

THE JOINT/PAN-CANADIAN ONCOLOGY DRUG REVIEW (JODR/pCODR)

APPRAISING CANADA'S JOINT/PAN-CANADIAN ONCOLOGY DRUG REVIEW
(JODR/pCODR) USING AN ECONOMIC PERSPECTIVE

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ABSTRACT

BACKGROUND AND OBJECTIVES: In 2007, the Joint Oncology Drug Review (JODR) (which ultimately evolved into a permanent body called the pan-Canadian Oncology Drug Review (pCODR)) was established to make recommendations to Canada's provincial and territorial public drug plans regarding the funding (i.e. reimbursement) of new cancer drugs. The JODR/pCODR exists alongside Canada's Common Drug Review, which provides reimbursement recommendations to Canada's provincial and territorial public drug plans for drugs in all other disease areas. Using an economic perspective, this thesis (composed of three separate papers) appraised: the rationale for the JODR/pCODR's establishment, the JODR/pCODR's resource allocation goals, and the JODR/pCODR's decision-making criteria and decision rules. The overarching theme linking the three thesis papers is whether the JODR/pCODR facilitates Canada's provincial drug plans' ability to achieve a goal of maximizing health benefits with available resources.

METHODS: For the first two papers, a series of questions regarding the JODR's establishment, resource allocation goals, decision-making criteria and decision rules were posed. The questions were answered by reviewing peer-reviewed literature and/or JODR/pCODR-published materials and by applying fundamental principles underlying an economic perspective. By again applying these same principles, the third paper in this thesis addressed the challenges associated with striving to simultaneously achieve the pCODR's resource allocation goals of maximizing health benefits with available

resources and striving to improve access to a more consistent standard of care across Canada.

FINDINGS AND CONCLUSION: The various issues identified in this thesis suggest that the JODR/pCODR is unlikely to facilitate Canada's provincial drug plans' ability to achieve a goal of maximizing health benefits with available resources for several reasons (which are described in detail in the thesis papers). It is my hope that this thesis will encourage further debate regarding the strengths and limitations of the pCODR and regarding other possible approaches for managing the public reimbursement of cancer drugs.

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LIST OF ABBREVIATIONS AND SYMBOLS

CADTH	Canadian Agency for Drugs and Technologies in Health
CCO	Cancer Care Ontario
CDEC	Canadian Drug Expert Committee
CDI	comparative drugs index
CDR	Common Drug Review
CEA	cost-effectiveness analysis
CED	Committee to Evaluate Drugs
CED-CCO	Committee to Evaluate Drugs – Cancer Care Ontario
CLL	chronic lymphocytic leukemia
DQTC	drug quality therapeutics committee
EAP	exceptional access program
EO	Executive Officer
FJC	Federal Joint Committee
FPT	federal/provincial/territorial
HTA	health technology assessment
HTD	high tech drugs
HYE	healthy years equivalent
ICER	incremental cost-effectiveness ratio
JODR	Joint Oncology Drug Review
MDS	myelodysplastic syndrome
MOHLTC	Ministry of Health and Long-Term Care
mRCC	metastatic renal cell carcinoma
NDFP	New Drug Funding Program
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NSCLC	non-small cell lung carcinoma
ODB	Ontario Drug Benefits
OS	overall survival
PBAC	Pharmaceutical Benefits Advisory Committee
pCODR	pan-Canadian Oncology Drug Review
PE	pharmacoeconomic
PFS	progression free survival
PSS	Personal Social Service
P/T	provincial/territorial
QALY	quality adjusted life-year
QoL	quality of life
RCC	renal cell carcinoma
SCCHN	squamous cell carcinoma of the head and neck
SCLC	small cell lung carcinoma
STA	single technology appraisal
TPD	Therapeutic Products Directorate
UK	United Kingdom

PREFACE / DECLARATION OF ACADEMIC ACHIEVEMENT

This thesis takes the form of a sandwich thesis and is comprised of three distinct papers, each prepared for publication in a peer-reviewed journal. The first paper, entitled “Is there an economic rationale for cancer drugs to be treated separately for resource allocation purposes? Critical appraisal of the Canadian approach to reimbursement decision-making for cancer drugs” was written in 2009/2010. This paper was originally submitted to the journal *Health Policy* and will next be submitted to *Health Affairs*. The second thesis paper, written in 2011, is entitled “Exploring Canada’s Joint Oncology Drug Review Using an Economic Perspective: Appraisal and Recommendations for Future Organizations.” Due to its volume, this paper will be separated into 2 manuscripts , each for submission to *The Milbank Quarterly*. The third paper in this thesis was written in 2012/13 and is entitled “Challenges in striving to simultaneously achieve multiple resource allocation goals: the pan-Canadian Oncology Drug Review (pCODR) example.” This paper will be submitted to *Social Science & Medicine*. The first author for all three papers is Heather McDonald. The authorship for each of the three papers is as follows: McDonald, H., Charles, C., Elit, L., and Gafni, A.

Heather McDonald, along with Dr. Amiram Gafni, conceived the idea and overall theme for each thesis paper. Heather McDonald was responsible for researching and writing each of the three papers, with guidance from Dr. Amiram Gafni. The research for each paper involved conducting formal literature reviews where required (i.e. Paper 1 and Paper 2), and reviewing all JODR and pCODR-related literature. For Paper 1 and Paper

2, Heather was responsible for abstracting all relevant information from the literature and interpreting and analyzing this information in order to address the research questions posed in each paper. For all three papers, Heather McDonald was responsible for drafting each manuscript and for revising each manuscript with guidance from Drs. Gafni, Charles and Elit. Drs. Gafni, Charles and Elit were all involved in providing input regarding the overall concept and approach for the three papers, for academic guidance regarding key concepts underlying each paper and for reviewing and providing feedback for each manuscript.

CHAPTER 1

INTRODUCTION

In Canada, the authorization to market pharmaceutical drugs is regulated by Health Canada's Therapeutic Products Directorate (TPD). In determining whether to grant market authorization, the TPD reviews the evidence of a drug's safety, efficacy and manufacturing quality (Health Canada, n.d.). The TPD does not evaluate the cost of a drug, nor does it determine whether anyone should pay for it. Therefore, while market authorization renders a drug suitable for sale in Canada it does not determine who pays for the drug or by what means.

Payment options in Canada for marketed drugs include: cash payment, payment via private health insurance and payment via public funds. In terms of public funding, each province and territory has its own drug plan to pay for outpatient medications for certain members of the population (e.g. people who are over 65 years of age or in significant financial need). There are also a number of federal drug plans that pay for outpatient drugs for specified groups of the Canadian population (e.g. first nations individuals, Department of National Defense employees). Individuals covered under these provincial, territorial and federal drug plans (i.e. beneficiaries) receive certain medications for free or at a subsidized cost. However, these publicly funded drug plans typically cannot afford to pay for all possible medications that are needed by beneficiaries. In other words, drug

budget resources (i.e. dollars) are scarce. Consequently, drug plan decision-makers must make choices regarding which drugs to fund (i.e. reimburse), for whom, at what stage of a disease, and for how long.

In 2003, the Canadian Agency for Drugs and Technologies in Health (CADTH), an independent pan-Canadian body funded by the provincial, territorial and federal Ministries of Health, established the Common Drug Review (CDR) to assist Canada's various public drug plans with the task described above. The CDR is a pan-Canadian process whereby a committee, known as the Canadian Drug Expert Committee (CDEC), provides formulary listing (i.e. drug funding/reimbursement) recommendations to Canada's provincial, territorial and federal drug plans (Canadian Agency for Drugs and Technologies in Health [CADTH], n.d.a). In making these recommendations, the CDEC reviews clinical data, cost-effectiveness information and input from patient groups (regarding the drug under review and the disease the drug is intended to treat) (CADTH, n.d.a). The CDEC is appointed by and reports to the CADTH president and Chief Executive Officer and is composed of experts in drug therapy, drug evaluation and drug utilization along with public members who are intended to bring a layperson's perspective (CADTH, n.d.b). The CDEC recommendations are not binding. Provincial, territorial and federal drug plans have full jurisdiction over their formularies and, therefore, once the CDEC makes a recommendation on a given drug, each participating public drug plan then makes its own decision on whether to reimburse the drug for eligible beneficiaries. All provinces except Quebec participate in the CDR process.

In 2007, a group known as the Joint Oncology Drug Review (JODR) was established (and funded) by the provincial and territorial Ministries of Health. The JODR's role was to make recommendations to Canada's provincial and territorial public drug plans (excluding Quebec) to guide their decisions regarding the funding of new cancer drugs. The JODR review process was considered to be an interim measure that would be formally evaluated before a permanent, national process for the reimbursement review of cancer drugs was established. The JODR ultimately evolved into a permanent body called the pan-Canadian Oncology Drug Review (pCODR), which was established in 2010 by the provincial and territorial Ministries of Health and which began accepting submissions in 2011 (pan-Canadian Oncology Drug Review [pCODR], 2011). The pCODR assesses the clinical evidence and cost effectiveness of new cancer drugs and uses this information to make recommendations to the provinces and territories (referred to as 'provinces' for simplicity from this point forward) to guide their cancer drug funding decisions (pCODR, n.d.a). Thus, in Canada there are now two similar groups that make recommendations regarding the public reimbursement of (i.e. the allocation of resources to) medications: one for cancer drugs and one for drugs in all other disease areas.

This thesis, composed of three separate papers, appraised: the rationale for the JODR/pCODR's establishment, the JODR/pCODR's resource allocation goals, and the JODR/pCODR's decision-making criteria (i.e. the specific criteria used to evaluate a drug) and decision rules (i.e. the how the decision-making criteria are combined in order to make a reimbursement recommendation) using an economic perspective. The

overarching theme linking the three thesis papers is whether the JODR/pCODR facilitates Canada's provincial drug plans' ability to achieve a goal of maximizing health benefits with available resources. The economic perspective (including the goal of maximizing health benefits with available resources) and details of each thesis paper are described further below.

An Economic Perspective

Economics is a discipline that studies how to allocate scarce resources in order to best achieve the stated goals defined, for example, by decision makers. It is based on three fundamental concepts: *scarcity* (whatever resources are available, they are insufficient to support all possible activities); *choices* (because resources are scarce, we must choose between different ways of using them) and *opportunity cost* (by choosing to use resources in one particular way, we forego opportunities to use the same resources in any other way).

I suggest that an economic perspective is an appropriate perspective to use in my thesis for several reasons. First, the very nature of the task with which the JODR/pCODR and provincial drug reimbursement decision-makers are involved (i.e. determining which drugs to reimburse with the available provincial drug budget dollars) is one of allocating scarce resources, and economics is a discipline that studies how to allocate scarce resources in order to best achieve the goals stated by decision makers. Second, the three fundamental concepts upon which economics is based - scarcity, choices and opportunity

cost - are relevant to the provincial resource allocation task that the JODR/pCODR recommendations are intended to guide. For example, due to resource scarcity (i.e. because there are a limited number of drug budget dollars available), provinces must make choices regarding which drugs to publicly reimburse. These choices are associated with opportunity costs: by choosing to spend drug budget dollars on reimbursing certain drugs, provinces forego the opportunity to use these same dollars in any and all other ways. Third, the JODR used and the pCODR uses cost-effectiveness analyses (CEA) to guide drug reimbursement recommendations. Cost effectiveness analysis is an economic tool that can be used to determine whether allocating resources in a particular way advances the goal of maximizing benefits with available resources. By using CEA as a key component of its reimbursement review, the JODR/pCODR has implicitly embraced an economic approach to guiding its resource allocation recommendations. Fourth, in the ‘Frequently Asked Questions’ section of the pCODR website, it is stated that: “The pCODR process also ensures that scarce health-care resources are used to fund the most effective cancer drugs” (pCODR, n.d.b). This pCODR statement is consistent with the economic perspective, because it recognizes that resources are scarce and that choices need to be made regarding how to allocate resources (i.e. regarding which drugs to fund). As such, I suggest that an economic perspective is an appropriate lens through which to appraise the JODR/pCODR.

As is described in my thesis papers, I assumed that the JODR/pCODR has a goal of maximizing the total aggregate health benefits that are conferred to Canada’s provincial

drug plan beneficiaries with the available drug budget dollars (i.e. the available resources). As will be described in further detail in my thesis papers, I assumed this because the JODR used and the pCODR uses CEA to guide its reimbursement recommendations, and the underlying premise of CEA is that the goal of society or society's decision-makers is to maximize the total aggregate health benefit conferred to the population for a given level of resources (Gafni & Birch, 2006; Gold, Siegel, Russel, & Weinstein, 1996; National Institute for Health and Clinical Excellence (NICE), 2004; Weinstein & Stason, 1977). The pCODR also wants to improve access to a more consistent standard of care across Canada, which will be addressed in detail in Paper 3.

Explanation for focusing on the JODR for Paper 1 and 2 vs. pCODR for Paper 3

The three papers in this thesis progress from focusing on the JODR (in Papers 1 and 2) to focusing on the pCODR (in Paper 3). While each thesis paper is described in detail in the next section, I briefly introduce them here to explain my focus on either the JODR or the pCODR for each respective paper.

