Regulatory Issues and Economic Efficiency

Economic analysis is defined as "the comparative analysis of alternative courses of action in terms of both their costs and consequences"[1]. In an economic evaluation the comparison of costs alone is generally not useful; it is important to view the cost of a given intervention as it relates to health outcomes[1]. The most informative economic evaluations are comparative, viewing an intervention against other possible interventions. The economic impact of interventions has been typically assessed by regulatory parties as ad-hoc evaluations of costs and consequences, without formal economic evaluation. The current trends, however, have been towards the increased use of full economic analyses, and mandatory submission by sponsors and manufacturers of evidence of efficiency: assessment of costs in relation to measurable health benefits[2].

The majority of users of health economic evaluations fall into one of 3 categories: central level policy makers, local level policy makers, or researchers. At the central level, economic evaluations may be used for reimbursement by national and provincial formularies, for practice guidelines, and for development of programs and policies. At the local level, economic evaluations are used for health plan formularies, for practice guidelines, and in managed care for program implementation. In research, economic evaluations are primarily used to assess outcomes and impact and to provide grounds for additional research.

Use of health economic evaluations at the central level is crucial, since resulting guidelines, policies, and programs may affect large populations. Several countries have begun making use of economic evaluations in the past decade; most of these have socialized health programs with some provision of universal health care. Australia and New Zealand were at the forefront of this change, as the first countries to require pharmaceutical companies to submit economic evidence in 1993, and to take into account cost effectiveness when making the decision whether or not to include drugs in their formularies[3,4]. In Canada, decisions are left to the individual provinces instead, and economic evaluation is currently required in 2 provinces: Ontario and British Columbia[3,5,6]. Many European countries also use economic analyses for regulatory decisions[3,4]. The United Kingdom (UK) has a very comprehensive program conducted by the National Institute for Clinical Excellence (NICE). NICE evaluates the clinical effectiveness and the cost effectiveness of pharmaceuticals, medical devices, and medical procedures. It then offers guidance to the National Health Service (NHS) rather than making reimbursement decisions directly. Many other European countries have developed economic guidelines as well, sometimes mandatory, sometimes voluntary, and some are planning to introduce economic analysis as a requirement for reimbursement[3]. In Japan, where the medical and policy-making climate tends to be conservative, health economic evaluations are not currently being used routinely, although small steps are currently being taken to introduce their use[3,7].

The United States possesses the largest and highest-priced pharmaceutical market in the world, dominated by the private sector. While decisions may be made at the central level under a system of socialized medicine, the state and federal governments in the US have little involvement in regulating pharmaceutical expenditures, except in the case of federally funded programs like Medicaid, Medicare, Veterans Affairs, and the Armed Forces. Efforts at this level have been haphazard, and no systematic guidelines for use of economic evaluations are available at these central, government-based provision levels. For the majority of the population, however, drug reimbursement decisions are made at the local level by third-party payers (e.g., Health Management Organizations, HMO). These providers may not always arrive at their decisions in systematic fashion, and they often rely more on cost analysis, rather than full economic evaluations.

Recently, there has been some interest in the use of health economic evaluation when making reimbursement decisions by managed care organizations. The first such organization to adopt pharmacoeconomic data as an element of its formulary decision-making process was Regence Blue Shield of Seattle, which did so in 1998[3,4]. Regence Blue Shield developed a set of stringent guidelines for formulary submissions, which have since been adapted by the Academy of Managed Care Pharmacy (AMCP) and made available to other HMO for their use on a voluntary basis. The extent, characteristics, and pace at which the movement towards health economic evaluation will continue in the United States is not yet clear.

Guidelines for the use of economic evaluations can be categorized into 3 groups: formalized guidelines, which are mandatory requirements for reimbursement; informal guidelines, which are voluntary recommendations; and methodological guidelines, which discuss and attempt to improve methodology in health economic evaluations. In a review conducted by Hjelmgren, *et al* of existing guidelines issued in North America, Europe, and Australia, 25 guidelines were identified[4]: 7 were classified as formalized, 8 as informal, and 10 as methodological. The 7 formalized guidelines were developed by the Australia Commonwealth Department, the Ontario Ministry of Health Guidelines, the Ministry of Social Affairs and Health in Finland, the Dutch Guidelines for Pharmacoeconomic Research, the Portuguese Pharmacy and Medicine Institute, Regence Blue Shield in the United States, and the National Institute for Clinical Excellence in the UK. Guidelines included recommendations on the following aspects (the recommendation most frequently

observed is in parentheses): perspective (societal perspective), costs/resource use (direct health care costs), valuation/pricing (country-specific costs), outcomes measured (effectiveness, as measured by natural units and quality-adjusted life-years gained), type of analysis (incremental ratios), treatment comparator (common practice, least expensive), methods of data capture (clinical trials, meta-analyses), modeling (acceptable), time horizon (long enough to capture relevant costs and outcomes), discount rate (5%), sensitivity analysis, reporting, and financial implications[4]. The formalized guidelines were observed to be slightly more homogeneous than the other 2 types, with agreement for the various features ranging from 40% to 100%. The disagreement between the guidelines was observed primarily in 3 different aspects: the range of costs/resource use to be considered, choice of discount rate, and methods of valuation/pricing.

