

## A Tale of Two (or More) Cities: Geographic Transferability of Pharmacoeconomic Data

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### Abstract

The economic evaluation of a new medicine often must be based on data gathered in multiple countries. Because replication of trials is an expensive and inefficient undertaking, analysts need to determine the validity of transferring cost-effectiveness data from one country to another. Threats to transferring data involve differences among countries with regard to demography and epidemiology of disease, clinical practice and conventions, incentives to and regulation of healthcare providers, relative price levels, consumer preferences, and opportunity cost of resources. Because of these differences, a drug can be cost-effective in one country and not cost-effective in another. Adapting a cost-effectiveness study conducted in one country to another country requires careful scrutiny of the relevance of comparators, practice patterns, and relative price weights.

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In recent years around the world there has been rapid growth in the application of economic appraisal techniques such as cost-effectiveness analysis to new pharmaceutical products.

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In an attempt to manage scarce healthcare resources more efficiently, public and private healthcare payers are demanding such studies to provide them with information on the value for money or "bang per buck" that a new medicine offers. The data are formally required by governments for pharmaceutical reimbursement throughout Australia<sup>1</sup> and

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Ontario, Canada.<sup>2</sup> In the multiple-payer healthcare system of the United States, managed care organizations are demanding cost-effectiveness studies on new drugs before listing the drugs on a formulary or granting them reimbursement status. The US Food and Drug Administration is requiring manufacturers to submit economic evidence that supports any promotional claim of cost effectiveness.<sup>3</sup>

Guidance documentation on what constitutes a valid and reliable economic appraisal is available specifically for pharmaceuticals in Australia<sup>1</sup> and Canada.<sup>2,4</sup> Under the auspices of the US Public Health Service, an expert panel has published general guidelines for conduct of economic evaluation for healthcare programs.<sup>5,6</sup> A key feature of a good economic study, emphasized in

such guidance documents, is that evidence of the effectiveness of a drug should be based on data from high-quality clinical experiments, such as randomized controlled trials. The primacy of the randomized controlled trial as the preferred method for drug evaluation has existed for a number of years, particularly for producing evidence required by regulators to license a drug as being safe and efficacious. A practical difficulty in conducting randomized controlled trials is that they often require large sample sizes to detect small but clinically important effects. For example, for the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial,<sup>7</sup> 41,021 subjects were recruited from 15 countries. Such trials proceed by means of pooling data from multiple countries to test the hypotheses of treatment effect.

The economic evaluation of a new medicine often has to be based on data, clinical or economic, gathered in multiple countries. In some instances it may be that the key clinical trial was conducted exclusively in one country (eg, the United States), but decision makers in another country (eg, Canada) want to determine cost effectiveness in their setting. Replication of all trials in all settings would be a costly and inefficient

undertaking for manufacturers, governments, and consumers. The question that emerges is which principles can the analyst follow to determine the validity of transferring economic evidence on a new medicine from one country to another. This paper examines the topic of transferability of pharmacoeconomic data. Using examples to illustrate points, six threats to the transferability of cost-effectiveness data from one country to another are examined.

### Six Threats to Transferability

Before examining the six issues, it is useful to review some basic concepts and terms. There are two basic approaches to conducting an economic evaluation of a new medicine.<sup>8</sup> The first is decision analytic modeling whereby the analyst draws on cost and outcome data from multiple sources and synthesizes this evidence using modeling techniques. The second approach is prospective "piggyback" trial-based studies, whereby the economic data are collected prospectively as part of a single randomized controlled trial. There are numerous advantages and disadvantages to the two approaches,<sup>8</sup> but both face issues of transferability. For example, to what extent is a decision analytic model of ulcer drug treatment in Canada<sup>9</sup> applicable in the United States?

**Table 1.** Costs, Effects, and Cost-Effectiveness Summary for Tissue Plasminogen Activator (tPA) Versus Streptokinase

	Treatment Group		Difference (tPA-streptokinase)	Difference Discounted @ 5%
	tPA	Streptokinase		
<b>Cost (US\$)</b>				
One-year healthcare costs (excluding thrombolytic therapy)	24,990	24,575	415	
Thrombolytic drug cost	2,750	320	2,430	
Total one-year cost	27,740	24,895	2,845	2,760 <sup>†</sup> (=ΔC)
<b>Effect</b>				
Life expectancy (y)	15.41	15.27	0.14	0.084 <sup>†</sup> (=ΔE)
<b>Incremental cost effectiveness of tPA</b>				ΔC/ΔE = \$32,678 per life-year gained

\*Treatment groups assumed to have no cost differences beyond one year

†These discounted differences were not reported in the paper but have been imputed.

