Achieving ‘value for money’ implies either a desire to achieve a predetermined objective at least cost or a desire to maximise the benefit to the population of patients served from a limited amount of resources. Cost-minimisation analysis relates to the first of these objectives.

Assumptions of clinical equivalence in cost-minimisation analysis should only be made if claims of equivalence can be supported by clinical evidence; that is, where measured outcomes have been shown to be equivalent; where this is not possible, a cost-minimisation analysis should not be conducted.

What steps can be taken to improve the quality and appropriateness of cost-minimisation analyses and in what circumstances is it appropriate to use cost-minimisation analysis as a methodology in the economic evaluation of healthcare technologies?

To what extent should healthcare professionals rely on cost-minimisation analyses to inform their decision-making?

How do we measure ‘clinical equivalence’ and what are the implications of potential sources of misinterpretation of clinical data within the framework of cost-minimisation analysis?

How can we enhance the reputation and value of cost-minimisation analysis as a method of health economic analysis to inform healthcare decision-making?
What is cost-minimisation analysis?

Cost-minimisation analysis should only be utilised in situations where the benefits of alternative treatments have been proven to be identical and, as such, this methodology is perceived as being the easiest to apply; however, such a perception is misleading. Prior to its use it is necessary to generate unambiguous evidence of clinical equivalence, which introduces a new and complex array of issues to be addressed. What is clear, however, is that it is highly inappropriate to simply assume clinical equivalence between competing therapies as a justification for the use of cost-minimisation analysis.

Cost-minimisation analysis is frequently perceived as being the ‘poor relation’ among health economic methodologies, with many analysts equating it as being a simple cost analysis. Such a perception is largely due to the poorly controlled and haphazard use made of this methodology to date. Cost-minimisation analysis has frequently been employed to support and justify the introduction of cheaper drugs into a therapeutic class. Such evaluations are frequently undertaken on the basis that the health benefits of competing healthcare technologies are assumed to be ‘similar’ and then dismissed, with the resultant analysis focusing entirely on costs. Such a perception is also found in health economics textbooks, which dismiss cost-minimisation analysis as a technique in which:

‘... the decision simply revolves around the costs’.¹

Cost-minimisation analysis turns to the assessment of costs only after the health benefits of the competing healthcare technologies have been demonstrated to be clinically equivalent. The cost side of the cost-minimisation analysis equation is equivalent to that of the other three methods of economic evaluation and, therefore, cost issues can be explored using well-validated tools. In cost-minimisation analysis the least expensive option is preferred and, as decision-makers intuitively understand the results of cost-minimisation analyses (‘cheapest is best’), scant attention is often paid to the sources of evidence used to establish the appropriateness of this choice of methodology.

Such a perception therefore ignores the rigorous evaluation of health benefits that should have been undertaken to prove them to be clinically equivalent before such a complete focus on costs can be justified. In cases where such a rigorous consideration of health benefits has not been undertaken, the appropriateness of the use of the cost-minimisation analysis methodology must be questioned. Structures of clinical evidence are, therefore, integral to the reliability that can be placed on any economic evaluation.

‘An economic evaluation is only as good as the medical evidence upon which it is based’.²

It is, therefore, perhaps surprising that the choice of health outcome measure and source of clinical evidence used in cost-minimisation analyses have not been subject to considerably more scrutiny. Recent advances have made it easier for analysts to confirm or refute the clinical equivalence of competing healthcare technologies, particularly through the use of non-inferiority trials and by switching from analyses of superiority to non-inferiority in appropriate cases. However, few if any analysts using cost-minimisation analysis have taken advantage of these richer data sets and it is likely to take a few more years before health economists catch up with advances in clinical trial design, allowing cost-minimisation analysis analyses to be undertaken in appropriate circumstances and using more rigorous methods. Only by taking advantage of such advances in clinical trial methodology will health economists be able...
What is cost-minimisation analysis?

to make efficient use of available clinical information and gain maximum value from the use of cost-minimisation analysis.

When should cost-minimisation analysis be used?

Given that the results of clinical trials cannot be known in advance, no prospective economic evaluation starts out as a cost-minimisation analysis; only when the health outcomes generated are demonstrated to be ‘identical or similar’ should this methodology be adopted by the analyst. But what do we mean by ‘identical or similar’ and what evidence is required to support this concept? Such issues need to be rigorously addressed if cost-minimisation analysis is to take its rightful place as a valid technique of economic evaluation.

