EVIDENCE AND VALUES: REQUIREMENTS FOR PUBLIC REIMBURSEMENT OF DRUGS FOR RARE DISEASES - A CASE STUDY IN ONCOLOGY

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ABSTRACT

Introduction
Doubts have been expressed about whether standard methods of health technology assessment are suitable for the evaluation of drugs for rare diseases. Under conditions of rarity, it may be more difficult to conduct large randomized trials in order to gather adequate evidence on efficacy, and the standard methods of economic evaluation may not adequately reflect societal preferences for the treatment of serious and/or life-threatening rare diseases.

Methods
A roundtable was held at the University of Toronto Joint Centre for Bioethics on February 18, 2008 to address these issues. While the focus was on evaluation and reimbursement decision-making for rare cancers, the discussion was broadened to consider the place of evidence and values in considering public reimbursement of drugs prescribed for rare disorders more generally.

Discussion
This paper explores the relevant issues in more detail, using the example of a new drug for treatment of renal cell carcinoma.

Conclusion
There should be a greater commitment by reimbursement agencies to a fair and transparent decision-making process with appropriate community input. Criteria should be developed to validate surrogate markers for rare diseases. It should also be acknowledged that the traditional measures of benefit in economic studies do not incorporate all elements of social value. The need should be recognized to balance equity with an efficient use of resources.

Key words: *Cost-effectiveness, ethics, health policy, clinical trials*

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Given the increasing pressures on healthcare budgets, many jurisdictions have begun to use health technology assessment, including economic evaluation, to assist in the decision-making process for the reimbursement of drugs and other health technologies. Several Canadian provinces were among the first jurisdictions to use this approach in the mid-1990s[1] and the Canadian Coordinating Office for Health Technology Assessment (now the Canadian Agency for Drugs and Technologies in Health (CADTH)) was one of the first organizations to develop methodological guidelines for the conduct of economic evaluations of drugs and other health technologies.[2] Since 2003, most Canadian provinces have participated in the Common Drug

Review (CDR), which assesses the clinical and cost-effectiveness of oral agents according to standardized methods.[3] Since 2007, most provinces have also participated in the Joint Oncology Drug Review for all cancer drugs.

Although the standard methods of health technology assessment, with their emphasis on evidence-based medicine and cost-effectiveness analysis, are gaining acceptance and are seen as important in improving the efficiency of healthcare provision, doubts have been expressed about whether they are entirely suitable for the evaluation of drugs for rare diseases.[4] For example, it may be more difficult to conduct large randomized trials in order to gather adequate evidence on efficacy. In addition, the standard methods of economic evaluation, which treat the gain of a unit of health (e.g., a life-year or quality-adjusted life-year (QALY)) as being of equal value no matter to whom it accrues, may not adequately reflect societal preferences for the treatment of serious and/or life-threatening rare diseases.

Laupacis, writing about the first three years' experience with the Canadian Expert Drug Advisory Committee (CEDAC) of the CDR, argued that the most difficult issue the committee faced was related to the ethics of reimbursement decisions for expensive drugs for rare diseases, most notably agalsidase alfa and agalsidase beta for Fabry's disease.[5] The annual cost of these drugs is greater than $Can 230,000 per patient, and the evidence of effectiveness is based on their impact upon surrogate markers of unknown clinical importance. Not surprisingly, CEDAC unanimously agreed that there was no evidence that enzyme replacement therapy for Fabry's disease met conventional cost-effectiveness thresholds. However, it also indicated that decision-makers might still decide to reimburse these drugs because it is unrealistic to expect drug manufacturers to produce inexpensive drugs for rare diseases, and it could be argued that these patients should not be denied access to potentially beneficial drugs.

Any discussion of drugs for rare diseases is likely to be complicated by the need to define "rarity" and to understand variations in approach taken by the jurisdictions that have addressed the issue. In Australia, a condition is considered to be rare if it affects 2000 individuals in the entire population (approximately 1 in 10,000). The European Union has defined 'rare' as a frequency of 1 in 2000 and the United States has set the bar at 75 per 100,000 or 1 per 1,333. The World Health Organization has defined a rare adverse reaction as affecting 1 in 1000 recipients of a target drug. Canada has no policy on rare diseases to offer guidance, although the National Pharmaceutical Study has been attempting to address the issue of "expensive drugs for rare diseases".

