Analytic Considerations in Economic Evaluations of Multinational Cardiovascular Clinical Trials

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ABSTRACT

Objectives: The growing number of economic evaluations that use data collected in multinational clinical trials raises numerous questions regarding their execution and interpretation. Although recommendations for conducting economic evaluations have been widely disseminated, relatively little guidance has been given for conducting economic evaluations alongside clinical trials, particularly multinational trials.

Methods: Building on a literature review that was conducted in preparation for an expert workshop, we evaluated a subset of methodological issues related to conducting economic evaluations alongside multinational clinical trials.

Results: We found wide variation in the types of costs included as part of the analyses and in the methods used to assign costs to hospitalization events. Furthermore, we found that the extrapolation of costs and survival outcomes beyond the trial period is an inconsistent practice and is often not dependent on whether a survival benefit was observed in the trial or on the epidemiology or practice patterns in the country to which the findings are directed.

Conclusions: Although the limited sample size precluded a quantitative analysis of trial characteristics and their associations with the methodologies employed, our findings highlight the need for more guidance to analysts regarding the execution of economic evaluations using data from multinational clinical trials. As the research community grapples with the complexities of methodological and logistical issues involved in multinational economic evaluations, the development of a standardized format to report the basic methodological characteristics of such studies would help to improve transparency and comparability for other analysts and decision-makers.

Keywords: cardiology, clinical trials, costs and cost analysis.

Introduction

Modern clinical trials must be designed to address several converging trends, including the diminishing magnitude of clinical benefit expected beyond what can be achieved with contemporary medical treatments, the growing desire for outcome-oriented end points, and expanding requirements for economic evaluations of new therapies. One consequence of these trends has been an increase in the number of patients enrolled in individual clinical trials [1,2]. The challenge of recruiting thousands of eligible patients in an expeditious manner has increasingly been met by crossing international borders. Also, to meet the needs of decision-makers in regulatory, reimbursement, and managed care settings, many clinical trials now incorporate economic end points that require collection of resource use data as part of the trial design. The joint effect of these trends has been the proliferation of economic evaluations conducted alongside multinational clinical trials.

The growth in the number of economic evaluations that use data from multinational clinical trials has raised questions concerning how best to conduct and interpret such analyses [3]. Although recommendations for conducting economic evaluations have been widely disseminated [4,5], relatively little guidance has been given for conducting economic evaluations alongside clinical trials [6], and even less attention has been given to issues specific to multinational trial settings. Nevertheless, several recent reports have addressed the difficult issues of generalizability and cross-national comparisons of costs in economic evaluations [3,7–11]. The complexities of multinational economic evaluations are neither minor nor academic, because the validity and generalizability of economic evaluations are critically important to decision-makers around the world who rely on cost-effectiveness information.

In a 2003 workshop on conducting economic evaluations alongside multinational clinical trials [9], experts focused on developing a categorization scheme for different approaches to conducting multinational economic evaluations, including advantages and disadvantages of various approaches and a literature review of economic evaluations conducted alongside multinational clinical trials in cardiology. Although this article draws on the literature review conducted in...
preparation for the workshop, our focus is different. Here we explore additional issues raised at the meeting—specifically, the types of costs included in the analysis, the costing strategies employed, and the extrapolation of costs and outcomes beyond the clinical trial period.

Types of Costs, Costing Strategies, and Extrapolation of Costs and Outcomes Beyond the Trial

Guidelines for conducting economic evaluations recommend that the time horizon for the evaluation of costs be consistent with the time horizon necessary to capture all downstream, health-related effects of the intervention [4,5]. This goal is usually accomplished through reliance on primary data to represent short-term effects and some type of modeling exercise to extrapolate costs and health outcomes to a longer-term time horizon. There is little debate that inclusion of disease-related costs, including downstream costs, is necessary in economic evaluations of medical interventions. Disagreement does exist, however, about whether medical costs not associated with the condition under study should be considered [4,5,12]. Some experts argue that both disease-related and unrelated medical costs should be included in economic evaluations, because it is often difficult to differentiate between costs that are associated with the disease and those that are not [13]. An opposing view holds that focusing only on disease-related costs allows greater precision in detecting the effects of the treatment by minimizing the “noise” that occurs when all costs are included [12]. In addition, there is debate regarding the inclusion of future costs for unrelated medical and nonmedical costs incurred during added years of life [5,14,15]. Reflecting this ongoing debate, the Panel on Cost-Effectiveness in Health and Medicine suggests excluding future unrelated costs from the reference-case analysis but exploring the impact of their inclusion in sensitivity analysis [4]. Lastly, the handling of indirect costs is another source of debate [13].

