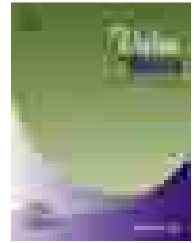


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EDITORIALS

Clinical Trials Provide Essential Evidence, but Rarely Offer a Vehicle for Cost-Effectiveness Analysis



All health care systems that are collectively funded through taxation or insurance make funding and coverage decisions considering value for money. Over the past 25 years or so, more systems have started to use formal cost-effectiveness analysis (CEA) to inform decisions, particularly those relating to the funding of new prescription pharmaceuticals. Inevitably and correctly, decision makers augment CEA with their own judgments about the reliability and relevance of evidence and the consequences of interventions, which may be poorly reflected in CEA outcomes. One important contribution of the greater use of CEA, however, has been to highlight some key principles that should be used in making resource allocation decisions. CEA undertaken alongside randomized controlled trials (RCTs) will often be inconsistent with these principles [1].

RCTs provide highly valuable evidence to support decision making. This is particularly true in the case of relative treatment effects, the estimation of which ideally requires randomization to reduce the risk of selection bias. Trials can provide other valuable information for CEA including data relating to the disease under current treatment(s), as well as resource use and health-related quality-of-life data. ISPOR's updated task force report on CEA alongside trials provides important guidance on how economic considerations should shape the design of the trials and the methods of data collection [2]. But a *trial-based* CEA goes beyond the use of evidence collected in RCTs in CEA. Such a study relates only to the population included in the trial, just includes the clinical and resource use evidence from that RCT, compares only those interventions to which patients were randomized, and has a time horizon defined by the trial's follow-up period. How often are these characteristics consistent with the key criteria for evidence-based decision making?

A number of important principles exist in undertaking CEA to support decisions. When assessing the relevance of *trial-based* CEA, four seem important to emphasize. The first is that CEA should relate to the population that will actually receive the interventions being evaluated. The task force provides a helpful summary of the challenges to the *external validity* of trials and some methods to address these. Often, concerns about external validity relate less to a trial's estimates of relative effectiveness and more to absolute benefits, which also drive cost-effectiveness. This can be dealt with using modeling. The relative treatment effect is taken from the trial (e.g., a hazard ratio) and is applied to a baseline measure. The latter should relate to the population of interest and can often come from locally available nonrandomized data because no treatment effects are being estimated. This use of modeling and multiple sources of evidence are also helpful in guiding decisions for subpopulations in whom

heterogeneity in baseline risks can drive important differences in cost-effectiveness. There are good examples in coronary stents [3] and treatments for acute coronary syndrome [4].

A second key principle is that the time horizon of the CEA should reflect the period over which the costs and benefits of the options being evaluated can differ. The task force is clear that follow-up periods in trials are often shorter than the necessary time horizons for CEAs and that extrapolation will generally need to be undertaken using modeling, sometimes using data other than from the trial.

The third principle that needs to be reflected in a CEA is to include all options (or comparators against a new intervention). For most diseases, there is an extensive range of interventions available. Furthermore, sometimes management is in the form of strategies such as treatment sequences or the use of starting or stopping rules for therapies. The designs of RCTs rarely reflect the full range of management options available, but CEA usually seeks to inform decisions such as the best way of treating patients, the most appropriate diagnostic strategy, or whether a new technology is better than existing alternatives. Undertaking a CEA based only on the options compared in a single RCT, rather than the full range of alternatives, risks generating misleading conclusions to guide decisions. Trial-based CEA may be suitable when, for example, a new treatment is being evaluated on top of usual care, which is represented in the trial's control group. More generally, however, bringing evidence together from a number of clinical studies is necessary to consider all alternatives, and this will need a modeling framework.

The final principle is one CEA holds in common with evidence-based medicine more generally: the need to incorporate all relevant evidence. Trial-based CEA is invariably, however, based on the evidence generated by one RCT, so any other evidence on treatment effects, outcomes, and resources is effectively ignored. In guiding decision makers about whether to fund a new technology, CEA would need to consider, for example, all RCTs (and perhaps observational studies) generating estimates of treatment effect for the new intervention and all comparators. This is why systematic review and evidence synthesis are such important components of health technology assessment [5]. The combination of the need to include all alternatives and relevant evidence in CEA is a major factor behind the development of network meta-analysis to estimate the relative effectiveness of treatments not directly compared in RCTs [6]. To bring together the full range of evidence on all parameters bearing on cost-effectiveness needs modeling, and good examples abound [7,8].

The importance of RCTs in generating evidence is beyond doubt, but what is the role of trial-based CEA? In principle, such analyses are consistent with the needs of decision making if they include the full range of alternative options, relate to the population for which the decision is being taken, represent the sole source of relevant evidence, and have a follow-up consistent with the appropriate time horizon. In practice, some trial-based CEAs exist that satisfy these criteria even if they do so more qualitatively than quantitatively. It remains the case, however, that analysts should design their studies on the basis of principles of evidence-based decision making rather than the availability of data from a particular trial, and this will generally lead them to conduct CEA using systematic review, evidence synthesis, and decision analytic modeling.

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