterwards.

To allow for the increased uncertainty (the traditional static parameter uncertainty plus the uncertainty around predicting future changes in dynamic parameters) to be fully explored, 5,000 iterations were undertaken. The code was programmed with Visual Basic (VBA)within Excel, and the annotated code is again provided in Appendix II.

Figure 8-4 Calculation algorithm



8.2.4 Model inputs

Most of the model parameters remained the same as in the simple ROA case study. For a description of how the stochastic process parameters were estimated see Section 7.1.3.1, while the calculation of the cost of reviews and changes in decisions can be found in Section 7.1.3.2. In addition, the real option game also required estimates of how long certain processes would take and of the costs falling on the new player, the manufacturer.

8.2.4.1 Decision times

In contrast to the simple application, where information was assumed to be revealed periodically independently of the previous decisions, here decision times are internal to the game itself. Previous decisions determine if and when new information will become available and when certain decisions need to be made. For the purposes of this example I treated the time to conduct an assessment (with and without a PAS) and the time to conduct research as fixed constants. However, one could introduce uncertainty over the durations alongside the traditional parameter uncertainty and the dynamic processes. It would involve moving the "Determine time when new information will be revealed" step in the calculation algorithm shown in Figure 7-1 into the loop so it varies in each iteration.

8.2.4.1.1 Length of assessments

Since the whole game was designed to reflect NICE's STA process, I considered guidance given by NICE itself on the process to determine a minimum interval between NICE decision points. An average assessment is expected to last 34 weeks with an additional 3 week period to register an appeal.(National Institute for Health and Clinical Excellence October 2009) Furthermore, if the manufacturer agrees a PAS with the DoH within 16 weeks of the publication of the original guidance, a rapid review facility is available and scheduled within 6 months.

NICE provides a list of its assessments that include a PAS on its website.(Natonal Institute for Health and Care Excellence)(accessed 24 April 2014, at which time the site was last updated on 24 March 2014) Each assessment on the list was examined. I extracted from the documents found on the NICE website: the date of the start of the review, the date of the Final Appraisal Determination (FAD) and the dates for the re-review with a PAS. The findings are presented in Table 8-3. Closer inspection of the 42 assessments including a PAS revealed that the scheme was agreed after an initial Appraisal Consultation Document (ACD) was published with negative recommendations, but before the final guidance was produced in 40 of the cases. In these cases the start of the PAS process was assumed to be the date of the last ACD with a negative determination.

Table 8-3 Timings of NICE assessments with a PAS (in months)

TA Ref	Treatment	Indication	Type	Review type	Review start	FAD	PAS*	Review time	Time for PAS
TA185	Trabectedin (Yondelis)	Advanced soft tissue sarcoma	Dose cap	STA	26/11/2008	21/12/2009	07/10/2009	12.8	0
TA155	Ranibizumab (Lucentis)	Macular degeneration (Acute wet AMD)	Simple discount	MTA	01/08/2006	02/04/2008	13/12/2007	20.1	0
TA171	Lenalidomide (Revlimid)	Multiple myeloma	Dose cap	STA	27/06/2008	23/04/2009	30/01/2009	9.9	0
TA162	Erlotinib (Tarceva)	Non small cell lung cancer	Simple discount	STA	23/05/2006	24/04/2008	29/09/2008	23.1	5.2
TA129	Bortezomib (Velcade)	Multiple myeloma	Response scheme	STA	28/02/2006	20/10/2006	30/08/2007	7.7	10.3
TA180	Ustekinumab (Stelera)	Moderate to severe psoriasis	Free stock	STA	08/01/2009	14/08/2009	01/03/2009	7.2	0
TA179	Sunitinib (Sutent)	Gastrointestinal stromal tumour	Free stock	STA	31/10/2008	12/08/2009	05/03/2009	9.4	0
TA176	Cetuximab (Erbitux)	Metastatic colorectal cancer (first Line)	Rebate	STA	08/04/2008	01/06/2009	29/01/2009	13.8	0
TA169	Sunitinib (Sutent)	Renal cell carcinoma	Free stock	MTA	01/10/2007	04/02/2009	07/08/2008	16.2	0
TA186	Certolizumab pegol (Cimzia)	Rheumatoid arthritis	Free initial stock	STA	22/06/2009	20/01/2010	19/10/2009	7.0	0
TA192	Gefitinib (Iressa)	Non small cell lung cancer	Single fixed price	STA	24/09/2009	27/05/2010	29/01/2010	8.1	0
TA215	Pazopanib (Votrient)	Advanced renal cell carcinoma	Discount+ poss rebate	STA	15/04/2010	24/12/2010	Sep-10	8.3	0
TA218	Azacitidine (Vidaza)	Myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia	Simple discount	STA	May-09	17/02/2011	08/10/2009	21.6	0
TA220	Golimumab (Simponi)	Psoriatic arthritis	Free stock	STA	15/06/2010	17/03/2011	05/10/2010	9.0	0

TA Ref	Treatment	Indication	Type	Review type	Review start	FAD	PAS*	Review time	Time for PAS
TA221	Romiplostim (Nplate)	Chronic idiopathic (immune) thrombocytopenic purpura	Simple discount	STA	24/10/2008	17/03/2011	04/01/2010	28.7	0
TA225	Golimumab (Simponi)	Rheumatoid arthritis	Free stock	STA	02/07/2010	13/05/2011	22/10/2010	10.4	0
TA233	Golimumab (Simponi)	Ankylosing spondylitis	Free stock	STA	18/08/2010	24/06/2011	18/05/2011	10.2	0
TA235	Mifamurtide (Mepact)	High grade resectable non-metastatic osteosarcoma	Simple discount	STA	28/10/2008	07/09/2011	08/10/2010	34.3	0
TA238	Tocilizumab (RoActemra)	Systemic juvenile idiopathic arthritis	Simple discount	STA	05/04/2011	27/10/2011	11/08/2011	6.7	0
TA241	Nilotinib (Tasigna)	Imatinib-resistant chronic myeloid leukaemia	Simple discount	MTA	29/04/2009	18/08/2011	09/02/2010	27.6	0
TA247	Tocilizumab (RoActemra)	Rheumatoid arthritis	Simple discount	STA	30/09/2011	23/12/2011	30/09/2011	2.8	0
TA251	Nilotinib (Tasigna)	First-line treatment of chronic myeloid leukaemia	Simple discount	MTA	25/05/2011	22/03/2012	25/05/2011	9.9	0
TA254	Fingolimod (Gilenya)	Highly active relapsing-remitting multiple sclerosis	Simple discount	STA	18/03/2011	16/03/2012	01/12/2011	12.0	0
TA258	Erlotinib (Tarceva)	First-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer	Simple discount	STA	10/10/2011	10/05/2012	17/02/2012	7.0	0
TA259	Abiraterone acetate (Zytiga)	Castration-resistant metastatic prostate cancer previously treated with a docetaxel containing regimen	Simple discount	STA	23/09/2011	16/05/2012	02/02/2012	7.8	0
TA265	Denosumab (Xgeva)	Skeletal related events in adults with bone metastases from solid tumours	Simple discount	MTA	15/07/2011	17/08/2012	15/07/2011	13.1	0
TA268	Ipilimumab (Yervoy)	Advanced melanoma, 2nd Line	Simple discount	STA	17/06/2011	02/11/2012	18/01/2012	16.6	0
TA269	Vemurafenib (Zelboraf)	Metastatic mutation positive melanoma	Simple discount	STA	01/02/2012	02/11/2012	10/08/2012	9.0	0
TA274	Ranibizumab (Lucentis)	Diabetic macular odema	Simple discount	STA	05/10/2012	04/01/2013	05/10/2012	3.0	0

TA Ref	Treatment	Indication	Type	Review type	Review start	FAD	PAS*	Review time	Time for PAS
TA276	Colistimethate (Colobreathe)	Pseudomonas aeruginosa for adults and children over 6 with cystic fibrosis	Simple Discount	MTA	12/05/2011	25/01/2013	24/10/2012	20.5	0
TA276	Tobramycin (TOBI Podhaler)	Pseudomonas aeruginosa for adults and children over 6 with cystic fibrosis	Simple Discount	MTA	12/05/2011	25/01/2013	12/05/2011	20.5	0
TA278	Omalizumab (Xolair)	Severe persistant asthma	Simple Discount	MTA	12/01/2012	07/03/2013	09/11/2012	13.8	0
TA280	Abatacept (Orencia)	Rheumatoid arthritis, polyarticular juvenile idiopathic arthritis	Simple Discount	STA	06/11/2012	08/03/2013	06/11/2012	4.0	0
TA282	Pirfenidone (Esbriet)	Mild to moderate idiopathic pulmonary fibrosis	Simple Discount	STA	01/12/2011	21/03/2013	29/11/2012	15.6	0
TA283	Ranibizumab (Lucentis)	Macular oedema secondary to retinal vein occlusion	Simple Discount	STA	10/05/2011	11/04/2013	24/11/2011	23.1	0
TA293	Eltrombopag (Revolade)	Chronic immune (idiopathic) thrombocytopenic purpura	Simple Discount	STA	10/08/2012	12/06/2013	10/08/2012	10.1	0
TA294	Aflibercept (Eylea)	Wet age-related macular degeneration	Simple Discount	STA	08/01/2013	31/05/2013	08/01/2013	4.7	0
TA298	Ranibizumab (Lucentis)	Choroidal neovascularisation secondary to pathologic myopia	Simple Discount	STA	10/06/2013	25/10/2013	10/06/2013	4.5	0
TA301	Fluocinolone (Iluvien)	Diabetic macula oedema	Simple Discount	STA	14/06/2013	01/10/2013	14/06/2013	3.6	0
TA303	Teriflunomide (Aubagio)	Active relapsing-remitting multiple sclerosis	Simple Discount	STA	28/05/2013	06/12/2013	18/09/2013	6.3	0
TA305	Aflibercept (Eylea)	Visual impairment caused by macular oedema secondary to central retinal vein occlusion	Simple Discount	STA	12/08/2013	31/12/2013	12/08/2013	4.6	0
TA306	Pixantrone (Pixuvri)	Multiple relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma	Simple Discount	STA	28/11/2012	31/12/2013	03/07/2013	13.1	0

* or last ACD with negative recommendation

Based on these findings, the STAs involving a PAS lasted on average 11.05 months, while MTAs lasted on average 17.72 months. Therefore, as a base case I assumed that the first and third assessments would each last 11 months. Since in most cases PAS were offered during the initial process, the manufacturer's decision whether to offer a PAS and the second assessment with the PAS also has to be made within this time period (thus no extra time was added for the PAS negotiation and second assessment, if required). However, the model structure was kept flexible to enable the introduction of additional time to agree PASs and to re-review the new technology under a PAS.

A further 3 month delay was also assumed until a new guidance is implemented, because "when NICE recommends a treatment 'as an option', the NHS must make sure it is available within 3 months (unless otherwise specified) of its date of publication". (National Institute for Health and Care Excellence)

8.2.4.1.2 Length of research

A need for further evidence on relative effectiveness was the most commonly cited reason by NICE for requesting further research to be undertaken. (Longworth et al. 2013) Therefore in the base case the model assumed that the form of further research to be undertaken would be a Phase 3 clinical trial. The average length of a Phase 3 clinical trial has been reported to be 780 days (~26 months) in 2005.(Tufts Center for the Study of Drug Development 2008)

Naturally, the type of research to be undertaken will be specific to each situation and may not require a full phase 3 clinical trial. The value of information analyses for parameters may also give an indication of which parameter groups are the ones about which more precise knowledge would be beneficial. In our case study, the calculations have shown that the EVPPI for resource use parameters and costs was the highest. On a population level, the EVPPI for resource use and cost information reached about £14 million and £10 million respectively. This type of information may be collected through other means such as an observational longitudinal study or through a retrospective analysis of patients' charts. These types of studies are usually shorter in duration and are less costly compared to a randomised clinical trial. Furthermore, the manufacturer may also have studies already running at the time of submission in anticipation of the need for further information. In this case the date when new information becomes available may be sooner than the full length of a study. In a sensitivity analyses, a shorter duration of one year was also tested to allow for such situations.

8.2.4.2 Costs to the manufacturer

The costs of producing the stents were already included in the impact calculations for the previous two analyses (see Section 6.2.2.5). It was also revealed by one of the manufacturers that in the case of stents, the costs associated with gaining approval for the new technology, producing the necessary documentation for technology assessments and the costs of marketing are all negligible compared to production costs.(Personal communication from Medtronic) I therefore assumed these costs to be zero. Therefore the novel items required for the evaluation of this real option game are the costs of conducting further research to reveal new information and the cost in terms of loss of profits due to offering an effective price reduction in a PAS.

8.2.4.2.1 The cost of further research

In 2005 the pharmaceutical industry spent $1.3 billion on research and development for the average drug approved by the US Food and Drug Administration.(Roy 2012) The amount is even larger today. The research and development spending from the 12 leading pharmaceutical companies from 1997 to 2011 totalled $802 billion to gain approval for 139 drugs.(Roy 2012) This means about $5.8 billion per drug, although some have argued that actual costs may be lower.(Light and Warburton 2011) In any case at the time of submission the majority of the sum has already been spent, and these costs are sunk costs and should not be taken into account in the current analyses.

The costs that matter here are the costs associated with carrying out the research to provide new information. As discussed in the section above, NICE requests further evidence on relative effectiveness most often (Longworth et al. 2013), therefore the base case model included an estimate of the costs of a Phase 3 trial. The average cost of conducting a Phase 3 clinical trial was reported to be $30.1 million (~ £18.06 million).by the industry.(Cutting Edge Information Nov 2013) However, the impact and use of a Phase 3 trial cannot be constrained to a single setting. Manufacturers operate on a global level and cannot expect to trade off the total costs of a Phase 3 trial against the profits in a single country. To account for this I decided to weigh the costs of the trial with the relative market size of the UK compared to the global market. 2.32% of the global value of biopharmaceutical sales at ex-factory prices came from the UK in 2011.(European Federation of Pharmaceutica Industries and Associations 2013) Therefore the UK-specific portion of the cost of conducting new research was assumed to be around £420,000.

Public funders tend to report lower overall costs. I also looked at the funding provided for all studies currently (2 December 2014) listed on the NIHR website for the Efficacy and Mechanism Evaluation Programme (EME).(NIHR EME 2014) The EME funds clinical studies to test interventions where proof of concept has already been demonstrated, including larger clinical trials. Treatment with drugs or biological compounds, psychological interventions, public health initiatives, diagnostic tests and medical devices are all within the remit of the Programme. The average funding provided for the 74 studies was £1,123,992 with a range between £123,998 to £3,525,623. The cost of research calculated above falls within this range, and may even be an underestimate of the cost of conducting clinical research in the UK.

Studies collecting information on local resource use patterns and costs are exempt from the above problem of allocating the costs of global research to local settings, because by definition local resource use patterns and costs relate to the local setting. The sensitivity analyses around the cost of performing new research have been undertaken using very wide ranges to capture the impact of different types of research, as well as the impact when the proportionate cost of research for a single setting does not correspond to the weight of that setting within sales.

8.2.4.2.2 The impact of a patient access scheme

It is not possible to calculate the exact level of discount involved in PASs, because most are commercial in confidence.

During the production of TA152, the guidance relating to the use of DES, PAS were not common. At the time it was NICE who requested that the price of DES should not exceed the price of BMS by more than £300.(National Institute for Health and Clinical Excellence July 2008) Taking the mean stent prices quoted in the final appraisal determination of £529 for DES and £131 for BMS, requiring DES not to exceed the price of BMS by more than £300 corresponds to an 18.52% effective price reduction on average.(National Institute for Health and Clinical Excellence January 2008) For the purposes of this analysis a 20% effective price reduction was assumed as a base case, but again this assumption was tested in the extreme (with a range between 5%-95% reduction) in the sensitivity analyses.

Note that it was assumed that once a PAS has been offered, the manufacturer cannot withdraw the offer. For example in strategies C to F profit and net benefit estimates were predicted for the times subsequent to the offer of the PAS with the reduced price, even though the technology was rejected the first time the PAS was offered.

As discussed in section 8.2.2.2 above, the model structure itself could be modified in future research to include multiple formulations of PAS with multiple levels of effective price reductions. Then the model itself could be used to identify the optimal PAS to be offered.

8.2.5 Analyses

As explained in Section 3.4.3.2.2.2, extensive form games with imperfect information cannot be evaluated using backward induction assuming subgame perfection, as there are no subgames.(Osborne and Rubinstein 1994) Furthermore, given that the assumed belief system is that nature may choose any value from the full distribution of the current INB, it is impossible to tell if there are any further dominant strategies besides the ones already ruled out. Therefore the game was solved using sequential equilibrium: for each information set of each player *i* the strategy of player *i* should be the best response to the other players' strategy, given player *i*'s beliefs at that information set.(Osborne and Rubinstein 1994) In this particular game this meant that at each decision point, since the players do not know the exact pay-off, the relevant player makes the choice that maximises their expectation of value (INB or profit), given their knowledge of the structure of the game and the choices that have already been made, and their beliefs about the initial distribution of value.

8.2.5.1 Model evaluation

To simulate nature's move, 5,000 iterations were run for the current state of the world and the predictions for how the future might unfold, simultaneously.