Additional Considerations Related to Extrapolation of Costs and Outcomes Beyond the Trial

In multinational settings, theoretical and methodological issues regarding unit costs and cost assignment are complex. First, unit costs for medical resources differ across countries. Second, the availability of medical resources differs across countries. Third, indirect costs resulting from lost productivity and friction costs vary because of wage rates and worker productivity. It is also likely that the propensity for patients with the same health status to drop out of the workforce differs across countries with various social welfare systems and sociocultural norms [16]. In addition, patient demographics, the epidemiology of disease, and clinical practice environments vary considerably across international borders [7]. The intensity of medical resource use for the same condition may similarly vary. These variations can complicate multinational clinical trials, because pooled resource use data may not apply to individual locales or their decision-makers [11]. This problem is exacerbated by the variation in methodological approaches in economic evaluations, particularly the extent to which analysts allow resource use to vary by country [10].

Additional Considerations Related to Extrapolation of Within-Trial Outcomes in Multinational Settings

As noted above, international differences in patient characteristics and clinical practice patterns exist. Assuming that these factors are associated with long-term survival and costs, methodological and interpretative difficulties arise when within-trial outcomes are extrapolated to a longer time horizon. For example, should extrapolation of survival be based on some parametric extrapolation of the data collected in the trial, thus producing estimates that reflect the study population? Or, for analysts attempting to customize the analysis for a particular country, should the extrapolation of survival be more specific? If sample size allows, parametric extrapolation based on a selected patient subgroup can be performed or epidemiological data from the country of interest can be applied to the trial population so that estimates might better reflect life expectancy in that country. Similar issues arise for extrapolation of costs beyond the trial period, because costs and the intensity of medical resource use vary across countries through different stages of disease.

How can these issues be handled adequately in a multinational economic evaluation? Using the basic framework of types of costs discussed above, this article focuses on three of these issues. Specifically, we sought to describe the types of costs that have been considered in published studies and how they have been estimated in economic evaluations conducted alongside multinational clinical trials in cardiology. We also sought to describe whether analysts extrapolated cost and survival outcomes beyond the trial period. In addition to the descriptive analysis, we also attempted to identify trial characteristics that may be associated with the methodological strategies employed in the studies.

Methods

The economic evaluations included in this analysis were identified in a previous literature review [9]. The literature search was conducted using MEDLINE and International Pharmaceutical Abstracts to identify economic evaluations conducted alongside multinational clinical trials in cardiology. Additional studies were located through contact with authors and by reviewing bibliographies of clinical and economic reports from multinational clinical trials. Relevant articles were limited to
those that used patient-level data as the basis for the analysis. Articles in which an economic model served as the primary analytic framework were excluded to maintain consistency among the analyses reviewed.

Results

Twenty-three studies met our inclusion criteria. The studies ranged in size from 471 to 41,021 patients and tested a variety of treatments, including angiotensin-converting enzyme (ACE) inhibitors, tissue plasminogen activator (tPA), and glycoprotein IIb/IIIa receptor inhibitors. The studies generally enrolled patients from Europe and North America, although some studies also enrolled patients from South and Central America. Of the 23 studies, 5 were limited to within-trial cost comparisons. The remaining 18 studies included cost-effectiveness (or cost-utility) analyses and form the basis of this analysis [17–34].

Table 1 provides a summary of the studies, including the names of the clinical trials on which the economic evaluations were based, the number of countries represented in the trials, and the interventions under study. Of the 18 studies, 3 were based on the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, which compared epifibatide to placebo in patients with acute coronary syndrome; 2 were based on the Heart Outcomes Prevention Evaluation trial, which evaluated the efficacy of the ACE inhibitor ramipril relative to placebo in patients at high risk for cardiovascular events; and 2 were based on the Studies of Left Ventricular Dysfunction trial, which compared the ACE inhibitor enalapril and placebo in patients with heart failure. The other trials included in our analysis were represented by only one economic evaluation each, thereby limiting our ability to evaluate the impact of methodological variations applied to the same trial data.