In practice, the extent to which cost-minimisation analyses are performed appropriately is largely determined by the source and nature of the clinical evidence available. For a cost-minimisation analysis to be a valid and reliable source of evidence to decision-makers requires the availability of high-quality clinical evidence that proves the equivalence of two treatments and, therefore, indicates the appropriateness of this method of economic evaluation. Box 1 provides a real-world case study outlining the use of cost-minimisation analysis in practice.

Whose views of clinical equivalence should we assess?

This section acknowledges that definitions of clinical equivalence will differ according to the perspective taken. This raises the question of whose views we should consider as being the most important (patients’, clinicians’ or society’s) in our evaluation of equivalence. Generally, lead investigators in clinical trials prespecify the primary and secondary health outcomes to be measured, with the identification of the primary outcome measure being based on relevant clinical experience, published clinical evidence and knowledge of patient needs. In a cost-minimisation analysis it is necessary to ensure that the choice of health outcome measure used to determine clinical equivalence is clinically meaningful to the patient; if not, use of cost-minimisation analysis should be considered inappropriate.

Over what time period should we assess clinical equivalence?

The benefits of healthcare technologies are likely to vary according to the time point at which they are measured. In a randomised controlled trial (RCT), the primary health outcome measure might be assessed as being statistically significant at six weeks; however,

Box 1. Case study

A study by Boland et al compared the cost-effectiveness of alternative methods for the insertion of Hickman lines with the single objective of facilitating the safe and effective delivery of chemotherapy. The healthcare technology is therefore simply an enabling technology which, in itself, does not impact on the health status of the patient. This case study therefore provides a useful illustration of the issues related to the application of cost-minimisation in practice in evaluating competing health technologies.

As with all such analyses, a range of potential adverse events (catheter tip misplacement, pneumothorax, arterial puncture, haematoma, infection) were acknowledged, but the potential clinical significance of such events was held to be very limited, thus justifying the use of cost-minimisation analysis. At the heart of this and any other analysis employing cost-minimisation analysis are two essential questions: from which perspective should we evaluate equivalence (patients’, doctors’ or both) and exactly at what point do ‘insignificant’ variations in clinical outcome achieve clinical significance?
if the same outcome was measured at 12 weeks, then there might be no statistically significant difference. As such, it is important to recognise that clinical equivalence is a dynamic and not a static concept and that the analyst must be sure that any demonstration of clinical equivalence is likely to be sustained over time.

Equivalence in what?
Even where a new intervention matches current standard treatment in its primary outcome, it is still necessary to scrutinise secondary outcomes. Such analyses of secondary outcomes may reveal significant differences in safety, cost or convenience.⁴

‘Provided that two therapies are equivalent in terms of efficacy and safety, one therapy may offer clinical benefits such as a more convenient administration schedule, less potential for drug interaction or lower cost.’⁵

Thus, even in cases where clinical equivalence is demonstrated between primary outcomes, there remain two other issues that must be addressed prior to unambiguously supporting the use of the cost-minimisation approach. First, the primary health outcome must encompass the main benefit(s) of the treatments being compared. Second, any differences in secondary health outcomes must be sufficiently small as to not attain clinical significance. If these assumptions cannot be substantiated, then it would still not be appropriate to adopt the cost-minimisation analysis methodology, despite the availability of evidence concerning equivalence in primary outcomes.

Sources of clinical evidence regarding clinical equivalence
Whether or not clinical evidence can be used to inform cost-minimisation analyses is very much dependent on the design of the RCT, with many cost-minimisation analyses being based on trials that were not specifically designed to prove clinical equivalence.

‘… in many studies in which this type of economic analysis was undertaken, the study was not designed to test the explicit hypothesis of equivalence in outcome’.⁶

Many sources of clinical evidence can be used to support economic evaluations; however, the ‘gold standard’ is normally considered to be the RCT. Such trials can be subdivided into superiority trials, equivalence trials and, as has been done more recently, non-inferiority trials. The framework of RCT evidence is crucial to the validity underlying the use of the cost-minimisation analysis methodology. The most common structure of clinical trial performed to inform clinical decision-making is the superiority trial. Given this fact, there is an inevitable incentive to make use of results obtained in the context of lengthy and expensive superiority trials to support more restricted claims of clinical equivalence in cases where original claims of clinical superiority are not supported by the evidence.

