RESEARCH NOTE

Use of pharmacoeconomics in prescribing research. Part 2: cost-minimization analysis – when are two therapies equal?

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SUMMARY
This is the second paper in a series looking at pharmacoeconomic methods. The first paper discussed how costs are identified for pharmacoeconomic studies. This article will examine one of the four main evaluation methods in health economics, cost-minimization analysis (CMA). The remaining three methods (cost-effectiveness, cost-utility and cost-benefit analysis) will be discussed in later papers.

Key messages
• Cost-minimization is the appropriate form of economic analysis to carry out whenever two drugs have the same clinical effect.
• True equivalence studies are uncommon; a more useful approach is to assess the size of the confidence interval around the difference between treatments and determine whether it excludes clinically relevant effects.
• The critical issue for cost-minimization analyses is determining equi-effective doses.

Keywords: cost-minimization analysis, equivalence studies, pharmacoeconomics

INTRODUCTION
Cost-minimization analysis (CMA) is the simplest of the four evaluation methods (1) (see Table 1). A CMA should be performed and is appropriate when two interventions have been shown to produce the same, or similar, effects. If two therapies are considered clinically equivalent, then only the costs of the interventions need to be considered. Economic efficiency (see Part 1 of this series [Robertson et al. Journal of Clinical Pharmacy and Therapeutics (2003) 28, 73–79]) then dictates selection of the least costly intervention. Thus, the critical first step before conducting a CMA is determining the therapeutic equivalence of the interventions.

STATISTICAL SIGNIFICANCE, CLINICAL SIGNIFICANCE AND EQUIVALENCE
The randomized controlled trial (RCT) is considered to be the ‘gold standard’ for comparing two interventions. A well conducted RCT provides the best estimate of any difference in efficacy by protecting against uncontrolled confounding variables (through randomization) and any potential subjectivity of outcome assessments (through blinding) (2).

Any potential differences between two therapies should be assessed from both a clinical and statistical perspective. A clinically significant difference is the smallest difference in an outcome that would have a clinical impact on the patient. However, deciding what a clinically important difference is can be problematic. Unlike bioequivalence studies, where there are standards for defining ‘equivalence’ that have been established by drug regulatory authorities, when it comes to assessing clinical equivalence there are few clear guides, and hence there is often considerable difficulty in deciding what is a clinically important difference (3).

The usual approach in assessing studies is to consider both statistical and clinical significance, based on the summary estimate of the size of the
effect of treatment (expressed as relative and absolute risk) and the $P$-value calculated using the appropriate statistical test. Statistical significance indicates the probability of any difference identified in a study is found by chance is small (usually $<5\%$), i.e. the probability that the true difference is zero is small.

However, care must be taken in interpreting statistically non-significant findings. There is a temptation to interpret a non-significant difference as indicating equivalence, but non-significance indicates an absence of evidence of a difference. Hence the phrase ‘absence of evidence is not evidence of absence’ (4). Some authors argue that unless a study has been designed to show equivalence, it is inappropriate to conduct a CMA on the basis of any observed lack of significance in the differences between treatments (5). However, there are a number of difficulties in conducting equivalence studies.

**Equivalence studies vs. superiority studies**

Equivalence studies aim to demonstrate that the true difference between two therapies is unlikely to be outside a predetermined range ($-\Delta$ to $+\Delta$) (6). The values of $\Delta$ represent the difference that would be considered clinically significant. Thus, if the confidence interval of the difference lies entirely between $\pm\Delta$, then equivalence is demonstrated (Fig. 1). In Fig. 1, Trials A and B provide evidence of superiority of one intervention over the other because the confidence intervals do not include 0, and the point estimates of the difference are greater than that considered to be clinically significant ($>+\Delta$). Trials C–E would be considered as having shown equivalence. In Trial F, although the confidence interval spans 0 (indicating statistical non-significance), the confidence interval also includes values that indicate potential clinically important differences ($>+\Delta$ and $<-\Delta$). Hence the equivalence of the therapies is considered uncertain.