Paper 1 explored whether a rationale that is derived from an economic perspective has been provided for cancer drugs to be separated from drugs in other disease areas for resource allocation purposes. Paper 1 focused on the JODR because the pCODR was not yet in existence when Paper 1 was written. Furthermore, while the JODR ultimately evolved into the pCODR, I expected that a rationale for the separation of cancer drugs

(even if not derived from an economic perspective¹) would have been provided by the JODR since it was the first incarnation of a national, cancer specific drug reimbursement review body in Canada.

Paper 2 focused on the transparency of and consistency among the JODR's resource allocation goals, decision-making criteria and decision rules, using an economic perspective. When Paper 2 was written, the pCODR had just been established and had not yet published any reimbursement recommendations. In contrast, the JODR had published 29 recommendations. Although it was ultimately given a different name, the permanent pCODR is very similar to the interim JODR. First, as with the JODR, the role of the pCODR is to “assess the clinical evidence and cost-effectiveness of new cancer drugs, and to use this information to make recommendations to the provinces and territories in guiding their drug funding decisions” (Sabharwal, 2010). Second, the pCODR's guiding principles are identical to those established by the JODR. Finally, as described in Papers 2 and 3, both agencies have the same underlying goal of maximizing health benefits with available resources and a stated goal of improving access to a more consistent standard of care across Canada. As such, I felt that focusing on the JODR for Paper 2 would provide an opportunity to offer recommendations to the newly-formed pCODR as it continues to evolve as Canada's “national collaborative platform” (pCODR, n.d.c) for cancer drug funding recommendations.

¹ In Paper 1 I included all rationales given for cancer drugs to be treated separately from drugs in other disease areas for resource allocation purposes and then appraised whether any of these rationales were derived from an economic perspective.

Paper 3 explored the challenges associated with striving to simultaneously achieve the pCODR goal of maximizing health benefits with available resources alongside a pCODR goal of improving access to a more consistent standard of care. By the time Paper 3 was written, the pCODR had been in existence for two years, had created a website where many aspects of the pCODR were described, was actively reviewing reimbursement submissions, and had published a number of recommendations. As such I felt that it would be most relevant to focus on the pCODR instead of the JODR for the third and final paper of this thesis.

Overview of Thesis Papers

As noted above, Paper 1 of my thesis explored whether a justification that is derived from an economic perspective has been provided for cancer drugs to be treated separately from drugs in other disease areas for resource allocation purposes. To address this I posed the following questions:

1. Was a justification that is derived from an economic perspective provided by the JODR for cancer drugs to be treated separately from drugs in other disease areas for resource allocation purposes?
2. Does justification that is derived from an economic perspective exist in the peer-reviewed literature for cancer drugs to be treated separately from drugs in other disease areas for resource allocation purposes?

3. Is there another health care system in the world where cancer drugs are treated separately from drugs in other disease areas for resource allocation purposes, and if yes, was a justification that is derived from an economic perspective provided for this separate treatment?

The questions addressed in Paper 1 are important because separating cancer drugs from drugs in other disease areas does not change the resource scarcity inherent to Canada's provincial drug plans. Canada's provincial drug plans still have a limited number dollars available to allocate towards reimbursing drugs and must determine how to allocate these resources in order to best achieve their goals. Therefore, it is important to understand whether there is a rationale for separating cancer drugs from drugs in other disease areas that is consistent with the economic perspective and achieving a goal of maximizing health benefits with available resources. Furthermore, the JODR may be viewed as a precedent for separating disease areas for (either drug or non-drug) resource allocation purposes. This potential for further compartmentalization of disease areas underscores the importance of examining whether a justification that is consistent with an economic perspective and achieving a goal of maximizing health benefits with available resources exists for such separation.

In my second thesis paper I appraised the transparency of and consistency among the JODR's resource allocation goals, decision-making criteria and decision rules, using an

economic perspective. In conducting this appraisal I addressed the following research questions:

1. a) Was a resource allocation goal that is derived from an economic perspective clearly stated, defined and operationalized by the JODR?

b) Is it possible to clearly infer a resource allocation goal for the JODR that is derived from an economic perspective?
2. a) Were there clear specifications regarding what information must be provided to the JODR when making a reimbursement submission?

b) Were the decision-making criteria and decision rules used by the JODR to make a reimbursement recommendation clearly stated, defined, and operationalized?

c) Did the JODR have the necessary information to make reimbursement recommendations that were consistent with its resource allocation goal(s)?
3. Were the JODR recommendations consistent with its resource allocation goals, decision-making criteria and decision rules?

OR

If the JODR's decision-making criteria and decision rule(s) for making a reimbursement recommendation were not clearly stated, defined and operationalized, can they be inferred based on the JODR's recommendations?

The questions addressed in Paper 2 are important because, despite questions around the appropriateness (from an economic perspective) of treating cancer drugs separately from drugs in other disease areas for resource allocation purposes, this separation has been cemented in Canada by the decision to evolve the interim JODR into the permanent pCODR. Consequently the pCODR is and will continue to directly influence the drug reimbursement landscape in Canada, impacting cancer stakeholders (which include patients, physicians, caregivers), stakeholders in other disease areas (as will be described in Paper 1) and the general public. As such, it is important to know what the agency's goals, decision-making criteria and decision rules are and whether the goals can be achieved based on the decision-making criteria and decision rules. While I use the JODR as the reference point for Paper 2, the findings from this paper are relevant to the pCODR given that, as noted earlier, the JODR and pCODR have the same role, the same guiding principles and the same resource allocation goals.

The objective of my third thesis paper was to explore, using an economic perspective, the challenges associated with trying to simultaneously achieve the pCODR's resource allocation goals of maximizing health benefits with available resources and improving access to a more consistent standard of care across Canada. The pCODR has highlighted

that its work will ultimately “improve access to a more consistent standard of care across Canada” (pCODR, n.d.d). From an economic perspective, improving access to a more consistent standard of care across Canada is an equity (fairness) goal that can be achieved through the allocation of resources. However, the pCODR also has an underlying goal that is derived from an economic perspective of maximizing health benefits with available resources. Therefore, the pCODR appears to have two simultaneous goals that will affect how scarce resources should be allocated. In Paper 3 I first examined the definition and operationalization of the pCODR goals to determine how resources would have to be allocated to achieve each goal. I then explored whether, from an economic perspective, both of the pCODR’s goals can be simultaneously achieved to the same extent that each goal could have been achieved alone with the same available resources. Finally, I discussed, using an economic perspective, the tradeoffs that may be involved in striving to simultaneously achieve the two pCODR goals.

The issues addressed in Paper 3 are important because trying to simultaneously achieve the goals of maximizing benefits with available resources and improving access to a more consistent national standard of care may seem like a positive undertaking that is beneficial both to patients and to society. However, from an economic perspective there are a number of challenges associated with trying to simultaneously achieve these two goals. Highlighting and making transparent the potential challenges of this complex undertaking will hopefully help Canada’s provincial drug plans and the stakeholders they represent understand the consequences that striving to simultaneously achieve the two

pCODR goals has on the ability to achieve a goal of maximizing health benefits with available resources.

The pCODR is still a relatively new agency that began accepting submissions in July, 2011 (pCODR, 2011). Consequently, it could be argued that it is too soon for an appraisal and that any criticisms of the pCODR are premature. However, the pCODR has the potential to significantly impact Canadian drug reimbursement decision-makers, patients, physicians and the general public. Furthermore, although still new, the pCODR has already issued a number of reimbursement recommendations (as had the JODR). Therefore, based on what is currently known about the pCODR, based on what is known about the preceding JODR, and based on the fundamental principles underlying an economic perspective, it is possible to predict (as is done in the following thesis papers) whether the pCODR will facilitate Canada's provincial drug plans' ability to achieve a goal of maximizing health benefits with available resources. Thus, I suggest that this thesis is both important and timely because it will advance the debate about whether cancer drugs should be treated separately from drugs in other disease areas (for resource allocation purposes) and whether the pCODR in its present form (with the present goals, decision-making criteria and decision rules) will enable provinces to achieve a goal of maximizing health benefits with available resources.

CHAPTER 2:

Is there an economic rationale for cancer drugs to be treated separately for resource allocation purposes? Critical appraisal of the Canadian approach to reimbursement decision-making for cancer drugs

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ABSTRACT

INTRODUCTION: In Canada two centralized groups make recommendations regarding the allocation of public dollars to outpatient medications: one for cancer drugs and one for drugs in all other disease areas. We explore whether a justification that is derived from an economic perspective has been provided, in Canada or elsewhere, for cancer drugs to be treated separately from drugs in all other disease areas for resource allocation purposes.

METHODS: A series of questions were developed to address our objective. Literature reviews and internet searches were undertaken to identify, collect and analyze relevant documents that would provide information to answer these questions. **FINDINGS:**

Although a number of reasons for cancer drugs to be treated separately from drugs in other disease areas for resource allocation purposes were cited, a rationale derived from an economic perspective did not appear to be documented, in Canada or internationally.

DISCUSSION AND CONCLUSION: From an economic perspective separating cancer drugs for resource allocation purposes is likely to impede drug plan decision-makers' ability to allocate resources in a manner that maximizes the total aggregate health benefit for the defined population. While we acknowledge the challenges that cancer drugs pose to drug reimbursement decision-makers, we suggest that separating the reimbursement review of cancer drugs requires further scrutiny given that it may reduce the total aggregate health benefits realized by the defined population.

Word Count: 216

Key Words: Resource allocation, cancer, reimbursement, Joint Oncology Drug Review, pan-Canadian Oncology Drug Review

INTRODUCTION

Health care systems everywhere face the complex challenge of determining how to provide healthcare to best achieve their goals within an environment of scarce resources. Resource scarcity (i.e. affordability) means that, whatever resources are available, they are insufficient to support all possible activities. As a result of scarcity, decision-makers responsible for drug plans (e.g. governments) must determine which drugs to reimburse, for whom, at what stage of a disease and for how long. In Canada, organizations have emerged to assist decision-makers with this task. In 2003, the Canadian Agency for Drugs and Technologies in Health established the Common Drug Review (CDR).[1] The CDR is a centralized organization (funded by Canada's federal, provincial and territorial (FPT) Ministries of Health) that provides formulary listing (i.e. drug funding/reimbursement) recommendations to Canada's publicly funded drug plans (which pay for outpatient medications for certain members of the population - e.g. people who are over 65 years of age or in significant financial need). All provinces and territories except Quebec participate in the CDR process. In 2007 a second centralized organization (funded by Canada's provincial and territorial Ministries of Health) known as the Joint Oncology Drug Review (JODR) was established specifically to make cancer drug formulary listing recommendations to Canada's provincial and territorial public drug plans. The JODR ultimately evolved into the permanent pan-Canadian Oncology Drug Review (pCODR), which was established in 2010 and which has been in operation since 2011. The overall role and the parameters upon which reimbursement recommendations are based are the same for the pCODR as they are for the CDR (i.e. clinical evidence,

cost-effectiveness, and patient evidence).[2] Thus, in Canada, there are now two centralized groups that make recommendations to the provincial and territorial drug plans regarding the allocation of resources to drugs: one for cancer drugs and one for drugs in all other disease areas.

This paper seeks to explore, using an economic framework, whether a rationale derived from an economic perspective has been presented to justify why having two separate drug reimbursement review bodies, one for cancer drugs and one for drugs in all other disease areas, is better than having one drug reimbursement review body for resource allocation purposes (i.e. better able to achieve the economic goal of maximizing benefits for the defined population with available resources¹). In doing so we ask the following questions:

1. Was a justification that is derived from an economic perspective provided by the JODR for cancer drugs to be treated separately from drugs in other disease areas for resource allocation purposes?
2. Does justification that is derived from an economic perspective exist in the peer-reviewed literature for cancer drugs to be treated separately from drugs in other disease areas for resource allocation purposes?

¹ The goal of maximizing health benefits with available resources will be explained in further detail in the next section.

3. Is there another health care system in the world where cancer drugs are treated separately from drugs in other disease areas for resource allocation purposes, and was a justification that is derived from an economic perspective provided for this separate treatment?

This paper focuses on the JODR instead of the pCODR. While the JODR ultimately evolved into the pCODR, we expected that a rationale for the separation of cancer drugs (even if not derived from an economic perspective²) would have been provided by the JODR since it was the first incarnation of a national, cancer specific drug reimbursement review body in Canada.

The next section describes why we chose an economic perspective for addressing the stated questions. This is followed by a brief description of the JODR. The research method for answering each question is subsequently outlined, followed by a summary and discussion of our findings.

USE OF AN ECONOMIC PERSPECTIVE

Economics is a discipline that studies how to allocate scarce resources in order to best achieve the stated goals defined, for example, by decision makers. Economics is based on three fundamental concepts: *scarcity* (whatever resources are available, they are

² In this paper we included all rationales given for cancer drugs to be treated separately from drugs in other disease areas for resource allocation purposes and then appraised whether any of these rationales were derived from an economic perspective.

insufficient to support all possible activities); *choices* (because resources are scarce, we must choose between different ways of using them) and *opportunity cost* (by choosing to use resources in one particular way, we forego opportunities to use the same resources in any other way).