There is an unambiguous argument for using cost-minimisation analysis when the results of an equivalence trial prove that two healthcare technologies are clinically equivalent. Equally, there is an unambiguous argument for not using cost-minimisation analysis when appropriately designed RCT evidence proves that the benefits of alternative healthcare technologies are significantly different. In between these extremes there are many ‘grey areas’ which require more careful analytical consideration. The following sections delve into such grey areas.

Superiority trials
Superiority trials are specifically designed to show a difference in health benefits between two healthcare interventions. Typically, the primary objective of the trial is to determine whether an experimental intervention is more efficacious than the established gold standard treatment. To identify whether or not there is a difference in health benefits between two healthcare technologies it is necessary to begin with a null hypothesis that treatment X yields the same health benefits as treatment Y. However, superiority trials are specifically designed to demonstrate a significant difference and, therefore, reject the null hypothesis by proving that the
observed difference is unlikely to be commensurate with equivalent health outcomes of the healthcare interventions being compared. The superiority trial then estimates the probability that the effect exists when the null hypothesis is true, using the test statistic (p-value). The smaller the size of the p-value, the more likely it is that the null hypothesis is false and that a difference does exist between the health benefits generated by the treatments. Therefore, p-values can identify statistically whether or not an effect is likely by conveying information about the probability of an incorrect inference given the observed effect, but can say nothing about the size of the effect or its clinical relevance.

In cost-minimisation analyses the clinical evidence from failed superiority trials is often misinterpreted as proving that the healthcare interventions being compared are clinically equivalent. As a result, the majority of published cost-minimisation analyses are fundamentally flawed. The methodological flaws that lead to the misinterpretation of clinical trial results can also:

‘... lead to false claims, inconsistencies and harm to patients’.

Lack of guidance regarding the interpretation and appropriate use of clinical evidence to support the use of cost-minimisation analyses may partly explain why cost-minimisation analyses are frequently based on the results of failed superiority trials without even acknowledging that the non-significant results regarding superiority are not necessarily indicative of clinical equivalence. There will be failed superiority trials that are well designed and do have adequate sample sizes and high power. To what extent data from these trials could be used to provide reasonable approximations of health benefits for use in cost-minimisation analyses is a question that is still open to debate.

Equivalence trials
In the case where a less expensive new healthcare technology has been introduced, the aim of the clinical trial programme may simply be to rule out significant clinical differences between the new treatment and the existing gold standard. Where this is the case, equivalence trials can be designed to show that two healthcare interventions have equivalent therapeutic effects. Equivalence trials are intended to demonstrate that the effect of a new treatment is not worse than the effect of the current treatment by more than a specified equivalence margin.

Briggs and O’Brien conclude that the only circumstance in which cost-minimisation analysis represents a legitimate methodology is when clinical equivalence has been unambiguously proven in an equivalence trial. They conclude by stating that:

‘... unless a study has been specifically designed to show the equivalence of treatments ... it would be inappropriate to conduct cost-minimization ... analysis’.

However, the difficulties of conducting equivalence trials are many and alternative approaches for demonstrating clinical equivalence should therefore be explored. The clinical results from an equivalence trial therefore represent the most appropriate evidence that could be used to inform cost-minimisation analyses. However, it cannot be unequivocally claimed that two healthcare technologies are clinically equivalent.

‘It is never correct to claim that ... there is no difference in the effects of treatments ... There will always be some uncertainty surrounding estimates of treatment effects, and a small difference can never be excluded’.

Thus, even where the results of equivalence trials indicate no difference, this may simply indicate that the true difference exists outside the specified probabilities of error. A negative study result from an equivalence trial can take two forms: the confidence interval around the treatment difference may lie partially within the equivalence margin, or it can lie entirely outside the clinical equivalence margin. In either case, it cannot be confirmed that the researchers have demonstrated equivalence; that is, the probability of a difference between the two treatments is not rejected.

In an equivalence trial, the hypothesis of
equivalence is supported when the confidence interval surrounding the point estimate of the treatment difference lies completely within the equivalence margin. In cases where the equivalence margin lies either partially or entirely outside the equivalence margin (Figure 1), the hypothesis of equivalence is rejected.