<table>
<thead>
<tr>
<th>Report</th>
<th>Trial, sample size</th>
<th>Number of countries</th>
<th>Comparison and patient population</th>
<th>Patients hospitalized at randomization</th>
<th>Costing begun with index hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bjoeholt et al. [17]</td>
<td>HOPE, n = 9297</td>
<td>19</td>
<td>Ramipril vs. placebo in patients at high risk of cardiovascular events</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Brown and Armstrong [18]</td>
<td>PURSUIT, n = 10,948</td>
<td>28</td>
<td>Eptifibatide vs. placebo in patients with acute coronary syndrome</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Brown et al. [19]</td>
<td>PURSUIT, n = 10,948</td>
<td>28</td>
<td>Eptifibatide vs. placebo in patients with acute coronary syndrome</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cathomas et al. [20]</td>
<td>PREVENT, n = 825</td>
<td>2</td>
<td>Amlodipine vs. placebo in patients with coronary atherosclerosis</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cook et al. [21]</td>
<td>SOLVD, n = 6797</td>
<td>3</td>
<td>Enalapril vs. placebo in patients with left ventricular dysfunction and hypertension</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dasbach et al. [22]</td>
<td>ELITE, n = 722</td>
<td>3</td>
<td>Losartan vs. captopril in patients with heart failure</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ekman et al. [23]</td>
<td>CIBIS II, n = 2647</td>
<td>18</td>
<td>Bisoprolol vs. placebo in patients with heart failure</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Erhardt et al. [24]</td>
<td>AIRE, n = 1986</td>
<td>14</td>
<td>Ramipril vs. placebo in patients with heart failure after acute myocardial infarction</td>
<td>Most*</td>
<td>Not reported</td>
</tr>
<tr>
<td>Glick et al., 1995 [25]</td>
<td>SOLVD, n = 2569</td>
<td>3</td>
<td>Enalapril vs. placebo in patients with heart failure</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Glick et al., 2002 [26]</td>
<td>RALES, n = 1663</td>
<td>16</td>
<td>Spironolactone vs. placebo in patients with severe heart failure</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Jonsson et al. [27]</td>
<td>4S, n = 4444</td>
<td>5</td>
<td>Simvastatin vs. placebo in patients with angina or prior myocardial infarction</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Lamy et al. [28]</td>
<td>HOPE, n = 9297</td>
<td>19</td>
<td>Ramipril vs. placebo in patients at high risk for cardiovascular events</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Mark et al., 2000 [29]</td>
<td>PURSUIT, n = 10,948</td>
<td>28</td>
<td>Eptifibatide vs. placebo in patients with acute coronary syndrome</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mark et al., 1995 [30]</td>
<td>GUSTO, n = 41,021</td>
<td>15</td>
<td>Tissue plasminogen activator vs. streptokinase for acute myocardial infarction</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Reed et al. [31]</td>
<td>Val-HeFT, n = 5010</td>
<td>18</td>
<td>Valsartan vs. placebo in patients with heart failure</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Schulman et al. [32]</td>
<td>FIRST, n = 471</td>
<td>14</td>
<td>Epoprostenol vs. placebo in patients with severe heart failure</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sculpher et al. [33]</td>
<td>ATLAS, n = 3164</td>
<td>19</td>
<td>Low-dose vs. high-dose lisinopril in patients with heart failure</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Topol et al. [34]</td>
<td>EPIDENT, n = 2399</td>
<td>2</td>
<td>Abciximab plus angioplasty vs. stenting plus abciximab vs. stenting plus placebo in patients undergoing percutaneous coronary revascularization</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*We assumed that most patients would have been hospitalized at the time of randomization, which occurred 3–10 days after an acute myocardial infarction.

AIRE, Acute Infarction Ramipril Efficacy Study; ATLAS, Assessment of Treatment with Lisinopril and Survival study; CIBIS II, Cardiac Insufficiency Bisoprolol Study II; ELITE, Evaluation of Losartan in the Elderly; EPIDENT, Evaluation of Platelet IIb/IIIa Inhibitor for Stenting; FIRST, Flolan International Randomized Survival Trial 4S, Scandinavian Simvastatin Survival Study; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; HOPE, Heart Outcomes Prevention Evaluation study; PREVENT, Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial; PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; RALES, Randomized Aldactone Evaluation Study; SOLVD, Studies of Left Ventricular Dysfunction; Val-HeFT, Valsartan Heart Failure Trial.
Types of Costs Considered During the Trial and Methods Used to Estimate Costs
In our sample of studies from the cardiology literature, the main focus of within-trial estimation of costs was on hospital care and study medications. Twelve studies focused their primary analyses on total medical costs (disease-related and unrelated medical costs); the remaining six studies were limited to medical costs related to cardiovascular disease (Table 2).

Four general approaches were used to assign direct medical costs for each hospitalization (Table 2). Analysts either 1) assigned a fixed cost to each hospitalization according to the reason for hospitalization; 2) assigned unit costs to individual resources used during the hospitalization; 3) assigned costs based on length of stay; or 4) relied on hospital billing data.