Given this background, and in spite of ambiguity about the definition of 'rare', the aim of this paper is to explore these issues in more detail, using the example of a new drug for treatment of renal cell carcinoma. This is one of the rarer cancers, having a prevalence of less than 650-1000 people per million population.

The specific questions addressed are:
1) What are the limitations of the current approach to priority setting for drugs, especially those for rare diseases?
2) How can priority setting for expensive drugs for rare diseases be improved?
3) What can be done to improve the evidence-base that contributes to these decisions?

A Case Study: Sorafenib for Renal Cell Carcinoma

Sorafenib is a multi-kinase inhibitor for the treatment of locally advanced/metastatic renal cell (clear cell) carcinoma in patients who have failed prior cytokine therapy, or are considered unsuitable for such therapy.

The main clinical data on the efficacy of sorafenib in this indication comes from the TARGET study, which randomized 903 patients to receive sorafenib (400mg twice daily) plus best supportive care (BSC) or BSC alone.[6] The trial, which is the largest so far conducted in advanced renal cell carcinoma, measured endpoints of progression-free survival (PFS) and overall survival (OS).

Although the primary trial endpoint was overall survival, a planned interim analysis of PFS showed a statistically significant advantage in favour of sorafenib. The drug was associated with a doubling of PFS compared to BSC alone (24 weeks versus 12 weeks; HR = 0.44, 95% CI = 0.35 to 0.55). The risk of progression was reduced

by 56% (P<0.000001). As a result of the overwhelmingly positive interim PFS findings, the FDA requested that all the subjects in TARGET be unblinded and offered treatment with sorafenib. (This action reflects the FDA's acceptance of PFS as evidence of efficacy in treatments for advanced disease[7] and the normal provision for allowing 'cross-overs' after a study is unblinded).

At the first planned overall survival analysis in TARGET, which occurred prior to the cross-over, sorafenib patients showed a 39% improvement compared with BSC (HR = 0.72, 95% CI = 0.55 to 0.95, P = 0.018). It was not possible to estimate a difference in median survival, as the median had not been reached for the sorafenib patients at the time of stopping the trial.[8]

A second analysis of OS took place approximately 6 months post-crossover. This showed an overall median survival advantage for sorafenib of 3.4 months (19.3 months versus 15.9 months; HR = 0.77, 95% CI = 0.63 to 0.95, P = 0.015). However, it is likely that the observed survival advantage is diluted due to the cross-over. Therefore, a secondary analysis was performed censoring patients who had crossed over. This showed a median overall survival advantage of 5 months (19.3 months versus 14.3 months, HR = 0.74, 95% CI = 0.58 to 0.93, P = 0.010).[9] It is likely that the estimated difference in overall median survival will increase with further trial follow-up, but subsequent analyses will also reflect the dilution in effect due to the cross-over.

Health technology assessments that include economic evaluation are heavily reliant on the data from clinical studies for the estimation of the denominator in the incremental cost-effectiveness ratio (e.g., life-years gained or quality-adjusted life-years gained). This was the case when the CDR considered whether or not sorafenib should be recommended for reimbursement.

The submission from the drug's manufacturer used a Markov model, with key parameter estimates based on the TARGET trial. These models estimate transition probabilities based on the data observed in the trial, in this case the transitions from PFS to progressive disease or death up until the point of cross-over. The Markov model estimated a difference in overall survival (over a lifetime) of 1.21 years and an incremental cost per life-year gained of $36,046. In its assessment of the evidence, the CDR concluded that, given the early termination of the trial, the overall survival advantage, and hence the true cost-effectiveness of sorafenib, were uncertain. Rather than accepting the manufacturer's projections, it conducted its own analysis, which assumed that once patients entered the progressive disease state, being treated with sorafenib had no further impact on survival.

The CDR analysis generated an estimate of overall survival gain of 4.5 months, which was closer to that actually observed in the trial at the time of the most recent analysis of outcome. Using this revised estimate of survival gain, the incremental cost-effectiveness ratio rose to $78,227, more than twice the manufacturer's estimate. Consequently, CEDAC recommended that sorafenib not be listed.