The model start date was set to January 2005.

The model generated the population net monetary benefit (at a £20,000 per QALY threshold) and the profits for the manufacturer that would occur each year if DES were accepted or rejected for each of the five strategy groups. The expected pay-offs for each of the 13 'pure strategies' (as reported in Table 8-1) were then determined from the 5,000 iterations taking into account the dates when DES were accepted (if at all) and the price associated with each strategy. The game-tree was then rolled back to determine the expected pay-offs at each decision node if the best response were to be chosen. That is, at each node, the player in question was assumed to choose the path with the higher expected pay-off. Finally, the model was rolled back completely to determine the optimal initial decision by the HTA decision-maker and optimal time to submit for the manufacturer.

8.2.5.2 Sensitivity analyses

Extensive sensitivity analyses were carried out around a number of parameters:

- the population size
- the costs of reviews and of the changing of decisions;
- the decision times, by varying the length of processes;
- the cost of further research;
- the magnitude of effective price reduction offered in a PAS

Since these analyses were exploratory, rather than testing the parameters at predefined ranges, they were tested to the extremes, to identify the threshold values (if any) that caused a change in the optimal strategy.

As described above, tests were also undertaken around the belief in the uncertainty of acceptance. One set of analyses removed this uncertainty, and assumed acceptance and rejection to be certain under and above the £20,000/QALY threshold, respectively. A second set of analyses recalculated the game pay-offs with a new threshold. Dakin and colleagues found that the probability of acceptance exceeded 50% if the ICER fell below £43,949/QALY. This implied threshold was also used to calculate the population level net benefits.

8.2.5.3 The complete information case

As with the value of information analyses in traditional economic analyses (see Section 2.2.2), I propose that one can determine the expected value of complete information (EVCI), that is perfect information on how both static and dynamic uncertainty resolves, by comparing the results, calculated as described above, with what could be achieved if nature were to "reveal his hand" at the beginning of the game, so that the players had complete information about their position in the game as well as the pay-offs. Since there is uncertainty over nature's move, the expected value of a decision taken with complete information was found by averaging the payoffs of the optimum solutions to the games with complete information over the distribution of nature's moves (i.e. over the distribution of the current INB and the dynamic changes over time predicted by the stochastic processes). As opposed to conventional VoI methods, EVCI includes dynamic uncertainty too. Furthermore, since the suggested calculation relies on a real option game, EVCI calculation methods could incorporate differences in the value of the technologies between players over time as well as the interdependence between decisions over time.

Calculation of the complete information results required a change in the calculation method and the programmed algorithm. Complete information games are usually solved using backward induction assuming subgame perfection (see Section 3.4.3.2.2.1).(Osborne and Rubinstein 1994) In other words, each decision node within the game is treated as a separate

game, and within each game, players were assumed to maximise their pay-off of interest (i.e. the decision maker maximised population net benefits while the manufacturer maximised profits).

In terms of the calculation algorithm, this meant that the game had to be solved for every one of the 5,000 iterations of nature's move separately rather than being solved based on the expected outcomes at each node. The annotated VBA code used to achieve this is reported in Appendix III.

8.3 Real options game model results

8.3.1 Determining the solution

The expected pay-offs after nature's move for the 13 strategies by year are shown in Table 8-4 and Table 8-5. As expected, we see higher profits and higher QALY gains with the strategies involving early acceptance, and higher NBs with the strategies involving a PAS and more research. Strategy C ("Submit – Reject – Offer PAS – Reject – Conduct more research – Re-submit – Accept") has the highest NB pay-off, while strategy A ("Submit – Accept") has the highest profit and QALY pay-offs.

Table 8-4 Expected pay-offs for strategies A to F by year

Strategies	A	B	C	D	E	F
NICE - QALY gains						
2005	37,857	37,857	37,865	37,865	37,865	37,857
2006	37,931	37,931	37,865	37,865	37,865	37,857
2007	42,921	42,921	42,830	42,830	42,830	42,821
2008	48,594	48,594	48,491	48,491	48,491	48,480
2009	55,068	55,068	55,059	54,951	54,951	54,939
2010	62,462	62,462	62,492	62,330	62,330	62,316
Total	246,975	246,975	246,737	246,468	246,468	246,413
NICE – NBs (at £20,000/QALY), including costs of reviews and change						
Cost of reviews and change	-193,846	-402,360	-575,212	-556,012	-381,675	-381,675
2005	512,914,735	512,914,735	517,482,444	517,482,444	517,482,444	512,914,735
2006	512,013,736	514,575,655	517,482,444	517,482,444	517,482,444	512,914,735
2007	578,907,941	582,386,372	585,308,590	585,308,590	585,308,590	580,131,143
2008	655,383,851	659,323,250	662,642,760	662,642,760	662,642,760	656,769,022
2009	742,654,103	747,119,756	754,665,795	750,893,682	750,893,682	744,224,171
2010	842,327,909	847,394,866	857,372,296	851,688,936	851,688,936	844,109,223
Total	3,331,093,694	3,350,397,539	3,376,896,672	3,367,460,400	3,367,634,737	3,337,766,620

Strategies	A	B	C	D	E	F
Manufacturer - profits + cost of research						
Cost of research	0	0	-419,001	-419,001	-419,001	0
2005	0	0	0	0	0	0
2006	8,553,556	6,842,845	0	0	0	0
2007	11,613,708	9,290,967	0	0	0	0
2008	13,152,890	10,522,312	0	0	0	0
2009	14,910,005	11,928,004	7,996,309	0	0	0
2010	16,917,636	13,534,109	12,053,566	0	0	0
Total	65,147,796	52,118,237	19,630,874	-419,001	-419,001	0

Table 8-5 Expected pay-offs for strategies G to M by year

Strategies	G	H	I	J	K	L	M
NICE - QALY gains							
2005	37,865	37,865	37,865	37,857	37,862	37,862	37,862
2006	37,865	37,865	37,865	37,857	37,862	37,862	37,862
2007	42,830	42,830	42,830	42,821	42,827	42,827	42,827
2008	48,491	48,491	48,491	48,480	48,701	48,487	48,487
2009	55,059	54,951	54,951	54,939	55,084	54,947	54,947
2010	62,492	62,330	62,330	62,316	62,481	62,325	62,325
Total	246,737	246,468	246,468	246,413	246,955	246,448	246,448

Strategies	G	H	I	J	K	L	M
NICE – NBs (at £20,000/QALY), including costs of reviews and change							
Cost of reviews and change	-387,384	-368,184	-193,846	-193,846	-179,923	-179,923	0
2005	517,482,444	517,482,444	517,482,444	512,914,735	515,950,704	515,950,704	515,950,704
2006	517,482,444	517,482,444	517,482,444	512,914,735	515,950,704	515,950,704	515,950,704
2007	585,308,590	585,308,590	585,308,590	580,131,143	583,575,523	583,575,523	583,575,523
2008	662,642,760	662,642,760	662,642,760	656,769,022	662,585,521	660,680,281	660,680,281
2009	751,697,371	750,893,682	750,893,682	744,224,171	748,828,570	748,669,575	748,669,575
2010	852,897,765	851,688,936	851,688,936	844,109,223	849,344,164	849,166,219	849,166,219
Total	3,369,641,547	3,367,648,229	3,367,822,566	3,337,954,449	3,360,104,560	3,357,862,380	3,358,042,303
Manufacturer - profits + cost of research							
Cost of research	-419,001	-419,001	-419,001	0	-419,001	-419,001	-419,001
2005	0	0	0	0	0	0	0
2006	0	0	0	0	0	0	0
2007	0	0	0	0	0	0	0
2008	0	0	0	0	8,153,471	0	0
2009	9,995,386	0	0	0	13,807,540	0	0
2010	15,066,958	0	0	0	15,666,972	0	0
Total	24,643,343	-419,001	-419,001	0	37,208,982	-419,001	-419,001

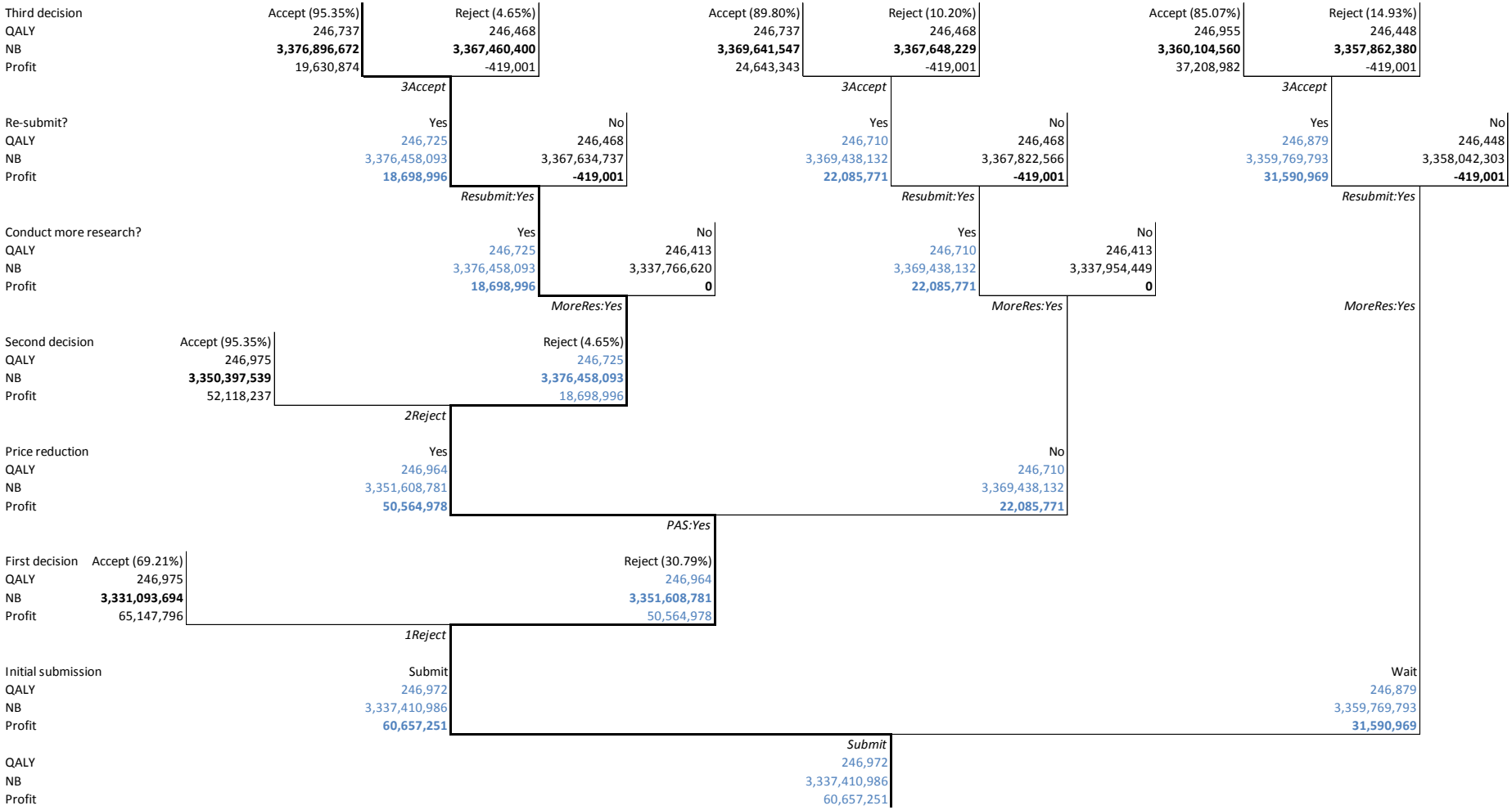
The calculated cost-effectiveness results at the time when new information would be revealed in the game (if at all), and expected probability of acceptance at the next assessment (if the manufacturer were to submit the new information) by strategy groups is reported in Table 8-6. Strategy group 1 shows that, although in the base case DES cannot be considered cost-effective at either a £20,000/QALY or £30,000/QALY threshold, the probability of acceptance is still nearly 70%. This reflects the higher implicit threshold found by Dakin and colleagues, where the probability of acceptance only fell below 50% if the ICER was above £43,949/QALY.(Dakin et al. 2013) Further research and time (as in strategy groups 3, 4 and 5) is expected to reduce the ICER, due to the net effect of the stochastic processes assumed for BMS TVR rate, the RRR with DES compared with BMS and prices (see Section 7.1.3.1), further increasing the probability of acceptance to above 85%. Cost-effectiveness of DES can also be improved with an effective price reduction (as in strategy groups 2 and 3). The assumed 20% price reduction in these cases made DES dominant.

Table 8-6 Probability of acceptance by date and information set

Strategy group	Date of effectiveness information	Price	Cost-effectiveness result	Probability of acceptance
1	January 2005	Original	£32,206/QALY	69.2%
2	January 2005	Reduced	DES dominates	95.4%
3	January 2008	Reduced	DES dominates	95.4%
4	January 2008	Original	£12,328/QALY	89.8%
5	March 2007	Original	£18,658/QALY	85.1%

The derivation of the optimum solution to this particular game is shown in Figure 8-5. Expected pay-offs at the final nodes (at the top of the tree) for the strategies are shown in black font. Note that there are 13 terminal nodes, corresponding to the 13 strategies (A to M) defined in Table 8-1, with pay-offs corresponding to the results reported in Table 8-4 andTable 8-5 above. The players have different maximands, therefore the pay-offs that are of interest to the relevant player making the decision at each stage are highlighted in bold font. The optimal decision for the relevant player to make at each decision junction is printed below the junction in italics. Expectations of pay-offs, taking into account the impact that the current decision has on later decisions, are shown in blue. Lastly, the decision path that provides the solution to the game is highlighted with a thick black line.

Figure 8-5 Game solution



As an example, NICE is faced with the choice between acceptance and rejection if the manufacturer decided to delay submission to conduct more research and then to submit the new information to NICE in March 2007. NICE is interested in the population NBs. If NICE were then to accept, DES would be available after the eleven month review and the three months implementation period from May 2008, resulting in a population NB between 2005 and 2010 of £3,360 million and profits of £37.2 million for the manufacturer (Strategy K). If NICE were to reject after the resubmission in March 2007, the NB would be £3,358 million and the manufacturer would be making a loss on the technology (Strategy L). Therefore the optimal final decision for NICE will be to Accept DES (shown in italics). With the new evidence, the ICER of DES compared to BMS is expected to fall to below £19,000/QALY, increasing the probability of acceptance to above 85%. So at the time of considering the resubmission, the manufacturer's expectation is for a profit of £31.6 million (~ 85.1%*£37.2 million + 14.9% * -£0.4 million), which is shown in blue at the decision junction around resubmission.

The solution to this particular game was the chain of actions "Submit – Reject – Offer PAS – Reject – Conduct more research – Re-submit – Accept", predicting that a positive recommendation for DES would be finally available at the end of 2008. Note that this is not just the best solution for NICE (the strategy with the maximum NB), but it is the stable solution to the game, which both parties will freely choose, given the beliefs, assumptions and information embodied in the game. The manufacturer will choose to take the necessary sequence of actions (Submit– offer PAS – Conduct more research – Re-submit) in order to maximise expected profit. Although there are other strategies that the manufacturer would prefer (A, B, G or K), in this case it is not worth risking a final rejection from NICE, as this would result in no profit or even a loss.

At the first assessment NICE expects a total NB of £3,337 million, and the manufacturer expects a profit of over £60 million. Note that due to the fact that the players have incomplete information, these numbers are markedly different from the actual expected pay-offs of pure strategy "C".

The optimal strategy also displays the advantages of the ROA approach. With a PAS, DES becomes dominant, that is traditional analyses would recommend accepting at the second evaluation. However, acceptance also means that no further research will be carried out, so given the current levels of uncertainty and its expectations about how the value of DES might change with time, it is better for the decision maker to reject DES even with a PAS at the second assessment to ensure that research is carried out.

8.3.2 Sensitivity analyses

8.3.2.1 Impact of population size

Similarly to the simple ROA, the size of the population to be treated over the lifetime of the new technology influences the magnitude of net benefits to be gained by changing decisions. In addition, the size of population is also important for the manufacturer, because it influences the magnitude of future sales and therefore profits. The smaller the population, the more expensive reviews and conducting research become in relative terms.

The size of the patient population was changed by the same fixed proportion for each of the years within the model time horizon. The solution remained the same until the population fell to below 5% of original size (less than about 3,000 patients treated per year, see

Table 8-7). Any fewer patients and conducting further research is not worthwhile for the manufacturer, because the costs of research cannot be recouped from future sales. In such a small population the benefits for NICE to hold out waiting for a PAS to be offered are also outweighed by the additional costs of conducting the second assessment. Therefore in this situation, the decision maker is better off accepting DES based on just the expectation and not the proof that DES will become cost-effective.