**Non-inferiority trials**

The rationale behind a non-inferiority trial is to demonstrate that a new health intervention is not worse than the current health intervention by more than a prestated clinical margin. This type of trial is useful when the clinical issue relates to the extent to which the new healthcare technology is as good as current therapy. In non-inferiority trials the analysis is focused entirely in one direction — typically that the new treatment is not worse than the established therapy by more than the non-inferiority margin specified. An improvement of any size fits within the definition of non-inferiority.

In non-inferiority trials, the null hypothesis assumes that a new treatment is inferior to current treatment. This hypothesis is supported when the confidence interval around the treatment difference lies entirely outside the lower bound of the non-inferiority margin. If the lower bound of the confidence interval lies above the non-inferiority margin (Figure 2), then non-inferiority is not demonstrated.
Conclusions
Where cost-minimisation analyses are based on valid claims of clinical equivalence, they represent an appropriate method of economic evaluation. However, there is currently inappropriate use of clinical evidence to support claims of clinical equivalence and, in such circumstances, healthcare professionals would be wise not to rely too heavily on the results of currently published cost-minimisation analyses. However, great efforts are being made to improve the reporting and interpretation of RCT evidence, and this provides potential for improvements in the conduct and interpretation of cost-minimisation analyses. The extent to which such potential improvements will be realised in practice depends on the extent to which a greater understanding can be generated of the need to enhance the quality and appropriateness of the cost-minimisation analyses being produced. If the results of cost-minimisation analyses are to form a reliable basis for healthcare decision-making, then due consideration must be given to the sources and appropriate uses of clinical evidence to support the claims of clinical equivalence that are crucial to the adoption of the cost-minimisation analysis methodology. Table 1 outlines the key characteristics of trial designs for assessing equivalence in therapeutic interventions.

Evaluators undertaking cost-minimisation analysis analyses need to be clear on what is meant by the phrase ‘identical or similar’ outcomes, as cost-minimisation analysis requires the clear demonstration of clinical equivalence. However, given the heterogeneous nature of patient populations and treatment outcomes, it may be not be possible to determine exact equivalence between competing healthcare technologies. Any analysis that uses the results of a failed superiority trial (without an \textit{a priori} statement of non-inferiority) to inform a cost-minimisation analysis should be interpreted with caution.

The cost-minimisation approach to comparing healthcare technologies has always been used in a more haphazard manner than other methods of economic evaluation, despite its enormous potential value in facilitating the introduction of cheaper but clinically equivalent health interventions. It is crucial to ensure that an appropriate economic methodology is being employed if health economic analyses are to effectively inform the future allocation of scarce healthcare resources. In addition, the analytical techniques that are incorporated within the chosen economic methodology must be valid, accurate and appropriate. Only techniques that prove to be robust and reliable in improving healthcare decision-making should form the basis of those advocated for use by health economists.

The current use of RCT evidence to support statements of clinical equivalence is inadequate, and clear and appropriate decision rules are required in the future to ensure that

### Table 1. Key characteristics of trial designs

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Superiority</th>
<th>Non-inferiority</th>
<th>Equivalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normally placebo</td>
<td>Active comparator</td>
<td>Active comparator</td>
</tr>
<tr>
<td>Objective of study</td>
<td>To compare clinical efficacy</td>
<td>To evaluate whether a new intervention is no worse by a pre-established margin</td>
<td>To identify any meaningful clinical difference between competing interventions</td>
</tr>
<tr>
<td>Null hypothesis</td>
<td>No difference between interventions</td>
<td>New intervention is inferior by more than the non-inferiority margin</td>
<td>A clinically significant difference exists between competing interventions</td>
</tr>
<tr>
<td>Criteria for estimating equivalence</td>
<td>Comparison of clinical event rates for each intervention</td>
<td>Non-inferiority margin measures the smallest difference between interventions that is clinically acceptable</td>
<td>Equivalence margin measures the largest difference between interventions that is clinically acceptable</td>
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unambiguous evidence of clinical equivalence is a feature of future cost-minimisation analysis analyses. In the absence of such evidence, it would be potentially misleading to use such flawed analyses as the basis for healthcare decision-making.

Clearly, a wide range of methodological questions remains to be addressed urgently. This report has addressed a number of these issues in an attempt to outline the criteria that will ensure cost-minimisation analysis becomes a legitimate and valuable method of economic evaluation. While acknowledging that many of the areas addressed would have benefited from far greater depth of analysis, it is hoped that this report has introduced important concepts that will guide and assist future analysts undertaking and interpreting cost-minimisation analyses.

References