

## Merging Regulatory and Reimbursement Needs in Clinical Trials



The ISPOR Cost-Effectiveness Analysis Alongside Clinical Trials Good Research Practices II Task Force Report achieves its stated objective, to refresh the 2005 Task Force Report with developments that have taken place over the past 9 years [1,2]. Certain fundamental components of the original report remain the same (e.g., data should be fully integrated into the trial; incremental analyses should be reported with appropriate measures of uncertainty based on an intention-to-treat analysis). However, the authors conveniently highlight in Table 1 several updates that should improve the quality of the economic evaluations conducted. Despite advances over the past 9 years, there remain areas in which further research and more detailed guidance are needed. Below are just a few areas in which I hope the (future) third Task Force will report that progress has been made.

As noted by the Task Force, early joint advice meetings with both regulatory and HTA agencies are now offered in some jurisdictions. These meetings have the potential for clarifying the issues in a comprehensive manner and ideally leading to greater harmonization of the evidentiary needs of the regulators and reimbursement agencies. With such alignment, the Task Force could emphasize that the choice of relevant patient population, comparator and study endpoints would be most important, in combination with a discussion of how well the sponsor's plan will meet these needs. Thus, earlier and closer alignment of the evidence generation plans for regulatory and reimbursements purposes are needed in the planning process. It is important to recognize that not all clinical trials lend themselves to conducting cost-effectiveness evaluations (either within the study period or thru extrapolation beyond the time horizon of the study). In these cases, clinical trials may still provide an opportunity to collect data that will inform a future cost-effectiveness model. Regardless of the intended purpose of the trial, there must be a shared, early understanding of the research objectives (both clinical and economic) to ensure the design adequately addresses these needs.

Randomized clinical trials (RCTs) commonly enroll patients across several countries. Because of questions about the generalizability of economic results and the desire for country-specific analyses by decision-makers, the design and analysis of these multinational RCTs continue to present challenges for the researcher. The selection of countries and the distribution of patients across the countries are critical design elements that are often decided without consideration of their impact on the economic evaluation. Thus, guidance is needed on how to determine whether a country should be represented (or not) in a specific RCT based on the potential impact of this decision on pricing and reimbursement. In multinational RCTs, the Task Force recommends the collection of provider-, site- and jurisdiction-specific baseline data, but we need a better understanding of what measures will be most useful to incorporate into the analysis. There also remain questions as to how trial-wide data can best be utilized to obtain country-specific estimates for participating countries as well as country-specific predictions for non-participating countries. Because decision-makers are most interested in economic evaluations tailored to their particular setting, additional research is needed to continue to refine the guidance.

Value of Information (VOI) continues to be touted from a theoretical basis, but has yet to take hold in practice. The report notes that VOI analyses should help inform the decision-makers on how much money they should be willing to spend in order to reduce uncertainty in the trade-off decisions they must make. In practice, however, the sponsor of a new technology remains responsible for providing evidence that supports recommended spending levels. Thus, it would seem VOI analyses might be best used to assess how much the sponsor should be willing to spend to collect additional data from an RCT(s) in order to reduce uncertainty in the decisions made by HTA agencies. Practical guidance on how to conduct VOI analyses from this perspective (to justify collection of key data for reimbursement purposes) would be quite useful for economic researchers.

For reimbursement needs to be fully integrated into the clinical trial program, guidance is needed to bring even greater analytic rigor to trial-based economic assessments. Pre-testing may be needed during Phase II trials in order to test the viability of collecting resource utilization or utility measures in the patient population of interest. If pre-testing occurs, it may also support VOI calculations used to identify and justify collection of critical data elements in subsequent trials for reimbursement purposes. Results from these early trials can also be used in power calculations to inform decisions on whether to include formal hypotheses around these measures. Finally, economic analysis plans must continue to increase in their scope and specificity. Key subgroups for reimbursement purposes should be identified early in the drug development process (early economic models can be used for this purpose). Guiding principles for subgroup analyses in trial-based cost-effectiveness evaluations should be followed [3]. In addition, if a beyond-trial projection will be made to assess cost-effectiveness, a pre-specified analysis plan should describe how it will be conducted. While plans may need to be adjusted to respond to unanticipated study findings, it doesn't negate the value of prespecification in elevating the scientific rigor (and shared understanding) of the intended economic evaluation.

Although progress has been made since the first report was issued in 2005, economic evaluations are still viewed as being conducted alongside clinical trials, as if an add-on or after thought to the regulatory objectives. Hopefully, by the time of the

Source of financial support: The author has no other financial relationships to disclose.

next Task Force report, guidelines will be provided for the conduct of economic evaluations "based on" clinical trials, where the regulatory and reimbursement needs are fully merged.

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1098-3015/\$36.00 - see front matter Copyright © 2015, International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Published by Elsevier Inc. http://dx.doi.org/10.1016/j.jval.2015.02.007

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