Table 8-7 Impact of population size on optimal strategy

Population size	E[QALYs]	E[NB]	E[Profit]	Strategy						
1%	2,470	33,113,391	603,896	Submit	1Accept	PAS:n/a	2N/A	MoreRes:No	Resubmit:n/a	3N/A
5%	12,349	166,623,059	3,019,481	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept
10%	24,697	333,506,634	6,038,963	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept
20%	49,394	667,273,785	12,077,926	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept
25%	61,743	834,157,360	15,097,407	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept
50%	123,486	1,668,575,235	30,194,814	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept
100%	246,972	3,337,410,986	60,389,628	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept
150%	370,458	5,006,246,737	90,584,442	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept
200%	493,943	6,675,082,489	120,779,257	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept
500%	1,234,859	16,688,096,995	301,948,142	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept
1000%	2,469,717	33,376,454,506	603,896,283	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept

8.3.2.2 Impact of changes in the costs of reviews and decision changes

The cost of reviews and the cost of changing the decisions were varied simultaneously, increasing them both by the same multiple. These costs have a direct impact on the payoff for the decision maker. A rise in these costs offsets the gains achievable by making sure that the right decision was made at each time point. One expects acceptance or an earlier decision about the new technology and fewer reviews as the costs increase. The sensitivity analyses confirmed this (see Table 8-8). Once the cost of reviews and decision changes increased more than 100 fold (increasing the cost of a review to above £2 million and the cost of changing the decisions to above £200,000) accepting DES right at the start becomes the optimal solution.

Table 8-8 Impact of change in cost of reviews and decision changes

Cost multiplier	E[NB] £ million	Strategy						
2	3,337	Submit	Reject	PAS:Yes	Reject	MoreRes:Yes	Resubmit:Yes	Accept
5	3,336	Submit	Reject	PAS:Yes	Reject	MoreRes:Yes	Resubmit:Yes	Accept
10	3,335	Submit	Reject	PAS:Yes	Reject	MoreRes:Yes	Resubmit:Yes	Accept
25	3,331	Submit	Reject	PAS:Yes	Reject	MoreRes:Yes	Resubmit:Yes	Accept
50	3,324	Submit	Reject	PAS:Yes	Reject	MoreRes:Yes	Resubmit:Yes	Accept
75	3,318	Submit	Reject	PAS:Yes	Reject	MoreRes:Yes	Resubmit:Yes	Accept
100	3,312	Submit	Accept	PAS:n/a	N/A	MoreRes:No	Resubmit:n/a	N/A
150	3,299	Submit	Accept	PAS:n/a	N/A	MoreRes:No	Resubmit:n/a	N/A

8.3.2.3 Sensitivity analyses around decision times

The base case assumed that the STA process with or without a PAS takes 11 months. The STA guide states that an average assessment is expected to last 34 weeks, while if the manufacturer agrees a PAS with the DoH within 16 weeks of the publication of the original guidance, a rapid review facility is available and is scheduled within 6 months. (National Institute for Health and Clinical Excellence October 2009) The 34 week length for the STA with again 0 length for the PAS (assuming the PAS will be agreed during the original assessment as was observed in most real life assessments), as well as the 34 week length for the STA plus an additional 6 months for the PAS were tested. The base case 11 month STA length was also paired with an additional 6 months for the PAS. Finally, very long processes were also tested, assuming a whole year for the STA plus an additional full year for the PAS as shown in Table 8-9.

Table 8-9 Impact of appraisal lengths

STA length (months)	PAS length (months)	E[QALY]	E[NB]	E[Profits]
7.84	0	246,089	3,320,361,289	64,836,178
7.84	6	246,451	3,323,324,076	62,188,170
11	6	245,382	3,312,280,213	59,848,233
12	12	242,094	3,258,451,114	57,107,512

Longer appraisal process times were generally associated with lower payoffs throughout, but none of the combinations tried changed the optimal solution.

8.3.2.4 The monetary and time cost of further research

Both the length and cost of further research depend on the type of research needed. Undertaking some types of observational studies may be shorter compared to randomised clinical trials. There is also great uncertainty around how much of a clinical trial's cost can be attributed to a single setting. Therefore wide ranges were tested in these analyses, pairing shorter and longer research times with a large range of costs. However, given the magnitude of profits to be made from the sales of DES, the burden of further research only becomes prohibitive if research takes longer than two years to conduct and costs more than £20 million (see Table 8-10). In these cases further research will not be undertaken, and it becomes optimal for NICE to accept DES at the first assessment.

Note that the change in optimal solution when the burden of research is very high is actually beneficial for the manufacturer. If the decision maker believes that the burden of research will prohibit carrying out further research, DES will be accepted, resulting in earlier sales as well as 'saving' the cost of research for the manufacturer.

Table 8-10 Impact of changing research time and monetary burden

Research length (months)	Research cost (£ million)	Decision 1	Decision 2	Decision 3	Decision 4	Decision 5	Decision 6	Decision 7	Strategy QALY	Strategy NBs	Strategy Profits
12	£0.5	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept	244,595	3,334,894,715	33,115,062
12	£10	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept	244,580	3,325,608,709	24,107,076
12	£20	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept	245,274	3,330,400,408	13,728,960
18	£0.5	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept	246,292	3,353,820,531	27,175,390
18	£10	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept	244,119	3,325,771,986	18,040,876
18	£20	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept	244,070	3,340,922,666	7,559,124
24	£0.5	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept	246,411	3,354,370,044	22,320,099
24	£10	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept	245,026	3,347,972,944	13,338,964
24	£20	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept	247,121	3,375,766,685	3,013,728
30	£0.5	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept	245,985	3,356,296,932	16,365,230
30	£10	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept	244,912	3,339,256,199	6,301,626
30	£20	Submit	1Reject	PAS:Yes	2Accept	MoreRes:No	Resubmit:n/a	3N/A	247,483	3,364,939,149	52,831,788
36	£0.5	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept	244,433	3,330,136,453	10,702,318
36	£10	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept	246,967	3,388,780,002	1,091,319
36	£20	Submit	1Reject	PAS:Yes	2Accept	MoreRes:No	Resubmit:n/a	3N/A	243,597	3,300,099,636	52,563,229

8.3.2.5 The magnitude of effective price reduction offered in a PAS

The effective price of the new technology is one of the most important factors determining the economic value of the new technology. Traditional analyses would judge DES to be cost-effective if its price was reduced by 10%. If the price is reduced by 20% or more, DES start to dominate BMS. However, the sensitivity analyses showed that the solution to the game remained to reject the offered PAS to ensure that further research is carried out, until the manufacturer offered an effective price reduction of at least 60%, as reported in Table 8-11 . At a 60% effective price reduction, the benefits achievable with more knowledge are surpassed by the gains achievable with the lower price, therefore it becomes optimal for the decision maker to accept the new technology with a PAS. Note that it is still worth it for the manufacturer to offer a PAS with a 60% effective price reduction. At price reductions of 70% or higher, the manufacturer will no longer consider offering a PAS a viable option. The optimal strategy for the manufacturer then becomes to keep to the original price, carry out further research to prove the economic value of DES and then resubmit for a new assessment.

Table 8-11 Impact of changes in the effective price reduction

PAS price reduction	E[QALY]	E[NBs]	E[Profits]	Decision 1	Decision 2	Decision 3	Decision 4	Decision 5	Decision 6	Decision 7
5%	246,894	3,339,177,891	61,104,430	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept
10%	248,485	3,373,180,108	60,486,000	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept
15%	245,566	3,314,592,115	62,022,473	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept
25%	245,345	3,315,851,455	59,367,161	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept
30%	245,773	3,324,937,030	60,117,517	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept
35%	244,163	3,294,677,706	57,417,601	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept
40%	242,568	3,265,550,949	55,264,928	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept
45%	247,510	3,353,181,550	56,503,404	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept
50%	245,341	3,318,489,362	55,133,876	Submit	1Reject	PAS:Yes	2Reject	MoreRes:Yes	Resubmit:Yes	3Accept
60%	244,805	3,326,410,672	52,397,134	Submit	1Reject	PAS:Yes	2Accept	MoreRes:No	Resubmit:n/a	3N/A
70%	245,362	3,328,427,248	52,287,257	Submit	1Reject	PAS:No	2N/A	MoreRes:Yes	Resubmit:Yes	3Accept
80%	244,483	3,296,766,575	53,386,039	Submit	1Reject	PAS:No	2N/A	MoreRes:Yes	Resubmit:Yes	3Accept
90%	246,758	3,339,372,722	53,267,072	Submit	1Reject	PAS:No	2N/A	MoreRes:Yes	Resubmit:Yes	3Accept

8.3.2.6 Testing the assumption around uncertainty of acceptance

As a form of structural uncertainty testing, tests were also undertaken around the belief in the uncertainty of acceptance.

The first set of analyses removed the uncertainty around the decision maker's choices altogether. It assumed acceptance and rejection to be certain under and above the £20,000/QALY threshold, respectively. As shown in Figure 8-6, the solution changed. If the decision maker's choices can be predicted with certainty, the manufacturer will be better off by no longer submitting for review in 2005. Waiting until the results of further research is available became the optimal strategy for the manufacturer.

A second set of analyses recalculated the game payoffs with a new threshold. Dakin and colleagues found that the probability of acceptance becomes higher than 50% if the ICER falls below £43,949/QALY, and this implied threshold was used to calculate the population level net benefits.(Dakin et al. 2013) More than doubling the threshold (from £20,000 to £43,949/QALY) meant that traditional analyses would find DES to be acceptable even at the time of the first assessment. However, the uncertainty around the ICER remains, and even at the higher threshold there is a 34% probability that in fact BMS are the better choice of treatment. Further research is still worthwhile with the population level EVPI being £16.7 million. Therefore the game solution also remained the same as in the base case (see Figure 8-7). The decision maker should still reject DES even with a PAS to ensure that further research is carried out.

Figure 8-6 Game solution with uncertainty around acceptance removed

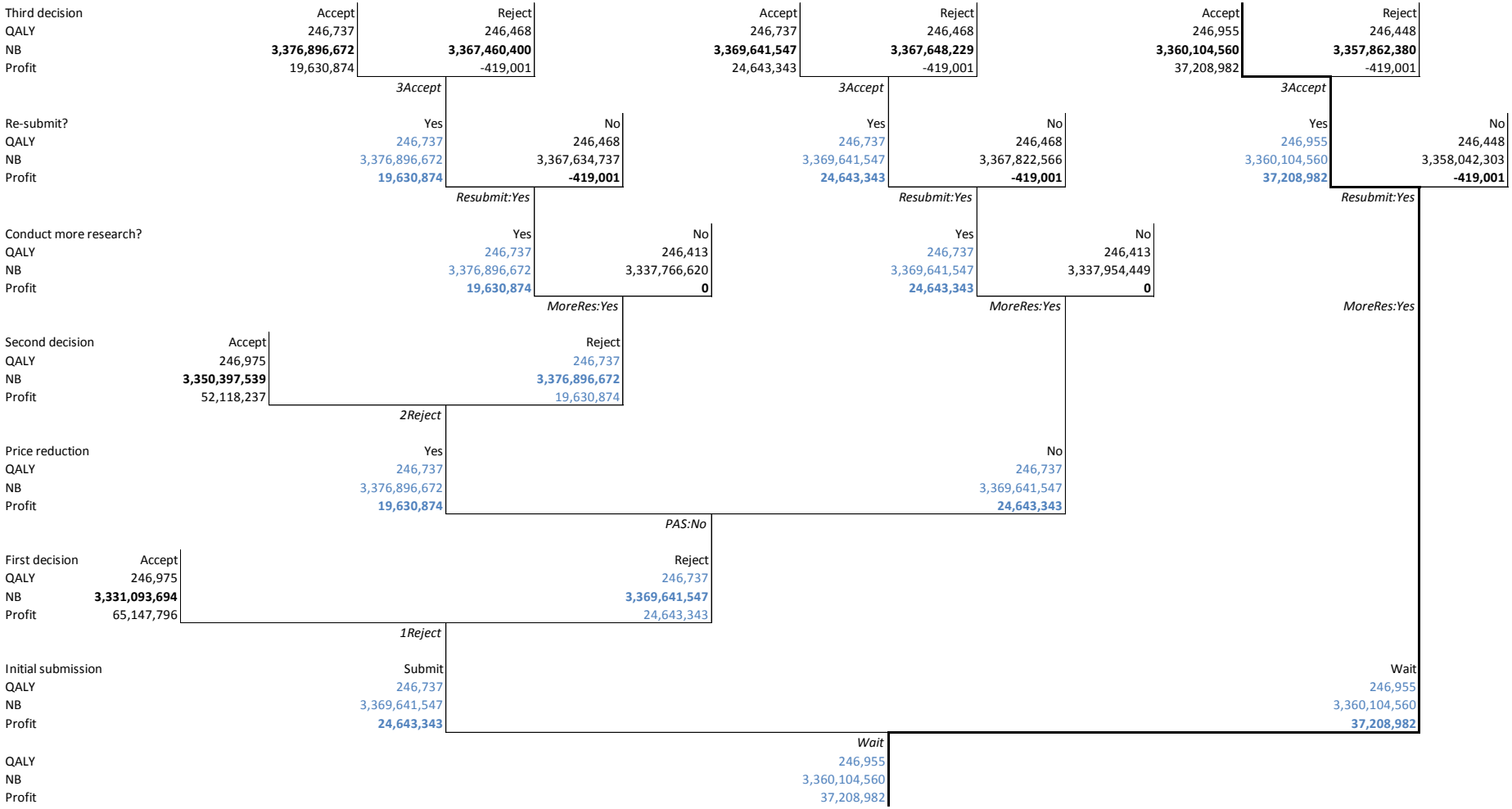
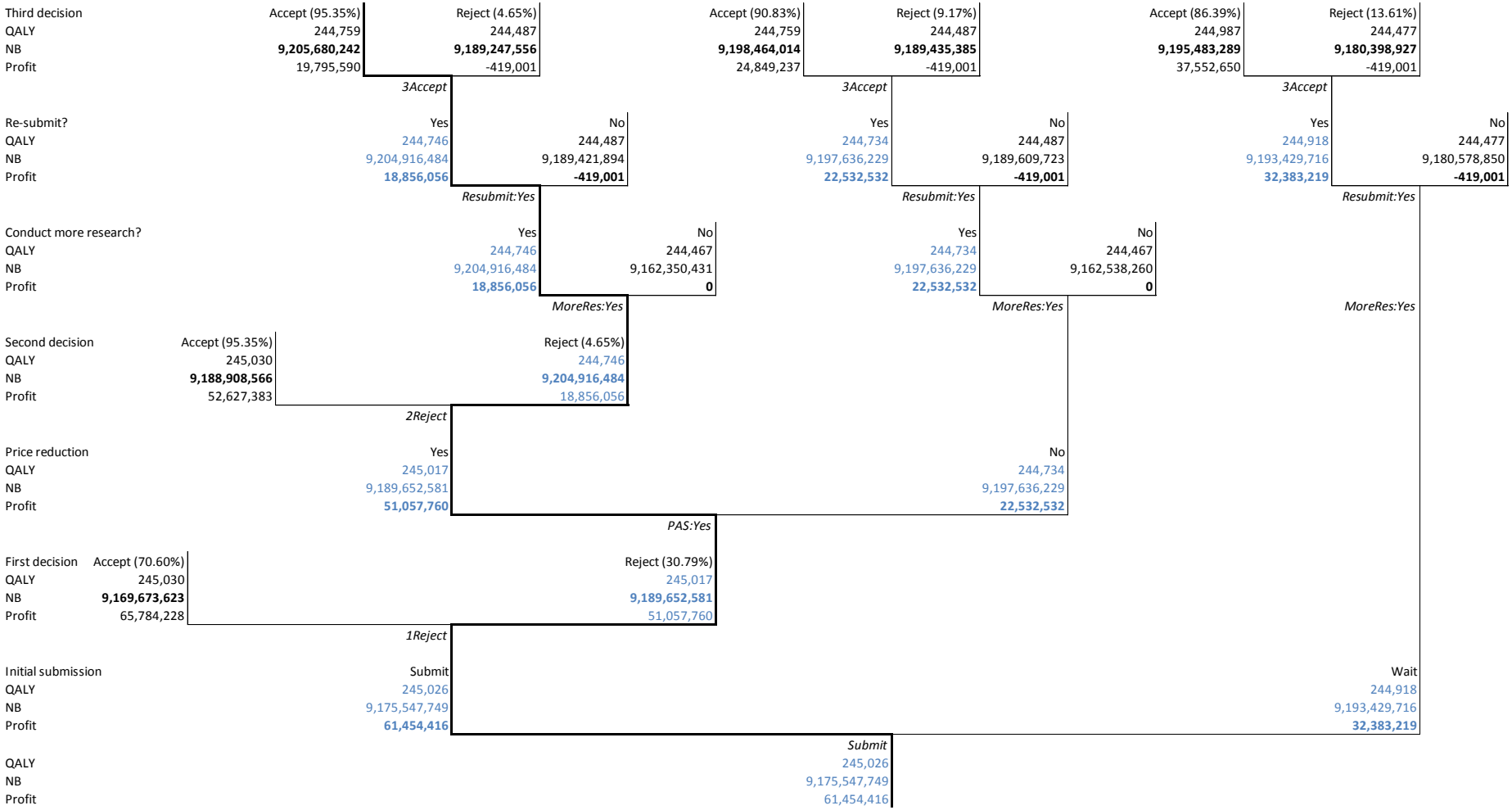


Figure 8-7 Game solution with higher threshold and with uncertainty around acceptance



8.3.3 The expected value of complete information

If all uncertainty was removed and the players had complete information about the value of the new technology and how it is going to change in the future, the situation would be easier. Accepting straight away, or after a PAS would be optimal in the majority of cases. The expected payoffs would also be much higher, since everyone would always make the right decision: with certainty, the expected NB was £3,850.7 million and manufacturer profits £60.4 million. I propose that in parallel to EVPI calculations in traditional analyses, the difference between expectation of the complete information results and the incomplete information results based on expectations of pay-offs may be thought of as the expected value of complete information, which was £513 million in this case study. This value exceeds the EVPI in the traditional analyses due to the value in resolving the added layer of dynamic uncertainty associated with predicting future changes in value.

