

## **Whither trial-based economic evaluation for health care decision making?**

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### **Abstract**

The randomised controlled trial (RCT) has developed a central role in applied cost-effectiveness studies in health care as the *vehicle* for analysis. That is, data are collected on resource use and health effects on all or a sample of patients in the trial. This proves the basis of a trial-based estimate of cost-effectiveness of the technology of interest relative to one or more comparator(s). Increasingly, economic evaluation is being used as an explicit input into formalised decision-making about new technologies by specific agencies (e.g. NICE in the UK). This paper considers the role of trial-based economic evaluation in this era of explicit decision making. It is argued that any framework for economic analysis can only be judged insofar as it can inform two key decisions and be consistent with the objectives of a health care system subject to its resource constraints. The two decisions are, firstly, whether to adopt a health technology given existing evidence and, secondly, an assessment of whether more evidence is required to support this decision in the future. We argue that a framework of economic analysis is needed which can estimate costs and effects, based on all the available evidence, across the full range of possible alternative interventions and clinical strategies, over a relevant time horizon and for specific patient groups. It must also enable the accumulated evidence to be synthesised in an explicit and transparent way in order to fully represent the decision uncertainty. These requirements suggest that, in most circumstances, the use of a single RCT as a vehicle for economic analysis will be an inadequate and partial basis for decision making. It is argued that RCT evidence, with or without economic content, should be viewed as simply one of the sources of evidence which must be placed in a broader framework of evidence synthesis and decision analysis. Given the reality that a large proportion of evaluative health services research is funded around RCTs, trials will remain an important source of all forms of evidence for economic evaluation, but economic components to trial proposals need to include an explicit evidence synthesis and decision modelling component.

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## 1. Introduction

The randomised controlled trial (RCT) occupies a central role in the evaluation of health care interventions. In the field of clinical evaluation, the role of the RCT is principally to generate estimates of relative treatment effect (e.g. odds or hazard ratios) relating to the population of interest [1]. In this context, appropriate randomisation minimises the risk of selection bias, although this will not ensure the generalisability of the estimates [2]. In the context of economic evaluation, the role of the RCT has extended much further than being a source of estimates of relative treatment effects. Since 1994, approximately 60% of published economic evaluations on the NHS Economic Evaluation Database have been based on data from a single RCT ([www.york.ac.uk/inst/crd](http://www.york.ac.uk/inst/crd)). That is, the RCT was used as the *vehicle* for economic analysis, providing the sole source of data on resource use, baseline event rates and, where appropriate, health values as well as relative treatment effects, and basing estimates of the costs and effects of interventions by averaging across all or a sub-sample of trial patients. It would not be an over-statement to suggest that this approach is widely viewed as the entirety of what economic evaluation (even health economics!) has to offer.

Since the mid-1990s, many health care systems have made explicit use of economic evaluation to make decisions about which new technologies should be funded from the systems' collective resources. This formal requirement for economic analysis has largely related to the need for manufacturers to submit economic studies to decision makers in order for their new pharmaceutical products to be reimbursed [3]. In the UK, economic evaluation plays a key part in the technology appraisal process at the National Institute for Clinical Excellence (NICE) which makes decisions about a range of health technologies, and is a major element in the independent technology assessment, as well as manufacturer submissions, which inform appraisals [4 5].

Given that economic evaluation exists to inform decisions about resource allocation, the explicit use of these methods as a basis for actual decisions about coverage and reimbursement raises some important questions about appropriate methodology. One of these relates to the role of trial-based economic evaluation. This paper discusses the requirements of economic evaluation for decision making and considers the extent to which the use of a single RCT as a vehicle for economic analysis is consistent with these requirements. It is argued that, in most cases, trial-based studies represent a partial and limited form of analysis. Given the reality that a large proportion of evaluative health services research is funded around RCTs, trials will remain an important source of all forms of evidence for economic evaluation, but economic components to trial proposals need to include an explicit evidence synthesis and decision modelling component.