Four studies applied a combination of costing methods [23,29,30,34]. Approximately one-third of the studies applied a “fixed” costing method, akin to diagnosis-related group (DRG) costs that, while indirectly incorporating the time patients spent in the hospital by using mean costs for specific diagnoses, did not adjust costs based on the duration of hospitalization or intensity of care experienced by individual patients [17,20,21,23,25,27,28,30]. Most of the studies estimated costs using methods that captured differences in length of hospitalization between patients [18,22–24,26,29–34]. Among these studies, four applied generic per diem unit costs to days in the hospital or days in various hospital wards, but did not vary costs according to the reason for admission [22–24,32]. Three studies combined the reason for admission with data on length of stay, thereby better approximating the variation in costs that occurs between patients [26,31,33]. Analysts relied on hospital bills to estimate inpatient costs in only two studies [29,34]. Bottom-up methods that rely on individual counts of resource use to estimate inpatient costs were applied in four studies [18,29,30,34].

In only a few cases did analysts explicitly present a rationale for their cost-estimation methods. In the study by Bjorholt et al. [17], which applied fixed costs to hospitalizations classified using DRGs, the authors stated that group differences were expected to be observed in the incidence of hospitalization, not in the management of patients after they were hospitalized. Topol et al. [34] used hospital bills and reported that they had decided during the trial’s design phase to

<table>
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<th>Table 2</th>
<th>Methods for cost determination and reporting in multinational cardiovascular clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Report</strong></td>
<td><strong>Trial, sample size</strong></td>
</tr>
<tr>
<td>Bjorholt et al. [17]</td>
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</tr>
<tr>
<td>Ekman et al. [23]</td>
<td>CIBIS II, n = 2647</td>
</tr>
</tbody>
</table>

(continued)
Table 2 continued

<table>
<thead>
<tr>
<th>Report</th>
<th>Trial, sample size</th>
<th>Source of cost data, country used for estimation, and sample size for estimation</th>
<th>Total vs. cardiovascular hospital costs</th>
<th>Method of cost estimation</th>
<th>Details of cost estimation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erhardt et al. [24]</td>
<td>AIRE, n = 1986</td>
<td>Swedish costs applied to Swedish patients (n = 162)</td>
<td>Primary: cardiovascular costs</td>
<td>Adjusted for length of stay$^4$</td>
<td>Data on length of stay and ward retrospectively collected from 4 Swedish clinics participating in trial and combined with unit cost data from 1 county hospital costing methods with others that used both reason for admission and data on length of stay.</td>
</tr>
<tr>
<td>Glick et al., 1995 [25]</td>
<td>SOLVD, n = 2569</td>
<td>US costs applied to all patients (n = 2569)</td>
<td>Total</td>
<td>Fixed$^3$</td>
<td>DRG-based costs assigned to hospitalizations for 9 cardiovascular reasons for admission plus noncardiovascular admissions plus randomized samples of US patients; linear regression models used to assign costs to patients without bills.</td>
</tr>
<tr>
<td>Glick et al., 2002 [26]</td>
<td>RALES, n = 1663</td>
<td>Country-specific costs applied to all patients (n = 1663)</td>
<td>Total</td>
<td>Adjusted for length of stay$^5$</td>
<td>Multiplied days in the hospital (by reason for admission) by admission-specific daily cost estimates for individual countries.</td>
</tr>
<tr>
<td>Jonsson et al. [27]</td>
<td>45, n = 4444</td>
<td>Swedish costs applied to all patients (n = 4444)</td>
<td>Cardiovascular</td>
<td>Fixed$^2$</td>
<td>DRG-based costs assigned to hospitalizations for 25 cardiovascular events.</td>
</tr>
<tr>
<td>Lamy et al. [28]</td>
<td>HOPE, n = 9297</td>
<td>US and Canadian costs applied separately to all patients (n = 9297)</td>
<td>Cardiovascular</td>
<td>Fixed$^2$</td>
<td>DRG-based costs assigned to hospitalizations for 11 cardiovascular events.</td>
</tr>
<tr>
<td>Mark et al., 2000 [29]</td>
<td>PURSUIT, n = 10,948</td>
<td>US costs applied to US patients (n = 3522)</td>
<td>Total</td>
<td>Hospital bills and adjusted for resource use</td>
<td>Hospital bills collected for 70% of US patients; linear regression models used to assign costs to patients without bills.</td>
</tr>
<tr>
<td>Mark et al., 1995 [30]</td>
<td>GUSTO, n = 41,021</td>
<td>US costs applied to US patients (n = 23,105)</td>
<td>Cardiovascular</td>
<td>Index hospitalizations adjusted for resource use; rehospitalizations fixed$^1$</td>
<td>Unit costs from 1 hospital cost accounting system applied to inpatient resources consumed for initial hospitalization; DRG-based costs assigned for 11 cardiovascular events for rehospitalizations.</td>
</tr>
<tr>
<td>Reed et al. [31]</td>
<td>Val-HeFT, n = 5010</td>
<td>Country-specific costs applied to all patients (n = 5010)</td>
<td>Total</td>
<td>Adjusted for length of stay$^3$</td>
<td>Multiplied days in hospital (by reason for admission) by admission-specific daily cost estimates for individual countries.</td>
</tr>
<tr>
<td>Schulman et al. [32]</td>
<td>FIRST, n = 471</td>
<td>US costs applied to all patients (n = 471)</td>
<td>Total</td>
<td>Adjusted for length of stay$^4$</td>
<td>Per diem costs for days in general ward, CCU, and ICU derived from 1 hospital cost accounting system and applied to length of stay for each ward.</td>
</tr>
<tr>
<td>Sculpher et al. [33]</td>
<td>ATLAS, n = 3164</td>
<td>UK costs applied to all patients (n = 3164)</td>
<td>Total</td>
<td>Adjusted for length of stay$^4$</td>
<td>Per diem costs for hospital days estimated for individual medical specialties assigned to hospital days based on reason for admission.</td>
</tr>
<tr>
<td>Topol et al. [34]</td>
<td>EPISTENT, n = 2399</td>
<td>US costs applied to US patients (n = 1438)</td>
<td>Total</td>
<td>Index hospitalizations based on hospital bills; rehospitalizations adjusted for resource use</td>
<td>Hospital bills used to estimate costs for initial hospitalization; costs for rehospitalizations estimated with linear regression model based on empirical follow-up cost data from another trial.</td>
</tr>
</tbody>
</table>