Although economics is just one perspective that could be used to address the questions in this paper, we suggest that it is an appropriate perspective for a number of reasons. First, as described by Luce et al[3] the three key questions that “evidence-based processes in health care seek to answer about an intervention” are “Can it work”, “Does it work?” and “Is it worth it?” Drug reimbursement review bodies must determine whether a drug is “worth it”, and economics provides an approach for determining whether allocating resources in a particular way advances the stated goal. Second, scarcity, choices and opportunity costs, the three fundamental concepts upon which economics is based, reflect the nature of the resource allocation problem facing drug reimbursement decision-makers. Third, the CDR uses and the JODR used cost-effectiveness analysis (CEA) as a key component of the reimbursement review process. The underlying premise of CEA is that the goal of society or decision-makers is to maximize the total aggregate health benefit conferred to a population for a given level of resources.[4,5,6,7]³ Therefore, the CDR and JODR’s use of CEA recognizes the relevance of applying economics to inform resource allocation decisions tasks.

³ Because only certain people are covered by Canada’s public drug plans, the allocation of public drug plan dollars can only maximize benefits for defined individuals (i.e. the drug plan beneficiaries). However, the underlying premise of CEA is that it is society’s goal (and the decision-makers that represent society) to maximize the benefits for this defined population.

Because the JODR implicitly embraced an economic approach to guiding its resource allocation recommendations (through the use of CEA), we suggest that the economic approach should have been consistently followed by the JODR, including in the rationale for its establishment. Furthermore, because, as noted above, the underlying premise of CEA is that the goal of society or decision-makers is to maximize the total aggregate health benefit conferred to a population for a given level of resources, we assume that maximizing health benefits with available resources was the JODR's (and the CDR's) resource allocation goal. Hence, the objective of this paper is to explore whether a rationale has been presented to justify why having two separate reimbursement review bodies, one for cancer drugs and one for drugs in all other disease areas, is better able to achieve the goal of maximizing health benefits with available resources than having a single reimbursement review body for drugs in all disease areas.

The maximization of benefits through the use of available resources is referred to as economic efficiency, while equity refers to the fair allocation of available resources. It is often wrongly argued that efficiency and equity are separable – i.e. that economics is only concerned with maximizing benefit and therefore ignores what is fair in terms of resource allocation. However, equity and efficiency are inextricably linked. Efficiency involves maximizing total aggregated benefits. In the case of health care, the total health benefits gained through the allocation of resources is calculated by aggregating the health benefits that accrue across individual patients. The aggregation requires a set of rules (known as equity criteria). These rules may describe, for example, how to value different types of

health benefits (e.g. a reduction in pain, a prolongation of life) or how to value health benefits based on the type of patients who have realized them (e.g. patients over 70 years of age, patients with a rare disease). The specific equity criteria should be chosen by the decision-maker. The equity criteria are then incorporated into resource allocation decision-making either by accounting for them when aggregating the health benefits (e.g. to weight health benefits gained for each particular type of disease differently) or by incorporating them as an additional constraint (e.g. by requiring that resources are equally available to everyone, regardless of the benefits gained). Equity considerations are thus inevitably incorporated into the task of determining how to efficiently allocate scarce resources. Consequently, our search for arguments related to how having two separate drug reimbursement review bodies (one specifically for cancer drugs) is better able to achieve the goal of maximizing health benefits with available resources than having a single reimbursement review body for drugs in all disease areas included any arguments based on equity considerations.

THE JOINT ONCOLOGY DRUG REVIEW

In 2006, Canada's provincial/territorial (P/T) premiers recommended that all provinces start working towards "a common, streamlined, evidence-based oncology drug review process."^[8] The establishment of the JODR was subsequently announced in 2007. The JODR was intended to be an interim process that would function until the establishment of a permanent centralized system for the reimbursement review of cancer drugs. The JODR made recommendations to Canada's provincial and territorial public drug plans

(except Quebec) to guide their drug funding decisions. Once the JODR made a recommendation, each participating drug plan then made its own decision on whether to reimburse the drug for eligible beneficiaries.

The JODR stated that “There is significant potential for Canada’s oncology drug review process to become the international gold standard.”[9,10] The establishment in 2010 of the pCODR as a permanent reimbursement review body solely for cancer drugs further entrenches the separation of cancer drugs from drugs in other disease areas for resource allocation purposes. As such, the questions raised in this paper remain relevant for the Canadian and international health policy communities.

METHODS

1) General

Because the JODR was only in existence from 2007-2010 we recognize that there may not be any peer-reviewed publications written by the JODR. As such we searched both the peer-reviewed literature and the internet for information to address Question 1.

Question 2 relates to whether a justification for cancer drugs to be treated separately exists in the peer-reviewed literature. Therefore, only the peer-reviewed literature was searched to address this question. Question 3 explores whether there is another healthcare system in the world that has separated cancer drugs from drugs in all other disease areas for resource allocation purposes. Given that, if such an example exists, it may not be

described in the published literature, we searched both the peer-reviewed literature and the internet to address this question.

For all three questions, the PubMed database was used to identify peer-reviewed publications, with literature searches limited to English-language articles published between January 1, 2000 and Dec 31, 2010. Relevant published articles were read in full by one reviewer (HM), and references from relevant articles were also scanned to see if they contained information related to the research questions.

2) Search Strategies and Data Collection

Question #1: Was a justification that is derived from an economic perspective provided by the JODR for cancer drugs to be treated separately from drugs in other disease areas for resource allocation purposes?

a) Peer-Reviewed Literature Search:

The following search terms were used:

- (Joint oncology drug review) OR JODR

Abstracts identified from the PubMed search were screened by one reviewer (HM).

Articles were considered relevant for full review if they discussed the establishment of the JODR in any way. Of the 72 abstracts identified using PubMed, none described establishment of the JODR and, hence, none were deemed relevant for review.

b) Internet Search:

The terms ‘JODR’ and ‘Joint oncology drug review’ were searched using the Google search engine. To be as broad as possible in this search, materials identified on the internet were deemed relevant if they were written by the JODR and described the JODR in any context. Four documents were deemed relevant for review.[8,9,10,11] All relevant materials were read in full by one reviewer (HM). Although not available on the internet, a presentation given in 2010 at a stakeholder meeting organized by the JODR[12] was also included.

Question #2: Does justification that is derived from an economic perspective exist in the peer-reviewed literature for cancer drugs to be treated separately from drugs in other disease areas for resource allocation purposes?

The following search strategy was used:

- [(oncology OR cancer) AND (reimbursement OR resource allocation)]
OR [(cancer OR oncology) AND (formulary OR funding)] OR [(oncology
OR cancer) AND (priority-setting OR priority setting)]

Search terms used in combination with (oncology OR cancer) were limited to abstract/title. Abstracts from the PubMed search were screened by one reviewer (HM). Articles were considered to be relevant for full review if they discussed: i) why cancer drugs should be given special consideration relative to other disease areas or ii) separating cancer from other disease areas for resource allocation purposes. Of the 1,709 abstracts identified, 32 references were deemed relevant for full review.

Question #3: Is there another health care system in the world where cancer drugs are treated separately from drugs in other disease areas for resource allocation purposes, and was a justification that is derived from an economic perspective provided for this separate treatment?

a) Peer-reviewed literature search: The search strategy used for question #2 was felt to also be the best strategy for identifying articles to address question #3. Abstracts from the PubMed search were again screened by one reviewer (HM). This time, articles were considered to be relevant for full review if they discussed resource allocation systems or reimbursement mechanisms for cancer drugs in countries outside of Canada. Relevant articles were then reviewed in full to see if cancer drugs had been given a separate reimbursement review process in any other country and, if so, whether a justification for this separate treatment had been provided. Of the 1709 abstracts identified, 11 primary references and five secondary references (identified by searching the reference lists of each primary reference) were deemed relevant for full review.

b) Internet Search: the Google search engine was used to find any examples of healthcare systems outside of Canada where cancer drugs are treated separately from drugs in other disease areas for resource allocation purposes. The same search terms used for the peer-reviewed literature search (described above) were used for the internet search. Similar to the peer-reviewed literature search for this question, materials identified through the internet search were deemed relevant if they discussed resource allocation systems or reimbursement mechanisms for cancer drugs in countries outside of Canada. These

materials were then reviewed in full to see if cancer drugs had been given a separate reimbursement review process in any other country and, if so, whether a justification for this separate treatment had been provided.

3) Synthesis and Analysis of Information

All relevant documents identified through the internet and peer-reviewed literature searches were reviewed for any statements justifying the separation of cancer drugs from drugs in other disease areas for resource allocation purposes. Such statements were abstracted and included in separate tables for each question (see Appendix A, Tables 1-3). We then examined whether any of these statements included a rationale to justify why having two separate drug reimbursement review bodies (one for cancer and one for drugs in all other disease areas) is better able to achieve the goal of maximizing health benefits with available resources than having one reimbursement review body for drugs in all disease areas.

FINDINGS

Question #1: Was a justification that is derived from an economic perspective provided by the JODR for cancer drugs to be treated separately from drugs in other disease areas for resource allocation purposes?

While the JODR cited various reasons for separating cancer drugs from drugs in other disease areas for resource allocation purposes (see Appendix A- Table 1), the focus of our paper was to determine whether any reasons that are derived from an economic

perspective (and the goal of maximizing health benefits with available resources) were provided. Overall, a rationale derived from an economic perspective was not provided by the JODR. We briefly address some of the rationales that were provided by the JODR below.

Differences Across Provinces in Structures, Processes, and Requirements for the Reimbursement Review of Cancer Drugs

The JODR highlighted interprovincial differences in structures, pharmacoeconomic requirements and review processes for cancer drug reimbursement as a rationale for its establishment.[11] However, the JODR did not explain why, from an economic perspective, these differences justify a separation of cancer drugs from drugs in other disease areas for resource allocation purposes.

Need for Transparency in Decision-Making

The JODR newsletters noted that one of the aims of a national oncology drug review process is to support more transparent decision-making.[8,9,10] Transparency is an important principle for public decision-making and is one of the four conditions (along with reasons or logic, appeals process, and enforcement) described in Daniels and Sabin's accountability for reasonableness framework for fair priority setting for resource allocation decisions.[13] However, the JODR did not provide any descriptions to explain how, from an economic perspective, a need for transparency in decision-making justifies a separate reimbursement review body for cancer drugs.

Different Reimbursement Status and Reimbursement Criteria Across Provinces

The JODR cited “different coverage in each jurisdiction” and “variation and inconsistency in coverage criteria across jurisdictions” as reasons its establishment.[8,9,10,11] The JODR also noted that one of the aims of a national cancer drug review process is to support “a more consistent standard of therapy.”[8,9,10] Establishing consistency across provinces in the drugs that are reimbursed and in the reimbursement criteria for these drugs is an equity criterion that, if specified by decision-makers, can be incorporated into the resource allocation task as a constraint (assuming the criterion is clearly defined and operationalized). However, if the drugs for which consistency in reimbursement across provinces is desired result in added costs, then provinces may need to forego currently funded interventions in order to satisfy this criterion. Because of differences in demographics and population preferences, the opportunity costs of adopting these drugs will vary across provinces.[14] That all provinces have agreed or would agree to an equity criterion of consistency in standard of therapy given the differing opportunity costs is questionable. Indeed, existing interprovincial differences in the reimbursement of cancer drugs that have entered the Canadian market since the establishment of the JODR suggest that the provinces have not agreed to this equity criterion. Moreover, even if provinces agreed to an equity criterion of consistency in standard of therapy, the JODR did not provide an explanation that is derived from an economic perspective for why this requirement would justify a separate reimbursement review body for cancer drugs.

Budget Impact of Oncology Drugs

Another rationale given for the establishment of the JODR was the high budget impact associated with cancer therapies. Under this heading, various reasons for the establishment of the JODR are provided, including the high prevalence of cancer, the rapid emergence of new cancer therapies, the increasing use of cancer therapies, and the high cost of new cancer therapies.[8,9,10,12] However, the JODR did not offer an explanation that is derived from an economic perspective for why budget impact justifies a separate reimbursement review body for cancer drugs.

Question #2: Does justification that is derived from an economic perspective exist in the peer-reviewed literature for cancer drugs to be treated separately from drugs in other disease areas for resource allocation purposes?

Additional reasons have been provided in the peer-reviewed literature for why certain cancer drugs should be given special consideration for resource allocation purposes (see Appendix A - Table 2). These reasons did not necessarily suggest that cancer drugs should be evaluated under a separate drug reimbursement review system (only that special consideration of some sort might be warranted). However, we still reviewed these arguments in case any of them would have justified the separation of cancer drugs from drugs in other disease areas for resource allocation purposes. In addition, the reasons identified in the literature were in some cases related to orphan drugs, with cancer drugs being used as examples or case studies. Therefore, while the rationale may apply to certain cancer drugs, they would not necessarily be specific only to cancer drugs.

Nonetheless, we briefly address some of these arguments below. Overall, similar to our findings for Question #1, a rationale derived from an economic perspective for cancer drugs to be treated separately from drugs in other disease areas was not provided.

Clinical Evidence Expectations of Reimbursement Review Bodies are Not Appropriate for Cancer Drugs

Some authors have noted that the evidence required by reimbursement review bodies is not available for cancer drugs due to the way clinical trials for cancer drugs are conducted.[15,16] For example, because cancer can be immediately life-threatening and because there is a lack of treatment options for many types of cancer, early trial results are often used to inform clinical practice. Furthermore, elements such as surrogate endpoints and cross-over trial designs are used to ensure that a drug's benefit (or lack thereof) can be detected early. The results from these trials often do not provide sufficient efficacy and safety information to meet the evidence requirements of reimbursement review committees. It has been argued that, as such, special considerations need to be granted when evaluating the clinical data for cancer drugs for reimbursement purposes. However, an argument derived from an economic perspective for why a discrepancy between the level of evidence generated in cancer drug studies and the level of evidence expected by reimbursement decision-makers justifies a separate reimbursement review system for cancer drugs is not provided.

