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THE DEATH OF COST-MINIMIZATION ANALYSIS?

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SUMMARY

Four different types of evaluation methods, cost-benefit analysis (CBA), cost-utility analysis (CUA), cost-effectiveness analysis (CEA) and cost-minimization analysis (CMA), are usually distinguished. In this note, we pronounce the (near) death of CMA by showing the rare circumstances under which CMA is an appropriate method of analysis. We argue that it is inappropriate for separate and sequential hypothesis tests on differences in effects and costs to determine whether incremental cost-effectiveness (or cost-utility) should be estimated. We further argue that the analytic focus should be on the estimation of the joint density of cost and effect differences, the quantification of uncertainty surrounding the incremental cost-effectiveness ratio and the presentation of such data as cost-effectiveness acceptability curves. Two examples from recently published CEA are employed to illustrate the issues. The first shows a situation where analysts might be tempted (inappropriately) to employ CMA rather than CEA. The second illustrates one of the rare circumstances in which CMA may be justified as a legitimate form of analysis. Copyright © 2001 John Wiley & Sons, Ltd.

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INTRODUCTION

Textbooks and guidelines on health economic evaluation typically distinguish four different types of evaluation method: cost-benefit analysis (CBA), cost-utility analysis (CUA), cost-effectiveness analysis (CEA) and cost-minimization analysis (CMA) [1–6]. Drummond et al. [7] consider all four of these techniques to be ‘full’ economic evaluation methods in that costs and effects are being compared between two or more alternative programmes. Among these techniques, CMA has considerable (and understandable) appeal to analysts and decision-makers who want to keep studies and evidence simple: if two treatments have the same outcome, then the lowest cost treatment is the treatment of choice.

In this note we pronounce the (near) death of CMA by showing the rare circumstances under which CMA is an appropriate method of analysis when sampled data on costs and effects are available. Donaldson et al. [8] have already noted that when designing a prospective economic evaluation, it is impossible to specify the technique of analysis (i.e. CEA versus CMA) because the data are unknown. Our contention is that even when the data are known, the use of CMA is rarely appropriate as a method of analysis.

The central focus of our discussion is how analysts determine whether programmes have ‘the same’ outcomes under uncertainty. Given recent advances in the analysis and presentation of cost-effectiveness under uncertainty—most notably net benefit analysis [9,10] and acceptability curves...
we argue that it is inappropriate for separate and sequential hypothesis tests on differences in effects and costs to determine whether incremental cost-effectiveness (or cost-utility) should be estimated. We argue that the analytic focus should be on the estimation of the joint density of cost and effect differences, the quantification of uncertainty surrounding the incremental cost-effectiveness ratio and the presentation of such data as cost-effectiveness acceptability curves.

CURRENT ANALYTIC CONVENTION WITH SAMPLED CEA DATA

Drummond et al. [7] present a matrix of nine possible situations that can arise when data on costs and effects are collected for two treatments, A and B. In Figure 1, each of the nine ‘boxes’ represents an area bounding the 95% confidence limits on observed differences in mean costs and effects. Where these boxes cross the axes of the cost-effectiveness plane, a ‘non-significant’ difference (at the 5% alpha level) in cost or effect difference is indicated. The standard interpretation of these boxes is as follows:

- **Situations 1 and 2** are cases of strong dominance: one treatment being more effective ($p < 0.05$) and less costly ($p < 0.05$) than the other, making it unambiguously the treatment of choice.
- **Situations 7 and 8** arise when one treatment has been shown to be both more effective ($p < 0.05$) and more costly ($p < 0.05$). By convention, the trade-off between costs and effects should be summarized by the incremental cost-effectiveness ratio (ICER).
- **Situations 4 and 6** are cases of weak dominance, arising when the difference in effect is not statistically significant ($p > 0.05$), but the difference in cost is significant ($p < 0.05$). These situations characterize conventional CMA, where the difference in effect is assumed to be zero and the least costly treatment is taken to be the treatment of choice.
- **Situations 3 and 5** are also cases of weak dominance, where the cost difference is not significant ($p > 0.05$), but the effect difference is significant ($p < 0.05$), with the decision rule to choose the most effective programme.