The sample size required for a trial is determined, in part, by the minimal difference that is to be detected. The larger the difference to be detected, the smaller the sample size required. In superiority studies the aim is usually to establish unequivocal clinical advantage over the comparator, often placebo, and hence the difference used is large. However, equivalence studies seek to show that two therapies are clinically indistinguishable (6). Thus, the difference to be detected is usually much smaller, and consequently the sample size required for equivalence studies is much larger than for superiority studies.
A second issue with equivalence studies is the rigour in which they are conducted and analysed. In trials designed to establish superiority, care is taken to minimize carelessness in the design, conduct and analysis as these may obscure any potential differences between therapies (6). Thus, a poorly designed superiority trial could be used as the basis for establishing equivalence. For example, if the dose of the comparative therapy is suboptimal it is possible to find therapeutic equivalence, when in fact the new therapy may have been inferior to the comparator had adequate doses of the comparator been used.

A third issue is that equivalence studies do not establish efficacy (i.e. they do not prove the therapy does something more than doing nothing at all). It is possible that neither therapy being compared is effective. One solution is to include a placebo arm in the equivalence study (3). If both therapies are more effective than placebo, but equal in efficacy to each other, then equivalence can be accepted. Alternatively, there should be sufficient evidence from other well-conducted clinical trials that the comparator has established efficacy over placebo before accepting equivalence.

There are also ethical issues concerning the conduct of equivalence trials (7). Current guidelines for the conduct of clinical trials are largely based on conventional trial designs where the aim is to determine superiority and reject the null hypothesis of no difference. The ethical principles that underpin these guidelines are based on the idea of clinical equipoise – that there is genuine uncertainty about the comparative clinical merits of two treatments (8). A defence of this argument appears to be more straightforward for superiority trials (i.e. that there is uncertainty whether one treatment is more effective than another) than for equivalence studies (i.e. that there is uncertainty whether the two therapies are the same).

Given the difficulties outlined above, it is not surprising that only a relatively small number of true equivalence studies are conducted. Further, as the pharmaceutical manufacturer performs most early studies with new medicines, it is logical that superiority studies are preferred. A pharmaceutical company would be more interested in claiming some advantage over its competitor, rather than equivalence, thus allowing them to argue for a higher price or promote the medicine to obtain a greater market share.

Therefore, although equivalence studies may be the ideal evidence for a CMA, in reality such analyses are often based on the results of a ‘superiority’ trial that has failed to detect a statistically significant difference. Those arguing against the acceptability of this do so largely from a ‘supplier’ perspective. Their position is that you do a disservice to the potential efficacy of the medicine by accepting an equivalent price, when a more statistically powerful study (i.e. larger study) may have found the differences to be significant. From a ‘purchaser’ perspective, it can be argued that it is unacceptable to risk paying more for a drug that has failed to equivocally show superiority to an existing therapy. This is the case in Australia when drugs are considered for subsidization on the Pharmaceutical Benefits Scheme. In the absence of data to support superiority, the drug is considered to be ‘no worse’ than its comparator and a cost-minimization approach is deemed the appropriate method of economic analysis (9).

One way forward in this argument is to move away from the distinction between ‘superiority’ and ‘equivalence’ trials. An alternative approach is to consider the size of the effect that is demonstrated in the studies and the width of the confidence interval around the size of the effect. A small study will have a large confidence interval – it is up to the reader to determine whether the interval includes or excludes potential clinically important differences between the two treatments. If it does not exclude these differences, then the conservative approach is to assume that the two drugs are not the same.

**Equi-effective Doses in Cost-minimization Analyses**

Once the decision to conduct a CMA has been made the greatest challenge is determining what the ‘equi-effective’ doses of the two therapies are; that is the doses of the drugs that produce the equivalent effect. There are several potential sources of this information.

**Data from randomized comparative studies**

Randomized clinical trials that form the basis of any claim of equal effectiveness are the logical
source of data on the equi-effective doses. However, the controlled nature of such trials can cast doubt on the equivalence of the doses used in such trials. Ideally, the dosing schedules in clinical trials should mirror those used in clinical practice. For example, if dose titration against a measure of clinical effect usually occurs in practice, then this should also occur in the clinical trials. A good example of this is the treatment of depression. Antidepressant doses are gradually increased until patients no longer suffer symptoms of depression. Some antidepressant trials, however, have used fixed doses without titration for one therapy, and variable doses of the other, or titration schedules that result in upward titration earlier than would occur in clinical practice. This approach can change the calculation of equi-effective doses to favour either drug, depending on the structure of the trial.

A second problem that can arise in determining equivalent doses is that the doses used in developmental studies of new drugs may not always end up being those that are used in clinical practice. Examples include the early studies of ondansetron (10) and sumatriptan, for which the original marketed dose of 100 mg was eventually halved. An economic analysis that compared sumatriptan with aspirin/metoclopramide based on the original studies would have ended up with quite different estimates of cost from those that would now be identified (11).