$^a$Adapted from Reed et al. [9].

$^b$Refers to sensitivity analyses or secondary/tertiary analyses.

$^1$Applied a “fixed” costing method, akin to DRG costs that, while indirectly incorporating the time patients spent in the hospital by using mean costs for specific diagnoses, did not adjust costs based on the duration of hospitalization or intensity of care experienced by individual patients.

$^2$Applied generic per diem unit costs to days in the hospital or days in various hospital wards, but did not vary costs according to the reason for admission.

$^3$Combined the reason for admission with data on length of stay to approximate the variation in costs that occurs between patients.

$^4$Because the analysis used reason for hospitalization to determine which medical specialty per diem estimate would be assigned, we categorized the costing methods with others that used both reason for admission and data on length of stay.

AIRE, Acute Infarction Ramipril Efficacy study; ATLAS, Assessment of Treatment with Lisinopril and Survival study; CABG, coronary artery bypass graft surgery; CCU, cardiac care unit; CIBIS II, Cardiac Insufficiency Bisoprolol Study II; DRG, diagnosis-related group; ELITE, Evaluation of Losartan in the Elderly; EPISTENT, Evaluation of Platelet IIb/IIIa Inhibitor for Stenting; FIRST, Flolan International Randomized Survival Trial; 4S, Scandinavian Simvastatin Survival Study; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries study; HOPE, Heart Outcomes Prevention Evaluation study; MI, myocardial infarction; PCI, percutaneous coronary intervention; PREVENT, Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial; PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; RALES, Randomized Aldactone Evaluation Study; SOLVD, Studies of Left Ventricular Dysfunction; Val-HeFT, Valsartan Heart Failure Trial.
collect hospital bills only for the index hospitalization as a means to “obtain an accurate estimate of any potential offset” from the study drug. Nevertheless, it appeared that characteristics of the trial were associated with cost assignment. All of the studies that used hospital bills [29,34] or bottom-up costing methods [18,29,30,34] were included among the trials that randomized patients when they were hospitalized [17,18,29,30,32,34].

The design of the clinical trial was also the main determinant as to whether inpatient costs were inclusive of the index hospitalization. Economic evaluations of the six clinical trials that randomized patients while they were hospitalized for an acute condition (e.g., severe heart failure, acute myocardial infarction) or surgical procedure (e.g., percutaneous coronary intervention) included the cost of the index hospitalization [17,18,29,30,32,34].

With regard to sources of unit cost data and assignment of these costs to patients from various countries, the most common approach—applied in nine studies—was to assign a set of unit costs from one country to resource use by all patients enrolled in the trial (Table 2) [20–23,25,27,28,32,33]. In six studies, cost estimation was limited to patients from one country [17,18,24,25,29,30,34]. For additional details about the unit costs and representation of countries for estimates of costs and health outcomes, see Reed et al. [31].