This table summarizes data in Mark DB, Hlatky MA, Califf RM, et al. Cost-effectiveness of thrombolytic therapy with tissue plasminogen activator as compared with streptokinase for acute myocardial infarction. *N Engl J Med* 1995;332:1418-1424.

Alternatively, how applicable to Canada is the US trial-based economic evaluation of tPA<sup>10</sup> from the GUSTO trial?

To guide some of this discussion, an example is used from the medical literature that received much publicity and has important policy relevance. Table 1 shows the basic findings of an economic appraisal of tissue plasminogen activator (tPA) versus streptokinase.<sup>10</sup> The study was based on two key data sources: (1) resource usage by a sample of US patients in the GUSTO trial; and (2) 1-year survival data for all 41,021 patients from all 15 countries. On the basis of US resources and healthcare prices, the data show that the cost of acquisition of tPA (\$2,750) is much greater than that of streptokinase (\$320). There is little difference, however, in the use of other healthcare resources (eg, subsequent revascularization) within the year between the groups. The observed difference in 1-year survival rate (a 1% all-cause mortality advantage in favor of tPA) is projected forward (data from a Duke University Cardiac Registry) to estimate differences in overall life expectancy due to treatment. With a discount rate of 5% per year to allow for time preference, the data show that over the remaining lifetime a tPA-treated person costs an additional \$2,760 (relative to streptokinase) and gains 0.084 life years; the ratio of this incremental cost to effect is \$32,678 per life-year gained. The question is: Are these pharmacoeconomic data applicable to patients and settings outside the United States?

*Demography and Epidemiology of Disease.* An important starting point to remember is that countries vary in terms of demography and the prevalence and incidence of a particular disease or condition. Such variation can influence the cost effectiveness of an intervention in a number of different ways. First, consider public health interventions such as screening or immunization. To the extent that the prior risk for a target condition is different from country A to country B, the economic implications of screening or immunization for that dis-

ease may be greatly different. If the denominator of cost effectiveness is the number of cases detected or prevented in a public health program, this number will be larger in countries with a higher baseline risk of this condition.

Another example of the influence of disease prevalence on the cost effectiveness of a treatment program is the eradication of *Helicobacter pylori* to manage peptic ulcer disease.<sup>9</sup> The cost effectiveness of attempts to eradicate the bacterium is a function of the prevalence of *H pylori* in the population and depends on rates of community resistance to antimicrobial agents, such as metronidazole, used in the therapy. It is likely that these disease prevalence and antimicrobial resistance data will vary between countries and settings and thus limit the transferability of study findings.

Of relevance to our tPA example, in which survival of an acute event is the treatment outcome, reducing the rate of premature death has different implications in countries where underlying life expectancy is different. For example, Table 2, Organization for Economic Cooperation and Development (OECD) data for men in 1990 shows that men live, on average, 2 years longer in Canada than they do in the United States. Therefore life-years lost per hundred thousand men because of heart disease is lower in Canada (477.8) than in the

**Table 2.** Life Expectancy at Birth and Life Years Lost to Heart Disease Among Men, 1990

Country	Life Expectancy (y)	Life Years Lost to Ischemic Heart Disease (per 100,000 Men)
Canada	73.8	477.8
France	72.7	257.0
Germany	72.7	562.0
Italy	73.6	387.0
Japan	75.9	116.0
United Kingdom	72.9	789.0
United States	71.8	528.0

Source: The Organization for Economic Cooperation and Development (OECD).

United States (528.0). Such variation in underlying life expectancy raises questions concerning the transferability of survival projections from one country to another.

*Clinical Practice and Conventions.* The results of an economic study conducted in one country may not be transferable to another country because a comparison therapy that is usual care in one country may not be typical practice in another country. For example, in evaluating the proton pump inhibitor omeprazole in the treatment of patients with

peptic ulcer disease, investigators conducting a study in Canada<sup>9</sup> used for comparison generic ranitidine as the H<sub>2</sub>-receptor antagonist. This comparison was chosen because evidence indicates that more than 80% of prescriptions written for ranitidine in Canada are for the generic rather than brand-name version, Zantac.<sup>11</sup> This comparison may not be transferable to the United States, where Zantac as a brand is still protected by patent and lower-priced generic ranitidine is not yet available.

A second issue arising out of clinical practice variation is that a physician's discretionary and nonprotocol treatment selections during a clinical trial may vary between study countries. For example, in Table 3, data from GUSTO split according to US patients versus patients outside the United States, shows that US patients were far more likely to receive invasive revascularization procedures such as angioplasty and bypass operations than were non-US counterparts.<sup>12</sup> There also were marked differences in medical treatments during hospital stays in the GUSTO trial (Table 4). Sixty-one percent of US patients received antiarrhythmic drugs as opposed to 27% of non-US patients. There was a similar gradient with respect to use of calcium antagonists (38% versus 21%).

