Extrapolation of survival data in cost-effectiveness analyses: the need for causal clarity

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Decision-makers require predictions of cost-effectiveness over a time horizon that is sufficient to capture material differences in costs and health outcomes across relevant comparators. The ideal Randomized Controlled Trial (RCT) for the purpose of cost-effectiveness analysis (CEA) would: include all relevant comparators; produce unbiased precise estimates when analyzed as randomized, and measure all endpoints relevant to the decision over a sufficient time horizon. Such trials are rare. To fill this gap, decision analytic models are developed to synthesize the available evidence in an attempt to recreate an "ideal trial". Decision models that include 'time to event' endpoints typically need to extrapolate from the observed data to account for censoring.

The method(s) chosen for extrapolation should minimize bias and maximize precision. However, in practice, it is challenging to assess and balance these criteria. It has been recognized that we are unlikely to obtain the best estimates simply by ever closer scrutiny of data from individual trials. Rather, we need to select methods that make use of the available evidence in its entirety - including trial and observational data, and expert opinion. The methods chosen should also be transparent and facilitate sensitivity analysis. This allows decision-makers to judge whether additional evidence is required, and to substitute their own judgements regarding uncertain parameters. This laudable goal raises important research questions regarding the appropriate selection of methods for synthesis and temporal extrapolation.

The eight papers published in this special issue highlight recent progress in methods for extrapolation in CEA. Several of these papers discuss different aspects of evidence synthesise. Guyot et al, harness Bayesian multi-parameter evidence synthesis to combine evidence from four sources: an RCT, general population database, cancer registry and expert opinion.[1] Negrin et al, argue in favour of Bayesian model averaging as a principled approach for weighting alternative parametric extrapolations.[2] Jackson et al's methodological review, defines the assumptions made by approaches for incorporating external data.[3] The authors also promote a future research agenda for developing methods to formally eliciting expert opinion for extrapolation methods. Hoogenveen et al present a mathematical modelling approach to predicting the effects of interventions on mortality across multiple disease areas.[4] Lousdal et al advocate an approach for estimating mean survival times when only published estimates of median survival are available.[5] Meacock et al consider some of the issues that may arise when attempting to extrapolate survival in the broader setting of health policy evaluations.[6] The papers by Williams et al. discuss the relative merits of extrapolation models with alternative structures, namely partitioned survival models (PSMs) and state transition models (STMs), for example multi-state and markov models.[7,8] In the Williams et al case study, the estimates of the Incremental Cost-Effectiveness Ratios (ICERs) range from £13,000 to £29,000 per QALY, according to precisely

which method is chosen.[7] Clearly, the choice of which model structure to use for extrapolation should take could be an important factor in the ultimate treatment recommendation (Bagust & Beale 2014).[9]

In PSMs, the relationship between treatment and eeach time to event endpoint, for example progression or death, is estimated independently. In this form of modelling, the cumulative probabilities of experiencing an event are estimated directly as a function of time - transitions between states are not explicitly modelled. By contrast, in STMs, transitions between states are explicitly modelled. Compared to PSMs, STMs are more complex in both implementation and estimation of model parameters. That said, the tutorial paper by Williams et al should help analysts armed with the requisite Individual Patient Data (IPD), implement even the more complex forms of STM, such as multi-state models.[8] We believe that an appreciation of the underlying causal relationships is pivotal when selecting an appropriate approach. We illustrate the causal frameworks for these two approaches in figure 1. Although these diagrams appear simple, the underlying causal assumptions are not.

In PSMs the causal relationships between endogenous variables are not explicitly modelled. Endogenous variables are those that are estimated within the model, such as time to progression and time to death. An example of a causal relationship between endogenous variables is the relationship between the time to progression, and the subsequent time to death (i.e. post-progression survival). In PSMs such relationships are not modelled explicitly. A natural consequence of keeping these relationships implicit is that this limits the scope for sensitivity analyses concerning the underlying causal assumptions. For example, it is difficult to make alternative assumptions about the effect of treatment cessation on outcomes, such as no, or tapering, additional effect beyond the end of treatment. When developing PSMs, it is essential to consider the underlying assumptions about the causal relationships between endogenous variables. By contrast, the causal relationships between endogenous variables are explicitly modelled in STMs. This facilitates sensitivity analyses related to these causal relationships and, in addition, external evidence on specific causal relationships can be included.

Both these model structures face important concerns regarding the potential for bias if the underlying causal assumptions are not met. With PSMs, a concern is that the extrapolation of overall survival typically does not account for the effects of endogenous variables such as progression or treatment status. Despite this omission, censoring is still treated as uninformative. With STMs, the outstanding concern is that the estimation of post-randomization causal relationships between endogenous variables, such as time to progression and subsequent survival time, may be subject to omitted variable bias. For example, if the model estimates the time to death post-progression, but ignores the causal effect of time to progression on subsequent survival time, the model will provide biased estimates of effectiveness and cost-effectiveness.

The chosen approach should make the best use of the available data, and allow decision-makers to understand and explore uncertainties about these fundamental causal relationships. STMs are attractive in allowing a wider synthesis of data and more extensive sensitivity analysis compared to PSM. However, we should not underestimate the challenge in obtaining unbiased estimates for all of the causal relationships underlying a STM. Likewise, we should be mindful of the credibility of the conditional independence relationships embedded in PSM models.

For either PSM or STM, there is a strong argument for considering the effects of endogenous variables, perhaps by incorporating time-varying variables in the survival modelling. Whichever method is chosen, access to IPD and careful consideration of causal assumptions is essential to improve the quality of CEA, and subsequent decisions about the choice of health care technologies and services. The stakes are high; as regulatory and government agencies move to ever faster access to new technologies specific to the individual patient's prognosis, there will be increased pressure to develop approaches that make the best use of available evidence when predicting the effects of alternative interventions on patients' long-term health.

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