The paper is structured as follows. The next section considers the requirements for economic evaluation for explicit decisions about resource allocation. Section 3 considers the extent to which trial-based economic evaluation compare with a framework of evidence synthesis and decision modelling would be considered 'fit for purpose' given these requirements. Section 4 discusses the role played by RCTs in economic evaluation given existing finding arrangements for evaluative health services research, and Section 5 offers some conclusions.

## 2. Requirements of economic evaluation for decision making

The formal use of economic evaluation as a basis for decision making about the reimbursement or coverage of health care technologies by health care systems places particular demands on the analytical methods used. The requirements of economic

evaluation for this purpose have been considered in detail elsewhere [6 7] Here we present a brief summary of the arguments.

There are two related questions which any health care system needs to address in making decisions about the cost-effectiveness of new technologies. The first is whether the new technology can be considered cost-effective based on existing evidence. Given its unavoidable nature, this *adoption decision* has to be taken on the basis of what is currently known about its costs and benefits relative to comparators. The second question is, whatever the adoption decision, is it a cost-effective use of resources to demand additional evidence through research? If the answer to the *research decision* is positive, further evidence will be used to review the adoption decision in the future. Although the adoption decision is central to most reimbursement agencies, many also consider the issue of research priorities. In the case of NICE, for example, guidance about a technology is accompanied by a statement of research priorities, several appraisals have stipulated the use of a technology only in the context of research (e.g. liquid-based cytology [8]) and a decision review date is specified in all guidance.

Given these two fundamental questions, a series of requirements for economic evaluation emerges.

- *Clear statement and measurement of the objective function.* As decisions are typically being taken by budget constrained health care systems, the analysis needed to inform the adoption and research decisions is essentially one of constrained optimisation in which an objective function is maximised subject to a budget constraint. A legitimate focus of the objective function is likely to be some measure of health gain. This would not preclude the inclusion of other arguments, but their ‘rate of substitution’ with health gain would need to be defined. The quantification of implications for the objective function in a given study is, of course, subject to much debate, but quality-adjusted life-year (QALY) remains a widely used measure of health gain with well understood strengths and weaknesses. A key requirement for decision making is the need for a consistent implementation of the measure of health gain in analyses informing decisions about different technologies.
- *A consistent perspective.* The need for consistency in perspective across adoption decisions is also a requirement for decision making. The appropriate cost and benefit perspective for a legitimate social decision maker would ideally be a broad societal one although, in reality, a somewhat constrained version might be the focus of actual decision makers.
- *Appropriate specification of the decision problem.* Any economic analysis informing decisions needs to be clear about which patient population(s) are being considered. Once this is defined, all relevant options need to be defined. These are likely to include a range of possible existing interventions and programmes, as well as one or more new technologies. The definition of alternative options may well need to include the specification of alternative sequences of interventions or diagnostic tests and different stopping and starting rules for treatments.
- *Appropriate time horizon.* A further requirement for decision making is the need for an appropriate time horizon – that is, the time period over which costs and benefits are likely to differ between the alternative options being compared. A lifetime time horizon will be appropriate in many instances. This is because, firstly, a large proportion of adoption decisions relate to new interventions for chronic conditions such as ischaemic heart disease and diabetes. The second reason is that, whenever options potentially differ in terms of their impact on mortality rates, the need to

quantify the implication of this in terms of changes in expected (mean) quality-adjusted survival duration requires full extrapolated survival curves.

- *All relevant evidence.* In order to inform social decisions about resource allocation, all sources of evidence need to be used. Anything that falls short of this will be a partial analysis with potentially misleading results. This relates not only to measures of relative treatment effect, but also to the full range of other parameters in an economic analysis.
- *Relevant to the decision context.* Decisions about new technologies are taken in specific contexts. This is defined by the jurisdiction of the specific decision-maker whom the economic evaluation is seeking to inform.
- *Appropriate characterisation of uncertainty.* In order to address the second question of whether or not additional research is required to inform future decision about a technology, the uncertainty associated with the adoption decision needs to be quantified. That is, in reimbursing a new technology, what is the probability that a wrong decision is being made? It is also necessary to consider the implications of making a wrong decision in terms of wasted resources and opportunities for health gain forgone.