Table 8-12 Chance of strategy being optimal with complete information

Strategies*	A **Initial acceptance**	B **Accept with PAS**	G **Reject, no PAS, accept after research**	J **Reject, no PAS, no research**	K **Wait for research**
Probability optimal	65.06%	34.26%	0.02%	0.36%	0.28%

* Other strategies were never optimal

8.4 Discussion

I noted in the previous chapter that the simple approach to application of real options analysis to health care is limited, because it does not take into account that in HTA information arrival is endogenous. This chapter therefore presented an extension to real options analysis incorporating the impact of the original decision on later decisions by combining real options analysis with game theory.

The real option game depicted here included two players, the manufacturer of the new technology and the decision maker. The game was envisaged as a sequential game, where each player was able to observe the previous moves. However, at the same time it was also an incomplete information game, where neither player knew the true value of the technology under evaluation, only the distribution of the INB of the new technology compared to the old one. The manufacturer had control over when to submit for appraisal and whether to offer a PAS. Most importantly, the manufacturer also decided whether to conduct further research, i.e. it had control over the arrival of new information.

Explicitly acknowledging in the model the impact of earlier decisions on information arrival resulted in decisions that seem to contradict traditional wisdom. My case study suggested that in the case of DES versus BMS, the optimal path would have been to reject DES at both the first assessment as well as after a PAS has been offered, even though the traditional analysis would recommend accepting DES with a PAS. This is because acceptance would cut off any new information, so in this case the decision maker should 'hold out' to ensure that further research is carried out to reduce the uncertainty around the cost-effectiveness of DES.

This is surprisingly close to what had actually happened in the production of TA152, where the final positive determination was published in July 2008, and the time delay enabled the manufacturer of the Endeavor stent to present the 2-year results of the ENDEAVOR II trial instead of the preliminary 9-month outcomes submitted in 2005.(National Institute for Health and Clinical Excellence July 2008) At the time PAS were not common, and it was NICE who requested that the price of DES should not exceed the price of BMS by more than £300.

The game theory extension required further assumptions to be made. These assumptions simplify the model and calculations, but do introduce some limitations to the realism of the ROG analysis. Most of these simplifying assumptions could be lifted, resulting in a more complex model. The impact of dropping these assumptions will be discussed in more detail in the next chapter.

The real option game in this chapter assumed a symmetry of knowledge between the players. Both players were assumed to use the best available evidence at the time, and to reach the same conclusions about the distribution of the INB of the new technology as well as the stochastic processes driving the change in the value of the technology in the future. Naturally in real life the players may have very different ideas about these factors. The manufacturer may have access to evidence that is not disclosed to the decision maker or the two players may decide to base their estimates on different sources. Even if both players work from the same pool of evidence, their interpretation of the data may be different, resulting in different model structures and results. These issues have been side stepped in the current analyses, but it is possible to modify the game to take into account differing information sets between players.

The formulation of the game itself imposes a structure on the decision problem that may not be correct. The case study was based on the processes of NICE's STA, and naturally, the game structure itself would probably need to be adapted to include other types of decision makers

and other assessment processes. But even within the current framework, other formulations are possible.

The current case study included a number of simple yes and no decisions to undertake a predetermined action. For example, the manufacturer was assumed to determine whether to offer a 20% reduction in the effective price or to conduct a research program that would take a fixed amount of time for a fixed cost. These simple binary decisions may be replaced with multi-choice decisions, looking at a range of possible actions and using the game itself to identify the optimal design for the planned action. The analysis may optimise the magnitude of effective price reduction to be offered in the PAS. Similarly, the question of what type of research in terms of length and cost could be determined within the game.

The real option game also requires estimation of further parameters that are currently not routinely measured. Estimating the costs of carrying out more research proved especially difficult. Our modelling framework assumed a single setting and only two players. This may be correct for the decision maker, but manufacturers operate on a global level. The results of most clinical research will be applicable in a large number of countries, and decisions about investing in new research are made on a global level too. Therefore the cost of further research is highly uncertain. I conducted extensive sensitivity analysis around this parameter, but the uncertainty could also be incorporated into the game itself making the cost of research a stochastic parameter. Furthermore, the impact of offering a PAS was also limited to the chosen single setting, whereas in real life it would set a precedent and as a result effective price could be reduced in other settings too.

The same argument holds for the variables predicting decision times in the model. The length of time required to undertake an assessment, the length of time required to agree a PAS with the DoH and have the technology reassessed, as well as the length of time it takes to carry out further research are all uncertain. The product's lifetime is also not known with certainty at the time when these real option game analyses would be carried out. Therefore future extensions of the game should incorporate this additional uncertainty and make all time-related variables stochastic too, which would not be difficult.

One of the limitations of the approach relates to the way NICE's decisions are modelled. As noted earlier, the £20,000/QALY threshold used to estimate the net benefit pay-offs for the decision maker does not seem to correspond to the tipping point for the probability of acceptance. NICE itself says that it does not make its recommendations based on economic arguments alone,(Rawlins and Culyer 2004) and its behaviour is at odds with the fundamental

assumption that NICE maximises population level net benefits calculated at a fixed threshold. The decisions are made assuming the players will want to maximise their expected pay-off of interest (a simple choice between the options), while the expected pay-offs are calculated as if NICE was playing mixed strategies at all of its decision points. A mixed strategy consists of possible moves and a probability distribution (a collection of weights) which corresponds to how frequently each move is to be played.(Shor 2005) There are many differing explanations why players might use mixed strategies.(Rubinstein 1991) The one that seems to be closest to the case of decision makers in HTA is the explanation provided by Harsanyi.(Harsanyi 1973) According to his theory of purification, mixed strategies merely reflect our lack of knowledge of the players' information and decision-making processes. In our case we know there are other factors besides cost-effectiveness that are taken into account. However, as opposed to usual games, where the probability distribution for the optimal mixed strategy is determined by the game, in the case of HTA these weights are determined outside the game and are driven by society's value judgements (or the Committee's judgements on that day). NICE also has an incentive not to fully reveal its objective function and its threshold as it retains bargaining power and keeps manufacturers from pricing everything "at the threshold".

Furthermore, the estimation of the probability of acceptance is based only on the ICER of technologies that are more costly and more effective than their comparators. These predictions cannot say anything about technologies in other quadrants of the cost-effectiveness plane. The probability of acceptance estimated based on the INB of all evaluated technologies may give a more useful estimate for the purposes of these type of analyses, but this was beyond the scope of this thesis.

The aim of the case study was to test the feasibility of using real options analysis in HTA. The analyses presented here show that although some methodological issues still need to be agreed upon, it is possible to carry out these analyses and that they provide more insight into the decision making processes during the adoption of new technologies compared to traditional economic evaluations.

9 Discussion

The aim of this thesis was to explore the feasibility of using ROA in HTA to explicitly incorporate the impact of uncertainty on decision making about new health technologies in the presence of irreversibilities. The previous chapters compared economic evaluation methods that dealt with uncertainty differently and showed what questions could be answered with the use of ROA that are currently left to the implicit consideration of decision makers.

The three economic evaluation methods compared were the following:

- A traditional economic evaluation which quantified the cost-effectiveness of the technology under evaluation assuming a single decision point in the present, assessed decision uncertainty and carried out value of information calculations, accounting for static uncertainty over input parameters ;
- A "simple" ROA incorporating future decision points and additional uncertainty relating to expectations over future changes in value, but with the simplifying assumption that information arrival is independent of the initial decision about adoption; and a
- A real option game combining elements of ROA with game theory in which decisions also took into consideration how other players might react and internalising information arrival.

The application of ROA allowed better description of the dynamic nature of the decision process with flexibility in decisions as well as incorporating all economic consequences of changing decisions. This evaluation method uncovers the value of waiting for more information and can also provide information about the optimal timing for review. Furthermore, combining ROA with a game theoretical approach allowed me to connect the decisions about adoption and further research providing the new information about the technology in the future, even if the decisions about these questions are made by different actors; while at the same time keeping the advantages of ROA in evaluating the adoption decision in a dynamic environment.

9.1 Findings from the case study

The three approaches to economic evaluation were illustrated with a case study based on the historical experience with the assessment of drug eluting stents (DES) for the treatment of coronary artery disease. In England, the assessment of DES by NICE started in 2005 with negative recommendations. The traditional analysis presented in Chapter 6 confirmed this initial decision based on the evidence that was available in 2005. The economic model used to calculate the treatment costs and health benefits for patients receiving DES rather than bare metal stents (BMS) showed the ICER of DES versus BMS to be above £30,000 per QALY gained. Adoption of DES could not be considered a cost-effective use of NHS resources at that time according to the usual standards applied by NICE. However, the probabilistic model evaluation enabled the quantification of parameter uncertainty, revealing considerable uncertainty over whether DES could or could not be considered cost-effective. The EVPI and EVPPI calculations showed that future research was warranted, especially around the main cost and resource use parameters.

Since, once implanted, the stents cannot easily be removed or replaced, there is irreversibility present on the patient level. This irreversibility paired with the uncertainty around its economic value made DES a relatively good candidate for ROA. In other situations, the irreversible costs of implementing a new technology may be greater, as they were, for example, for the implementation of liquid based cytology for cervical cancer screening. In these cases explicitly considering option value may be even more important. The first set of RO analyses (in Chapter 7) were performed from the payer's perspective only, with the simplifying assumption that new information about DES would be revealed continuously and independently of the original decision about its adoption. ROA requires a description of how value of the new technology is expected to change in the future. But in the case of new health technologies there is no historical data that would enable prediction of this change in value. I proposed that possible changes in the components of net benefit could be predicted with less uncertainty. Therefore the model included a prediction of change in the components that generate value in health care (i.e. in the evolution of prices and in the evidence base underlying estimates of effectiveness of the compared treatments) rather than trying to model change in value directly. By modelling change in the components of value, it became possible to empirically predict the process that net benefit would follow over time. The simple ROA application helped determine the optimal first decision and, as a novelty, the optimal time to review the first decision, by balancing the costs of undertaking the reviews and the likelihood and consequences of having to change the original decision. The case study showed that given

the high levels of uncertainty surrounding the value of DES and the relatively small estimated cost to conduct reviews and to change decisions compared to the gains achievable in a large population, the optimal solution would have been to reject the use of DES in 2005, but review the evidence annually. The sensitivity analyses showed that the optimal time between reviews initially increased as the cost of reviews and decision changes increased. However, if reassessment and decision changes are very costly, it becomes more efficient to simply make a decision based on the expectation of future effectiveness without further reviews even if the new technology was not shown to be cost-effective at the time of the analysis. The size of the population to be treated over the lifetime of the new technology was also shown to be important, since it influences the magnitude of net benefits to be gained by changing decisions. With a fixed INB per patient, more benefit can be gained by changing decisions that turn out to be wrong in light of new evidence with larger populations. Recommended review time increased to two years if the population fell below about 15,000 patients per year. With fewer than 3,000 patients per year conducting further reviews are simply not worthwhile any more. However, in contrast to what a traditional analysis would suggest (i.e. rejecting DES), the optimal strategy was to accept DES based on the expectation of change in its cost-effectiveness.

To make the analyses more applicable to HTA, it was necessary to lift the assumption about new information arriving exogenously. Adoption decisions have a clear impact on the incentives to perform further research. However, if the actor deciding whether to adopt the new technology is different from the actor deciding whether to conduct more research, then the ROA method has to be extended. Pairing ROA with game theory allowed me to make information arrival endogenous in the evaluation. The real option game depicted in Chapter 8 included two players, the manufacturer of the new technology and the payer making decisions about adoption of the new technology. The game was envisaged as a sequential game. Games in HTA will always be incomplete information games, neither player knowing the true value of the technology under evaluation. The manufacturer had control over when to submit for appraisal and whether to offer a PAS. Most importantly, the manufacturer also decided whether to conduct further research, i.e. it had control over the arrival of new information. The payer decided whether or not to adopt the technology at three different points in the game. This incomplete information game was turned into an imperfect information game assuming that both players' belief systems corresponded to the same distribution of the INB of DES compared to BMS and a common set of stochastic processes driving the change of INB over time. The game was then solved using the concept of sequential equilibrium.

Explicitly acknowledging the impact of earlier decisions on information arrival in the model recommended decisions that seemed to contradict traditional wisdom. The case study suggested that in the case of DES versus BMS, the optimal path of action would have been to reject DES at both the first assessment as well as after a PAS has been offered even though traditional analyses would recommend accepting DES with a PAS. Acceptance would have meant that the manufacturer no longer had any incentive to carry out further research and provide new information about DES. The real option game suggested that DES should have been rejected even with the 20% effective price reduction offered in the PAS to ensure that further research were carried out to reduce the uncertainty around the cost-effectiveness of DES. According to the ROG the manufacturer should have carried out more research and DES (with a PAS) was predicted to be accepted in 2008 based on the expected results of this new research.

Similarly to the simple ROA, the size of the population to be treated over the lifetime of the new technology and the cost of reviews and changing the decisions has high impact on the results. In the ROG, compared to the simple ROA, the size of population is also important for the manufacturer, because it influences the magnitude of future sales and therefore profits. The smaller the population, the more expensive reviews and conducting research become relatively. If the population was less than about 3,000 patients treated per year, conducting further research is not worthwhile, because the costs of research cannot be recouped from future sales. Therefore, the decision maker would also be better off by accepting DES based on the expectation of changes in its cost-effectiveness. Similarly, one expects an earlier decision about the new technology and fewer reviews as the costs of assessments increases. The sensitivity analyses confirmed that with high costs (increasing the cost of a review to above £2 million and the cost of changing the decisions to above £200,000) accepting DES right at the start becomes the optimal solution. The length and cost of further research is dependent on the type of research needed. Given the large population size with coronary heart disease, and therefore the magnitude of profits to be made from the sales of DES, the burden of further research only became prohibitive if research were to take longer than two years to conduct and cost more than £20 million. However, this threshold would be lower for smaller patient populations. In these cases further research will not be undertaken, and it became optimal to accept DES at the first assessment. Interestingly, the change in optimal solution when the burden of research is very high is actually beneficial for the manufacturer. If the decision maker believes that the burden of research will prohibit carrying out further research, DES will be accepted, resulting in earlier sales as well as 'saving' the cost of research

for the manufacturer. The effective price of the new technology was also an important factor determining the economic value of the new technology and therefore the solution of the ROG. Traditional analyses would have judged DES to be cost-effective if its price was reduced by 10%. If the price is reduced by 20% or more, DES dominate BMS. However, the sensitivity analyses showed that the solution to the game remained to reject the offered PAS to ensure further research is carried out until the manufacturer offered an at least 60% effective price reduction. At a 60% effective price reduction level the benefits achievable with more knowledge are surpassed by the gains achievable with the lower price, therefore it becomes optimal for the decision maker to accept the new technology with a PAS. Only at price reduction levels of 70% or higher did offering a PAS become a non-optimal action for the manufacturer.

In the case of DES, the magnitude of the irreversible consequences of treatment is small and present only on the individual level. Furthermore, the size of the patient population is large, therefore the cost of reviews and decision changes are relatively small compared to the population level benefits achievable, and the costs of research can be balanced by future sales. NICE reached the same decisions (rejected the technology in 2005 and accepted it with a cap on price differential compared to BMS in 2008) based on repeated traditional analyses. However, as shown in the sensitivity analyses, thinking through the strategies from the start and analysing the possible actions of the other decision makers in the HTA process may lead to results that contradict recommendations based on traditional evaluations if the irreversible consequences of the implementation of the new technology or its assessment in terms of reviews and further research are larger compared to the achievable population level INB.

9.2 Strengths and novel contributions to the field

The thesis showed that although there is yet no consensus on some of the assumptions made and the value of inputs required, real options analyses can be carried out to aid health technology assessment. ROA can provide answers to some questions that are currently left to the implicit consideration of decision makers. The advantage of applying ROA techniques is in the development of an explicit structure to the long term consequences of actions stemming from a decision as well as providing a way to quantify the impact of assumptions. ROA seems to be in a similar situation now as modelling methods were about two decades ago when people needed convincing that a quantitative, explicit method is preferred to implicit considerations.

The approach to ROA in this thesis differs from previous works in the following three main areas:

- Modelling information arrival for separate components that contribute to the value of the new technology;
- Including not just uncertainty in the current estimate of the value of the technology (static uncertainty), but also trends in information over time (dynamic uncertainty);
- Explicitly modelling strategic interactions between actors and thereby internalising information arrival through the use of an incomplete information game.