Limitations of Current Approaches to Priority Setting for Drugs, Especially those for Rare Diseases

Drug priority setting in most jurisdictions worldwide relies heavily on evidence-based medicine (EBM) and cost-effectiveness analysis (CEA). This approach is helpful in that it provides useful information that supports three key values (evidence, benefit, and efficiency), but limited because these are not the only values relevant to drug priority setting. Other values relevant to drug priority setting decisions include: equity, equality, need, precedent, and solidarity.

It is hardly surprising that committees whose membership consists of experts in EBM and CEA focus mainly on the assessment of evidence on clinical and cost-effectiveness. However, the pursuit of an objective, quantifiable approach does not provide an adequate *a priori* justification for excluding these other values, which may be equally relevant.

It would be wrong to suggest that drug reimbursement committees like CEDAC pay no attention to other factors. In Australia, George et al[10] argue that the Pharmaceutical Benefits Advisory Committee (PBAC) probably considered factors such as the seriousness of the condition and the availability of other treatments, over the five year period studied. Also, in the United Kingdom, Rawlins and Culyer[11] give an example where, in the case of a cancer drug, some

patients were allowed access on equity grounds, in situations where care would not be considered cost-effective according to normal criteria.

Adjudicating among clusters of relevant values is the core of priority setting, especially for drugs.[12] Unfortunately, there is no overarching principle for resolving the cluster of value-conflicts that arise when, for example, the incremental cost-effectiveness is high, the evidence is weak, the benefit is small, the cost is high, and the patients have no feasible alternative therapy. Different individuals will resolve this conflict differently according to the values that they emphasize.

Therefore, decisions about drug reimbursement from a publicly funded drug program require, as Culyer has suggested, a process that blends algorithmic and deliberative approaches.[13] That is, drug reimbursement committees should adhere to a process that is unbiased and ethically acceptable.

TEXT BOX 1

Stakeholder Engagement: Rationales for priority setting decisions must rest on reasons (value-based) that stakeholders can agree are relevant in the context. Only participation by the full range of stakeholders can ensure that the full range of relevant reasons is brought to the deliberations. Only by deliberation between conflicting viewpoints can context-specific solutions be found.

Publicity: Priority setting decisions and their rationales must be publicly accessible. Publicity means that leaders must take action to disseminate the message out to all segments of the public. Thus, publicity goes beyond mere transparency.

Revisions: There must be a mechanism for challenge, including the opportunity for revising decisions in light of considerations that stakeholders may raise. This provides a quality assurance mechanism to difficult and controversial decision making and demonstrates responsiveness on the part of leaders.

Leadership: Leaders in each context are responsible for ensuring that the first three conditions are met. This requires periodic ongoing monitoring and evaluation of progress with respect to *stakeholder engagement*, *publicity* and *revisions*.

Adapted from Daniels and Sabin (2002)

How Can Priority Setting for Expensive Drugs for Rare Diseases be Improved?

The real difficulty in priority setting for expensive drugs for rare diseases is that the inherent value-conflicts are actually people-conflicts. Within a range of different people - i.e., different stakeholders – it is possible to identify reasonable, but mutually exclusive, value-positions. Consequently, when a small group of 'experts' make drug priority setting decisions that exclude individuals who hold different value positions, they usually generate public controversy.

To ameliorate such controversy, leaders in drug priority setting contexts must create a decision-making environment that is, and is seen to be, ethically acceptable. Daniels and Sabin argue that fair priority setting must meet four conditions: *stakeholder engagement*, *publicity*, *revisions*, and *leadership* (Text Box 1).[14]

This framework can be used as an analytic lens to facilitate social learning about drug priority setting,[15] and it connects priority setting to broader, fundamental, democratic, deliberative processes that should ground all public policy making. Drug priority setting decisions that are fair are those that involve the full range of relevant stakeholders, deliberating about the full range of relevant values, within a process that is transparent and responsive.

What Can be done to Improve the Evidence-base that Contributes to these Decisions?

Epidemiological Approaches
The sorafenib example above raises two important epidemiological issues:

1) What can we reasonably expect to learn from RCTs in advanced disease?
2) What other studies could be conducted to improve interpreting evidence from RCTs?