![Figure 1. Nine possible situations that can arise concerning the significance (or otherwise) of cost and effect differences illustrated on the cost-effectiveness plane. Boxes indicate the area bounded by the individual confidence limits on cost and effect: statistically significant differences are indicated where the box does not straddle the relevant axis. (Adapted from Drummond et al. [7] and Laska et al. [23])](image-url)
Situation 9 arises when no statistically significant difference in costs or effects is observed. In summary, the decision to estimate incremental cost-effectiveness or conduct CMA is driven by the observed data, and based on simple hypothesis testing of differences in mean costs and effects, using arbitrary type I error rates, such as 5%. But the deficiencies of hypothesis testing (in contrast to estimation) are well known and gave rise to the memorable adage that ‘absence of evidence is not evidence of absence’ [12]. The concern is that a focus on hypothesis testing leads to an overemphasis on type I errors (the rejection of the null hypothesis of no difference when there is, in fact, no difference) at the expense of type II errors (the failure to reject the null hypothesis of no difference when in fact a difference does exist). In a review of clinical evaluations, Freiman et al. [13] showed how a substantial proportion of studies reporting ‘negative’ results had insufficient power to detect quite important differences in treatment effect.

Consistent with these recent debates in the clinical evaluation literature, our contention is that the goal of economic evaluation is the estimation of a parameter—incremental cost-effectiveness—with appropriate representation of uncertainty, rather than hypothesis testing. The point estimates (means) from the cost and effect distributions provide the best estimates of the cost and effect of the alternative treatments and should be used in the primary analysis. While confidence intervals for cost-effectiveness ratios are valid approach to addressing uncertainty in CEA for situations 7 and 8, problems arise when uncertainty is such that the ICER could be negative [14]. However, these problems can be overcome either through the appropriate representation of uncertainty on the cost-effectiveness plane [11,15], or through the use of the net-benefit statistic that represents a new framework for handling uncertainty in CEA, and which does not suffer from the problems associated with the ICER in situations where negative ratios arise [9].

EXAMPLE 1: IMPLANTABLE CARDIOVERTER DEFIBRILLATORS

In the Canadian Implantable Defibrillator Study (CIDS) [16], 659 patients at high risk of ventricular arrhythmia were randomly assigned to receive an implantable cardioverter defibrillator (ICD) or drug therapy with amiodarone. Over 6 years of follow-up, the annual rate of all-cause mortality was 10.2% with amiodarone and 8.3% with ICD; a relative risk reduction of 19.7%, but with 95% confidence interval (CI) from $-7.7\%$ to $40\%$ (a two tailed $p$-value of 0.14). An economic evaluation was also conducted alongside the trial [17]. The primary measure of effectiveness for economic analysis was pre-specified as life expectancy. Mean survival among the amiodarone group (with 3% annual discounting) was 4.35 years, compared with 4.58 years with ICD; a difference of 0.23 years (95% CI $-0.09–0.55$; $p = 0.16$) in favour of ICD.

Using the conventional 5% alpha level, the gain in effect associated with ICD is not statistically significant, and the trial is ‘negative’. One option for economic evaluation would have been to conduct CMA based upon the assumption that life expectancy is identical for ICD and amiodarone treated patients. Based upon the reasoning above, the authors decided to estimate the incremental cost-effectiveness of ICD therapy with uncertainty. In 1999, in Canadian dollars, the mean cost per patient in the amiodarone group was $38600 versus $87715 for ICD; a statistically significant difference of $49115 with 95% confidence interval $41793–$56610. The incremental cost-effectiveness of ICD was computed in the usual way ($49115/0.23$) at $213543 per life-year gained.

Figure 2(a) shows the uncertainty associated with ICD cost-effectiveness as an elliptical joint density of mean cost and effect differences; the 95% confidence region for cost-effectiveness runs from a low of $88187 per life-year to amiodarone being dominant (less costly, more effective). The figure gives the reader a good sense that the key uncertainty that drives the ICER upwards is the size of the treatment effect, with the ellipse representing the joint density straddling the $y$-axis. ICD therapy having the same or worse effectiveness as amiodarone is consistent with the data, but the mass of the distributions are over the means with the best estimate of cost-effectiveness being $213543 per life-year gained.