There are several barriers to the use of economic data by decision makers. One major problem is the difficulty in interpreting the data[3,5,6]. Currently, there is a lack of confidence in the methodological rigor and a concern that it may be difficult to generalize results across different settings[2,3]. In several sectors of the health care industry, there is still a "silo mentality" — a narrow sense of budgetary responsibility, where individual decision makers focus solely on the costs that they are personally responsible for, rather than what would be best with respect to the total costs to their organization, their patients, or society as a whole[3]. There can be a lack of timeliness to health economic evaluations, or poor information on budget implications[3,6]. Reimbursement decisions are based on a variety of factors when economic analysis is mandatory[3,5,6]. Cost-effectiveness is not always used as expected in decision-making, and overall cost may play an important role[5]. Other factors that may be important to decision-making include efficacy of the drug, disease severity, prevalence of the disorder, social and political influences, legal issues, and unexplained variation, perhaps related to personal preferences[3,5,6].

Anis and Gagnon reviewed all 95 submissions made to the British Columbia Pharmacoeconomic Initiative from 1996 to 1999, and evaluated what types of economic analyses were included. Of the 95 applications, 7 included no economic analysis whatsoever, 25 used cost-consequences analysis, 14 used cost-effectiveness, 11 used cost minimization, 9 used cost utility, and 25 used budget impact analysis. In 74% of the applications, the guidelines were not complied with. Over 75% of the cost comparisons and budget impact analyses were industry-conducted. Cost-effectiveness and cost-utility analyses were more often subcontracted to academics or consultants, and applications that relied upon either of these analyses were more often funded than others. Overall, 74% of the applications were not recommended for approval, 9% were fully approved, and 16% were given restricted approval. Of the applications that failed to comply with the guidelines, 80% were not approved. The lack of compliance could potentially be due to the lack of expertise in pharmacoeconomics in the industry, dubiousness as to the importance of following the guidelines in decision-making and/or corporate strategy[6].

Since 1996, the provincial Government of Ontario (Canada) has required a formal economic analysis from any pharmaceutical manufacturers applying for listing of products on the provincial formulary. The Drug Quality and Therapeutics Committee (DQTC) is responsible for assessing which drugs should be listed on the formulary and making recommendations to the Ministry of Health. In a qualitative study by PausJenssen, *et al*, 9 consecutive DQTC meetings were observed and 7 committee members were interviewed. The clinical factor (the product's perceived efficacy and safety) dominated issues of cost. The type of drug being discussed also affected the discussion. For generic drugs, only bio-equivalence had to be proven (costs for generic drugs are regulated in Ontario). For "me-too" drugs, the associated costs were more of an issue. Innovative products often prompted the most complex discussions, as they tend to have high costs and may be the only treatment available for a certain disease, making it difficult to make clinical and economic comparisons. The listing decision was influenced when the submissions from the manufacturers were of poor quality. Impact analysis was typically discussed but was secondary to the economic analysis. The more complex economic analyses were often considered unnecessary (e.g., for generic or "me-too" products), or were not discussed in depth. Cost-consequences analyses were most frequently used by the committee[5].

NICE in the UK has a comprehensive approach to assessing products for approval. External experts from academic settings often review data. A technology assessment is performed and experts write recommendations. The Appraisal Committee then develops provisional recommendations, which are sent to the manufacturer, who then provides feedback and can appeal the NICE decision. British Medical Association and Royal College specialists also provide feedback. Once all feedback is gathered, NICE gives its final recommendation to the National Health Service. For example, in forming guidelines on the use of anti-tumor necrosis factor (anti-TNF) agents in rheumatoid arthritis, the assessment report was prepared by the University of Birmingham. Submissions were also accepted from the manufacturers/sponsors, professional/specialist groups, patient groups, external experts, and patient advocates. The professional/specialist group and patient group submissions, for example, included those from the Royal College of General Practitioners and the British League Against Rheumatism. Clinical effectiveness and cost effectiveness were both examined. Data from 6 randomized controlled trials (RCT) for etanercept and 4 RCT for infliximab were relied upon to assess clinical effectiveness. Cost-

effectiveness was assessed using 3 published evaluations, a cost-utility model developed by the Assessment Group, and cost-utility models for etanercept and for infliximab developed by their respective manufacturers. Based on the clinical and economic data, NICE recommended the use of anti-TNF in the treatment of adults with continuing clinically active rheumatoid arthritis who have not responded to at least 2 disease modifying antirheumatic drugs, including methotrexate (unless contraindicated). NICE also made recommendations in relation to administration, monitoring, maintenance, and other similar issues[8].

It is clear that economic evaluations will be required with increasing frequency for drug approval[2,3]. The trend in many countries is towards the requirement for an analysis more complex than simple cost analysis[3,4,6]. However, the data from economic evaluations is not always used as expected, as decisions about pharmaceutical products are sometimes driven more by budget impact analysis[5]. The quality of data is crucial, as poor quality methods or lack of compliance with guidelines are often factors in the decision not to recommend a pharmaceutical product[3,5,6]. Another vital issue as the use of economic evaluations becomes widespread is the training of the decision makers, who need to be sufficiently able to understand data from these analyses to utilize them appropriately in their decision-making processes[3,5].

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