Turning to the first issue, there is a growing tension between, the trend towards quicker approval in the US for drugs in advanced diseases, versus, the need for better quality data for formulary committees in Canada and elsewhere. It is becoming much more common for the FDA to give approval based on PFS or time to progression (TTP) and to allow cross-overs. The paradox, under such circumstances, is that the more

effective the drug, the shorter the time to cross-over and hence the lower the chances of showing an advantage in terms of overall survival.

In the context of sorafenib, it is difficult to see how the manufacturer could have behaved any differently following the FDA's recommendation. Patients with advanced disease are often reluctant to enter into RCTs since they only have a 50% chance of receiving the new therapy. Therefore, it is common (and indeed ethical) to allow cross-over to the new therapy once efficacy has been demonstrated.

Thus, the manufacturer was caught in an ethical 'no man's land', in that 1) it has lost the opportunity to continue the trial in its original form to the point where the outcome would have become clear, 2) it is not able to prove/disprove a statistically significant benefit of its drug in terms of overall survival, 3) it is not ethically able to conduct another RCT, and 4), it is in the position of having these reasons used to deny listing of its drug.

The ethics surrounding the early termination of cancer trials, based on improvements in PFS, clearly require more debate. On the one hand, continuing the trial would mean that patients are being randomized to a therapy that is potentially inferior. On the other hand, early termination of the trial means that less will be known about the long term benefits and harms of the therapy than otherwise might be the case. Trotta et al argue that this may compromise the treatment of future patients once the drug is used in regular clinical practice.[16] Therefore, the ethical dilemma concerns the extent to which participants in the trial should be denied potentially effective therapy, for the benefit of future patients. However, in the case of rare diseases, where there are already problems in recruiting sufficient patients for clinical trials, any policy that makes participation in such trials less attractive should be considered carefully.

One possible countervening strategy is to use statistical approaches, such as multivariate regression, to link PFS/TTP to overall survival. The likely success of this depends on being able to identify appropriate baseline variables to use as co-variates in the model. Such an approach would also need to be tumour-site specific.

In some fields, such as rheumatology, efforts have been made to find ways of validating biomarkers and surrogate endpoints.[17,18] The OMERACT Filter[19] uses the criteria of truth, discrimination and feasibility to judge particular study endpoints. More generally, the benefits and harms of therapies should be assessed using a standardized general metric, such as GRADE.[20]

Given the fact that RCTs will always have a relatively short follow-up period or be terminated early, more effort needs to be put into establishing registries and conducting other observational studies in rare diseases. Although the absence of a control group limits the usefulness of such studies for estimating relative treatment effect, they can be useful in studying adherence to therapy, the use of the drug in regular practice, and the natural history of disease. However, given the small numbers of patients, conduct of such investigations may require substantial national and international collaboration.

Economic Evaluation

It is clear from the above discussion that the clinical data available to decision-makers on drugs for rare diseases are never going to be as comprehensive, or concise, as those for drugs for more common conditions. These uncertainties are compounded by the fact that other societal considerations may be important, alongside health gain (as measured in QALYs). Thus, the issue for economic evaluation is whether these uncertainties make assessments impossible, as suggested by Clarke,[21] or whether approaches can be devised to cope with the uncertainty.

Three approaches merit further examination. First, more effort could be put into developing standardized approaches for economic evaluation at the disease level. These approaches would conform with the general methodological principles of conducting studies, but go into more detail about the appropriate outcomes to assess and features that are particular to the disease in question. Such disease-specific 'reference cases' have already been developed for several musculoskeletal conditions.[22-24]

Secondly, alongside the decision about whether or not to reimburse the technology, more attention should be paid to the decision about whether or not to collect more data. Formal approaches, that compare the expected benefits of gathering more information with the costs of

conducting the research, have proved useful in determining whether further data collection is worthwhile and, if so, what data to collect.[25]

Indeed, in association with data collection, innovative approaches could be developed to reimburse therapies for which there are considerable doubts about long-term cost-effectiveness. For example, 'coverage with evidence development', or 'conditional reimbursement' is gaining popularity in a number of jurisdictions.[26] In this approach, the new health technology is allowed reimbursement on the condition that further research is conducted (e.g., into long-term outcomes). Then, the reimbursement decision is reviewed after 2-3 years. This approach appears to be particularly well-suited to drugs for rare diseases; although, there must be recognition and acceptance by patients and physicians of the key principle that therapy will be withdrawn if it appears not to be beneficial.