Society or the Decision-Maker May Place a Higher Value on Health Gains in Cancer Than on Health Gains in Other Disease areas

Whether the assumptions currently used by drug reimbursement review bodies accurately reflect societal preferences for health gains for serious and/or life-threatening diseases, including certain cancers, has been discussed in the literature.[16] For example, it has been posited that society may place a higher value on health gains in cancer than on health gains in other disease areas. If true, special consideration would be warranted to ensure that the benefits derived from cancer drugs are valued properly within the cost-effectiveness analysis framework. However, decision-makers have not explicitly stated that benefits from cancer drugs should be valued more highly than benefits from drugs in other disease areas, and there generally does not appear to be evidence of a greater societal preference for health gains in cancer over health gains in other disease areas. Furthermore, even if this preference existed, a single reimbursement review body covering all disease areas could incorporate it into the resource allocation decision-making task (i.e. it still does not justify the separation of cancer drugs from drugs in other disease areas from an economic perspective).

Question #3: Is there another health care system in the world where cancer drugs are treated separately from drugs in other disease areas for resource allocation purposes, and was a justification that is derived from an economic perspective provided for this separate treatment?

There does not appear to be another country where a separate drug reimbursement review system has been established specifically for cancer drugs. However, our literature search identified a few countries where a separate budget was set aside for cancer drugs (see Appendix - Table 3). For example, in Denmark funding has been earmarked for cancer drugs [17] and in Belgium, high cost inpatient cancer drugs are funded through increases in drug budgets or are reimbursed separately.[18] However, an economically-derived rationale to justify these separate budgets was not provided.

Our literature search also identified a few countries where special consideration is incorporated into drug reimbursement decision-making based on specific drug or disease characteristics such as disease severity (Norway, Sweden),[18] prognosis (National Institute for Health and Clinical Excellence (NICE)), [19] need for and cost of drugs (France), [20] or chronicity of illness (Portugal, Greece, Finland, Ireland). [20] Some cancer drugs may qualify for special consideration as a result, but this special consideration is not specific only to cancer drugs. In some countries national cancer plans have been launched (e.g. France, United Kingdom). [17] However, while these national cancer plans emphasize the need for access to new cancer drug therapies, they do

not constitute separate reimbursement review processes or special mechanisms for the reimbursement review of cancer drugs in and of themselves.

DISCUSSION

Reimbursement of cancer drugs is a subject of increasing interest and controversy, both in Canada and in other countries around the world. As noted by Mittmann et al, “there has been a great deal of discussion within the health technology assessment community about whether cancer should be treated as a special case, which implies that the agents used to treat cancer need to be evaluated differently from other health care technologies.”[21] In Canada, cancer drugs are now treated separately from drugs in other disease areas for resource allocation purposes. We sought to explore whether a rationale that is derived from an economic perspective has been presented to describe why having two separate drug reimbursement review systems, one for cancer drugs and one for drugs in all other disease areas, is better (i.e. better able to achieve the goal of maximizing health benefits with available resources) than having one system for resource allocation purposes.

As we noted earlier, by using CEA as a key component of its reimbursement review, the JODR implicitly embraced an economic approach to guiding its resource allocation recommendations. While it may be argued that there are other reasons justifying the separation of cancer drugs from drugs in other disease areas for resource allocation purposes, the JODR’s adoption of the economic approach to guide its decision-making

suggests that its reason for existence should also be derived from (and at least, not in contradiction to) this approach.

While various rationales were given for the establishment of the JODR, we did not identify an explanation that was derived from an economic perspective. We similarly did not identify an economically derived rationale in the peer-reviewed literature or from another country for the separation of cancer drugs from drugs in other disease areas for resource allocation purposes.

One limitation of our study is related to the literature search (both PubMed and internet) used to address question #3. Although we were looking for international examples, our search was limited to postings written in English. Therefore, there may be an example of another country where cancer drugs are treated separately for reimbursement review purposes (and where an economically derived rationale for this separation has been provided), but where our search did not retrieve the relevant information.

From an economic perspective, the establishment of the JODR and subsequently the pCODR does not seem to be justifiable. Separating the reimbursement review of cancer drugs from drugs in all other disease areas prevents reimbursement review committees from evaluating cancer drugs within the context of all possible uses of drug budget resources. This interferes with their ability to determine what drugs (from among all possible drug options) will, if reimbursed, confer the maximum aggregate health benefits

for the population. Consequently, if provincial drug plan decision-makers follow the JODR/pCODR recommendations, they may end up reimbursing drugs that confer fewer health benefits with available resources relative to other (non-cancer) drugs that are competing for the same (scarce) drug budget dollars. As a result, patients suffering from diseases other than cancer may be denied access to drugs that would better achieve the goal of maximizing health benefits with available resources. Thus, based on an economic perspective, separating the reimbursement review of cancer drugs may do more harm than good because it may ultimately reduce the total aggregate health benefits that are gained for the defined population.

In addition to the limitations described above, separation may disadvantage cancer drugs. Some cancer drugs may confer more health benefits for a given level of resources than drugs in other disease areas. In these cases, considering cancer drugs under a separate budget (if a separate budget is set aside for cancer drugs), that only represents a portion of the total resources that are available for all drugs, may lead to fewer cancer drugs receiving funding than would be possible if drugs for all disease areas were evaluated together. This is because the funding for the non-cancer drugs would then come at the expense of cancer drugs that could have offered more health benefits for the same resources.

In addition to the economic challenges posed by the establishment of the JODR/pCODR, allowing cancer drugs to be treated separately from drugs in all other disease areas for

resource allocation purposes opens the door for other disease areas to request a separate reimbursement review body for their drugs. If it is not clear why cancer drugs were given a separate reimbursement review body, then it may be difficult to deny other disease areas the same option. This further compartmentalization may lead to even more interference with achieving a goal of maximizing health benefits with available resources.

Although we challenge the justification for the establishment of the JODR and pCODR, we also acknowledge that there are considerable challenges associated with managing the reimbursement of cancer drugs. There has been a rapid emergence of new drugs to treat various forms of cancer, many of these drugs are associated with a high cost, and there is a high prevalence of cancer in Canada and around the world. Consequently, payers need to find a way to balance the potentially large financial impact of cancer drugs against the health care needs of society. As such, further consideration regarding how to best manage cancer drugs in an environment of resource scarcity is both warranted and needed.

CONCLUSION

Our review of the literature found that a justification derived from an economic perspective has not been provided for cancer drugs to be treated separately from drugs in other disease areas for resource allocation purposes. In fact, separating cancer drugs may be inconsistent with an economic perspective and the goal of maximizing health benefits for a defined population with available resources. Based on these findings we suggest

that separating the reimbursement review of cancer drugs from drugs in all other disease areas requires closer scrutiny, both in Canada and by other countries that may be considering a similar approach.

APPENDIX

Table A1 Reasons Provided by the JODR for its Establishment

Theme	Statements	Source
Differences Across Provinces in Structures, Processes, and Requirements for the Reimbursement Review of Cancer Drugs	<p>“Environmental Scan - Differences in structures and processes for the review and approval of oncology drugs”</p> <p>“Environmental Scan - Variation in pharmacoeconomic (PE) submission requirements and expectations for manufacturers”</p>	<p>JODR presentation, 2008[11]</p> <p>JODR presentation, 2008[11]</p>
(Need for) Transparency in decision-making	<p>“The joint oncology drug review (JODR) is a provincial/territorial collaborative initiative and the first step towards building a permanent, national oncology drug review process to support <u>more</u> consistent and <u>transparent decision-making</u> and ultimately, a more consistent standard of therapy.” (underlining added)</p> <p>“The vision for a permanent national oncology drug review process that is emerging from the evaluation and consultations with key stakeholders is one characterized by best practices, in particular with respect to transparency.”</p>	<p>JODR newsletters-April, July, Fall 2008[8,9,10]</p> <p>JODR newsletter – July, Fall 2008[8,9,10]</p>

<p>Different Reimbursement Status and Reimbursement Criteria Across Provinces</p>	<p>“The joint oncology drug review (JODR) is a provincial/territorial collaborative initiative and the first step towards building a permanent, national oncology drug review process to support more consistent and transparent decision-making and ultimately, <u>a more consistent standard of therapy.</u>” (underlining added)</p> <p>“Faced with the increasing utilization of cancer therapies, the rapid introduction of new and high cost oncology drugs and <u>different coverage in each jurisdiction,</u> Canada’s premiers recommended in 2006 that all provinces and territories work toward a common, streamlined, evidence-based oncology drug review process” (underlining added)</p> <p>“Environmental Scan - Variation and inconsistency in coverage criteria across jurisdictions”</p>	<p>JODR newsletters-April, July, Fall 2008[8,9,10]</p> <p>JODR newsletters-April, July, Fall 2008[8,9,10]</p> <p>JODR Presentation, 2008[11]</p>
<p>Increasing budget impact of oncology drugs</p>	<p>“Faced with the <u>increasing utilization of cancer therapies,</u> the <u>rapid introduction of new and high cost oncology drugs</u> and different coverage in each jurisdiction, Canada’s premiers recommended in 2006 that all provinces and territories work toward a common, streamlined, evidence-based oncology drug review process” (underlining added)</p> <p>“Environmental Scan - Changing paradigm: cancer increasingly viewed as a chronic disease.”</p> <p>“Opportunity for a collaborative initiative deemed possible because of...Rapidly rising expenditures for oncology drugs and corresponding increase in financial pressures on P/T drug plans”</p>	<p>JODR newsletters-April, July, Fall 2008[8,9,10]</p> <p>JODR Presentation, 2008[11]</p> <p>JODR Presentation, 2008[11]</p>

	<p>“The annual sales growth of oncology drugs is outpacing that of the overall pharmaceutical market by as much as double, and the therapeutic category is currently the biggest area of drug development”</p> <p>“With the increasing utilization of cancer therapies and the rapid introduction of new high-cost cancer drugs, provinces and territories require rigorous reviews of the clinical effectiveness and cost- effectiveness of these drugs”</p> <p>“Expenditures on cancer drugs and biologics now occupy approximately 30% of provincial cancer budgets”</p>	<p>JODR/pCODR presentation, 2010[12]</p> <p>JODR/pCODR presentation, 2010[12]</p> <p>JODR/pCODR presentation, 2010[12]</p>
Prevalence of disease	<p>“Cancer is Canada’s leading cause of premature death, with approximately 2.5-2.8% of the population, or over 850,000 Canadians, living with a cancer diagnosis”</p>	<p>JODR/pCODR presentation, 2010[12]</p>
Duplication of effort by cancer experts in conducting drug reviews	<p>“Opportunity for a collaborative initiative deemed possible because of...Duplication of effort by cancer experts in conducting drug reviews”</p>	<p>JODR presentation 2008[12]</p>
Limitations in human capital	<p>“Environmental Scan - Variation in pharmacoeconomic (PE) capacity amongst jurisdictions”</p> <p>“Opportunity for a collaborative initiative deemed possible because of...Limited access to a small pool of experts and resources”</p>	<p>JODR presentation, 2008[11]</p> <p>JODR presentation, 2008[11]</p>

Table A2: Reasons Identified in Peer-reviewed Literature for Why Cancer Drugs Should be Given Special Consideration for Resource Allocation Purposes^{1,2}

Theme	Supporting Statements (underlining added)	Reference
<p>Clinical Evidence Expectations of Reimbursement Review Bodies are not Appropriate for Cancer Drugs</p>	<p>“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. <u>For example, it may be more difficult to conduct large randomized trials in order to gather adequate evidence on efficacy.</u>” (underlining added)</p>	<p>Drummond, Evans, LeLorier et al, 2009[15]</p>
	<p>“<u>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.</u> 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, or whether approaches can be devised to cope with the uncertainty.” (underlining added)</p>	<p>Drummond, Evans, LeLorier et al, 2009[15]</p>
	<p>“Second, because of the small number of persons suffering from rare diseases, it is often difficult to enroll sufficient patients into a</p>	<p>Drummond, Wilson, Kanavos et al, 2007[16]</p>

¹ As noted in the results section, the references in this table did not necessarily suggest that cancer drugs should be treated separately from drugs in other disease areas for resource allocation purposes (only that special consideration of some sort might be warranted for cancer drugs). However, we still reviewed these arguments in case any of them would have justified the separation of cancer drugs from drugs in other disease areas for resource allocation purposes.

² Most of the references cited in this table refer to orphan drugs/drugs for rare diseases and include cancer drugs, either as an example or as a discussion point. The arguments made in these papers are included in Table 2 for comprehensiveness. However, as noted in the results section of this paper, the arguments are not specific only to cancer drugs.