**Extrapolation of Costs and Outcomes Beyond the Trial Period**

Of the 18 cost-effectiveness evaluations reviewed, 12 were based on trials that demonstrated a significant difference in within-trial, all-cause mortality (Table 3). In 3 of these 12 trials, analysts did not extrapolate costs or survival beyond the duration of the trial [24,26,28]. Lamy et al. [28] reported cost-effectiveness ratios as the incremental cost per end point saved. Erhardt et al. [24] and Glick et al. [26] based the denominators of the incremental cost-effectiveness ratios on differences in within-trial survival, thereby generating conservative estimates of cost-effectiveness. The remaining 9 of 12 studies demonstrated significant reductions in within-trial, all-cause mortality and extrapolated survival to a lifetime perspective using a variety of methods (Table 4).

Four studies did not demonstrate a significant difference in mortality but did estimate lifetime survival (Table 2). Three of the four were based on PURSUIT, a trial of eptifibatide for acute coronary syndromes. The trial showed a significant reduction in the primary end point—death or acute myocardial infarction at 30 days—but not in overall mortality. In the subsequent economic evaluations, estimation of survival after 6 months was based on Cox proportional hazards models that used long-term survival data from an observational data set of postmyocardial infarction patients from one medical center in the United States [18,19,29]. Survival estimation for the United States and Canadian economic evaluations was based on characteristics of trial patients from North America, whereas the European adaptation was based on characteristics of patients from Western Europe. Because this trial demonstrated a reduction in the primary end point among US patients but not among Western European patients, these studies are important in that they demonstrate the potential for variations in the results of multinational clinical trials that can have important effects on the results of economic evaluations. The other economic evaluation that extrapolated survival estimates despite a nonsignificant reduction in all-cause mortality was based on the Prospective Randomized Evaluation of the Vascular Effects of Norvase Trial (PREVENT), which showed no reductions in mortality, progression to atherosclerosis, or risk of major cardiovascular events, but was associated with a reduction in hospitalizations for unstable angina and coronary revascularization procedures [20].

Although it is not necessary that a clinical trial demonstrate a statistically significant mortality benefit to extrapolate life expectancy beyond the trial period, assessment and reporting of uncertainty associated with the study’s results is warranted. For example, in the economic evaluation of the PREVENT trial, although sensitivity analyses were conducted to vary the point estimate of a 0.083 gain in life expectancy by ±20%, these analyses were insufficient to represent the underlying uncertainty associated with the nonsignificant mortality effect observed in the clinical trial. In fact, fewer than half of the studies we evaluated included information on the stochastic uncertainty associated with the studies’ cost-effectiveness findings (e.g., confidence intervals for cost-effectiveness ratios, cost-acceptability curves) (Table 4). We did not observe a temporal trend indicating that more recently reported studies were more likely to have included information on uncertainty; about half of the studies (43%) that reported measures of uncertainty predated 2000, similar to the proportion of studies that did not report measures of uncertainty (45%).

### Table 3 Within-trial mortality findings and survival projection in economic evaluations

<table>
<thead>
<tr>
<th>Survival extrapolated beyond trial period</th>
<th>Significant difference in all-cause mortality</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>No</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>18</td>
</tr>
</tbody>
</table>

*In the three studies based on data from PURSUIT, there was a significant reduction in the incidence of death or acute myocardial infarction in the US subset at 30 days (P = 0.002) but not in the Western European subset (P = 0.39).*
In 13 of the 18 studies reviewed, analysts did not extrapolate the cost of study treatment beyond the trial period in the primary analyses (Table 4). Nevertheless, in five of these studies, this approach was appropriate because the interventions under study (i.e., tPA and eptifibatide) were administered only once in an acute care setting. In an additional five studies, the focus of the analyses was on within-trial benefits, and the time frames for the evaluations of costs and clinical outcomes were consistent. In the primary analyses of the remaining three studies, the time frames were not consistent [17,20,27]. In these studies, the long-term effect of chronic medication use on survival was estimated, but costs for treatment were not extrapolated over the same time period (although Bjorholt et al. [17] did project costs in a sensitivity analysis).

In four studies, both treatment and nontreatment costs were projected over a lifetime perspective in the primary analyses [21–23,25]. The cost projections made in all four of these studies relied on the extrapolation of within-trial resource use or costs. These four studies also projected survival and were thus consistent in projecting total medical costs and survival [21–23,25].
cost per life-year gained was 13,094 SEK exclusive of future costs and 168,858 SEK when future net consumption was considered.