These requirements of economic evaluation for decision making are the starting point for considering an appropriate framework for analysis. It is certainly true that, in their methods guidelines, many decision makers are not prescriptive about preferred methods [3]. Indeed, some elements of existing guidelines are inimical to these requirements. However, unless these requirements are recognised and implemented, the value of formal economic evaluation for resource allocations decisions will be limited.

### **3. What analytical framework for economic evaluation?**

#### **3.1 Trial-based economic evaluation**

Given the requirements for economic evaluation defined in the last section, to what extent can trial-based economic evaluation be considered ‘fit for purpose’? An economic analysis based on a RCT will have the advantage of the relative effectiveness of the intervention being derived from a design which should be free of selection bias. However, using a trial as *a framework* (vehicle) for economic analysis falls short in terms of many of the requirements described above.

##### *3.1.1 A failure to compare all relevant options.*

Given the costs and implications for patient numbers, few RCTs will include more than two options – typically a new technology plus one ‘standard’ intervention. However, it is usually the case that a range of existing interventions exist, used to varying degrees in routine practice. Indeed, it will often be the case that new technologies for a given condition come in clusters – for example, classes of pharmaceuticals, or drugs in different but related classes. In a recent technology assessment of alternative therapies for different types of epilepsy in adults, between 1 and 6 newer anti-epileptic drugs were compared with 2 older therapies [9]. Not surprisingly, no trial directly comparing all therapeutic options had been undertaken.

For many chronic diseases, therapies are used in sequence. Although RCTs exist comparing alternative treatment sequences (e.g. the FOCUS trial in colorectal cancer (<http://www.ctu.mrc.ac.uk/studies/CR08.asp>)), this is typically a sub-set of all the possible sequences. In looking at the cost-effectiveness of new biological therapies for rheumatoid arthritis, for example, NICE had to consider the appropriate point in a

therapeutic sequence of 2 new biological therapies and 8 existing disease-modifying anti-rheumatic drugs [10].

The implication is that RCTs will usually only compare a sub-set of relevant options for a given patient population. Using a single trial as a vehicle for an economic evaluation will, therefore, invariably represent a partial analysis. If one or more relevant options have not been included in an analysis, there is a clear risk of inappropriate adoption and research decisions.

In considering this issue, the weaknesses of the ‘pragmatic’ trial are also evident [11]. One feature of such studies is that the selection of intervention (usually in the ‘control’ group) is sometimes left to the individual investigator. Although this feature of their design is intended to make pragmatic trials more generalisable by reflecting a range of clinical practice. However, for economic evaluation, it precludes an estimate of the incremental costs and effects of individual interventions and becomes an analysis of ‘average’ practice.

### 3.1.2 *A truncated time horizon*

For many trial-based economic evaluations, the maximum follow-up in the trial will be shorter than the appropriate time horizon for the economic analysis. For trials concerned with the treatment of particular acute conditions or with alternative forms of management for terminally ill patients, this may not be the case. However, trial-based economic evaluations relating to interventions in many areas of health care will exhibit a gap between the costs and benefits which can be estimated in the trial, and those which are needed for decision making. This gap will relate to numerous evaluations in areas such as heart disease, most types of cancer and diabetes.

In some studies, simply providing a within-trial estimate of cost-effectiveness with a truncated time horizon can be misleading. For example, in Mark *et al*'s cost-effectiveness analysis of alternative thrombolytic therapies following myocardial infarction, after one year's follow-up 91% and 89.9% of patients randomised to TPA and streptokinase, respectively, had survived, and mean costs were higher in the TPA group [12]. Any within trial-estimate of cost per life-year (or QALY) gained would only allow for differences in survival duration *until 1-year*. This fails to acknowledge that the additional patients surviving during follow-up in the TPA arm of the trial will live for some period beyond one year. In other words, a within-trial estimate effectively assumes all patients drop dead at the end of the study! To provide reliable estimates of cost-effectiveness, therefore, Mark *et al* moved out of a trial-based paradigm and used decision modelling to extrapolate the survival curves over patients' lifetimes assuming that, after one year, the mortality hazards were equal in the two arms of the trial.