	<p>standard randomized controlled trial. This means that, at the time of product launch, there may not be the same breadth and quality of clinical evidence for orphan drugs, compared with those for more common diseases.”</p> <p>“With orphan diseases, it is usually difficult to recruit a sufficient number of patients and medical centres for clinical trials. Furthermore, trials of an anti-cancer medicine may be halted early on ethical grounds when an interim analysis demonstrates clinical superiority in terms of an intermediate outcome measure such as progression-free survival.”</p>	<p>Simoens & Doods, 2011 (epub 2010)[22]</p>
<p>Standard methods of health technology assessment may not be suitable for cancer (rare diseases)</p>	<p>“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, <u>doubts have been expressed about whether they are entirely suitable for the evaluation of drugs for rare diseases.</u> For example, it may be more difficult to conduct large randomized trials in order to gather adequate evidence on efficacy.” (underlining added)</p> <p>“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). <u>Thus, the issue for economic evaluation is whether these uncertainties make assessments impossible, as suggested by Clarke, or whether approaches can be devised to cope with the uncertainty.</u>” (underlining added)</p>	<p>Drummond, Evans, LeLorier et al, 2009[15]</p> <p>Drummond, Evans, LeLorier et al, 2009[15]</p>

<p>Societal values may be different for cancer (rare diseases)</p>	<p>“In addition, the standard methods of economic evaluation, which treat the gain of a unit of health (e.g., a life-year or qualityadjusted 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.”</p> <p><u>“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.”</u> (underlining added)</p> <p>“Although standard methods of health technology assessment are important in improving the efficiency of healthcare provision, there are concerns about whether they adequately reflect societal preferences for the treatment of serious and/or life-threatening rare diseases.”</p> <p>“Standard HTA procedures may not fully capture the societal value of some health technologies and there are currently serious shortcomings in the evaluation of orphan drugs.”</p> <p>“The legitimacy for the availability of orphan drugs, therefore, rests on whether the “standard” methods of HTA adequately reflect societal preferences.”</p> <p>“The economic evaluation of orphan medicines in cancer care is challenging. Given their high price for an often modest effectiveness, orphan medicines are unlikely to provide value if their cost-effectiveness ratio is compared to a fixed threshold value. However, other societal considerations may matter when evaluating</p>	<p>Drummond, Evans, LeLorier et al, 2009[15]</p> <p>Drummond, Evans, LeLorier et al, 2009[15]</p> <p>Drummond, Wilson, Kanavos et al, 2007[16]</p> <p>Drummond, Wilson, Kanavos et al, 2007[16]</p> <p>Drummond, Wilson, Kanavos et al, 2007[16]</p> <p>Simoens & Dooms, 2011 (epub 2010)[22]</p>
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	an orphan cancer medicine, such as the fact that these medicines tend to target life-threatening rare diseases for which there is no alternative therapy, and that these medicines have a considerable financial on patients if they had to incur the costs themselves.”	
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Table A3: Health Care Systems Outside of Canada where Cancer Drugs are Given Special Consideration for Resource Allocation Purposes¹

Country	Details	Reference	Comments
Denmark, Belgium, Canada (Ontario), Ireland, New Zealand	Denmark earmarks grants for high priority areas such as cancer treatments; in Belgium, high-cost inpatient cancer drugs are funded by increased drug budgets or reimbursed separately; in Canada, the Province of Ontario has established the ‘New Drug Funding Programme’ to reimburse hospitals and cancer centres for certain new and expensive intravenous cancer drugs; Ireland and New Zealand also operate special schemes for cancer treatments.	Mason & Drummond, 2009[18]	These are examples of special funding mechanisms for cancer drugs, but a justification for these special mechanisms was not provided.
UK	<p>Within the United Kingdom (UK), several bodies make decisions on National Health Service (NHS) funding for new drugs, but none uses a separate process for cancer treatments.</p> <p>Not every new health technology is reviewed by NICE. The selection is made by the Ministry of Health on the basis of a number of criteria, the most important of which is whether the new technology is likely to have a large clinical or financial impact on the NHS...Several cancer drugs have been assessed by NICE, because many of them have been judged to have a major clinical or economic impact on the</p>	<p>Mason & Drummond, 2009[18]</p> <p>Drummond & Mason, 2007[23]</p>	Many cancer drugs have been reviewed by NICE, but there is not a separate system for cancer drugs.

¹ As noted in the results section, the countries noted in this table did not necessarily have a separate reimbursement review system for cancer drugs. In many cases, the countries instead had a special mechanism for managing the reimbursement either of cancer drugs or of certain types of drugs (and cancer drugs met the criteria for the special mechanism). However, we still reviewed these arguments in case any of them would have justified the separation of cancer drugs from drugs in other disease areas for resource allocation purposes.

	NHS...Cancer drugs have also featured heavily in the new single technology appraisals (STAs), with 12 of the first 28 appraisals being of cancer drugs. In general, the guidance issued by NICE for cancer drugs has been positive, with 52% of the recommendations being for first-line use only. Only in a few instances have the indications for use suggested by NICE been more restrictive than those granted in the license.		
Germany	The Federal Joint Committee (FJC) has by law some possibilities to regulate pharmaceutical expenditures. For instance, it can list medications on their negative list. According to the Social Code Book V, the list consists of pharmaceuticals which contain active ingredients which do not help to achieve the therapy goal or reduce risks (for instance painkillers in combination with vitamins) or whose efficacy cannot be assessed conclusively due to the containment of various combinations of active ingredients or whose benefit cannot be proved....To date, no medication for cancer treatment has been set on the negative list.	Von der Schulenburg et al, 2010[24]	Not a separate reimbursement review system or payment mechanism for cancer drugs
Ireland	The High Tech Drugs (HTD) scheme introduced in November 1996 facilitated the supply by community pharmacies of certain high-cost medicines (e.g., those used in conjunction with chemotherapy and IFN-[beta]), which had previously been supplied primarily in the hospital setting. The cost of medicines dispensed under the HTD scheme is paid directly to the wholesalers and pharmacists are paid a standard patient care fee of E54.82 per month to cover dispensing.	Barry and Tilson, 2007[25]	Cancer is in some cases managed under HTD scheme. However, HTD scheme is not only for cancer – it is for high cost drugs.

Finland	The Higher Special Refund Category includes 36 chronic illnesses...The category covers illnesses where drug treatment is necessary and effective to maintain the patient's health status and where the drug restores or replaces normal bodily functions. Drugs used to treat diabetes and cancer are examples of drugs belonging to the Higher Special Refund Category.	Martikainen and Rajaniemi, 2002[20]	The higher refund category is not specific only to cancer drugs (i.e. includes 36 chronic illnesses). Also not a separate resource allocation system for cancer drugs.
France	There are three reimbursement categories: The 100% reimbursement category which includes essential and particularly expensive drugs, such as drugs to treat diabetes, AIDS and cancer as well as drugs used in certain chronic illnesses (approximately 30 illnesses are listed)	Martikainen and Rajaniemi, 2002[20]	The 100% reimbursement category is not specific only to cancer drugs. Also not a separate resource allocation system for cancer drugs.
Greece	Insurance companies usually pay 75% of the drug costs, but there are some exceptions. Certain patient groups, such as pensioners, children and patients with some chronic illnesses, e.g. diabetes or cancer, are exempt from any payment.	Martikainen and Rajaniemi, 2002[20]	Categories that cancer drugs fall under are not specific only to cancer. Also not a separate resource allocation system for cancer drugs.
Portugal	Drugs in Group A are reimbursed in full. This group includes essential drugs to treat chronic illnesses, such as cancer drugs and drugs used in diabetes and tuberculosis. Group A contains 5% of all pharmaceutical products.	Martikainen and Rajaniemi, 2002[20]	Categories that cancer drugs fall under are not specific only to cancer. Also not a separate resource allocation system for cancer drugs.

<p>Denmark, France, UK</p>	<p>In some countries (such as France and Germany), separate lists of innovative drugs exist. These may include special funding for the drugs to be accessed outside of the hospital systems or enables hospitals to apply for new cancer drugs placed on the list, allowing them to switch to innovative drugs within the restrictions of their hospital budgets.</p> <p>In other countries (such as Denmark), there are special initiatives to make budgets available for new medicines, such as the recent decision to allocate 200 million DKK for new cancer drugs.</p> <p>In addition, in some countries (such as France, Denmark and the UK) national cancer plans that emphasise the need for access to new cancer drug therapies have been put in place.</p>	<p>Wilking and Jönsson, 2005[17]</p> <p>Wilking and Jönsson, 2005[17]</p> <p>Wilking and Jönsson, 2005[17]</p>	<p>This is an example of earmarking funds for cancer drugs. However, a justification consistent with the economic perspective for this earmarking was not provided.</p> <p>These plans emphasize the need for cancer research, but are not separate resource allocation systems for cancer drugs.</p>
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CHAPTER 3

Exploring Canada’s Joint Oncology Drug Review Using an Economic Perspective: Appraisal and Recommendations for Future Organizations

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ABSTRACT: The pan-Canadian Oncology Drug Review (pCODR) makes recommendations to Canada’s provinces and territories to guide their cancer drug funding decisions. The cited rationale for establishing the pCODR was the success of the pCODR’s predecessor, the Joint Oncology Drug Review (JODR), in demonstrating that “a pan-Canadian collaborative platform for assessing new cancer drugs provides significant value to cancer care decision-making.” However, that the JODR was successful in demonstrating this value has not been publicly documented. We felt that an appraisal of the JODR’s resource allocation goals, decision rules and recommendations would provide an opportunity to offer recommendations to the newly formed pCODR.

METHODS: We posed a series of questions to appraise, using an economic perspective, the transparency of and consistency among the JODR’s resource allocation goals, decision-making criteria, and decision rules. To answer the questions, documents published by the JODR and by Ontario’s Committee to Evaluate Drug’s-Cancer Care Ontario (CED-CCO) subcommittee (which conducted reviews on behalf of the JODR) were reviewed.

RESULTS AND CONCLUSION: The JODR had a stated goal of supporting a more consistent standard of therapy, but this goal was not clearly defined or operationalized. While not clearly stated, we inferred that the JODR also had a goal of maximizing health benefits with available resources. The decision-making criteria and decision rules used by the JODR to determine whether a drug was given a positive or negative reimbursement recommendation were not clearly stated and could not be clearly inferred. Furthermore, we suggest that the JODR had insufficient information to make reimbursement recommendations that were consistent with the inferred resource

allocation goal. Based on these findings we offer recommendations for the pCODR. It is our hope that these recommendations can be considered by the pCODR as it continues to evolve as Canada's national collaborative platform for cancer drug funding recommendations. **Word Count: 299**

INTRODUCTION:

Drug plan expenditures on cancer drugs have grown substantially in recent years. In Canada, provincial expenditures on oral cancer drugs, for example, rose by 25% - 70% between 2002 and 2007.[1] Despite this rapid and substantial growth, resources (dollars) for funding of medications remain scarce (i.e. whatever resources are available, they are insufficient to pay for all possible medications for all eligible individuals). As such, drug reimbursement decision-makers (e.g. governments) must continue to make choices regarding which drugs will be funded (from a basket that includes drugs across multiple disease areas), for whom, for how long, and at what stage of the disease. The rapidly rising cost (and potential budget impact) of cancer drugs coupled with the resource scarcity inherent to all drug formularies has led to much discussion regarding how best to manage the public reimbursement of cancer drugs.

One response to the challenge of managing the public reimbursement of cancer drugs was the establishment in Canada of the Joint Oncology Drug Review (JODR). The JODR was established (and funded) by the provincial and territorial Ministries of Health to make recommendations to Canada's provincial and territorial public drug plans to guide their

decisions regarding the funding of new cancer drugs. All provinces except Quebec participated in the JODR process. The JODR recommendations were not binding: after the JODR made a recommendation on a given drug, each provincial/territorial drug plan then made a decision on whether to add the drug to its public formulary. In place from 2007-2010, the JODR process was considered to be an interim measure that would be formally evaluated before a permanent national collaborative platform for cancer drug funding recommendations was established.[2] While the JODR was in existence, Ontario's cancer drug reimbursement review committee (the Committee to Evaluate Drugs - Cancer Care Ontario (CED-CCO) subcommittee) functioned as the JODR review committee, making cancer drug reimbursement recommendations on the JODR's behalf.[2,3]

The permanent body that evolved out of the interim JODR, the pan-Canadian Oncology Drug Review (pCODR), was established in 2010. The cited rationale for the establishment of the permanent pCODR process was the success of the interim JODR in demonstrating that “a pan-Canadian collaborative platform for assessing new cancer drugs provides significant value to cancer care decision-making.”[4] However, that the JODR was successful in demonstrating the value of a pan-Canadian collaborative platform for assessing cancer drugs has not been publicly documented. While a formal review of the JODR was conducted by IBM Canada (an independent healthcare consulting firm) and a selection of recommendations from the review were presented during meetings held by the pCODR,[5] the full IBM review was never made public.[6]

Given the lack of a transparent, publicly available review of the JODR, we aimed to conduct an appraisal of the JODR using an economic perspective. Our appraisal investigates the transparency of and consistency among the JODR's resource allocation goals, decision-making criteria and decision rules.

Although it has a different name, the permanent pCODR is very similar to the JODR. First, as with the JODR, the role of the pCODR is to “assess the clinical evidence and cost-effectiveness of new cancer drugs, and to use this information to make recommendations to the provinces and territories in guiding their drug funding decisions.”[7] Second, the pCODR's guiding principles are identical to those established by the JODR. Finally, the JODR's resource allocation goals (which will be described later in this paper) are the same as the pCODR's resource allocation goals (which we describe in detail elsewhere).[8] As such, we felt that an independent appraisal of the JODR would provide an opportunity to offer recommendations to the newly formed pCODR as it continues to evolve as Canada's national collaborative platform[9] for cancer drug funding recommendations.