The third approach would be to explicitly address the value-conflicts that are implicit in economic approaches – for example, the trade-off between efficiency (i.e., maximizing health gain given the available budget) and equity (i.e., fairness in access to therapies). One way of addressing this particular conflict would be to acknowledge that the maximum willingness-to-pay for a QALY (the so-called threshold value) may vary according to the level of social value ascribed to the therapy. This would require a

unique decision process featuring deliberation that considers context. Design of such a process will be challenging.

For example, a diverse committee of stakeholders, including the community, might consider composite outcomes and decide that providing access to therapy for sufferers of a rare genetic disease has a high social value, which might justify a high incremental cost-effectiveness ratio for a drug to treat the disease in question.

This is illustrated by Figure 1. For therapies in Group A, there is no great deviation between social value and cost-effectiveness, so a standard technology assessment, based on an assessment of cost-effectiveness alone, is likely to deliver a result which most members of the community would find acceptable. However, therapies in Group B are relatively cost-effective yet are judged to have a low social value. Therefore, members of the community may argue that they should not be publicly funded, even if they are cost-effective. An example may be drugs to treat male impotence, which are not generally funded despite being highly cost-effective.[4] Conversely, therapies in Group C have a high social value, although they are not very cost-effective. Drugs for rare diseases and some cancers may be in this category, if their use is intended in serious conditions for which there are no effective alternative therapies.

FIG. 1 The relationship between social value and incremental cost per quality-adjusted life-year (QALY)
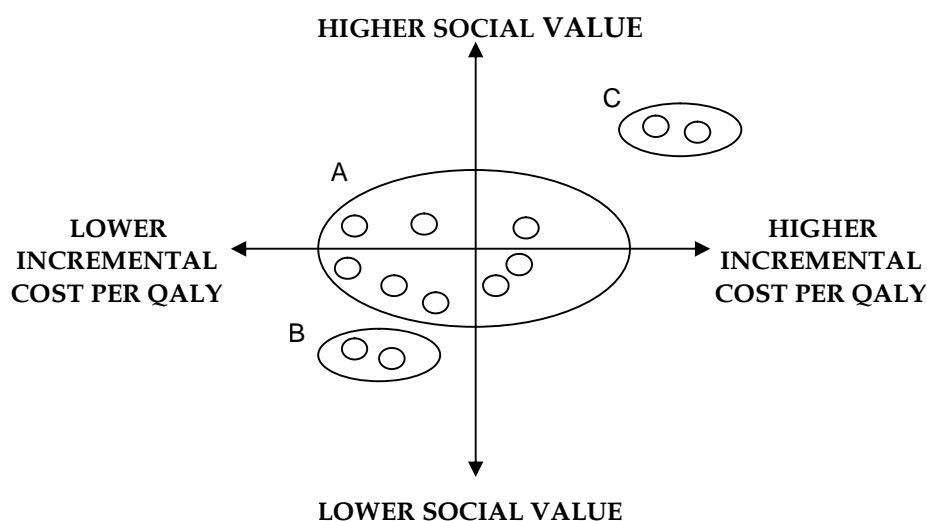
Current Canadian Responses to the Problems

The problems outlined in this paper are beginning to be acknowledged in Canada. For example, a recent report of the Standing Committee on Health (2007) on the Common Drug Review recommended that "the federal government work with its provincial and territorial CDR counterparts to urge CADTH to establish a specifically designed approach for the review of drugs for rare disorders and for first-in-class drugs."[27]

In Ontario, the challenges in cancer drug evaluation and reimbursement have been known for some time. Since 1995, intravenous cancer drugs have been reimbursed according to evidence-based guidelines developed by Cancer Care Ontario (CCO). Recently the program was changed to include cost-effectiveness criteria, since the original program was based only on efficacy. Nowadays, the Joint Oncology Drug Review, coordinated by CCO, receives its information on clinical benefits and harms as systematic reviews conducted by its program on Evidence-based Care. The Joint Oncology Review also reviews economic evaluations prepared by the pharmaceutical industry.