The literature search summarised in Chapter 4 has identified applications of ROA relating to many differing aspects of health technology evaluation. Since investing in the development of a new health technology is the closest to traditional investment decisions in corporate finance, most studies identified concerned new health technologies from the perspective of the developing firm. ROA has been applied to HTA before in only seven studies in six publications. All identified studies focused on the timing of the adoption decisions in relationship to the body of evidence that is available and that is expected to be available in later time periods. However, only four of the seven studies included actual data.(Attema 2010, Grutters 2011, Favato 2013, Forster-Pertile 2013) The scarcity of studies may be explained by the difficulties in predicting future changes in value in health care. Eckermann and Willan through a series of publications suggest estimating the option value of delaying the adoption decision on a new health technology through expected value of information calculations: expected value of information from requested new research should exceed the expected opportunity costs.(Eckermann and Willan 2007; Eckermann and Willan 2008a; Eckermann and Willan 2008b; Willan 2008; Eckermann and Willan 2009; Eckermann, Karnon, and Willan 2010; Willan and Eckermann 2012a; Willan and Eckermann 2012b; Eckermann and Willan 2013) However, the framework's underlying assumption is that there exists a true INB that remains constant through time and therefore the suggested method incorporates only static uncertainty). Other methodological works on ROA in HTA suggested that the value should follow a predetermined stochastic process to describe dynamic uncertainty.(Palmer and Smith 2000; Driffield 2003) However, in the case of new health technologies there is no historical data that would enable estimation of the trend and/or volatility of change in value.

The current literature on ROA related to health technology development also provides very little guidance about how uncertainty and, more importantly, how expected future changes should be described. Only two studies were identified that compared different ROA methods

from the viewpoint of the developer of a new technology.(Kellogg and Charnes 2000; Willigers and Hansen 2008) Kellog and Charnes valued a new medical entity and compared results using a multi stage decision analytic method (MSDA, decision tree with multiple decision nodes) with a binomial lattice approach to describing change in value. They did not find significant differences between the risk characterisation methods. Technology specific assumptions about the main ROA parameters (e.g. time to launch, market size and probability of success) seemed to matter more than the method used to describe the evolution of uncertainty. On the other hand, when Willigers and Hansen compared valuing a new drug with MSDA, a binomial lattice and a specific mean-reverting stochastic process, they did find significant differences between risk characterisation methods. However, the difference in results between the methods could potentially be explained by differences in the scope of the options included in the methods. The authors did not examine the predictions of the more flexible methods if they were restricted only to the options depicted by the less flexible methods. The DES case study I presented in this thesis used a relatively simple Wiener process to describe evolution of components of value. There is yet no evidence on the impact of the risk characterisation method, nor any guidance on how to choose between them. The comparison of different risk characterisation methods is an important area for further research (details will be provided in section 9.5 below).

The application of ROA to the evaluation of health technologies may have been hindered by the uniqueness of new health technologies and therefore the lack of long term, historical data upon which to base expectations for future changes. By decomposing change in value to change in components in value, it became possible to draw the distribution around future value of the new technology empirically. This approach has been applied before in ROA studies valuing potential new pharmaceutical products,(Schwartz 2004; Willigers and Hansen 2008; Hoe and Diltz 2012) but, as far as I could ascertain, has not been applied in ROA studies in HTA.

The “simple” ROA has shown how uncertainty, the cost of carrying out reviews and changing decisions and the population size might affect the decision about adoption of the new technology. As a novelty I have also shown how the simple ROA can be used to determine the optimal time to review the original decision.

Willan and Eckermann were the first applying their approach from a dual perspective.(Willan and Eckermann 2012b) Their suggested value of information calculations may be carried out by both the payer and the company to determine the maximum price acceptable to the payer

and the minimum price acceptable to the company. However, in their framework both the payer and the company optimise only within their own jurisdiction to find the price boundaries within which price negotiations may take place.

Forster and Pertile also viewed adoption, treatment and research decisions as a single economic project.(Forster and Pertile 2013) They examined the full dynamic impact of delaying decisions on the adoption of new technologies until uncertainty is resolved. They presented analytical solutions for a two-period framework. However, their model assumed that all uncertainty is completely eliminated by the second period. In their model research will be carried out regardless of what decision has been made about the adoption.

To the best of my knowledge, all previous applications of ROA to HTA to date assumed that arrival of information on the health technology under evaluation in the future is independent from the initial decision to be made about its adoption. However, the assumption of independent information arrival does not hold. Furthermore, these decisions may not fall into the jurisdiction of the same decision maker. If there are separate decision makers deciding over these important aspects, then real option analysis needs to be extended to include their strategic interactions.

A game theory approach can account for interdependency between agents' decisions and the endogeneity of information arrival. The major methodological innovation of the thesis is the proposal to combine ROA with a game theoretical approach that allows us to connect the decisions about adoption and further research providing the new information about the technology in the future even if the decisions about these questions are made by different actors; while at the same time keeping the advantages of ROA in evaluating the adoption decision in a dynamic environment. The real option game approach kept the elements of flexibility in decisions in the light of new information, while at the same time allowing for the fact that these decisions have to be made in consideration of how the other players might react.

The standard real option game model concerns competing firms wanting to invest, where the value of the investment is treated as a state variable that follows a known process, the investment problem is studied in isolation as if it is the only asset on the firm's balance sheet (i.e., the game is played on a single project); and there are usually two players, that is two firms holding the option to invest.(Azevedo and Paxson 2014) The three studies that have been identified that apply a real options game all followed the standard approach focusing on the biotechnology industry, modelling the decisions of whether and when to ally with a

pharmaceutical company to develop a new product.(Fujiwara 2010; Nigro et al. 2013; Fujiwara 2014) The case study presented in Chapter 8 presents the first real option game in the context of HTA, modelling the strategic interaction between the payer and the manufacturer of the new technology.

As an additional novelty compared to standard real option games usually seen in the literature, the use of an incomplete information game was suggested here to represent uncertainty around the value of the new health technology at each time point. As there are certain similarities between ROA and value of information methods, the possibility of calculating the value of complete information (complete in the sense that it includes both the perfect information about the current value of the technology as interpreted in value of information analyses and perfect information on how that value will change in the future) was explored by looking at the difference between the incomplete information and the complete information real option game solutions.

9.3 Limitations

Several questions remain regarding both the estimation of some of the model parameters, the framework chosen for the case studies as well as the scope of the uncertainty to be included. These questions will be explored in more detail in the next sections, starting with the more specific questions regarding some of the parameters in the models presented in this thesis (in Section 9.3.1), then moving to the issues of how the set-up could be changed and the assumptions of the analyses lifted (in Section 9.3.2) and finishing with the limitations of the framework itself (in Section 9.3.3) as shown in Figure 9-1 and Table 9-1.

Figure 9-1 Scope of discussion

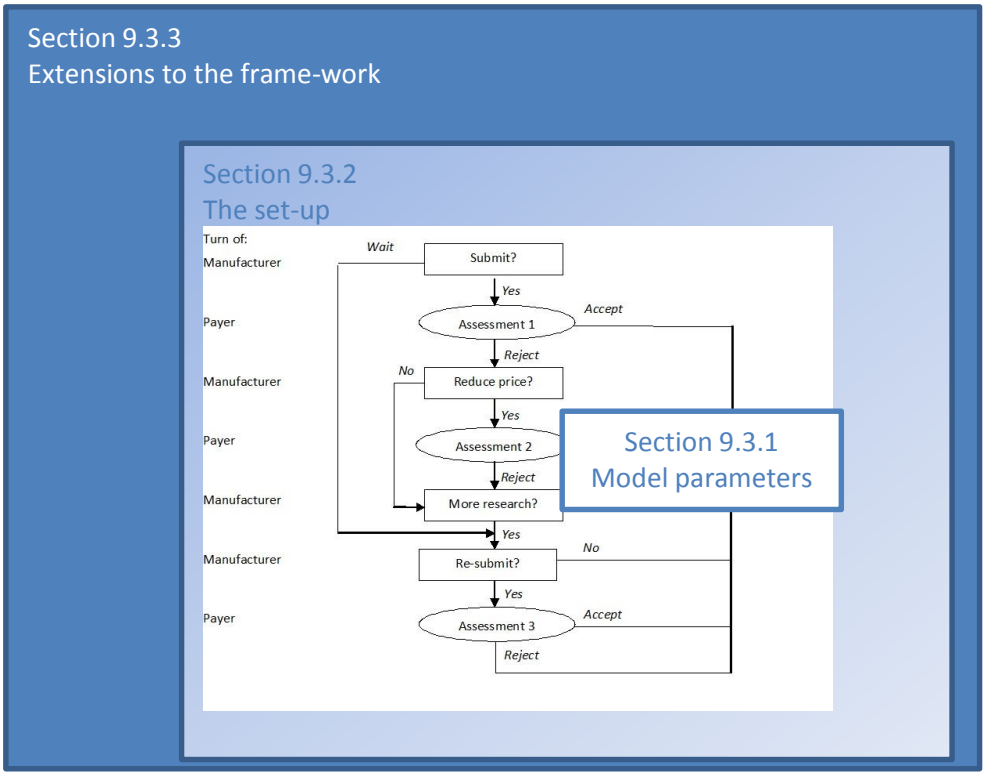


Table 9-1 List of limitations

Section 9.3.1 HTA specific model parameters
• The lifetime and uptake of the technology • Change in best estimate of effectiveness over time • Change in prices • Cost of reviews and changing decisions • Expectation of acceptance
Section 9.3.2 The set-up of the examples
• Modelling of future changes • Characterisation of information arrival • The type of payer • Additional actions for the players • Changing the threshold • Fixed belief system
Section 9.3.3 Extensions to the framework
• Scope of uncertainty • Multiple settings • Inclusion of competitors • Differentiating patients participating in research • Alternative objective functions • Differences in information • Attitudes toward risk • Taking into account payer reputation

9.3.1 HTA specific model parameters

If ROA is to be used routinely, economists will need to reach a consensus on some of the methods and parameters to predict future changes.

9.3.1.1 The lifetime and uptake of the technology

Similarly to population level value of information calculations, the lifespan of the technology (*T*) has been assumed to be constant in the examples used in this thesis. Furthermore, it was based on personal communication from the manufacturer of one of the DES rather than on any analysis of the lifetime of past medical devices.

It has been suggested by Philips and colleagues in the context of value of information calculations that it may be useful to consider the possibility of using empirically based estimates of *T*.(Philips, Claxton, and Palmer 2008) Their suggestion is valid in the case of ROA too, and not just about the lifespan of the technology, but also in relation to its predicted uptake. However, the speed of innovation may be different in different disease areas as well as across different health technologies. Empirical studies will be needed to estimate the lifetime and speed of uptake of different types of health technologies and across different patient groups (e.g. whether the lifecycle of medical devices is shorter or longer than the lifecycle of pharmaceuticals or whether the lifecycle of coronary artery stents is of different length compared to, say, hip replacements).

Philips and colleagues also pointed out that estimates of *T* are themselves uncertain.(Philips, Claxton, and Palmer 2008) Therefore the impact of variability in any estimates of *T* should ideally be quantified in the analyses too. Since variability in the lifetime of the technology is just an additional source of uncertainty, representing this uncertainty could be accomplished by including *T* among the stochastic variables in the model and drawing randomly from the pre-specified distribution for each iteration of the probabilistic analyses. For example, in the real option game it would be a part of nature's move to decide on the lifetime of the technology impacting both the expected population net benefits and profits (i.e. the payoffs of the game). In the simple ROA it would have structural implications too, since more or fewer updates to the guidance may be done within a longer or shorter technology lifespan, respectively.

Similary to *T*, other variables related to time could also be made stochastic. The duration of the different stages of the HTA process or the duration of further research were assumed to be constant in the examples, but in future analysis these can also be uncertain parameters.

The uptake of the new technology in the case studies was assumed to be an exogenous factor in the objective functions of the players. However, uptake is not necessarily exogenous, and arrival of new information in any ROA as well as some decisions in the ROG could have an impact on the uptake of the new technology. For example, new and positive information about the effectiveness of the new technology or simply the reduction of uncertainty around effectiveness due to the additional information from a new piece of research and/or offering or changing the effective price reduction in the PAS may speed up uptake of the new technology. Future extensions of the approach can incorporate an explicit relationship between decisions and uptake.

9.3.1.2 Furthermore, by incorporating uptake into the objective functions, and allowing it not to reach 100% in the case studies, the analyses assume an imperfect implementation of the recommendation about the use of the new technology. This approach potentially keeps the value of implementation constant while at the same time limiting the value of perfect information rather than allowing an optimal allocation of resources between further research and better implementation.(Fenwick, Claxton, and Sculpher 2008; Andronis and Barton 13 Nov 2015) One could argue that uptake should not be included in the objective function of the payer, the question should be simply if the new treatment should replace the old treatment for all eligible patients. Then resources should be allocated optimally towards further research versus implementation to ensure that the recommendations are followed through. However, as I argued in Chapter 2, in the presence of irreversibilities, the true value of the new technology and the option value of delay to wait for more information cannot be determined without knowing the size of the patient populations using the new and the old technologies at any given point throughout the lifetime of the new technology. Furthermore, the objective function of the manufacturer (maximising profits) is also directly linked to the uptake. In real life variability in patient preferences also necessitates the allowance for less than perfect implementation. Therefore, I believe uptake should be included in the objective functions, although this masks differences between value of information and value of implementation in ROA. Change in the best estimate of effectiveness over time

There are different ways to characterise future uncertainty about effectiveness. There is currently very little evidence to determine the right assumption about the existence of a trend

in the mean estimates of effect. The case studies here assumed there would be an evolution of knowledge, and the mean (the best) estimate of effectiveness would follow a stochastic process. I carried out a cumulative meta-analysis, adding in studies as and when they were published and therefore continuously updating the best estimate of effectiveness. Analysis of trends from the studies that were published prior to the time of the original assessment (in 2005) suggested different trends for DES and BMS.

The small negative coefficient for the trend variable of the BMS TVR suggests a slightly improved efficacy for BMS over time. Better results over time can be explained by a learning effect. Manufacturers may recognise the patient subgroups for whom their technology works best and focus the trials on these patients. In this interpretation the improved efficacy is only artificial. However, there may be true learning effects, where manufacturers or the medical profession learns about the particular characteristics of the new technology and truly increase efficacy by better use of the technology (e.g. by developing more skill in surgical techniques, or fine tuning medication dosages).

The RRR of DES also had a negative trend coefficient. This negative variable however means decreased effectiveness for DES compared to BMS over time. This could partly be explained by the improved effectiveness of BMS over time. In fact, the estimated effectiveness of DES themselves worsened over time with the first trial (RAVEL in June 2002) to report a TVR of 0.83%, but the best estimate of DES TVR increased to almost 8% by 2005 with the additional information from further five trials. The limited evidence on trends in effectiveness over time available today seems to confirm the existence of this negative trend.(Ioannidis 2005; Gehr, Weiss, and Porzsolt 2006) This finding may be explained by publication bias, with the dissemination of very positive trials being expedited by the manufacturers, while they may be more reluctant to publish not so positive results. Changes in patient populations within trials over time could also be a cause. Rather than selecting the best subgroups (as in the logic used to explain improved effectiveness), technologies that clearly work in specific subgroups may be tried in a more heterogeneous population. Neither of these explanations mean any real change in effectiveness over time, only the impact of selective reporting of follow-up trials or the impact of heterogeneity. The most appropriate way to describe future uncertainty and if there is a trend, and the direction of that trend in HTA are very exciting topics for future research.

9.3.1.3 Change in prices

The prices of the two stents were assumed to follow a similar trend to pharmaceuticals observed by Hoyle and colleagues, decreasing by a relatively small amount annually.(Hoyle 2008) Competition between drugs in the same therapeutic category may act to reduce prices over time. However, there is no evidence how the prices of medical devices behave over time, therefore using the above trend implied the very strong assumption that stent prices follow the same process as pharmaceutical prices over time. To test the impact of this assumption I repeated the analyses assuming that there was no change in stent prices over time, but this did not change the conclusions of any of the analyses.

Furthermore, the results of Hoyle seem to suggest a gradual decline in price, because in that study drug classes were pooled and examined together. In real life the price of a single product may remain constant until there are changes in the regulatory environment, or the appearance of a new product by the same company or a competitor. At the time when the patent is lost there may be another sudden drop in price. Evidence suggests that the average prices of pharmaceutical products in Europe falls by approximately 20% during the first year of loss of patent, and a further 5% over the next two years as a result of generic competition.(Costa-Font, McGuire, and Varol 2014) This suggests that changes in prices for individual drugs may be better modelled through the use of jump processes with expected negative jumps at the time of new product entry and loss of patent, but currently there is limited information about price changes of medical devices.

9.3.1.4 Cost of reviews and changing decisions

Since the switch from BMS to DES is a relatively easy one, with doctors only having to insert a different type of stent but all other procedures before, during and after the operation remaining the same, I have been very conservative in the calculation of the cost of reviews and changing the decisions, but varied these costs in the sensitivity analysis. For example the costs of the decision to change current practice only included the cost to disseminate the information by NICE. In other disease areas it may be necessary to retrain staff, assign dedicated staff or dedicated areas within the facilities to perform tasks associated with the new technology. The purchase or selling of specialist equipment may be also required to implement a new technology. In these cases all these costs should also be counted in the cost of changing decisions.