In the next section we describe the economic perspective and explain why it is an appropriate lens through which to appraise the JODR's resource allocation goals, decision-making criteria (i.e. the specific criteria used to evaluate a drug) and decision rules (i.e. the how the decision-making criteria are combined in order to make a

reimbursement recommendation). We then describe the framework used for our appraisal. Finally, our findings are presented and discussed.

AN ECONOMIC PERSPECTIVE

Economics is a discipline that studies how to allocate scarce resources in order to best achieve the stated goals defined, for example, by decision makers. Economics is based on three fundamental concepts: scarcity (whatever resources are available, they are insufficient to support all possible activities); choices (because resources are scarce, we must choose between different ways of using them) and opportunity cost (by choosing to use resources in one particular way, we forego opportunities to use the same resources in any other way).

We suggest that an economic framework is an appropriate perspective through which to evaluate the JODR for a number of reasons. First, as described by Luce et al[10] the three key questions that “evidence-based processes in health care seek to answer about an intervention” are “Can it work”, “Does it work?” and “Is it worth it?” The key question that the JODR (and the pCODR) must answer is whether a drug is “worth it”, and economics provides an approach, including methodology and criteria, that enables one to determine whether allocating resources in a particular way (i.e. to a specific drug) advances the stated goal. Second, scarcity, choices and opportunity costs, the three fundamental concepts upon which economics is based, reflect the nature of the problem facing the JODR (and the pCODR). Due to resource scarcity (i.e. because there are a

limited number of dollars available in the drug budgets), provinces must make choices regarding which drugs to publicly reimburse. Furthermore, these choices are associated with opportunity costs: by choosing to spend drug budget dollars on reimbursing certain drugs, the provinces forego the opportunity to use these drug budget dollars to reimburse any other drugs. Third, the JODR used and the pCODR uses cost-effectiveness analyses (CEA) as a key component of their review process. Cost effectiveness analysis is an economic tool that can be used to determine whether allocating resources in a particular way advances the goal of maximizing benefits with available resources. Therefore, the JODR's use of CEA recognizes the relevance of applying economics to inform resource allocation decisions. Fourth, the pCODR states that "The pCODR process also ensures that scarce health-care resources are used to fund the most effective cancer drugs." [11] This statement is consistent with the economic perspective, because it recognizes that resources are scarce and that choices need to be made regarding how to allocate resources (i.e. regarding which drugs to fund).

APPRAISING THE JODR FROM AN ECONOMIC PERSPECTIVE

In appraising the JODR from an economic perspective we first examined whether the JODR had a resource allocation goal (derived from an economic perspective) that was clearly stated, defined and operationalized (and, if not, whether a resource allocation goal could be clearly inferred). We next examined whether the JODR clearly stated, defined and operationalized the decision-making criteria and the decision rules it used to make a reimbursement recommendation. We then sought to determine whether the JODR had

the necessary information to make recommendations that were consistent with the stated (or inferred) goal(s). Finally, we set out to review the extent to which the JODR recommendations were consistent with its decision-making criteria and decision rules and, ultimately, its stated or inferred resource allocation goals. In the event that the JODR's decision-making criteria and decision rules were not clearly stated, we planned to review the JODR's recommendations to see if the decision-making criteria and decision rules could be clearly inferred.

In conducting our appraisal, the following questions were posed:

1. a) Was a resource allocation goal that is derived from an economic perspective clearly stated, defined and operationalized by the JODR?

b) Is it possible to clearly infer a resource allocation goal for the JODR that is derived from an economic perspective?

2. a) Were there clear specifications regarding what information must be provided to the JODR when making a reimbursement submission?

b) Were the decision-making criteria and decision rules used by the JODR to make a reimbursement recommendation clearly stated, defined, and operationalized?

- c) Did the JODR have the necessary information to make reimbursement recommendations that were consistent with its resource allocation goal(s)?
3. Were the JODR recommendations consistent with its resource allocation goals, decision-making criteria and decision rules?

OR

If the JODR's decision-making criteria and decision rule(s) for making a reimbursement recommendation were not clearly stated, defined and operationalized, can they be inferred based on the JODR's recommendations?

METHODS FOR ANSWERING THE RESEARCH QUESTIONS

To conduct our appraisal, publicly available documents written by the JODR were identified by searching the peer-reviewed literature (PubMed) and the internet using the terms: “Joint oncology drug review” and “JODR.” In addition, because the JODR relied on the Ontario Ministry of Health's CED-CCO subcommittee to review drug submissions on its behalf, we also reviewed publicly available documents from the CED-CCO subcommittee (found on the Ontario Ministry of Health and Long-Term Care (MOHLTC) website). The following documents, which we label as primary documents, were reviewed:

- JODR April 2008, July 2008 and Fall 2008 newsletters [3,12,13]

- Ontario MOHLTC website. “Drug Submissions – Inter-Provincial Joint Oncology Drug Review Process” [2]
- 2008 JODR presentation [14]
- 2010 pCODR presentation [5]
- Ontario MOHLTC website: “How Drugs are Approved: Funding Decisions – The CED-CCO Subcommittee” [15]
- Ontario Public Drug Program Guidelines: CED-CCO Joint Drug Review Process[16]
- Overview of Submission Process for Cancer-Related Drugs (CED-CCO document) [17]

One publication related to the JODR was identified in our search of the peer-reviewed literature.[18] This document did not appear to be written by the JODR. Therefore, we did not include it for review as a primary JODR document. Where provided, references cited in the primary documents (i.e. secondary references) were also reviewed to determine whether they contained relevant information that could be used to address our first two questions. The following secondary documents were reviewed:

- Ontario Guidelines for Drug Submission and Evaluation [19]
- Ontario Guidelines for Economic Analysis of Pharmaceutical Products [20]

To answer our first two questions, all primary and secondary documents listed above were reviewed. To answer our third question, we first reviewed the Inter-Provincial Joint

Oncology Drug Review Process section of the Ontario MOHLTC website for the list of cancer drugs that had been reviewed by the JODR.[21] We then cross-referenced this list against the Ontario Public Drug Programs: ‘EO Decisions and CED Recommendations’ section of the Ontario MOHLTC website to find the corresponding published CED-CCO subcommittee recommendation (which would also represent the JODR recommendation).[22] The published CED-CCO subcommittee recommendations are summarized in Appendix A.

RESULTS

Question 1a: Was a resource allocation goal that is derived from an economic perspective clearly stated, defined and operationalized by the JODR?

The JODR released three newsletters during its existence: one in each of April 2008, July 2008 and December 2008. All three newsletters state that: “The Joint Oncology Drug Review (JODR) is...the first step towards building a permanent, national oncology drug review process to support more consistent and transparent decision-making and, ultimately, a more consistent standard of therapy.”[3,12,13] As described in Daniels’ accountability for reasonableness framework for fair priority setting, consistency and transparency (in decision-making) are important principles for public decision-making.[23,24] However, these principles describe characteristics of a decision-making approach instead of the desired end goal of a resource allocation task. Having a more consistent standard of therapy is an equity (fairness) goal that can be incorporated into the resource allocation decision-making task either by accounting for it when aggregating

benefits or incorporating it as an additional constraint (e.g. by requiring that resources are equally available to everyone, regardless of the benefits gained). However, the phrase “more consistent standard of therapy” is not clearly defined or operationalized by the JODR, which leaves it open to multiple interpretations. This poses a challenge for provincial drug plan reimbursement decision-makers because different interpretations may have different implications in terms of the mix and type of drugs that should be reimbursed in order to achieve the goal. We explore this particular challenge in detail elsewhere.[8]

There were no other statements in the published JODR documents that clearly stated a resource allocation goal derived from an economic perspective. Therefore, we next sought to determine whether the JODR had any resource allocation goals derived from an economic perspective that could be clearly inferred.

Question 1b: Is it possible to clearly infer a resource allocation goal for the JODR that is derived from an economic perspective?

The JODR’s reliance on the CED-CCO subcommittee to review drug submissions on its behalf suggests a subscription by the JODR to the CED-CCO subcommittee’s resource allocation goals.¹ Therefore, we reviewed the publicly available primary and secondary documents from the CED-CCO subcommittee (listed in the methods section above) to determine whether a resource allocation goal that is derived from an economic

¹ This also holds for the JODR’s decision-making criteria and decision rules, which we address in question #2b.

perspective could be clearly inferred. In providing an overview of the submission process for cancer-related drugs, the CED-CCO subcommittee states that one of its mandates is “to establish, refine and apply criteria to evaluate the therapeutic value and cost-effectiveness of cancer drug products.”[17] As such, we explored whether the CED-CCO subcommittee provided any further information that could offer insights into how the subcommittee’s evaluation of therapeutic value and cost-effectiveness might contribute to achieving a resource allocation goal (discussed below).

Therapeutic Value: The term ‘therapeutic value’ is not defined or operationalized in the CED-CCO subcommittee documents. However, the Ontario MOHLTC website states that: “the CED-CCO subcommittee has committed to using the same criteria for evaluation as the CED.”[15] Therefore, we also reviewed the CED drug reimbursement submission guidelines to find a definition for and/or operationalization of the term therapeutic value.[19,20] Neither a definition of therapeutic value nor a methodology or criteria through which therapeutic value was assessed were clearly stated in the CED documents. Consequently, it was not possible to clearly infer a related resource allocation goal.

Cost-effectiveness: The Ontario Guidelines for Drug Submission and Evaluation note that a pharmacoeconomic analysis must be included in reimbursement submissions, and state that “if the new product has an incremental cost (drug price and/or total therapy cost) with an incremental gain in efficacy or other outcomes, then a cost-effectiveness,

utility or benefit analysis would be indicated.”[19] Cost-effectiveness analysis is presented in the health economics research literature as a methodology for determining a drug’s value for money. Both the methodology literature and CEA guidelines published by reimbursement review bodies are consistent in defining the goal of CEA as the maximization of the total aggregate health benefit for a given level of available resources.[25,26,27,28]

Because the CED-CCO subcommittee uses CEA to make reimbursement recommendations, we infer that the subcommittee and, in turn, the JODR, had an underlying resource allocation goal of maximizing the total aggregate health benefits gained from the available resources (i.e. the available drug budget dollars). In terms of how health benefits are quantified, the guidelines followed by the CED-CCO subcommittee (i.e. the Ontario Guidelines for Economic Analysis of Pharmaceutical Products) state that quality-adjusted life-years (QALYs) are commonly used to quantify health gains.[20] A QALY is a year of life that has been adjusted for quality of life. With QALYs, an individual’s health is measured as the product of a person’s total years of life adjusted for quality, and a population’s health is measured as the sum of QALYs for all individuals in the population. The guidelines also indicate that other measures, such as healthy years equivalents (HYEs) can be used to quantify health benefits, and that generally QALYs and HYE are valued equally regardless of who gains or loses them.

In summary, the JODR had a stated goal of supporting a more consistent standard of therapy and, we infer, an underlying goal of maximizing health benefits with available resources. Given the challenges that we have briefly discussed regarding the definition and operationalization of the consistency goal, we focus for the remainder of this paper on the JODR's decision-making criteria, decision rules and recommendations as they relate to the goal of maximizing health benefits with available resources.

Question 2a: Were there clear specifications regarding what information must be provided to the JODR when making a reimbursement submission?

The JODR did not provide a specific set of guidelines regarding what must be included in a reimbursement submission. Therefore, we assumed that the CED-CCO subcommittee's submission guidelines also represented the JODR's submission guidelines. The CED-CCO Joint Drug Review Process Guidelines[16] indicate that submissions should follow the requirements outlined in the Ontario Guidelines for Drug Submission and Evaluation.[19] These guidelines describe the information that must be provided when making a reimbursement submission. Among other items, a reimbursement submission had to include data from clinical studies, pharmacoeconomic evidence demonstrating the benefit of the product in relation to the cost of the product and to any alternative products or treatments, and a financial impact analysis. Overall, while the JODR did not explicitly provide their own specifications, the information required in a reimbursement submission appears to be clearly listed in the guidelines followed by the CED-CCO subcommittee.

Question 2b: Were the decision-making criteria and decision rules used by the JODR to make a reimbursement recommendation clearly stated, defined and operationalized?

To organize our discussion of decision-making criteria and decision rules we use the following terms and definitions. We define ‘constructs’ as the themes that are evaluated by the reimbursement review committee. In this context, therapeutic value and cost-effectiveness are both examples of constructs. We define ‘decision-making criteria’ as the specific criteria used to evaluate a drug (on a given construct such as therapeutic value or cost-effectiveness). For example, the decision-making criteria for therapeutic value might require that a specific degree of incremental benefit be shown via a specific clinical endpoint in a specific type of study (e.g. a drug must demonstrate an improvement in overall survival of six months relative to the current standard of care in a randomized controlled trial). As shown in this example, there could be multiple decision-making criteria that an intervention must meet to satisfy a review committee’s expectations for a given construct. A decision rule is defined as the way the decision-making criteria are combined in order to make a reimbursement recommendation. For example, one of the JODR’s decision rules might have been that a negative recommendation should be given if an intervention meets a committee’s expectations (i.e. satisfying the decision-making criteria) for therapeutic value, but not cost-effectiveness.