For some studies, the failure to estimate cost and benefits over the full time horizon may not be a major problem if the within-trial estimate of the incremental cost-effectiveness ratio is considered acceptable relative to a threshold, and longer follow-up would only further confirm the adoption decision. An example of such a study was a trial-based comparison of the cost-effectiveness of high-dose versus low-dose ACE inhibitors in heart failure [13]. Within the trial, high-dose therapy was observed, over 4-years of follow-up, to have a lower mortality risk and to result in lower mean costs. The fact that, within the trial, it was not possible to observe the survival durations of all patients may not have been a problem if it could be safely assumed that mortality rates with low-dose therapy would never become lower than those with high-dose. That is, life-years gained

from high-dose would only increase as follow-up continued, and its cost-effectiveness would only improve. However, this justification of within-trial estimates of cost-effectiveness has its limitations. The first relates to the fact that patients living longer on one therapy are likely to incur greater costs relating to diseases other than that for which the interventions are being evaluated. In the heart failure example, patients living longer under high-dose therapy will be at risk of other diseases such as cancer. These additional 'unrelated' costs are unlikely entirely to prompt a change in the adoption decision from that based on a within-trial analysis, especially when discounting is considered. However, in finely balanced decisions, these additional costs may result in an important change.

A more important limitation of the justification for a within trial estimate of cost-effectiveness relates to further research. Although it may be possible to reach robust adoption decisions on the basis of a study with a truncated time horizon if further follow-up would be expected just to confirm the result, analysis to inform decisions about the value of further research cannot make such a simplification. Value of information analysis involves the quantification of the costs of decision uncertainty in terms of forgone health and resource costs. These methods depend on all sources of parameter uncertainty being included in an analysis, including full life expectancy. Value of information methods based on a truncated time horizon could, therefore, generate misleading results.

### 3.1.3 *Lack of relevance to the decision context*

A further problem with some RCTs as used as a vehicle for economic evaluation is their lack of relevance to the specific jurisdiction in which the decisions are being made. This is often the case with trials undertaken by pharmaceutical and medical device manufacturers who focus their patient recruitment in countries which represent important potential markets and/or where they can recruit quickly and inexpensively. Using such trials as a vehicle for economic analyses will mean that estimates of costs and benefits may reflect considerable variability in patient case-mix and routine clinical practice. Although methods have recently been described to handle this variability in economic evaluation alongside multi-location trials [14], they will not help if the jurisdiction making the decision recruited relatively few patients or was not part of the study at all.

This was the case with NICE's appraisal of the glycoprotein 2b/3a antagonists for non-ST-elevation acute coronary syndrome [15]. Although nearly 50,000 patients had been randomised to relevant trials of these therapies, these were predominately undertaken outside the UK, largely in continental Europe or north America where the management of heart disease has traditionally shown some important differences compared to that in the NHS. The economic analysis to support NICE's decision making required the use a decision analytic framework to combine relative treatment effects from the trials with baseline event rates specific to the UK in an attempt to 'transfer' trial results to a NHS setting [16].

For publicly-funded RCTs supporting economic evaluation it may be expected that patients and clinical practice is more representative of the jurisdiction in which the decision will be taken. This might be expected to be the case, for example, in trials funded by the NHS Health Technology Assessment programme and the Medical Research Council in UK with respect to NHS practice. However, the centres recruited into such studies are typically based on their willingness to participate rather than whether they contribute to a representative picture of NHS patients and practice. For

economic evaluation based on these trials, therefore, it may not be reasonable to assume generalisability with respect to the context of the decision.