9.3.1.5 Expectation of acceptance

The expectation of acceptance in the real option game was calculated based on the study by Dakin and colleagues using an estimate that included only the ICER as an explanatory variable.(Dakin et al. 2013) The study included only those technologies that fall in the north-east quadrant of the cost-effectiveness plane, i.e. technologies that were both more costly and more effective than their comparators. Since DES could become dominant under some circumstances I had to make some (rather arbitrary) assumptions about the expectation of acceptance for dominant technologies.

Other studies examining the factors influencing NICE decisions could have been used to predict the probability of acceptance, or if the equations including further explanatory variables besides just the ICER from Dakin and colleagues were available, the model could have been expanded to take into account other factors influencing the acceptability of technologies such as the number of randomised controlled trials available evaluating the intervention, the number of patients in the reported trials, whether the new technology is the only treatment in a disease area, whether the patients are children, the type of appraisal, the type of the disease itself and uncertainty in the reported ICERs.(Devlin and Parkin 2004; Dakin, Devlin, and Odeyemi 2006; Jena and Philipson 2009; Mason and Drummond 2009; Dakin et al. 2013)

The regression equation assumed that the relationship between the ICER and the probability of acceptance is quasi linear. However, the linearity of this relationship is hard to accept, and a more complex lognormal or logarithmic relationship would comply better with our current understanding of the workings of NICE.(Rawlins and Culyer 2004)

As shown in the sensitivity analyses around expectation of acceptance in Chapter 8, other structural formulations are possible here as well. Players may also take the threshold for granted and assume that everything below a certain cost-effectiveness threshold will be accepted. Although this formulation would imply that the payer's decisions are based solely on cost-effectiveness. In real life we know that this is usually not the case and there are many other factors that decision makers take into account when considering acceptance of a new technology.

9.3.2 The set-up of the examples

The previous section discussed the limitations in the estimation of the new parameters required for the ROA in the presented case studies. However, the case studies themselves could have been presented in different formats too.

9.3.2.1 Modelling of future changes

Whether known or anticipated future changes in components of the value of the new technology should be modelled is relevant question even in situations where there is no flexibility in the decision making process, that is, it is relevant in evaluations not relying on ROA too. Only if there is absolutely no irreversibility, can ignoring future changes be appropriate. In these situation, if there will be a change in the value of the new technology, decisions can be changed at no additional cost. Therefore the current evaluation does not need to take the possibility of these changes into account. However, in all other cases when there is some irreversibility in the decisions the anticipated changes should be included to properly capture the economic value of the technology over the decision's time horizon.

Although future changes should be routinely included in economic models (see for example Hoyle recommending incorporating a decrease in future drug prices)(Hoyle 2008), these recommendations are usually ignored in everyday practice. As shown in Chapter 7 in the simple ROA analysis, if anticipated changes in the effectiveness of the stents and their prices are taken into account, accepting DES with no review yield higher population NBs than rejecting DES with no review. This means that if these were included in the traditional evaluation presented in Chapter 6, the conclusion of the analysis would have been to recommend DES. Furthermore, the ROG in Chapter 8 also assumed that parameters would not change after an "accept" decision. Although this assumption is correct for effectiveness parameters if no further research is undertaken, prices could still change over time. Therefore in future applications future price changes should be incorporated into the game even in situations where an accept decision was made at the first or second decision points.

9.3.2.2 Characterisation of information arrival

The most ambiguous aspects of the analyses presented here are the methods and parameters for predicting the arrival of new information. As shown in Chapter 4, the current literature on ROA related to health technologies provides very little guidance about how uncertainty and, more importantly, how expected future changes should be described. The use of stochastic processes is borrowed from financial economics. (Eckermann and Willan 2008b) These processes assume an immediate and continuous updating with new information which is at odds with how research is conducted and information is revealed in health care. The lumpy arrival of information may suggest the use of a different type of stochastic process, e.g. a mean-reverting process with possible Poisson jumps to depict the impact of a new trial reporting.

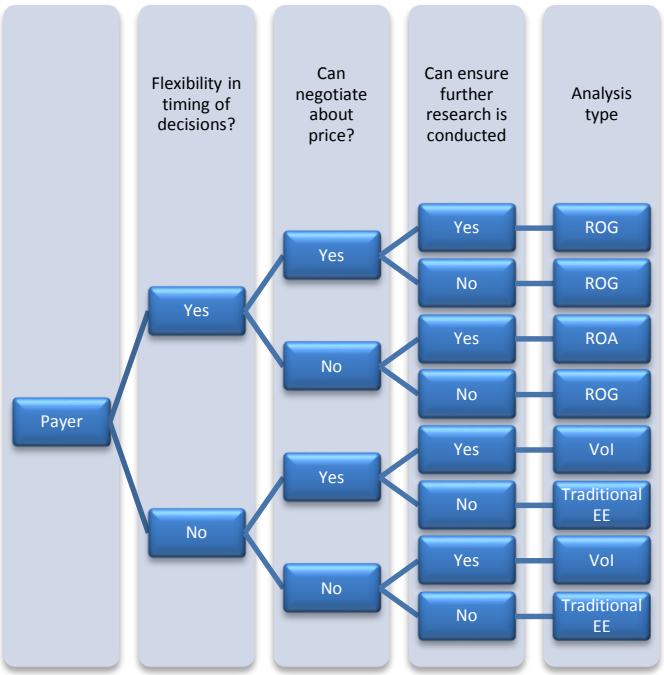
One could also assume that the information does not change, i.e. the distribution of the INB remains the same until the next study reports, then use Bayesian methods to calculate a posterior distribution incorporating the results of the new study.(Burman and Senn 2003) Taking this idea to the extreme, Pertile and colleagues recommended updating the economic evaluations after every single patient to determine the optimal time to stop carrying out research.(Pertile, Forster, and Torre 2014)

If no evolution of information is assumed, i.e. the current uncertainty represents future uncertainty too, expected value of sample information calculations could also be used to predict the impact of future studies.(Eckermann and Willan 2008b; McKenna and Claxton 2011). It is a question for future research to determine whether there is an evolution of the expected value of health technologies, therefore it remains to be determined what the most appropriate way to describe future uncertainty in HTA is.

9.3.2.3 A different type of payer

ROA will only be helpful for payers who have some flexibility over the timing of their decisions or who have the ability to review those decisions at a later date.(Palmer and Smith 2000) But Walker and colleagues categorised purchasers according to two additional dimensions: whether they can negotiate about price and whether they can ensure further research is conducted as shown in Figure 9-2.(Walker et al. 2012) I have assumed in the thesis that the payer cannot directly negotiate price and cannot ensure that further research is conducted. If the payer does have the remit to negotiate on price or conduct research, the set-up of the analyses will change. In these cases the payer's options would need to be extended with the actions of finding a mutually agreeable price and conducting more research.

Figure 9-2 Suggested methodology by type of payer in the presence of irreversibilities



Legend: ROG - real option game; ROA - real option analysis; VoI - value of information analysis; EE - economic evaluation

If the payer does not have direct influence on the price but can ensure research is conducted, the decision may be analysed using the "simple" ROA approach. The set-up of the ROA would then be similar to what has been described by Eckermann and Willan.(Eckermann and Willan 2008b) The payer's options would include all possible combinations of rejection/adoption and conducting/not conducting further research which could be simultaneously evaluated in the analyses. How to simultaneously evaluate the question about adoption and the need and design for further research is currently a topic of interest to many. Chalabi and colleagues suggested a two-stage stochastic mathematical programming approach to allocate resources between and within healthcare programmes.(Chalabi et al. 2008) Claxton and colleagues advocated that even results of standard meta analyses can directly inform the questions posed in research prioritisation and commissioning.(Claxton et al. 2013) To incorporate the dynamic nature of these decisions, Bayesian approaches have also been suggested to identify an optimal portfolio of research (Conti and Claxton 2009) or the optimal stopping rule for sampling.(Pertile, Forster, and Torre 2014) Bregantini developed a sequential approach to value of information calculations to minimise the costs of sampling.(Bregantini 2014) Any of these optimisation methods can theoretically be incorporated into a "simple" ROA, which would further extend these methods by modelling expectations over change in value.

On the other hand, negotiating about price is still a gaming situation. If there is a single novel health technology and a single payer, in effect there is a bilateral monopoly situation. The price of the new technology will be set in negotiations, but both actors (the payer and the manufacturer) need to consider the impact that different price levels may have on the incentives and decisions of the other decision maker. Therefore modelling a payer who can negotiate about price still requires a real option game approach.

9.3.2.4 Additional actions for the players

9.3.2.4.1 Inclusion of only in research, only with research options

The real option game limited the payer's actions to approving or rejecting the new technology. Many payers do have the chance to consider new technologies as part of evidence generation schemes.(Claxton et al. 2011b; Longworth et al. 2013) These options can be easily included into the analyses as separate actions available to the payer. If the scheme is implemented perfectly, the pay-offs can be calculated with all necessary data already included in the analyses, with the exception of the size of the patient population expected to participate in the research. Separating the patients participating in further research from the population currently included in the analyses will be discussed in more detail in section 9.3.3.4 below.

9.3.2.4.2 Different types of research

The game in the thesis included the question whether to conduct a fixed type of research with a fixed expected cost and a fixed timeline. However, the players (the manufacturer in this example, but the payer may also have the option to conduct research in other settings) may have different research options. Different types of research might also be used to inform different parameters. For example, a randomised controlled trial may be conducted to get a better estimate of the relative effectiveness, a cohort study to estimate the baseline risk, retrospective case note review or analysis of routine data for costs, or a patient survey for utilities. As a relatively simple extension one could experiment with different research lengths and sample sizes with the associated differences in the costs of conducting the research. However, currently new information about the technology is predicted through the use of stochastic processes which are assumed to be independent from the type and size of the research. If different types, lengths or sizes of research are to be included then the impact they have on the information and level of uncertainty around the value of the technology cannot be assumed to be the same. As a minimum one would need different jump processes to describe the evolution of parameters with the frequency or timing of the jumps linked to

the length of research and/or the magnitude of the jumps linked to the size of the research population.

As a more complex solution, optimising the type, size and length of future research could form a part of the evaluation process.(Conti and Claxton 2009) In reality, the research decision requires an examination of much wider dimensions over a range of possible combinations of different types of studies. Conti and Claxton performed such an optimisation by simultaneously estimating the expected net benefit of sampling across all dimensions of the design space including different study designs to identify the optimal sample sizes and allocations within such a research portfolio.(Conti and Claxton 2009) Pertile and colleagues and Bregantini both advocated updating the models to find the optimal sample size for the research.(Pertile, Forster, and Torre 2014; Bregantini 2014) However, such optimisation processes provide a huge computational and monitoring challenge, exponentially increasing the number of game branches with every research dimension added, and may not be feasible in the routine application of ROA.

9.3.2.4.3 Different types of PAS

The representation of a PAS was also quite simplistic in the case study. The decision whether to offer a fixed reduction in the effective price may be replaced by a multi-choice decision looking at a range of possible formulations for a PAS.

Similarly to the optimal research design, the analysis itself could be used to identify the optimal magnitude of effective price reduction to be offered in the PAS if the manufacturer was faced with a number of actions each offering a different level of effective price reduction instead of just the binary option to offer a 20% effective price reduction or not. There is also no a priori obstacle to including the actual formulation of the PAS into the structure of the model. The only restriction being that if the PAS is formulated on a patient level (e.g. it is conditional on treatment continuation or linked to an outcome) then the model structure has to be able to track either individual patients or at least patient groups falling into different PAS categories.(Walker et al. 2012) Also in parallel with optimising research types within the model, identification of the optimal PAS with the model may pose a computational challenge.

9.3.2.5 Changing the threshold

Claxton and colleagues point out that, over time, there may be changes to the value we attach to health (the consumption value of health) or the budget that is available to be spent on health care.(Claxton et al. 2011a) In my analyses the threshold was assumed to remain constant over time. Health benefits of DES were converted to monetary value in the NB

calculations using a £20,000/QALY threshold in 2005 as well as in 2010. In the evaluation of technologies with longer lifetimes, this assumption may not be acceptable. The threshold in the analysis should not remain constant if there is evidence that the monetary value of health gains will change over time, although research conducted to this day has not found significant temporal trends.(Dakin et al. 2013) This change could be implemented in the calculations by using the predicted (stochastic) threshold value in future years to calculate expected NBs, although establishing expectations over change in the threshold would be very challenging.

9.3.2.6 Actions influencing the belief systems

In the ROG example, players did not adjust their assessment of the probability of each action in Nature's initial move at any decision throughout the game. That is, the belief systems about nature's move were constant between information sets. Although the information set for the payer during the first assessment is different from the information set if the technology has been rejected but then resubmitted for a second assessment with a PAS, i.e. the payer knows that it was worth it for the manufacturer to resubmit with a PAS, this knowledge was assumed not to influence the payer's belief system about the original distribution of INB. Therefore pay-offs for all strategies were calculated using the complete distribution of the INB, regardless of what information could be deduced from the actions of the other player.

In real life, in the presence of information asymmetries the payer might truly take some of the manufacturer's decisions (e.g. whether to submit a PAS or resubmit after further research) as a signal for the true value of the technology. For example, strategies in which a PAS was not offered after an initial rejection were rarely optimal. Given the current distribution around the INB of DES and the expectations for future change, these strategies would only be optimal less than 1% of the time (as shown in Table 8-12 in Chapter 8 in the complete information case). In fact, not to offer a PAS would only be chosen with particularly unfavourable effectiveness predictions, when the population QALY gain and NB would be magnitudes smaller than on average. Therefore if the other player's actions indicate that he is playing one these more obscure strategies, the payer making the decision could adjust his belief about the distribution of INB depending on the perceived actions of the manufacturer.

9.3.3 Extensions to the framework

Over and above the set-up of the examples within the modelling framework described in Chapter 5, the framework itself could also be extended to cover a range of other, broader examples.

9.3.3.1 Scope of uncertainty to be included in ROA

As shown throughout the thesis, ROA is well suited to incorporate quantifiable uncertainty (risks, if we follow Knight's distinction).(Adner and Levinthal 2004) The case studies shown here incorporated parameter uncertainty only. However, there is no reason why other types of uncertainties could not be included in the analysis too.

There are often a number of credible structural assumptions that can be made to characterise the underlying natural disease process or the impact of treatment. This type of structural uncertainty could also be parameterised as suggested by Bojke and colleagues.(Bojke et al. 2006) If alternative model structures are thought of as special cases of a general meta-model, then the general model could be analysed including the additional uncertain parameters turning specific structural assumptions on or off.

Incorporation of heterogeneity, that is where differences between patients can be explained by differences in patient characteristics, depends on whether it is feasible and acceptable to make different recommendations according to the patient characteristics defining the patient subgroups. If separate recommendations are possible, the ROA should be performed separately for each identified patient subgroup, just like in the case of traditional economic evaluation methods. If for some reason (e.g. deemed unethical or impractical) separate recommendations are not possible, results from the subgroups should be pooled. In this case heterogeneity should still be modelled to properly characterise uncertainty, but there will be more noise around the estimates and an increase in decision uncertainty.

Any type of uncertainty that can be characterized in terms of means and variance of key parameters can be included in a ROA. It is possible to include catastrophic events by the use of jump processes that could, for example, immediately wipe out the value of the new technology if one could quantify the expected probability of such an event. Jumps in the opposite direction are also possible. As seen in some of the studies found in the literature,(Loch and Bode-Greuel 2001; Cook et al. 2011) one could include a growth option, for example to model the chance that the new technology which was developed for one indication may be shown to be successful in some yet unspecified other indication. Although we know of a few instances where such events have happened, to the best of my knowledge, the probability of these types of positive or negative events has not been quantified. Only the truly unknown, the Knightian uncertainty cannot be incorporated and analysed with ROA methods.

9.3.3.2 Multiple settings

In the case study, a single, well-defined patient population was considered. In real life, decision makers may need to optimise for multiple geographical locations (especially on the manufacturer's side) and multiple patient populations. From the payer's point of view, a decision in their jurisdiction might influence decision makers in other settings, and vice versa. To include these effects, the other settings/populations would either have to be modelled directly or the monetary value of the externalities quantified and included in the pay-offs of the single setting analysis.

9.3.3.2.1 Impact on manufacturer behaviour

The manufacturers of new health technologies operate on a global market. In a fully rational world their decisions would be optimised globally considering the research needs in a number of settings as well as the impact of setting price or PAS precedents in one setting that will influence the price expectations in other settings. In real life, price setting may be more heuristic than described above. Nonetheless, the influence of the price in one large market on other important markets is taken into account. The inclusion of the external effects in other settings would make the analyses more realistic.

9.3.3.2.2 Impact on number of payers

Health care systems differ widely, and therefore the number and level of actors involved in the decisions about adoption of new health technologies also differs substantially. If the framework is to be extended to multiple settings, one needs to determine whether interactions between payers exist. If there is no interaction, and each payer assesses the technology independently, then the analyses can be carried out separately for each setting. However, in many cases the settings are linked through mechanisms such as reference pricing. There is also the anecdotal effect of "reputation bias", e.g. if NICE approves a new technology, the probability of acceptance becomes much higher in other settings too. If these interactions could be quantified, the impact of change in one setting on other settings could be modelled directly.