Discussion

In this article, we have focused on a subset of issues involved in the economic analysis of multinational clinical trials—the types of costs considered, the costing methods employed, and whether analysts extrapolated within-trial costs and outcomes beyond the follow-up period in major multinational cardiovascular trials. We found that the studies reviewed were remarkable both for similarities in their general approaches and for subtle but important variations in the details of their methods.

Overwhelmingly, the studies we examined focused on assessment of direct medical costs. Moreover, most of the studies were based on total medical costs (i.e., not costs limited to cardiovascular disease), but few studies incorporated nonmedical or indirect costs. Although these studies reflect the state of the art in clinical trial-based economics research, they may also be indicative of inconsistency among decision-makers with regard to the importance of indirect costs, as well as the compromises required to carry out economic evaluations alongside large, multinational trials. Data collection in these trials is expensive, requiring resources for case report form design, data collection, data monitoring, and data entry. Therefore, in conditions for which cost drivers are well understood, such as cardiovascular disease, truncated data collection limited to the direct medical costs that are expected to dominate total and incremental costs may be a reasonable compromise. To the extent that there is a desire for a broader perspective in assessing costs of new medical therapies, the incremental costs and benefits of collecting these additional data should be weighed against their exclusion from the analysis or their inclusion through some type of modeling effort that relies on secondary data.

Although all of the studies included hospital costs, there was variation in the costing methods employed. Some analysts assigned the same costs regardless of the patient's hospital experience (e.g., length of stay, complications), whereas others attempted to account for between-patient variation. It appears that the selection of costing method was associated primarily with the characteristics of the resource use data available from the clinical trial. In some studies, only information regarding the number of hospitalizations related to cardiovascular disease was available to analysts (e.g., Jonsson et al. [27]), thereby restricting the analysts to the “fixed” costing method. In other analyses, data on the number of cardiovascular-related hospitalizations from the trial were supplemented with per diem cost estimates and data on length of stay collected retro-

spectively from local centers that participated in the trial to calculate total hospital costs (e.g., Erhardt et al. [24]). Even in multinational trials from which more detailed information, such as length of stay and reason for admission, is available for all hospitalizations, analysts may be justified in the application of “fixed” costing methods that do not account for variation in length of stay between patients. Although this approach reduces variance, which may not be desirable from a statistical perspective, variations in length of stay in a multinational setting may be more closely related to variations in practice patterns between countries than to variations in disease severity between patients. One approach to address both issues is to apply country-specific unit costs to hospital days experienced by patients from those countries (e.g., see Reed et al. [31] and Glick et al. [26]).

As noted previously, the application of one country's unit costs to resources consumed by all patients in the trial is a frequently applied method [9]. Nevertheless, this approach may be problematic for at least two reasons. First, numerous studies demonstrate that patterns of resource use vary across countries [35–38]. Second, assignment of one country's unit costs to resource use across patients in many countries runs counter to the theoretical relationship between relative prices and the use of substitutable resources that exists across countries [39]. Nevertheless, there are many practical reasons why analysts would choose to overlook these considerations. One of the most important reasons may be the accessibility of cost data from different countries. A related issue is the variation in methods used to derive unit costs in individual countries [40]. Because many countries finance health care through a centralized system, patient-level cost accounting data may be nonexistent, and cost estimates may include tariffs or other markups that do not reflect opportunity costs. Another reason that analysts assign country-specific costs may be that they consider them to be most applicable and transparent to their target audience. Two studies have shown that the cost assignment methodology has very little impact on qualitative findings from cost-effectiveness analyses across countries with similar levels of economic development [10,41]. Variations in results across countries are more likely to be evident when analysts allow for patient characteristics and resource use patterns to vary between countries [10,41].

Although the inclusion of disease-related medical costs as the basis for cost-effectiveness analysis has been supported by consensus recommendations [12], it has also been suggested that a more accurate evaluation of costs would include costs for comorbidities, loss of productivity, and consumption of nonmedical resources brought about by improved survival due to therapy [42]. Whether to project unrelated costs is an area of ongoing research and debate and has impor-
tant implications for the results of such studies. Although the number of studies included in our review is limited, it is notable that the only two studies that included future medical and nonmedical costs were conducted by analysts in Sweden [17,23], possibly reflecting the extensive social welfare system that exists in that country. When future costs were included, both studies yielded cost-effectiveness ratios that were approximately 12 times greater than ratios excluding such costs. As noted by Ekman et al. [23], when these costs are included, they “clearly dominate” other costs. This conclusion is supported by assertions in the literature that the inclusion of both disease-related and unrelated future costs can significantly alter the cost-effectiveness ratio in economic evaluations [42,43].