**Data from non-randomized and post-marketing studies**

Data from non-randomized and post-marketing studies may be used in CMA. The most obvious reason to use these types of data is that described above, where the dose of a drug used in a Phase II/III study turns out to be different from that used in practice. Other aspects of such studies that may be applied in CMA include the assessment of adverse events in clinical practice and measures of compliance. The measurement of these types of variables can often be unreliable and may introduce bias into economic evaluations.

**Expert opinion**

Another approach to identifying equi-effective doses is obtaining advice from clinicians who are familiar with the drugs of interest. Like post-marketing data, expert opinion can be useful when there is uncertainty that the doses in clinical trials reflect normal clinical practice. However, there are a number of problems with this approach. First, only a small number of ‘experts’ are usually involved in the data collection. Secondly, the types of clinicians approached may affect the results. For example, if psychiatrists at a large public hospital are asked what the average dose of an antidepressant used to treat depression is, this is very likely to be much greater than the average dose used by a general practitioner in the community, who would tend to see less severe cases. Finally, there is the issue of conflict of interest; if an ‘expert’ is being paid to provide his/her views, as is often the case, the likelihood of unbiased opinion will decrease.

**INCLUSION OF OTHER COSTS**

An important consideration in a CMA, once equi-effective doses have been established, is the consideration of other costs. Perhaps the best example of this is the cost of administering a drug and monitoring its usage. A theoretical example of how inclusion of conservative estimates of the cost of monitoring a drug can change the estimate of its cost-effectiveness is shown in Table 2. The effectiveness of the two drugs in terms of prevention of thrombosis is the same, but low molecular weight heparin (LMWH) is significantly more expensive than heparin for a course of treatment. If only drug costs are considered, then arguably the price of LMWH should be reduced substantially. As soon as one takes into account the cost of monitoring heparin therapy, the comparative costs of the two treatments are reversed – in fact, LMWH is cheaper and possibly more effective – economically dominant.

The difficulty that arises in the assessment of non-drug costs in CMA is where to draw the line.

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<th>Table 2. Heparin vs. LMW heparin</th>
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<td>Monthly drug costs ($AU)</td>
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<td>Monthly monitoring costs ($AU)</td>
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<td>Total monthly costs ($AU)</td>
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Most texts suggest that costs such as intravenous equipment for drug administration, tests used to monitor treatments, and clear differences in the time of health professionals involved in administering treatments should be included in economic analyses. More contentious is the inclusion of costs such as those arising from inpatient vs. outpatient care, time off work and other intangibles – and these can substantially alter the outcome of an economic evaluation.

**CHOICE OF COMPARATOR**

There are two issues with the comparator used as the basis of a CMA. First, the comparator should represent the accepted ‘best’ treatment for the condition. For example, a new antidepressant should be compared with say, selective serotonin reuptake inhibitors (SSRI) rather than older tricyclic antidepressant agents. Secondly, a new drug should be compared with an adequate dose of the comparator. As noted above, evidence that two drugs are equi-effective is not necessarily evidence that either drug is effective if subtherapeutic doses are used.

**EXAMPLES OF COST-MINIMIZATION ANALYSES**

Just as there are few published equivalence studies, there are only a relatively small number of published CMA. As with equivalence studies, this may reflect the resistance to publish studies that only claim a new drug is no better than existing therapies, that is, a form of publication bias. Examples in the literature include comparisons of the newer antiepileptic drugs (12), antibiotic treatment for various types of infections (13, 14) and comparisons of some chemotherapy regimens (15, 16).

**SUMMARY AND CONCLUSION**

Cost minimization analysis is appropriate where the two therapies being compared are considered equal in efficacy and safety. Although ideally clinical equivalence should be based on well conducted equivalence studies, in reality it is often taken from superiority trials that have failed to show any significant difference. One approach to resolving the issues of ‘non-superiority’ vs. ‘equivalence’ is to consider the size of the difference and the confidence interval around the difference in the analysis.

Although on the surface CMA appears to be the most straightforward of the four common types of economic analysis, careful consideration must be given to establishing the equi-effective dose, the appropriate comparator and the inclusion of costs other than drug therapy alone.

**REFERENCES**


American Journal of Health System Pharmacy, 56, 1521–1524.