#### *3.1.4 Failure to incorporate all evidence*

Arguably the most damning criticism of trial-based economic evaluation is the fact that a single trial is very unlikely to include all evidence relevant to a given evaluation. One aspect of this problem is relatively trivial. In some trial-based economic studies not all the data necessary for cost-effectiveness analysis are collected. For example, there may be an absence of resource utilisation data and measurements of health-related quality of life (HRQL). This tends to be the case, for example, in RCTs undertaken to support pharmaceutical companies' applications for licences for new products, although these studies are often the main source of evidence when the cost-effectiveness of these therapies is initially considered for reimbursement. One approach in these cases is to limit the economic evaluation to those data that were included – for example, only include those costs where resource use data were collected or that can be inferred. This sort of partial analysis can lead to wholly misleading results if important costs or effects are excluded. Another example is to report estimates of life-years, rather than QALYs, gained, when no HRQL data were collected. This was true of the two trial-based studies in cardiology described above [12 13]. This, of course, implicitly assumes that all surviving patients are in 'perfect' health. A second approach would be to augment the data collected in the trial with evidence from other sources which is a movement away from trial-based economic evaluation towards synthesis and modelling.

The more fundamental problem, however, is that single trials will invariably fail to reflect all the available evidence relating to a particular decision problem. Trial-based studies have the advantage of reflecting an unbiased estimate of relative treatment effect. However, in many situations there will be other trials relating to the technology of interest and, even if they do not include resource use and HRQL data to sustain full trial-based analyses, ignoring their estimates of treatment effects would risk presenting a partial and misleading analysis.

This principle also extends to other parameters such as baseline event rates, resource use and HRQL. Additional estimates of these parameters may be available (wholly or partially) in other trials. It is perhaps more likely, however, that estimates of these non-treatment effect parameters would be available in non-experimental studies such as longitudinal or cross-sectional studies. Given that these parameters are not susceptible to selection bias in the same way as for treatment effects, it would be inappropriate not to consider evidence from the full range of data sources within an economic analysis.

In principle, the need to bring to bear all available evidence does not stop there. Sources additional to the single trial will probably be available to provide estimates of functions of parameters with an economic analysis. For example, for a surgical intervention, some studies may present estimates of the risks of individual complications, and others may indicate the overall risk of an adverse event. Ideally, the evidence presented in all studies would be incorporated into an economic analysis despite this inconstancy in reporting. Although the rates of complications are presented differently, the mathematical relationship between them could be used to provide a full synthesis.

One response to the failure of trial-based economic evaluation to use all available evidence is that, once such a study has been published, it can be synthesised with other evidence in a more detailed analysis for decision making. This would be analogous to

what happens with clinical measurements in RCTs. That is, a single trial publishes its results and then meta-analysis is used to synthesise these estimates with those from other trials [17]. However, although this makes sense in the context of individual clinical measurements, there can be no sense in meta-analysing estimates of cost-effectiveness such as an incremental cost-effectiveness ratio or incremental net benefit. This is because these cost-effectiveness estimates are derived from a range of parameters, many of which would not be of relevance in all decision making contexts. This would certainly apply to unit costs – for example, a cost-effectiveness ratio based on US unit costs would not be relevant to NICE decisions. This may also be true of other parameters such as resource use, utilities and baseline event rates. Standard meta-analysis for clinical measures typically focuses on relative treatment effects which are assumed exchangeable across different decisions contexts. This assumption cannot be made with measures of cost-effectiveness.

### *3.1.5 Inadequate quantification of decision uncertainty*

As described above, to address the second key decision question – whether additional research is required to revisit the adoption decision in the future – requires a full quantification of decision uncertainty. A failure fully to characterise the uncertainty in all parameters in an analysis can have a major influence on the expected value of perfect information and the expected value of sample information [18-20]. As argued above, the use of a single trial as the sole basis for economic evaluation will usually ignore evidence from other trial and non-trial sources on relevant parameters and functions of parameters. As well as a potential impact on expected cost-effectiveness (which may lead to an inappropriate adoption decision), failure to use all available evidence can lead to less precision in parameter estimates which, all things being equal, will result in over-estimates of the expected value of perfect information.