In principle, practice variation by country for a disease may not bias the inferences we draw from a cost-effectiveness study provided there is no statistical interaction with treatment assignment. In other words, in Table 1 the 1-year healthcare costs excluding thrombolytics for both the tPA and streptokinase groups are approximately \$25,000 with a difference of \$415. In another country with lower rates of bypass operations the absolute dollar values for each treatment group may be smaller but the difference may be similar. More worrisome yet is the possibility that the more aggressive use of revascularization in the United States had a favorable impact on overall mortality and that this had an interaction

**Table 3.** Performance of Invasive Procedures for Acute Myocardial Infarction (GUSTO)

Procedure	Percentage of Patients	
	United States (n = 23,105)	Outside United States (n = 17,916)
Angioplasty	31	10
Surgical bypass	13	3
Intra-aortic balloon	6	1
Mechanical ventilation	17	5
Pacemaker insertion	10	3
Cardioversion	11	8

*P* < 0.001 for US versus non-US comparison for all procedures. Adapted from Van der Werf F, Topol EJ, Lee KL, et al. Variations in patient management and outcomes for acute myocardial infarction in the United States and other countries. *JAMA* 1995;273:1586-1591.

**Table 4.** Nonprotocol Medical Treatments During Hospital Stay (GUSTO)

Treatment	Percentage of Patients	
	United States	Outside United States
Antiarrhythmic drugs	61	27
Calcium antagonists	38	21
Digitalis or other inotropic agent	31	18
Angiotensin-converting enzyme inhibitors	20	25

Adapted from Van der Werf F, Topol EJ, Lee KL, et al. Variations in patient management and outcomes for acute myocardial infarction in the United States and other countries. *JAMA* 1995;273:1586-1591.

with treatment. For example, Table 5 shows the overall 30-day mortality among US patients was 6.8% versus 7.2% among non-US patients with a *P*-value for treatment-by-country interaction of 0.07. Although we should always be extremely cautious about *post-hoc* subgroup analysis, these data do offer food for thought about whether the treatment effect in favor of tPA can be transferred beyond the US patients.

*Incentives and Regulations for Healthcare Providers.* Different healthcare systems in different countries impose varying regulatory frameworks and financial incentives on healthcare providers, and these factors can explain some degree of practice variation. Obvious examples include payment of physicians by fee-per-item-of-service versus salary or capitation. In a country or setting where providers are paid for providing items of service, theory and evidence support the proposition that these providers will provide more items of this service.<sup>13</sup> In managed care settings and other healthcare systems such as in the United Kingdom, where primary care physicians are paid by capitation (for a fixed pool of patients served on an annual basis), different incentives operate. The way in which hospitals are reimbursed also can influence the transferability of economic appraisal data. A good example is the introduction of prospective payment in the United States through the use of diagnosis-related groups. The incentive for the hospital under fixed remuneration by diagnosis-related group is to discharge the patient earlier and therefore be in "profit." In the GUSTO trial the US patients had an average length of stay of 8 days in the hospital; non-US patients had an average stay of 10 days. In other words, US patients received more procedures but

**Table 5.** Thirty-Day Mortality and Stroke Rates (GUSTO)

	United States (n = 23,034)	Outside United States (n = 17,796)	Treatment by Country Interaction ( <i>P</i> value)
30-day mortality (%)	6.80	7.20	0.07
Stroke rate (%)	1.53	1.34	0.29
Rate of hemorrhagic stroke (%)	0.66	0.64	0.03
Rate of death or nonfatal stroke (%)	7.80	7.90	0.09

Adapted from Van der Werf F, Topol EJ, Lee KL, et al. Variations in patient management and outcomes for acute myocardial infarction in the United States and other countries. *JAMA* 1995;273:1586-1591.

in a shorter period of time, probably because of the pressures of prospective payment.

*Relative Price Levels.* Although overall price levels (ie, the so-called cost of living) vary between countries, it is the variation in the price of one resource relative to another that is a threat to the transference of economic data from one country to another. For example, if prices for all goods and services are twice as high in the United States as they are in Canada, then the relative cost effectiveness of one treatment versus another is the same in both settings. However there is considerable international variation in relative prices of some healthcare resources, such as drug prices. In the sensitivity analysis of the GUSTO economic appraisal,<sup>10</sup> it was shown that although the price of streptokinase was about the same in Italy as in the United States, the price of tPA in Italy was almost half that of the price in the United States. Researchers showed that using the Italian relative drug prices would yield a cost per life-year gained of approximately \$14,000, which is markedly more attractive than a \$33,000 per life-year gained.