With regard to extrapolation of within-trial outcomes beyond the trial period, in trials where a significant survival benefit was shown, most of the analyses were based on projected estimates of costs and survival. Nevertheless, some analysts extrapolated outcomes to a lifetime perspective when a survival benefit was not observed in the trial, and others chose not to extrapolate even when a significant mortality benefit was observed. A commonly used method of extrapolating within-trial mortality to long-term survival estimates was to apply the same mortality rate to patients in both arms. This approach is often interpreted incorrectly to be as conservative as limiting findings to those observed within the trial period, but accumulation of benefit occurs over time to a greater extent in the treatment arm with improved survival at the end of the study period [44].

It is interesting to note that, although the majority of the articles reviewed provided substantial detail regarding the methods they used for survival projections, few discussed the rationale behind the choice of methodology. Thus, any interpretation of the authors’ choices of analytic methods would be speculative. Nevertheless, we noted that in approximately half of the studies, the analysts appeared to apply methods to customize the analysis for an individual country through the use of actuarial data from the target country [17,20,22,27] or through the use of survival data representing a relevant patient cohort from the target country [29,30,34]. In other studies, an intermediate method was applied whereby patient characteristics from the target country were used to customize survival projections that originally were based on mortality data from another country [18,19]. In the remaining analyses, analysts used information from the trial itself to extrapolate beyond the follow-up period (e.g., parametric survival extrapolation), thus representing the experience of the multinational mixture of patients enrolled in the study.

Although we found that the methods employed in the economic evaluations were generally consistent with expert recommendations, we also noticed a great deal of variation in the methodological details. These subtle differences in methodology, which may go unnoticed by many potential users of cost-effectiveness analyses, could have important effects on the studies’ findings and could ultimately affect decision-making. Another issue of concern was the amount of time that was necessary to identify and decipher the methods that had been employed. Even for decision-makers with sufficient training to appreciate the potential implications of various analytic strategies, the time required to compare methods and findings of economic evaluations is substantial. It is likely that many decision-makers would abandon such an undertaking, thus undermining the potential impact of cost-effectiveness analyses in the selection of the most efficient medical technologies.

Because the field of economic evaluation alongside multinational clinical trials continues to mature, a reasonable interim step toward uniform standards by which the majority of trial-based multinational economic analyses could be conducted would be to continue development of both new methodologies to evaluate variability in study results across countries and consistent reporting frameworks for such analyses and their results. The International Society for Pharmacoeconomics and Outcomes Research Task Force on Good Research Practices: Randomized Clinical Trials—Cost-Effectiveness Analysis (RCT-CEA) has recommended three analytical approaches that could be used to address between-country variation in economic evaluations [6]. These include testing for homogeneity of study results across countries [45], use of multivariate regression models to adjust for country-level effects [41], and use of multilevel modeling [46]. In addition, Drummond et al. [11] recently published recommendations for reporting the results of trial-based economic evaluations for the purpose of increasing their generalizability, or at least the ability to assess their generalizability. Recommendations that specifically address issues that arise in the multinational context include the reporting of important features of the different health-care systems in countries in the trial and the reporting of variability in the study’s results by location using quantitative analysis, such as multilevel modeling, or sensitivity analysis.

We also recommend adoption of standard terminology that can be used to classify multinational economic evaluations based on which countries are the sources of clinical effectiveness data, which are the sources of resource use data, and which are the sources of unit costs [9]. Standard terminology may also reduce problems caused by space restrictions in scientific journals that often necessitate truncation of methods sections. We also agree with other commentators that another step forward would be the publication of selected primary data (such as country-level or patient-level data) and detailed methods on the
Internet to allow for more thorough, critical evaluation of economic studies performed alongside multinational trials and to allow individual analysts to apply local cost data to resource use data collected in such trials.

Questions about which costs to consider in a multinational economic analysis, which costing methods to use, and how to extrapolate within-trial outcomes remain matters of ongoing debate. In many cases, these decisions are dictated by practicality—that is, analysts must rely on the data that are collected in the clinical trial and, in many cases, the requests of decision-makers and journal reviewers trump theoretical and methodological considerations. Nevertheless, we should recognize that the globalization of clinical trials is likely to continue, as is the increasing reliance on health technology assessment for coverage decisions. Thus, continued dialogue among methodologists and decision-makers about the issues discussed in this article is essential to move the field forward.

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