## **3.2 Evidence synthesis and decision modelling**

If trial-based economic evaluation is a limited framework for cost-effectiveness analysis for decision making, what is the alternative? The use of decision analytic models, coupled with full evidence synthesis, is the only framework that has the potential to meet all the requirements for economic evaluation for decision making. These methods provide a framework within which an appropriate structure for the underlying disease and the impact of all relevant options under evaluation can be developed, all existing evidence can be brought to bear and, through, probabilistic sensitivity analysis, the joint implications of parameter uncertainty on the uncertainty in the decision (and the value of additional research) can be quantified.

This role of decision models is contrary to how it has been portrayed in the literature [21]. Models have sometimes been characterised as alternatives to trials [22], but this is to misunderstand their respective roles. The RCT provides estimates of particular parameters in a specific sample of patients at a particular point in time. Decision models provide a structure within which evidence from a range of sources can be directed at a specific decision problem for a defined population and context. Being clear about this distinction between measurement (undertaken in trials and other primary studies) and decision making (which needs an analytical structure within which to direct the evidence at the decision problem being addressed), emphasises that models and trials are complements not substitutes. Although they can generate measures of a range of parameters, RCTs are the key source of estimates of relative treatment effects which should be free of selection bias. These are central to economic evaluation as they

provide the driver for differences between options in costs and health effects. However, trials should be seen as a source of inputs into, not as a vehicle for, economic evaluation.

Of course, there are numerous methodological challenges to be addressed in using decision models [7]. These include the choice of an appropriate structure for a model, particularly for complex disease processes where future prognosis is dependent on a patient's past history [23]; how structural uncertainty in decision models is to be handled and reflected in decision uncertainty and value of information analysis; and various computational issues associated with the calculation of the expected value of perfect information for individual parameters, and of sample information [20].

Arguably, however, the greater methodological challenges within the framework relate to evidence synthesis; that is, the process of bringing together all relevant evidence on parameters and functions of parameters. As soon as the primacy of using all available evidence in decision making is accepted, the analytical issues this throws up are clear. These issues go well beyond standard meta-analysis, and are being addressed (usually within a Bayesian framework) more generally than just for purposes of economic evaluation [24]. To date most of methodological work in this area has focussed on complex synthesis problems relating to treatment effects. For example, obtaining absolute effectiveness measures for several interventions when these have not been compared head-to-head in trials [25 26]; synthesising data from trials with different points of follow-up with different endpoints [27]; and obtaining estimates of relative treatment effects from non-randomised studies. However, there are also important methodological questions to be considered in synthesising other parameters relevant to economic evaluation such as utilities and resource use.

The use of evidence synthesis to 'feed into' decision models also raises interesting questions. For example, multi-parameter synthesis relates to the methods used to bring together not just individual parameters, but also to include evidence on mathematical functions of those parameters [28]. Advanced methods of evidence synthesis, particularly undertaken using Bayesian methods, emphasise the importance of reflecting in models all available evidence and a complete picture of parameter uncertainty. In addition, they clearly show the importance of fully incorporating the correlations between parameters as these can effect estimates of expected cost-effectiveness, and measures of decision uncertainty and value of information will inevitably be sensitive to the degree of correlation. The importance of appropriately coupling decision models with evidence synthesis has resulted in a set of methods which have been termed 'comprehensive decision models', where these two stages are essentially undertaken jointing in order the all evidence, uncertainties and correlations are captured in the economic analysis [29 30].

#### **4. What is the role for trials in economic evaluation?**

The last section argued that the primary purpose of RCTs is to measure specific parameters in particular samples of patients, and that these provide one source of parameter estimates for economic evaluations undertaken within the framework of evidence synthesis and decision modelling. This implies a radically different approach to funding evaluative health services research than is currently the case. Ideally, funders such as the Medical Research Council (MRC) would support the following evaluation sequence. Firstly, identify potentially important decision problems relating to the management of particular populations and sub-populations of individuals. These would typically be patients but would include others in the context, for example, of preventative

services. The second stage would be the funding of systematic reviews, evidence synthesis and decision modelling to address the adoption and research questions described in Section 2. Thirdly, and based on the results of this the second stage, one or more primary studies may be commissioned. The number and design and these studies would be determined by the second stage. For example, value of information analysis would determine the importance of collecting additional data on relative treatment effects (requiring an RCT) and other parameters (which may be estimated using an observational design). In other words, the question of whether additional primary studies are required and, if so, their design is an *empirical* question informed by the second stage. A fourth stage is to update the evidence synthesis and decision modelling when the additional primary studies report. At this stage, the whole process would start again, which emphasises the iterative nature of the evaluation process [31].