*Consumer Preferences.* In the evaluation of some diseases and treatments in which outcomes span changes in both survival and health-related quality of life, it is often useful to undertake a form of economic appraisal known as cost-utility analysis, whereby outcomes are quantified in terms of quality-ad-

justed life years (QALYs). [See "Preferences for Health Outcomes and Cost-Utility Analysis," S8.]

There is no necessary reason why preferences for health states and trade-offs between survival and quality of life should be a universal constant across all countries and nations. As part of the program of research into cross cultural validation of quality-of-life measures, important research for the future is examination of the transferability of utility weights for health states. In other words, it is unclear whether QALYs measured in one country are applicable to another country.

A related issue of preference is the topic of discounting, where future streams of costs and benefits are discounted to their present value to allow for time preferences of consumers and society in general. There has been protracted debate about whether and by how much costs and outcomes in health economic appraisals should be discounted.<sup>14</sup> In the United States Gold et al<sup>5</sup> argued that the discount rate should be set equal to the real riskless rate of return on government bonds (they currently recommend a rate of 3% per year). Looking to the government bond market for an indication of a society's rate of time preference (ie, how much they wish to consume today versus tomorrow) is a logical strategy and one that has been the basis of the discount rate in the

United Kingdom for many years. Such an approach, however, raises some interesting international transferability issues. For example, the 10-year government bond rate for 1996 shows that the percentage return per year varies widely among countries (6.7% in the United States, 7.6% in Canada, 3.3% in Japan, and 9.5% in Italy). An intriguing (but unanswered) question is whether individual country appraisals should use indigenous government bond rates for time preference adjustments or whether all studies should adhere to one international rate. Furthermore, it is unclear whether the bond rate in, for example, "Country A" necessarily reflects time preference for citizens in that country because bonds are bought and sold internationally.

*Opportunity Cost of Resources.* As indicated in Table 1, the bottom line of the GUSTO economic appraisal was an incremental cost effectiveness of approximately \$33,000 per life-year gained. Is this good value for money? In their discussion of this analysis, Mark et al<sup>10</sup> suggest that \$50,000 per life-year gained is a rough benchmark for an acceptable cost-effectiveness ratio. By this criterion, the authors argue that tPA at \$33,000 per life-year is a good value for the money. But is this benchmark and interpretation applicable to other settings? The answer is a simple no.

There is no reason why all countries should have the same values and be willing to pay similar amounts to achieve improved health outcomes. The opportunity costs of implementing a program are the other programs that will be forgone and the benefits that would have arisen. These opportunity costs will vary between countries, all of which spend different percentages of their gross national product on healthcare (Table 6). Even if the data are applicable from one country to another the interpretation and value of the information will vary depending on what each country is willing to pay or sacrifice to have the program put in place. There is no obvious reason why all countries should value

**Table 6.** Total Healthcare Expenditures as a Share of Gross National Product (GNP), 1992

Country	Percentage of GNP	Relative Rate (Canada = 100)
Australia	8.5	83
Canada	10.2	100
Germany	8.6	84.3
Japan	7.0	68.3
Austria	9.0	87.4
Spain	7.2	70.6
United Kingdom	7.0	68.5
United States	13.8	134.8

Source: The Organization for Economic Cooperation and Development (OECD)

health relative to other goods at the same rate.

### Conclusion

"It was the best of times, it was the worst of times . . ." wrote Charles Dickens in the mid-19th century comparing the cities of London and pre-Revolution Paris. The theme this paper has attempted to draw out is that a drug can be cost effective in one country and not cost effective in another. This paper illustrates the various ways in which economic and clinical data may not be transferable from one setting to another. Although variation in the prices of healthcare inputs explains some of the international variation, a large part of the difference in costs or treatments is attributable to differences in clinical practice patterns. Adapting a cost-effectiveness study conducted in one country to another country is not a trivial task. It requires careful scrutiny of the relevance of comparators, practice patterns, and relative price weights.<sup>15</sup> The implications of this reasoning apply at all levels of geographic grouping. The focus of this paper has been international, but for large heterogeneous countries, there may be much intranational variation.

As the conduct of economic appraisal moves more toward piggyback analyses as part of prospective randomized trials, new analytic tools will be needed to examine the extent to which resource data can be combined from multiple centers and countries. Limited intellectual resources have been expended on this problem to date, but this is a challenging and important topic for the future of pharmacoeconomic analysis.

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