The JODR clearly cited therapeutic value and cost-effectiveness (also referred to as “value for money”) as key constructs that were evaluated during a reimbursement review.

However, it did not provide specific decision-making criteria for what constituted demonstration of therapeutic value or cost-effectiveness. Furthermore, the JODR did not specify what decision rules were used to combine the therapeutic value and cost-effectiveness constructs in order to make a reimbursement recommendation. Therefore, we again reviewed the CED-CCO subcommittee documents in an attempt to identify the subcommittee's, and in turn the JODR's, decision-making criteria and decision rules.

Decision-Making Criteria

Therapeutic Value: The guidelines used by the CED-CCO subcommittee (i.e. the Ontario Guidelines for Drug Submission and Evaluation[19]) state that the Ministry of Health and the CED place greater reliance on well-designed, comparative clinical trials than on other sources of data and refer manufacturers to a clinical data checklist for information regarding what is important to the committee. Some examples of the questions listed in the clinical data checklist are provided below.

- “What are the conclusions of randomized controlled trials supporting the efficacy (i.e. when used under optimal circumstances) of the product? Are trials published in peer-reviewed journals?”[19]
- “What are the results of randomized trials comparing the product to listed alternatives on the Formulary/CDI (Comparative Drug Index)? Are there randomized trials comparing the product to the least costly and most widely used alternative products listed in the Formulary/CDI?”[19]
- “What are the conclusions of randomized controlled trials supporting the effectiveness (i.e., when used under usual, real world circumstances) of the product? Are trials published in peer-reviewed journals?”[19]
- “Do the randomized trials use the most clinically relevant outcome measures, or do they use the surrogate outcomes requiring extrapolation to the relevant outcome? Are the end-point(s) sufficiently justified?”[19]

Although cited as information that is important to the committee, no detail is provided regarding how the items in the checklist are operationalized into decision-making criteria for demonstration of therapeutic value. For example, what constitutes “sufficient justification of the endpoints”, and what are “the most clinically relevant outcome measures”? Furthermore, do all of the items in the checklist need to be provided or just certain ones? Therefore, while some of the information used to evaluate a new drug’s therapeutic value is described, the specific decision-making criteria used to determine whether a new drug, in the opinion of the CED-CCO subcommittee, demonstrates therapeutic value are not clearly stated.

Cost-Effectiveness: The Ontario Guidelines for Drug Submission and Evaluation state that: “The Ministry (of health) and the DQTC (Drug Quality and Therapeutics Committee) are interested in evaluating the value-for-money of new drug product(s), particularly in comparison to alternatives already listed in the ODB (Ontario Drug Benefits)”[19]², and refer manufacturers to the Ontario Guidelines for the Economic Analysis for Pharmaceutical Products[20] for more information. The Ontario Guidelines for Economic Analysis of Pharmaceutical Products state that:

“...those who produce and interpret cost-effectiveness studies often do so by comparing the incremental cost-effectiveness ratio for a particular intervention with that for other programs, to determine its relative economic attractiveness.”[20]

However, the guidelines are vague regarding whether this is how the CED or the CED-CCO subcommittee actually interpret the ICERs that result from cost-effectiveness

² The DQTC is now known as the CED

studies (and instead simply state that this is how it is “often” done). The guidelines also acknowledge that the approach of comparing ICERs for a particular intervention with that for other programs “does not directly address the issue of what constitutes low (economically attractive) or high (economically unattractive) ratios”, stating that “This is a qualitative and subjective judgment, that will vary according to the resources available to the jurisdiction making that decision.”[20]³ Thus, while the guidelines indicate how information on a drug’s ICER is “often” used, the guidelines do not clearly state that this is how the CED (or, in turn the CED-CCO subcommittee) uses this information.

Decision Rules

The CED-CCO subcommittee primary and secondary documents do not clearly state what decision rules are used (i.e. how the constructs of therapeutic value and cost-effectiveness are combined and whether there are any additional constructs that are incorporated into the decision rules) to make a reimbursement recommendation.

Question 2c: Did the JODR have the necessary information to make reimbursement recommendations that were consistent with its resource allocation goal(s)?

We suggest that the CED-CCO subcommittee (and, in turn, the JODR) did not have the necessary information to make reimbursement recommendations that were consistent

³ As we will describe in Section 2c, using ICERs to determine whether allocating resources to a particular activity (e.g. to a particular drug) will advance a goal of maximizing health benefits with available resources is neither a qualitative nor a subjective judgement.

with the goal of maximizing health benefits with available resources. Our explanation for this suggestion is described below.

First, as noted earlier, economics provides a methodology, via CEA, to determine whether allocating resources in a particular way (i.e. to a specific drug) advances the goal of maximizing health benefits with available resources. The results of a CEA are expressed as an ICER, which is calculated by dividing the difference in costs between two health care programs by the difference in outcomes between the programs, with one program typically being a new intervention and one being the current standard of care. The theoretical underpinnings of the ICER have been discussed extensively by Gafni and Birch [25,29] and we briefly summarize these below. Gafni and Birch highlight Weinstein and Zeckhauser's [30] description of how the ICER can be used to determine whether the allocation of resources to a specific intervention will lead to maximization of health benefits from available resources. Weinstein and Zeckhauser [30] demonstrate that, under the conditions of perfect divisibility and constant returns to scale for all interventions, total health benefits will be maximized in one of the following two scenarios:

- all interventions are ranked from the lowest to the highest ICER and adopted in descending order until the available resources are exhausted (league table approach), or
- specification of the critical ratio, λ , and adoption of all interventions that have an ICER less than or equal to λ , where λ represents the opportunity cost (i.e. what is

given up by allocating resources to a particular activity instead of to any and all other activities) of available resources at the margin (the threshold approach)

If the CED-CCO subcommittee evaluates cost-effectiveness via the method that the Ontario Guidelines for the Economic Analysis of Pharmaceutical Products suggest is “often” used (i.e. comparing the ICER for a new drug to ICERs for other interventions), then the CED-CCO subcommittee’s method is not consistent with either of the above two approaches. This is even recognized in the guidelines endorsed by the CED-CCO subcommittee (i.e. the Ontario Guidelines for the Economic Analysis of Pharmaceutical Products), which stated the following:

“Although this [comparing the incremental cost-effectiveness ratio for a particular intervention with that for other programs, to determine its relative economic attractiveness] does not result in meeting the objective of maximizing net benefits derived from a fixed budget, for a variety of reasons (Birch & Gafni 1992), comparison of incremental ratios does give a measure of the economic consequences of investing in those programs.”[20] (emphasis and text in brackets added)

Thus, it is unclear how the subcommittee’s use of the ICER can facilitate achievement of the goal of maximizing health benefits with available resources.

Second, as noted by Gafni and Birch,[25,29] the two scenarios described by Weinstein and Zeckhauser will lead to maximization of total health benefits with available resources only under conditions of perfect divisibility and constant returns to scale for all interventions. Under a scenario of constant returns to scale, the marginal benefit derived from an intervention is constant, regardless of how many units are purchased. For example, if one mammogram test provides 10 units of benefit, then one-tenth of a

mammogram test will provide 1 unit of benefit and 10 tests will provide 100 units of benefit. The condition of perfect divisibility requires that it be possible to purchase all interventions in incremental units (e.g. that it be possible to purchase one-tenth of a mammogram test). These conditions, as noted by Gafni and Birch, are theoretical and invalid in most, if not all, decision-making settings (including the JODR's decision-making setting).[29,31] When these theoretical assumptions do not hold, neither the league table or threshold approach will ensure that the goal of maximizing health benefits with the available resources will be achieved.

Third, even if the assumptions of perfect divisibility and constant returns to scale existed in the real world scenario in which decision-makers must allocate resources, both the league table and threshold approach require that the incremental costs and incremental benefits (e.g. the ICERs) for all current and potential interventions are known. This information is not available for all interventions in the real world and therefore, a ranking of all interventions cannot be done. Consequently, the opportunity cost at the margin cannot be identified such that decision-makers can determine whether allocating resources to a particular intervention advances the goal of maximizing health benefits with the available resources.

Fourth, even if all theoretical and practical requirements were realized, ICERs do not take opportunity costs into account.[25,29] As noted by Gafni and Birch, “the ICER ignores the simple reality that, if overall funds are fixed, the additional funds required for a new

program must come from other uses, that is, cuts to other programs.”[32] If the goal is to maximize health benefits with available resources then a new drug should only be adopted if the total health benefits gained by reimbursing the new drug exceed the total health benefits foregone by choosing not to reimburse other drugs with the same available resources. Decision-makers therefore need to know: the total amount of the resources required to reimburse the new drug, where the resources will come from (i.e. which currently funded activities will be discontinued), and the total health benefits that will be foregone as a result of discontinuing currently funded activities. Cost-effectiveness analysis does not provide this information. While the CED-CCO subcommittee does require manufacturers to submit a financial impact assessment, which can inform decision-makers of the total resources required to reimburse the new drug, a financial impact assessment does not provide information on where these resources should come from (i.e. which activities should be discontinued) and the total benefits that will be foregone as a result.⁴ Therefore, even if there were no theoretical or practical limitations to using ICERs, the CED-CCO committee and, in turn, the JODR still would not have all of the information required to achieve the goal of maximizing the health benefits with the available resources.

⁴ While it is possible that opportunity costs and program discontinuations are considered by the CED-CCO subcommittee during its deliberations, this was not clearly or transparently described in any public documents.

Question 3: If the JODR’s decision-making criteria and decision rule(s) for making a reimbursement recommendation were not clearly stated, defined and operationalized, can they be inferred based on the JODR’s recommendations?

As noted above, neither the JODR nor the CED-CCO subcommittee clearly stated what decision-making criteria or decision rules were used to make reimbursement recommendations. We therefore reviewed the published CED-CCO subcommittee recommendations (for drugs that were listed as having been reviewed by the JODR [21]) to see if these decision rules could be inferred. In doing so, we sought to answer three key questions: a) Can the decision-making criteria used by the CED-CCO subcommittee to determine whether an intervention demonstrates therapeutic value be clearly inferred? b) Can the decision-making criteria used by the CED-CCO subcommittee to determine whether an intervention is cost-effective be clearly inferred? and c) Can the decision rules that are used by the CED-CCO subcommittee to make a reimbursement recommendation based on a drug’s therapeutic value and cost-effectiveness to be clearly inferred? A summary of the published CED-CCO recommendations for drugs that were listed as being reviewed by the JODR is shown in Appendix A. The Ontario MOHLTC website indicates that 54 submissions were reviewed by the JODR between March 2007 and December 2011. Of these, 29 recommendations were published by the CED-CCO subcommittee as of September, 2013. Once the CED-CCO subcommittee makes a recommendation, Ontario’s Executive Officer (EO) then decides whether to reimburse the

drug on the Ontario Drug formulary.⁵ We do not incorporate the EO's decision or the final reimbursement status of a given drug into our appraisal because this is an activity specific only to the province of Ontario as opposed to an activity undertaken on behalf of the JODR. Of the 29 recommendations that are publicly available, eight recommended that the drug in question be funded (referred to from this point forward as a 'positive recommendation'), eight recommended that the drug in question be funded through an Exceptional Access Program (EAP)[33]⁶, and 13 recommended that the drug in question not be funded (referred to from this point forward as a 'negative recommendation'). Two of the eight drugs given an EAP recommendation were simultaneously given a negative recommendation for another line of therapy for the same indication. For simplicity, we have kept these categorized as EAP recommendations (instead of classifying them as negative recommendations) because they are akin, we believe, to a recommendation to fund a drug for a subgroup of patients.

a) Can the decision-making criteria used by the CED-CCO subcommittee to determine whether an intervention demonstrates therapeutic value be clearly inferred?

When describing an intervention's therapeutic value, the CED-CCO subcommittee consistently cited the need for comparative evidence from a clinical trial. Five of the 13

⁵ Some drugs that are listed as having been reviewed by the JODR may not yet have a final recommendation because recommendations are only published once the final funding decision is made by Ontario's Executive Officer.

⁶ Ontario's Exceptional Access Program (EAP) facilitates patient access to drugs not funded on the Ontario Drug Benefit (ODB) Formulary, or where no listed alternative is available. A recommendation to fund a drug under Ontario's EAP is a recommendation to reimburse the drug on a case-by-case basis instead of listing the drug on the formulary.

negative recommendations cited a lack of comparative evidence in the published recommendation document. In one case there were no direct comparison studies between the drug under review and alternative treatments (bevacizumab for recurrent glioblastoma multiforme); one drug was cited as having “limited evidence of clinical benefit” for the line of therapy in question (topotecan for second-line treatment of small cell lung cancer); one drug lacked comparative evidence against what the CED-CCO subcommittee considered to be the Canadian standard of care (gemcitabine for metastatic breast cancer); one drug lacked clinical trial evidence to support the line of therapy for which reimbursement was requested (fulvestrant for metastatic breast cancer); one drug lacked any comparative evidence whatsoever at the time of the review (alemtuzumab for chronic lymphocytic leukemia). A sixth negative recommendation highlighted that only interim comparative data were available for a drug (capecitabine as part of a combination therapy regimen for gastric cancer). Furthermore, many of the drugs that the CED-CCO subcommittee recommended for funding (either positive recommendations or EAP recommendations) were restricted to the specific subgroups of patients or lines of therapy for which comparative evidence existed (e.g. azacitidine for myelodysplastic syndrome and dasatinib for chronic myeloid leukemia, respectively). Therefore, we infer that evidence derived from a clinical trial that both mimics the scenario for which reimbursement is requested (i.e. line of therapy or for a specific patient population) and that compares the intervention to what the CED-CCO subcommittee considers to be the current Canadian standard of care for that scenario is required by the CED-CCO subcommittee. When comparative evidence was provided, there were no clear statements

in any of the recommendations about a specific level or grade of evidence that was required (i.e. a specific criterion or set of criteria) in order to meet the committee's expectations for demonstration of therapeutic value.