To tackle the problems of global markets and the impact on other payers, the analysis could be extended by including a composite 'rest of the world' market and payer incorporating all external effects rather than having to model every country and payer separately.

9.3.3.2.3 Impact on strategies

Some of the strategies of the players were omitted from the case study analyses, because they would always be dominated in the single setting. If the impact of decisions on other settings

were to be included the analysis, then some strategies that were dominated may become viable options. Depending on the expectations on future value and, for example, the threshold used or the probability of acceptance in a different setting, it may become necessary for the manufacturer to consider conducting further research even after acceptance. If the expectation on future value is pessimistic, it can also be a viable strategy to not conduct more research after not submitting, in order not to jeopardise acceptance elsewhere with potentially bad news about the technology. Furthermore, if the new technology is already accepted in some settings and if the technology behaves in the same way as pharmaceuticals with its price gradually decreasing over time, and if prices in other settings influence the price in the analysed setting and the technology's lifetime is long enough to permit the wait, it may become a viable strategy to just wait until the price decreases enough to make the new technology cost-effective without the need for further evidence on its effectiveness.

9.3.3.3 Inclusion of competitors

It was assumed in the analyses in this thesis that there will be no similar technologies entering in the near future. The impact of other new technologies or competitors to the manufacturer was not included directly, although the impact of competitors was included indirectly by assuming less than 100% uptake.

This framework is realistic if the new technology is truly innovative, i.e. there are no other technologies on the market or in development that would provide a similar improvement in the quality of life of the patients. If, however, there are other technologies with a similar impact, the framework could be extended to include other manufacturer(s) as additional player(s). The relationships between the second manufacturer and the payer could be modelled in a similar fashion as the relationship between the single manufacturer and the payer in the game presented in the thesis. The relationship between the competing manufacturers resembles the situation described in standard real option games.(Azevedo and Paxson 2014) The standard real option game model concerns competing firms wanting to invest, the game is played on a single project, and there are usually two firms holding the option to invest. In the standard games the two firms are assumed to be identical. The two manufacturers could be assumed to play a "pre-emption game" (PE). Real option theory shows that when an investor has a monopoly over an uncertain investment decision, there is an option value to wait, to delay the investment. When competition is added to the investment problem, all else being equal, the value of the option to wait tends to erode. Pre-emption games assume an initial period where the first mover may reap monopolistic rents, giving an incentive to be the first to invest. The competitors may also be assumed to play a

"war-of-attrition game'' (WOA). In this type of games the second mover has the advantage by learning from and using the results of the first mover. Both types of competition games are usually formulated as non-zero-sum games. Typically the advantage of investing first/second is assumed to be limited, so the investment of the leader (PE) or the follower (WOA) does not completely eliminate the revenues of its rival. Further extensions to more than two players or asymmetries between the firms can also be incorporated. However, the addition of payers in different jurisdictions as well as additional manufacturers could make the gaming situation very complex.

9.3.3.4 Patients participating in research

I have assumed the treatable population to be independent from the population participating in further research. This is an acceptable assumption for large patient populations, where trials do not become too lengthy due to the lack patients available to participate, and the impact of treating patients in research situations is negligible on future sales. In the case of diseases with smaller incidence this assumption will not hold. Trials could be (and often are) delayed due to difficulties in recruiting patients. Conducting large trials could also significantly diminish the treatable patient population, later reducing the profits achievable. In these circumstances it will be necessary to track the numbers and the benefits of the patients participating in the research efforts, and also to calculate what impact participation in research has on the need for treatment later and therefore the numbers requiring treatment after approval and hence profits. This issue has been addressed in value of information calculations already.(McKenna and Claxton, 2011) By distinguishing patients enrolled in clinical trials from the rest of the patient population, it is possible to account for the full opportunity costs of conducting research, not just the direct costs of the research. As shown through the sensitivity analyses around population size, it is anticipated that with smaller patient populations the "costs" of further research (including profits lost due to reduced patient sales) will become prohibitive earlier.

9.3.3.5 Alternative objective functions

In the examples the payer was assumed to maximise the net monetary benefits for its population over the lifetime of the new technology. The manufacturer was assumed to maximise profits. It is possible to envisage other formulations for the objective functions too.

The manufacturer may just want to hit a sales target or achieve at least some minimum level of profit without necessarily maximising its value as described by the behavioural theory of the firm.(Cyert and March 1992; Argota and Greve 2007) The payer may also want to optimise

other outcomes, e.g. QALY gains or life expectancy or waiting times. Any objective function is feasible as long as its components can be calculated with the disease model.

9.3.3.6 Differences in information

For the purposes of these analyses I assumed that the payer and the manufacturer share a common knowledge set about the value of the new technology under evaluation and a common set of assumptions about how that value might change. The same model, with the same inputs and assumptions, was used for the evaluations undertaken from both the payer's and the manufacturer's perspective. The ROG case study assigned the first action to the manufacturer, the decision whether to submit for an assessment. Naturally, if the payer conducts the analysis, this first step should be omitted. The game from the payer's perspective only starts when they receive the first submission of evidence from the manufacturer.

As mentioned in 9.3.2.6 above, the payer (or its HTA body) and the manufacturer may have different understandings and interpretations of the available evidence, or one may have privileged access to some evidence. These differences in evidence base are clear with hindsight, but may be difficult to anticipate a priori. It is also a question of who performs the analysis. If it is one of the players, then the disease model and assumptions will naturally reflect the knowledge (and beliefs) of that particular player. Differences in the evidence base may still be incorporated if the conductor of the analysis wilfully withheld information from the other party. Even in the absence of informational asymmetry, there may be differences between the players about what evidence they feel is acceptable and what weight they place on different types of evidence. Differences may also be incorporated if the analysis is to be performed by a third party who would have access to the sources and evidence weights of both players. However, this set-up raises difficult questions of confidentiality and deliberate concealment of information. Although assuming that both players use the best available evidence is not an unrealistic assumption, there is some empirical evidence that cost-effectiveness estimates differ depending on who performs the analysis.(Miners et al. 2005; Chauhan, Miners, and Fischer 2007) Manufacturers tend to estimate lower average benefits for the comparator technology and lower costs relating to the technology under evaluation compared with estimates of the Assessment Groups in the UK.(Chauhan, Miners, and Fischer 2007) In future analysis one could introduce a difference in these estimates between the two players, either making payers pessimistic or the manufacturer optimistic.

The one place where agents' beliefs could diverge is around the probability of acceptance. If the analysis is performed by the payer, they more or less know whether a new health

technology with a certain ICER should be accepted. In a different type of analysis one could remove the uncertainty around acceptance from the payer's evaluations, but still keep the uncertainty around acceptance from the manufacturer's point of view. Similarly, the payer may be uncertain about the manufacturer's objective function if there were uncertain externalities in other markets or impact on sales of other products through reputational damage. In a two tiered analysis the payer could choose their actual threshold while the manufacturer could form their own expectations over what value the payer would use, and conversely, the manufacturer might know their own objective function in a given situation, but the payer might not know with certainty.

The symmetry in knowledge assumed in these analyses also implies that the payer takes into account the financial implications of carrying out more research on the decisions of the manufacturer. The sensitivity analyses showed that if the payer believes that the burden of research will prohibit carrying out further research, the new technology is more likely to be accepted earlier. This type of consideration is evident for example in the handling of orphan drugs. But it remains a question for future research whether decision makers are truly as rational as to fully take into account the motives and financial incentives of the manufacturer too. Also note that in a world of asymmetry in information about costs of research, it is financially highly rewarding for the manufacturer to exaggerate the burden of carrying out more research, to threaten to abandon the development of the new technology in the hope of earlier acceptance without the need for further evidence.

9.3.3.7 Attitudes toward risk

The case study assumed both players to rank options according to their expected values. More precisely, the players were assumed to be risk neutral and the same discount rates were used for both players. However, the manufacturer and the payer may have very different attitudes toward risk and how this risk should be represented in the analyses.

For the manufacturer, the development of a new health technology is a capital investment. The basic assumption in finance and therefore in all option pricing models is that in efficient financial markets the expected return of an investment has a clear relationship with its riskiness with investors demanding higher expected returns for riskier investments (Capital Asset Pricing Model).(Sharpe 1964) Therefore more uncertain outcomes in the future should be discounted at a higher, risk-adjusted rate. Therefore risk is incorporated into the discount rate and the resulting present values of projects with different levels of risks are directly comparable. Since real life research projects are highly specific, it is usually very difficult to

find a replicating asset or portfolio to estimate the risk-adjusted rate in ROA. Therefore risk needs to be incorporated more explicitly into the evaluation through the use of chance nodes and simulating the distributions of pay-offs as opposed to simply incorporating it into the discount rate. This way, future pay-offs may be discounted using the risk-free rate. However, risk-free in ROA does not mean the interest rate of government bonds as it would be in finance. The risk-free rate is where no risk premium is added for the specific project, and the discount rate should reflect the weighted average cost of capital if funds are plentiful or the average expected return on investments in R&D projects if funds are scarce for the manufacturer.(Loch and Bode-Greuel 2001)

The payer's discount rate is likely to be different. In the UK, the use of the Social Time Preference Rate is recommended representing the value society attaches to present, as opposed to future, consumption.(HM Treasury 2011) Besides pure time preference, the discount rate of the payer should also incorporate the expectation about changes in the budget for health care, the expected growth in the cost-effectiveness threshold, and the expected growth in the consumption value of health.(Claxton et al. 2011a). However, according to the Arrow-Lind Theorem, the payer's recommended discount rate should not incorporate risk. (Arrow-Lind 1970)

In effect, both players need to be aware of their own and the other's discount rate: using their own discount rate to work out what is the best course of action for them, as well as using the other player's discount rate to work out the implications of the actions for the other player and therefore their likely reaction.

The assumption of the risk neutrality of the payer can be easily lifted. A known level of risk aversion (or, although it is highly unlikely, a risk seeking attitude) can be incorporated into the analysis by using the certainty equivalents of uncertain pay-offs.(Loch and Bode-Greuel 2001; Attema, Lugner, and Feenstra 2010) The models can also be modified to accommodate prospect theory.(Kahneman and Tversky 1979) According to prospect theory, preferences depend on a reference point, with outcomes better than a reference point considered as gains, while worse outcomes are considered losses. Prospect theory states that losses loom larger than gains, and that probabilities are not evaluated linearly. Decision makers can be assumed to be loss averse by the inclusion of a loss aversion parameter with a value higher than 1, while probabilities can be transformed by giving them a decision weight, which is not necessarily equal to the probability itself (small probabilities tend to receive more weight and large probabilities less weight).(Attema, Lugner, and Feenstra 2010)

9.3.3.8 Payer reputation

The analyses assumed no other implications to the payer of changing decisions than the monetary costs associated with disseminating the new recommendation. Some strategies in the real option game and some decision paths in the simple real option analysis required a change in the recommendation every time a new review was carried out. Real life agencies have to think about their reputation too and how the public might view frequent changes in the recommendations. They might be unwilling to change decisions too often even if the changes would benefit society as a whole.

Applying ROA in real life would require a change in attitude from the decision makers and a change in how their decisions are viewed by the public to accept the need for continuous change in recommendations. Practical implications of ROA in assessing the economic value of new technologies are parallel to the implication of the concept of adaptive licensing.(Eichler et al. 2012) Adaptive licensing approaches are based on stepwise learning under conditions of acknowledged uncertainty: *"Adaptive licensing is a prospectively planned, flexible approach to regulation of drugs and biologics. Through iterative phases of evidence gathering to reduce uncertainties followed by regulatory evaluation and license adaptation"*. These approaches also require the explicit acknowledgement in the evaluation methods themselves that decisions are expected to be changed. Until such change in attitudes towards decisions occurs, the application of both adaptive licensing and ROA methods will be hindered by the lack of a price tag on the non-economic aspects of issuing guidance about new health technologies.

9.4 Policy implications

I believe that for payers that have the flexibility in the timing of their decisions, ROA methods will become the norm for evaluation of technologies that entail some level of irreversible investment. In the UK specifically, HM Treasury's Green Book already contains the recommendation that if the project under evaluation involves irreversible investments, then the *"appraisal of different proposals should not ignore the 'option' value of avoiding or delaying irreversible actions, and the benefits of ensuring flexibility to respond to future changed conditions"*.(HM Treasury 2011) The real option methods described in this thesis provide an example of how this recommendation could be implemented.

ROA will not always be necessary. Figure 9-2 in Section 9.3.2.3 above already demonstrated that for payers who do not have flexibility in the timing of their decisions and cannot review those decisions at a later date, there is no need to employ real option methods (e.g. if new technologies are assessed only at the time of their introduction to the market, as in Scotland).

Payers who do have flexibility in timing and/or can reassess technologies and can ensure future research is conducted if necessary may employ simple ROA, while if the burden of conducting research falls on other actors beside the payer and/or if the payer can negotiate over price, a ROG approach can be considered.

Currently there is limited capacity to undertake ROA, therefore it is important to identify areas where it is most worthwhile to do it. ROA methods will be most useful in situations where there are apparent (and sizable) irreversible consequences associated with the introduction of the new health technology. Some technologies are truly irreversible on an individual level, so there is only one time the decision about their implementation can be made. For individual patients, undergoing a surgical procedure may be an irreversible decision if the impact of the procedure cannot be undone at a later date, and if the operation will become impossible if the patients' condition deteriorates. On the population level, decisions about the adoption of new health technologies are always reversible. New patients after the change in the decision can always receive another treatment. However, the change in decision may not be costless. Facilities or new protocols developed for the new technology will need to be changed and rewritten if the decision is reversed, not to mention other political implications associated with reversing a decision. ROA approaches will be most useful if the new technology requires substantial investments (either in terms of capital investment or staff time). Although, even in the absence of large initial investments to introduce the new technology, the treatment of patients between the current decision and the time when the decision may be reconsidered will always have irreversible consequences. Therefore ROA approaches should be considered for all technologies where treatment cannot be delayed without an impact on the health status of the patients.

The proposed ROA approaches will only be meaningful if the future can be reliably characterised in the analyses. As shown by Kellog and Charnes, having technology-specific information is crucial.(Kellogg and Charnes 2000) Therefore initially ROA methods will likely be used in situations where there is more technology-specific information available on the parameters that drive the analyses, e.g. on the expected change in the best estimate of the effectiveness, likely price changes and/or the lifespan of the technology.

The case study on DES in the UK fit most of these requirements. NICE can delay decisions and reassess technologies. Although the change from BMS to DES does not require capital or training investments, the implantation of the stents is irreversible on the patient level. I did not have technology-specific information on the price changes, but the evolution of the best

effectiveness estimate was based on clinical trials of DES available at that time and the technology life time included in the analyses reflected the manufacturer's expectations.

In the current NICE assessment process, the economic evidence based on the traditional methods is considered by the review committee. They also consider the uncertainty surrounding the evidence in making recommendations for further research and the date when the guidance should be reconsidered.(Claxton et al. 2005) The appraisal committee is also supposed to assess the costs associated with a possible change in the decision about the technology in the future, and the impact on issuing guidance on ongoing research. If ROA methods would be recommended, these implicit considerations undertaken by the appraisal committee would be made explicit. The cost of changing the decision would be one of the model inputs, while the impact of issuing guidance on ongoing research is incorporated into the structure of the ROG. The economic model itself could be used to determine the optimal times to review the decision. The assessment process would not have to change, but ROA approaches conducted from the perspective of the payer could provide a more transparent way to analyse the committee's views and assumptions about all the above-mentioned additional considerations.

9.5 Further research

9.5.1 Empirical research

Application of ROA approaches to HTA does seem feasible. However, ROA requires estimation of parameters that are currently not routinely measured or estimated and no consensus exists on the best methods to calculate them. Given their importance for the reliability of ROA value estimates, priority should be given to estimation of HTA-specific parameters.

Historical time series of prices of health technologies could be examined to answer the question whether prices of medical devices follow the same trends as the prices of pharmaceuticals. It would be important to know what factors influence the trend in prices: e.g. does the disease area or the number of competitor products or the size of the patient population treated with the drug have an impact on prices? Once the time series of prices are compiled, standard tests are available to test for cointegration between selected groups. Cointegration is a statistical property of time series variables, with two or more time series said to be cointegrated if they share a common stochastic drift.(Engle and Granger 1987)

The evolution of evidence in terms of reduced uncertainty over time has been shown by meta-analyses.(Moher and Olkin 1995) However, ROA requires a different type of information, a

prediction of how the best estimate of effectiveness may change over time. This prediction was based on the limited data available on DES a priori to the evaluation date in the case study. However, it should be examined if other health technologies follow the same trends over time. Similarly to understanding the driving forces behind trends in prices, we should try to understand what characteristics determine the trends in the estimates of effectiveness. Meta-regression analyses could examine which variables are significant predictors of a positive, or a negative trend in the best estimate of effectiveness and under what circumstance could one assume no expected change in the estimate of effectiveness over time.(Ioannidis 2005; Gehr, Weiss, and Porzsolt 2006) The presence of the identified technology characteristics would then determine the best method to represent future changes of value.