In addition, a broader debate is taking place about the adequacy of 'standard' assessment methods and ways of incorporating societal judgements into the decision-making process. Ontario's Bill 102 (2006) encourages more public involvement through:

1) adding patients to the Committee to Evaluate Drugs;
2) increasing the transparency of the decision-making process-- both of which have been done; and
3) establishing a Citizens Council to advise on controversial value-laden drug policies-which is happening in the Fall of 2008.

Finally, in the case of devices and procedures, the Medical Advisory Secretariat of the Ministry of Health and Long-Term Care in Ontario has established an extensive Health Technology Policy Analysis process. A key component of this is Conditionally Funded Field Evaluations, where studies are launched in collaboration with academic centres.[28] As mentioned earlier, such an approach may be particularly suited to drugs for rare diseases.

CONCLUSIONS / RECOMMENDATIONS

The evaluation of drugs for rare diseases raises a number of complex methodological and policy issues. These require extensive debate, involving ethicists, epidemiologists, clinicians, economists, and decision-makers. To help structure this debate, the following tentative suggestions are made.

An Improved Approach to Drug Priority Setting

There should be a commitment to a fair decision-making process for drugs for rare diseases, recognizing that inevitably this has a value-based foundation. This process should, therefore, include appropriate community input, including patients and tax paying citizens.

Existing decision-making processes need to be reviewed to assess their suitability for dealing with the challenges posed by drugs for rare diseases, including some cancers. Promising initiatives, such as attempts to engage stakeholders, including patients and the public, or to undertake conditional field evaluations, need to be supported and built upon.

An Improved Approach to Evidence Development Regarding Rare Disorders

Epidemiology
Criteria should be developed to validate surrogate markers for rare diseases. In evaluating drugs for rare cancers and other rare diseases, a range of outcomes (including patient-reported outcomes) should be considered alongside survival. In addition, a standardized approach for assessing benefits and harms, such as GRADE, should be used.

In the case of cancer therapy, the conditions under which extrapolation from PFS or TTP is acceptable should be defined and appropriate methods developed.

The greater use of approaches, such as 'coverage with evidence development' should be explored, so as to provide access to therapy, whilst helping reduce decision-makers' uncertainties about the clinical and cost-effectiveness of new treatments. To generate more data on the long-term outcomes of therapies, the use of existing data sources (e.g., clinical series and administrative databases) needs to be explored and, if necessary, new registries established. As a

complementary activity, clear stopping rules and criteria for the removal of technologies from reimbursement need to be developed.

Economic Evaluation

It should be acknowledged that the traditional measures of benefit in economic studies do not incorporate all elements of social value. However, these latter factors (e.g., equity of access to therapy) need to be explicitly balanced against the efficiency objective (i.e., maximizing the health gain, given the available budget). The methods of economic evaluation require more standardization at the disease level (e.g., cancer), whilst maintaining conformity with the existing general guidelines/standards.

Decisions to reimburse new technologies need to be more closely integrated with the decisions to undertake more research. Bayesian approaches, incorporating assessments of the value of information, would be helpful in determining what research should be carried out.

Declaration of Interests

Drs. Drummond and MacLeod are principal consultants for i3Innovus, a contract research organization that conducts health economics and outcomes research for pharmaceutical and biotechnology companies. Neither has provided consultation to i3Innovus directly relevant to this work and i3Innovus has no responsibility for the manuscript. Dr. MacLeod has chaired advisory board meetings for a pharmaceutical company on matters unrelated to the subject matter of this paper.

Dr. LeLorier has, in the past three years, received research funding from Pfizer Inc, Merck-Frosst (Canada) Inc, and Novartis Pharmaceuticals. He has been paid as a consultant by a company with a vested interest in the product being discussed on issues related to the product, and as a consultant by a company with a vested interest in the product under discussion on issues unrelated to the product. He has also received unrestricted research or educational support from a company with a vested interest in the product(s) discussed.

Dr. Karakiewicz has provided consultations to Bayer Inc, Pfizer Inc, Novartis Pharmaceuticals Inc, and Wyeth Canada. Some consultations were relevant to the subjects discussed in this paper.

Drs. Evans, Martin, and Tugwell declared no relevant conflicting interests.

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