There is some indication that some research funders recognise the strengths of this iterative framework. For example, the NHS Health Technology Assessment programme consists of secondary research (systematic reviews and decision modelling) which informs the selection and, to some extent, design of primary research studies (mainly RCTs). It might be expected that, as formal use of economic evaluation in reimbursement decisions about new technologies becomes more widespread internationally, this will encourage greater use of an iterative framework to research sequencing and funding.

In the main, however, to the extent that economic evaluation is seen as important by any research funder, it fits into their funding plan through RCTs. For example, the MRC's only funding of applied economic evaluations comes through trials. Furthermore, the economic evaluation undertaken by pharmaceutical companies is focussed on having analyses available to inform reimbursement decisions at product launch. This puts the main emphasis on the collection of data for economic analysis within the products' regulatory trial programmes. As things stand, therefore, the trial is central to how applied economic evaluation is funded. How can researchers within the field adopt an appropriate framework for economic evaluation whilst recognising that the one of the few ways resources are going to be made available for economic analysis is as part of this trial?

It is possible to identify two scenarios regarding how an economics component might be contribute to a trial. The first is where a particular research question has been established, the decision to run a RCT has been made but the design of that trial (options compared, endpoints, follow-up etc.) has yet to be determined. In this situation, the ideal would be to be able to identify funds to undertake some initial synthesis and modelling to get a rough idea of the expected cost-effectiveness of all alternatives based on current evidence, the key uncertainties and the most appropriate primary research design. In essence, this might be seen as a constrained version of Stage Two as described earlier. There may be an opportunity to undertake such work as part of a trial pilot study, but it is probably unlikely that it would be able to feed into trial design in an unconstrained manner.

A more likely situation is that there will be no opportunity for modelling, that the options being compared will have been selected and will be a sub-set of the relevant alternatives and the size and follow-up period will be determined by the (expected) available budget. In these circumstances, one option would be for the economic evaluation researcher not to participate in the research given the absence of any coherent approach to its

specification. However, this would lose the opportunity to collect data which may be expected to be important in establishing cost-effectiveness. The marginal cost of such data collection may be quite modest given that the trial will be going ahead anyway. Furthermore, by remaining involved in the trial, it would hopefully be possible to secure a budget for economic analysis when the trial data emerge. However, the purpose of this funding would not be to undertake a standard trial-based economic evaluation based only on the sample of trial patients. Rather, it would be to use the data collected in the trial as part of a wider drawl of available evidence, and to synthesise this within a decision modelling framework based on a potentially broader specification of the decision problem. Clearly, this approach would require a carefully written proposal which would have to emphasise the added value of this more comprehensive approach to economic evaluation. There are also important methodological questions to address such as how to synthesise patient-level and aggregated data for decision models.

## **5. Conclusions**

For many years the RCT has been a convenient way of getting economic evaluation studies funded and undertaken. However, for a large proportion of that period, once the study was published, it played little role in actual decisions about resource allocation. Many health care systems in developed countries now use economic evaluation as a formal input to decisions about whether to fund new interventions. This use of economic analysis for specific decisions raises a series of questions about appropriate methods. It has been argued in this paper that the use of a single trial as a vehicle for economic analysis will, in most situations, lead to a partial and limited analysis with which to inform decision making. The more appropriate framework for economic analysis is evidence synthesis and decision modelling where all available data are brought to bear on fully specified decision problems. Given that a large proportion of funding for economic evaluation currently flows through the RCT, however, it will be necessary to use trials as a key source of data collection but to ensure that analysis includes an explicit evidence synthesis and decision modelling component.

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