Similarly to prices and effectiveness, the factors influencing the lifespan and speed of uptake of new technologies should also be examined through the use of regression techniques. We need to understand what drives the speed of innovation in certain areas: the disease area; the magnitude of unmet need, i.e. the size of the potential patient population to be treated and therefore the size of sales and/or profit to be made; and the number of competitors are all likely candidates as explanatory variables in the regression.

For ROA to work for novel health technologies, it will be important to understand the similarities and differences across new technologies. How far one may go to predict future price, effectiveness or lifespan of new technologies? Can we assume similar trends within a drug or device class, within a disease area, or even within all drugs and/or devices?

Another area where more precise information could be collected relatively easily is what that actual cost of an assessment is. Rather than the top-down approach followed here that started from the overall annual budget of NICE and the number of assessments undertaken future research might follow a micro-costing approach. The study should establish the number of people involved in the assessment and determine how much time they spend to undertake the assessment. Similarly, the cost of changing decisions should be examined by establishing who are involved when a recommendation is changed and what time commitment is required from the identified participants to ensure the new guidance in implemented in everyday clinical practice. Once we have a better understanding of the time commitment required for an assessment and to implement changes in the guidance, we can examine the feasibility of repeating assessments more frequently, e.g. biannually or annually as suggested by the simple ROA case study in this thesis given current capacity of NICE and the NHS.

Different risk characterisation methods may have large influence over the findings of ROA, however, there is currently no guidance on how to choose between methods. An analysis employing a number of different methods may show the importance of the risk characterisation methods chosen and provide guidance about the appropriateness of selected methods to describe dynamic risks during the development of a health technology.

9.5.2 Software and programming considerations

Since the simple real options analysis looked at the need for reviews in annual cycles (i.e. the model had to be re-evaluated only 5 times, once every year) and the real option game assumed fixed time requirements to undertake research and to conduct an assessment (again, the model had to be evaluated only for a limited number of time points and pricing scenarios) the calculations could be undertaken in Excel. However, some of the extensions discussed in the previous sections would drastically increase the number and complexity of calculations and evaluations needed. Increasing the number of actions available to players is not a problem per se. However, since every time an assessment of value is made by any player a full "traditional" probabilistic analysis is required, increasing the number of nodes when decisions are to be made can increase the number of calculations beyond the capabilities of Excel. If the model is to be used to optimise the type of research to be undertaken (see section 9.3.2.4.2) or to determine the best type and best formulation of PAS (see section 9.3.2.4.3), a simulation software or a programming language enabling a large number of calculations might be required. Furthermore, if the number of players is to be increased (see sections 9.3.3.2 and 9.3.3.3), there might be a need to employ software developed for agent based models.

The uncertainty around future changes in value is additional to the uncertainty surrounding the current value of the new technology. To allow for this increased uncertainty to be captured fully, the models were evaluated using 5,000 iterations. This value was chosen arbitrarily. The necessity of performing more iterations, or the possibility that fewer iterations might be enough could be tested in the future. By performing the analysis a number of times the variability of the mean of the estimates can be calculated. One expects the variability to decrease with an increase in the number of iterations. The "right" number of iterations may be determined by requiring this variability to be below some pre-specified threshold. However, there is currently no consensus about what is an acceptable level of variability between mean estimates of probabilistic models.

9.6 Conclusions

The aim of the thesis was to explore the feasibility of using ROA in HTA to explicitly incorporate the impact of uncertainty on decision making about new health technologies in the presence of irreversibilities. Three methods were compared that deal with uncertainty differently. I have argued that due to the assumption of complete and costless reversibility, uncertainty plays a limited role in decisions based on traditional economic evaluations. When decisions cannot be completely and costlessly reversed, the uncertainty surrounding the value of the new technology starts to matter.

Although further research is needed to determine the best methods to forecast change in demand, cost and health effects, as required for these types of analyses, ROA is a feasible method to evaluate health technologies in the presence of irreversibilities. The best course of action for both the decision maker and the manufacturer may be different from the one suggested by traditional analyses depending on the current levels of uncertainty, the expected change in evidence base and the costs of decision reversal.

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11 Appendix I: Visual Basic code for simple ROA calculations

```
Sub Option_calc()
'
' Option_calc Macro
'Created by Edit Remak on 10/03/2014

‘ Switch off screen updating to speed up calculations and enable status bar to be able to follow progress of simulations
    Application.ScreenUpdating = False
    Application.StatusBar = True

‘ Cell Results H12 switches the model between deterministic (value 0) and probabilistic (value 1) calculations
    Sheets("Results").Select
    Range("H12").Select
    ActiveCell.FormulaR1C1 = "1"
‘ Clear previous simulation results  to speed up calculations
    Sheets("Trends").Select
    Range("ROAresults").Select
    Selection.ClearContents

' Backup existing formulas that chose either the deterministic value or a random draw from the pre -specified distributions for model inputs in Model inputs column AH
    Sheets("Model inputs").Select
    Range("Q10:Q73").Select
    Selection.Copy
    Range("AH10").Select
    ActiveSheet.Paste
    Range("R76:R122").Select
    Selection.Copy
    Range("AH76").Select
```

```
    ActiveSheet.Paste
    Range("Q123:Q124").Select
    Selection.Copy
    Range("AH123").Select
    ActiveSheet.Paste
    Range("R127:R166").Select
    Selection.Copy
    Range("AH127").Select
    ActiveSheet.Paste

‘ Start iterations
    Index2 = 0

    Do While Index2  < 5000

' Record one realisation from distributions around current knowledge
        Sheets("Model inputs").Select
        Range("P10:P73").Select
        Selection.Copy
        Range("Q10").Select
        Selection.PasteSpecial Paste:=xlValues, Operation:=xlNone, SkipBlanks:= _
            False, Transpose:=False
        Range("P76:P122").Select
        Selection.Copy
        Range("R76").Select
        Selection.PasteSpecial Paste:=xlValues, Operation:=xlNone, SkipBlanks:= _
            False, Transpose:=False
        Range("P123:P124").Select
        Selection.Copy
        Range("Q123").Select
        Selection.PasteSpecial Paste:=xlValues, Operation:=xlNone, SkipBlanks:= _
            False, Transpose:=False
        Range("P127:P166").Select
        Selection.Copy
        Range("R127").Select
```

```
    Selection.PasteSpecial Paste:=xlValues, Operation:=xlNone, SkipBlanks:= _
      False, Transpose:=False

' Record one realisation of future changes
    Index = 0
    Sheets("Trends").Select
    Range("randinputs").Select
    Selection.Copy
    Range("paste_randinputs").Select
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
      :=False, Transpose:=False

    Do While Index < 5
' Change time-point of analyses so that model inputs are updated to whichever year the analyses are taking place in (2006-2010)
      Range("current_year").Select
      ActiveCell.Value = 2006 + Index
' Record model results for each year
      Range("results").Select
      Selection.Copy
      Range("paste_results").Offset(Index, 0).Select
      Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
        :=False, Transpose:=False

      Index = Index + 1
    Loop

' Store outcomes by year
    Application.StatusBar = "Calculating option strategy impacts for trial " & Index2
    Range("results2006").Select
    Selection.Copy
    Range("paste2006").Offset(Index2, 0).Select
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
      :=False, Transpose:=False
```

```
    Range("results2007").Select
    Selection.Copy
    Range("paste2007").Offset(Index2, 0).Select
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
      :=False, Transpose:=False

    Range("results2008").Select
    Selection.Copy
    Range("paste2008").Offset(Index2, 0).Select
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
      :=False, Transpose:=False

    Range("results2009").Select
    Selection.Copy
    Range("paste2009").Offset(Index2, 0).Select
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
      :=False, Transpose:=False

    Range("results2010").Select
    Selection.Copy
    Range("paste2010").Offset(Index2, 0).Select
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
      :=False, Transpose:=False

    Index2 = Index2 + 1

  Loop
' Copy of simulation results is made to base graphics and strategy impact calculations on –
speeds up calculations
    Range("ROAresults").Select
    Selection.Copy
    Range("copyROAresults").Select
    Selection.PasteSpecial Paste:=xlPasteValues
' Restore model time-point to start
  Range("current_year").Select
```

```
    ActiveCell.Value = 2006

' Restore original setup on Model inputs sheet
    Sheets("Model inputs").Select
    Range("AH10:AH73").Select
    Selection.Copy
    Range("Q10").Select
    ActiveSheet.Paste

    Range("AH76:AH122").Select
    Selection.Copy
    Range("R76").Select
    ActiveSheet.Paste

    Range("AH123:AH124").Select
    Selection.Copy
    Range("Q123").Select
    ActiveSheet.Paste

    Range("AH127:AH166").Select
    Selection.Copy
    Range("R127").Select
    ActiveSheet.Paste

    Range("AH10:AH166").Select
    Selection.ClearContents

‘ Turn off probabilistic calculations
    Sheets("Results").Select
    Range("H12").Select
    ActiveCell.FormulaR1C1 = "0"

‘ Return to sheet  where the macro has been started from
    Sheets("ROA").Select
    Range("H11").Select
```

```
' Switch screen updating back on and hide status bar
    Application.StatusBar = False
    Application.ScreenUpdating = True

End Sub
```

12 Appendix II: Visual Basic code for ROG calculations

```
Sub Option_calc()
'
' Option_calc Macro created by Edit Remak on 07/04/2014

‘ Switch off screen updating to speed up calculations and enable status bar to be able to follow progress of simulations
    Application.ScreenUpdating = False
    Application.StatusBar = True

‘ Cell range ‘type’ switches the model between deterministic (value 0) and probabilistic (value 1) calculations
    Sheets("Model").Select
    Range("type").Value = 1
‘ Clear previous simulation results  to speed up calculations
    Sheets("Trends").Select
    Range("ROAresults").Select
    Selection.ClearContents

' Backup existing formulas that chose either the deterministic value or a random draw from the pre -specified distributions for model inputs in Model inputs column AH
    Sheets("Model inputs").Select
    Range("Q10:Q73").Select
    Selection.Copy
    Range("AH10").Select
    ActiveSheet.Paste
    Range("R76:R122").Select
    Selection.Copy
    Range("AH76").Select
    ActiveSheet.Paste
    Range("Q123:Q124").Select
```

```
    Selection.Copy
    Range("AH123").Select
    ActiveSheet.Paste
    Range("R127:R166").Select
    Selection.Copy
    Range("AH127").Select
    ActiveSheet.Paste

‘ Start iterations for Nature’s move
    Index2 = 0

    Do While Index2 < 5000

 ' Record one realisation from distributions around current knowledge

        Sheets("Model inputs").Select
        Range("P10:P73").Select
        Selection.Copy
        Range("Q10").Select
        Selection.PasteSpecial Paste:=xlValues, Operation:=xlNone, SkipBlanks:= _
            False, Transpose:=False
        Range("P76:P122").Select
        Selection.Copy
        Range("R76").Select
        Selection.PasteSpecial Paste:=xlValues, Operation:=xlNone, SkipBlanks:= _
            False, Transpose:=False
        Range("P123:P124").Select
        Selection.Copy
        Range("Q123").Select
        Selection.PasteSpecial Paste:=xlValues, Operation:=xlNone, SkipBlanks:= _
            False, Transpose:=False
        Range("P127:P166").Select
        Selection.Copy
        Range("R127").Select
        Selection.PasteSpecial Paste:=xlValues, Operation:=xlNone, SkipBlanks:= _
```

```
        False, Transpose:=False
'Record one realisation for predictions of future population size and market share
    Sheets("Impact").Select
    Range("K15:K49").Select
    Selection.Copy
    Range("L15").Select
    Selection.PasteSpecial Paste:=xlValues, Operation:=xlNone, SkipBlanks:= _
      False, Transpose:=False

 ' Record one realisation of future changes by date of arrival of new information for each strategy group
    Index = 1
    Sheets("Trends").Select
    Range("randinputs").Select
    Selection.Copy
    Range("paste_randinputs").Select
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
      :=False, Transpose:=False

' Generate results for each strategy group
    Do While Index <= 5

      Range("current_year").Select
      ActiveCell.Value = Index
' Record model results (the multipliers, the population level impact and the recalculated ICER components) for each year between 2006 and 2010
      Range("mults").Select
      Selection.Copy
      Range("pastemults").Offset(Index2, (Index - 1) * 50).Select
      Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
        :=False, Transpose:=False

      Range("results2006").Select
      Selection.Copy
      Range("paste2006").Offset(Index2, (Index - 1) * 50).Select
```

```
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
    :=False, Transpose:=False

Range("results2007").Select
Selection.Copy
Range("paste2007").Offset(Index2, (Index - 1) * 50).Select
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
    :=False, Transpose:=False

Range("results2008").Select
Selection.Copy
Range("paste2008").Offset(Index2, (Index - 1) * 50).Select
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
    :=False, Transpose:=False

Range("results2009").Select
Selection.Copy
Range("paste2009").Offset(Index2, (Index - 1) * 50).Select
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
    :=False, Transpose:=False

Range("results2010").Select
Selection.Copy
Range("paste2010").Offset(Index2, (Index - 1) * 50).Select
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
    :=False, Transpose:=False

Sheets("Simulation").Select
Range("D7:G7").Select
Selection.Copy
Sheets("Trends").Select
Range("pasteICER").Offset(Index2, (Index - 1) * 50).Select
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
    :=False, Transpose:=False
```

```
        Index = Index + 1
    Loop

    Application.StatusBar = "Calculating option strategy impacts for trial " & Index2
    Index2 = Index2 + 1

  Loop
'Reset time in base model to starting point
  Sheets("Trends").Select
  Range("current_year").Select
  ActiveCell.Value = 1

'Store outcomes by strategy group – a copy of simulation results is made to serve as the base
for all further calculations – speeds up calculations
ORIG = original time point, original price;
ORIGRED = original time point, reduced price;
PASRES = time point after original assessment, PAS and research, reduced price;
NoPASRES = time point after original assessment and research, reduced price;
WAITRES = time point after research only, original price;
  Range("ORIG").Select
  Selection.Copy
  Sheets("Orig info").Select
  Range("B8").Select
  Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
    :=False, Transpose:=False

  Sheets("Trends").Select
  Range("ORIGRED").Select
  Selection.Copy
  Sheets("Orig red").Select
  Range("B8").Select
  Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
    :=False, Transpose:=False

  Sheets("Trends").Select
```

```
    Range("PASRES").Select
    Selection.Copy
    Sheets("PAS res").Select
    Range("B8").Select
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
        :=False, Transpose:=False

    Sheets("Trends").Select
    Range("NoPASRES").Select
    Selection.Copy
    Sheets("noPAS res").Select
    Range("B8").Select
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
        :=False, Transpose:=False

    Sheets("Trends").Select
    Range("WAITRES").Select
    Selection.Copy
    Sheets("Wait res").Select
    Range("B8").Select
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
        :=False, Transpose:=False

'Restore original setup on Model inputs and Impact sheets
    Sheets("Model inputs").Select
    Range("AH10:AH73").Select
    Selection.Copy
    Range("Q10").Select
    ActiveSheet.Paste
    Range("AH76:AH122").Select
    Selection.Copy
    Range("R76").Select
    ActiveSheet.Paste
    Range("AH123:AH124").Select
    Selection.Copy
```

```
    Range("Q123").Select
    ActiveSheet.Paste
    Range("AH127:AH166").Select
    Selection.Copy
    Range("R127").Select
    ActiveSheet.Paste
    Range("AH10:AH166").Select
    Selection.ClearContents

    Sheets("Impact").Select
    Range("L15:L49").Select
    Selection.ClearContents

' Turn off probabilistic calculations
    Sheets("Model").Select
    Range("type").Value = 0

' Return to sheet  where the macro has been started from
    Sheets("ROA").Select
    Range("H11").Select

' Switch screen updating back on and hide status bar
    Application.StatusBar = False
    Application.ScreenUpdating = True

End Sub
```

13 Appendix III: Visual Basic code for calculation of complete information strategies

```
Sub Strategies()
' Strategies Macro created by Edit Remak on 15/04/2014
'
   Application.ScreenUpdating = False
   Index = 0

   Do While Index < 5000
‘Select the results of a single iteration for all five strategy groups
      Sheets("Orig info").Select
      Range("B8:AR8").Offset(Index, 0).Copy
      Range("B5").Select
      Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
         :=False, Transpose:=False

      Sheets("Orig red").Select
      Range("B8:AR8").Offset(Index, 0).Copy
      Range("B5").Select
      Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
         :=False, Transpose:=False

      Sheets("PAS res").Select
      Range("B8:AR8").Offset(Index, 0).Copy
      Range("B5").Select
      Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
         :=False, Transpose:=False

      Sheets("noPAS res").Select
      Range("B8:AR8").Offset(Index, 0).Copy
      Range("B5").Select
```

```
        Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
          :=False, Transpose:=False

        Sheets("Wait res").Select
        Range("B8:AR8").Offset(Index, 0).Copy
        Range("B5").Select
        Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
          :=False, Transpose:=False
'Solve the game treating the single iteration as a full game of complete information, and store the results
        Sheets("Strategies CI").Select
        Range("strategy").Copy
        Range("D105").Offset(Index, 0).Select
        Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
          :=False, Transpose:=False

        Index = Index + 1
    Loop

    Application.ScreenUpdating = True

End Sub
```