Figure 2(b) summarizes the information from Figure 2(a) as an acceptability curve showing the evidence in favour of the intervention being cost-effective for different values of the maximum...
Figure 2. (a) Uncertainty in costs, effects and cost-effectiveness on the plane. Horizontal ‘I’ bar indicates the confidence interval for effect difference alone; the vertical ‘I’ bar indicates the confidence interval for the cost difference alone; the ellipses show the estimated contours of the joint density function (assuming joint normality of cost and effect differences) covering 5, 50 and 95% of the integrated joint density. (b) Uncertainty in cost-effectiveness summarized as an acceptability curve

acceptable incremental cost-effectiveness (ceiling) ratio appropriate for decision-making. The 50% point on the acceptability curve corresponds to the point estimate of cost-effectiveness. The acceptability curve is tending to 0.921, which is one minus the one-sided $p$-value on the effect difference. A 95% interval for cost-effectiveness can be obtained by reading across from the 0.025 and
0.975 points to where they intercept with the acceptability curve. This shows the lower limit on cost-effectiveness to be $88187 per life year gained, while the upper limit is undefined (since the effect difference is not significant). Note that this method of obtaining a confidence interval for cost-effectiveness from the acceptability curve does not give a confidence interval on the ICER statistic, as the ceiling ratio is defined only in positive quadrants of the cost-effectiveness plane. Therefore, statistical problems associated with negative ICERs are avoided [14], and the interval is equivalent to that obtained under the net-benefit framework [9].

An important post-script to CIDS is that a subsequent pooled analysis of the three trials comparing ICD and amiodarone (CIDS, The Antiarhythmics versus Implantable Defibrillators (AVID) Investigators [18] and the Cardiac Arrest Study Hamburg (CASH) [19]) found a significant 27% relative risk reduction in all-cause mortality ($p = 0.002$), suggesting that CIDS may have been underpowered. Overall, we feel that CMA would have been wasteful of information, proceeding as it does from simple hypothesis tests rather than estimation.

**EXAMPLE 2: DEEP VEIN THROMBOSIS TREATMENT**

One possible circumstance where it might be viewed as legitimate to conduct CMA is where a randomized trial has been designed to test the explicit hypothesis of equivalence in outcome between two therapies. An example of this situation is the study by O’Brien et al. [21] comparing two treatments for deep vein thrombosis (DVT): in-hospital treatment with unfractionated heparin versus at-home therapy with low molecular weight heparin (enoxaparin). This economic evaluation was a conducted alongside a clinical trial predicated on a safety and efficacy equivalence hypothesis: that the group sent home to self-inject with enoxaparin would experience no greater rates of bleeding or DVT recurrence as those kept in hospital. Accordingly, the primary economic hypothesis was one of weak dominance: that home treatment was as safe and effective as hospital treatment, while being less costly. The data were consistent with this hypothesis: there were 11 thromboembolic events in 151 heparin-treated patients, and ten events in 149 enoxaparin-treated patients ($p = 0.88$) and no significant difference in bleeds. Over 3 months, the hospital group mean cost per patient was $5323 versus $2278 for home treatment, a saving of $3045 in favour of home treatment, with 95% CI on savings from $2012 to $4050.

We consider this DVT study to be a legitimate case for prospective CMA design and analysis. However, we should add that the protocol did call for a secondary analysis of cost-effectiveness if the data had shown clinical effectiveness to differ significantly between groups. One possibility might have been slightly higher rates of DVT recurrence, or bleeds in the home treatment group accompanied by large cost savings, suggesting the need to estimate incremental cost-effectiveness. We believe that this form of CMA—conducted alongside an equivalence trial—is the exception rather than the rule. Equivalence trials are rare because they require a much larger sample size than those designed to test for differences [22].

It should be noted that the more comprehensively one defines outcome or effectiveness, the less likely it becomes that equivalence between treatments will be established. Hence, in the DVT example, a CUA would have likely yielded an outcome difference in favour of home treatment by virtue of the improvement in quality of life.

**CONCLUDING COMMENT**

It is clear that when undertaking a CEA of a treatment intervention, it is not possible to specify the evaluative technique in advance. Furthermore, since ‘absence of evidence is not evidence of absence’, we argue that unless a study has been specifically designed to show the equivalence of treatments (in terms of costs or effects), it would be inappropriate to conduct cost-minimization or outcome-maximization type analysis on the basis of an observed lack of significance in either the effect or cost differences between treatments. Instead, analysts should focus their attention on estimation of cost-effectiveness rather than on hypothesis testing of cost or effect differences.
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REFERENCES