Overall survival (OS) was cited in a number of recommendations as part of the rationale either for a negative or positive recommendation. For example, pemetrexed (which was given a negative recommendation for the second-line treatment of non-small cell lung carcinoma (NSCLC)) was cited as having an “absence of survival or QoL (Quality of Life) advantage over docetaxel”[34] while fludarabine in combination with rituximab (which was given a positive recommendation for the treatment of chronic lymphocytic leukaemia) was cited as having “significant improvements in PFS (progression free survival), OS and disease response rates.”[35] However, a specific criterion regarding the degree of improvement in OS that is required before a product is considered to have demonstrated therapeutic value was not clearly stated in any of the recommendations. Furthermore, some drugs showing improvements in other clinical endpoints, but not in OS, were given positive recommendations (e.g. panitumumab for metastatic colorectal cancer). Therefore, while OS appears to be important, it was not necessary in all cases for a positive recommendation. Clinical trial components such as sample size, study duration, and quality of life data were also cited in some of the recommendations. However, specific decision-making criteria through which these elements were operationalized were not clearly stated.

In summary, while we were able to observe some patterns in the CED-CCO subcommittee's evaluation of therapeutic value, we were not able to infer the specific decision-making criteria that were applied by the committee for this construct.

b) Can the decision-making criteria used by the JODR/CED-CCO subcommittee to determine whether an intervention is cost-effective be clearly inferred?

In attempting to infer the CED-CCO subcommittee's decision-making criteria regarding an intervention's cost-effectiveness, we searched the published recommendations for any statements made by the CED-CCO subcommittee regarding a drug's cost-effectiveness, value for money, price, cost, or economic benefits. While we reviewed each published recommendation in its entirety, we focused in particular on two sections of the recommendations: the 'CED Recommendation' section and the 'Highlights of Recommendation' section.

Of the eight positive recommendations, seven cited "value for money", "cost-effectiveness" or "costs" in the 'CED Recommendation' section or the 'Highlights of Recommendation' section. Of the eight EAP recommendations, four mentioned drug cost, cost-effectiveness or value for money. Of the 13 negative recommendations, 12 cited price, cost, economic advantage, cost-effectiveness or value for money. These statements are summarized in Appendix B.

None of the recommendations listed above cited the ICERs for the drugs under review. This was true for positive, negative and EAP recommendations alike. Therefore, although general statements regarding cost-effectiveness were made in most of the CED-CCO subcommittee recommendations, we were not able to clearly infer what decision-making criteria were applied to evaluate this construct (with the exception of drugs that have higher costs and no additional clinical benefit relative to the standard of care, which we discuss below).

Drugs with a higher cost than what the CED-CCO subcommittee considered to be the Canadian standard of care that were deemed not to have additional benefits were either given negative recommendations (e.g. pemetrexed for second-line treatment of NSCLC) or were recommended for reimbursement only under the EAP for patients in whom the standard of care could not be used (e.g. oxaliplatin for first-line treatment of metastatic colorectal cancer). Therefore, for interventions deemed to have similar clinical benefits to the standard of care, the cost-effectiveness decision-making criterion appears to require that the drug cost no more than what the CED-CCO subcommittee considered to be the Canadian standard of care.

c) Can the decision rules that are used by the CED-CCO subcommittee to make a reimbursement recommendation be clearly inferred?

Drugs for which therapeutic value and cost-effectiveness were, in the opinion of the CED-CCO subcommittee, both clearly demonstrated were given positive reimbursement

recommendations in all cases. Drugs for which therapeutic value was, in the opinion of the CED-CCO subcommittee, not clearly demonstrated were given negative recommendations, regardless of their cost-effectiveness in all but one case (the exception being imatinib for the treatment of acute lymphoblastic leukemia, where the committee gave an EAP recommendation, stating that “current evidence was not strong enough to support formulary listing of imatinib and consideration on a case-by-case basis is reasonable”).[36] Drugs for which therapeutic value was clearly demonstrated but where cost-effectiveness was a concern for the CED-CCO subcommittee received positive recommendations in some cases (e.g. azacitidine for myelodysplastic syndrome) and either negative recommendations (e.g. everolimus for metastatic renal cell carcinoma) or EAP recommendations (e.g. oxaliplatin for metastatic colorectal cancer) in other cases. Based on these patterns, we infer that the committee’s expectations for demonstration of therapeutic value must be satisfied for a positive recommendation (and, in most cases, for an EAP recommendation) to be given. What is less clear is how the cost-effectiveness construct is incorporated into the decision rule, because some drugs that demonstrated therapeutic value but not cost-effectiveness were also given positive recommendations.

The fact that there are limited treatment options was cited in some EAP recommendations (e.g. sorafenib for the treatment of hepatocellular carcinoma, imatinib for acute lymphoblastic leukemia). Therefore, the availability of alternative treatments may be another factor that is incorporated into the CED-CCO subcommittee’s decision rule. However, similar to therapeutic value and cost-effectiveness, there are no clear statements

describing how this construct is operationalized into decision-making criteria or how it is incorporated into a decision rule.

In summary, a review of the CED-CCO subcommittee recommendations (which also represent the JODR's recommendations) did not allow us to infer the decision-making criteria that must be met in order to satisfy the committee's expectations for demonstration of therapeutic value or cost-effectiveness.⁷ In terms of combining the assessment of therapeutic value and cost-effectiveness into a decision rule we infer that one decision rule was that drugs demonstrating both clinical value and cost-effectiveness were to be given positive recommendations. We also infer that demonstration of therapeutic value was a necessary condition for positive recommendations (and usually necessary for EAP recommendations). However, in situations where therapeutic value was demonstrated but the CED-CCO subcommittee had questions around cost-effectiveness or felt cost-effectiveness was not demonstrated, it was not clear what decision rules were used to make a recommendation.

SUMMARY

The JODR was intended to be an interim measure that would undergo a formal evaluation before a permanent, national collaborative platform for cancer drug funding recommendations was established in Canada. Since the formal evaluation was never made public, a transparent account of the strengths of the JODR and areas for

⁷ With the exception of drugs that have similar clinical benefit to but cost more than what the CED-CCO subcommittee considers to be the Canadian standard of care.

improvement is not available. Our appraisal provides an opportunity to highlight some areas for the pCODR's consideration as it continues to develop in its role as Canada's national collaborative platform for cancer drug funding recommendations.

We demonstrate in this paper that there was a lack of clarity regarding the JODR's resource allocation goals. While one goal appeared to be clearly stated (i.e. supporting a more consistent standard of therapy), this goal was not clearly defined or operationalized. Another goal (i.e. maximizing health benefits with available resources) was not clearly stated and instead could only be inferred. There is also a fundamental challenge associated with striving to simultaneously achieve multiple resource allocation goals, which we explore in detail elsewhere.[8] The JODR also did not clearly describe the decision-making criteria or decision rules used to make a reimbursement recommendation, and we were not able to identify them based on a review of the CED-CCO subcommittee guidelines or infer them based on a review of the CED-CCO subcommittee recommendations (with the exception of the decision rule for drugs that have similar efficacy to but cost more than what the CED-CCO subcommittee considers to be the Canadian the standard of care). From a public accountability perspective, not having clearly stated resource allocation goals, decision-making criteria and decision rules is problematic because it prevents stakeholders from knowing what the JODR, a publicly funded agency, set out to accomplish and from determining the extent to which the JODR's decision-making criteria, decision rules and recommendations were consistent with its resource allocation goals.

We suggest, for the reasons we provided while answering question #2c, that the CED-CCO subcommittee and, in turn, the JODR did not have sufficient information to make reimbursement recommendations that were consistent with the goal of maximizing health benefit with available resources. Interestingly, some of these reasons are also acknowledged in the guidelines used by the CED-CCO subcommittee.[20] In addition to not having sufficient information to make recommendations that are consistent with the inferred JODR goal, using the information that was required by the CED-CCO subcommittee (and, in turn, the JODR) can actually lead to recommendations which, if adopted by participating provinces and territories, result in unsustainable drug budget growth. Indeed, evidence from Ontario (Canada), England and Australia suggests that the adoption of the ICER approach has been associated with substantial increases in healthcare expenditures without any evidence of an increase in total health benefit.[25,29,37]

Our appraisal of whether the CED-CCO subcommittee (and, in turn, the JODR) had the necessary information to make reimbursement recommendations that were consistent with the goal of maximizing health benefits with available resources rests on two key assumptions. The first assumption is that the JODR subscribed to the CED-CCO subcommittee's goal. The second assumption is that maximizing health benefits with available resources is a goal of the CED-CCO subcommittee. As relates to the first assumption, the JODR clearly deferred to the CED-CCO subcommittee to review and make recommendations regarding a drug's cost-effectiveness. Therefore, we suggest that

it is reasonable to assume that, by subscription to the CED-CCO subcommittee's processes and criteria, the JODR also subscribed to the subcommittee's resource allocation goal. As relates to the second assumption we suggest that, even without this goal being explicitly stated, maximizing health benefits with available resources is an implied goal that underpins the CED-CCO subcommittee and the JODR's work. This is because the CED-CCO subcommittee uses CEA as a key component of its reimbursement review process and, as noted in the CEA methodology literature, the underlying premise of CEA is that the goal of society or society's decision-makers is to maximize the total aggregate health conferred to the population for a given level of resources.[25,26,27,28]

It might be argued that an economic perspective is not an appropriate perspective through which to address the questions posed in our appraisal. However, we suggest that an economic perspective is appropriate for a number of reasons, and we have described these reasons in detail at the outset of our paper. Another possible criticism of our appraisal is that the JODR had other resource allocation goals, decision-making criteria or decision rules that we have not captured. However, if there are other resource allocation goals, it would have been incumbent upon the JODR to be specific and transparent about what these goals were. This also holds for potential criticisms regarding other constructs, decision-making criteria or decision rules that were not captured in our appraisal.

A theme that is highlighted throughout this paper is the lack of transparent, explicit or clear statements from the JODR/CED-CCO subcommittee regarding resource allocation

goals, decision rules, decision-making processes etc. This lack of transparency is not unique to the JODR. Rather, drug reimbursement review committees are consistently challenged to describe their recommendations more thoroughly as this would enable stakeholders to understand and evaluate reimbursement committees' decisions regarding allocation of public dollars. For example, Canada's Common Drug Review,[38] Australia's Pharmaceutical Benefits Advisory Committee (PBAC),[39] and the United Kingdom's National Institute for Clinical Excellence (NICE)[40] have all been challenged to improve the transparency of their processes and recommendations.

There are examples where drug reimbursement review committees have provided clear statements regarding resource allocation goals, decision rules, and the decision-making process. For example, although it has been challenged to improve transparency even further, the National Institute of Clinical Excellence (NICE) clearly states that one resource allocation goal is "the maximisation of health benefits from the use of NHS (National Health Service) and PSS (Personal Social Service) resources"[41] and that another goal is "to remove unfairness in the availability of technologies in different localities and to minimize the possibility of further examples of unfairness or inequity being introduced." [41] The Institute also provides a clear description of how evidence is appraised, and while stating that a precise ICER threshold is not used, notes that it is most appropriate to use a threshold of £20,000-30,000 per QALY gained.[42] While we have highlighted the concerns with using an ICER-based approach to achieve the goal of maximizing health benefits with available resources and while there are challenges

associated with striving to simultaneously achieve this goal alongside an equity goal of removing unfairness in the availability of technologies in different localities (discussed in detail elsewhere [8]), NICE's transparency about its goals and decision rules at least allows for a comparison of the decisions against the stated goals and rules.

Based on the issues laid out in this paper we have developed a number of recommendations for the pCODR. Some of these recommendations (i.e. #2 and #3) are derived from an economic perspective while recommendations #1, 4 and 5 are more general. Our recommendations are as follows:

1. The pCODR's resource allocation goal (or goals), decision-making criteria and the decision rules through which goal achievement will be facilitated should be clearly stated, defined, and operationalized by the pCODR.
2. If the goal is to maximize health benefits with available resources, then the practice of using ICERs to guide resource allocation decision-making should be re-evaluated given the theoretical and practical limitations of this approach.
3. If the goal is to maximize health benefits with available resources, then what payers have to give up in order to reimburse a new drug (i.e. the opportunity cost of reimbursing a new drug) needs to be incorporated into the pCODR's evaluation framework in order to determine whether the health benefits that will be gained by

reimbursing a new drug will exceed the health benefits that have to be foregone in order to free up enough resources to reimburse the new drug.

4. The pCODR should transparently describe how the decision rules were applied to reach each reimbursement recommendation such that stakeholders can understand the extent to which the pCODR's recommendations are consistent with the stated resource allocation goals, decision-making criteria and decision rules (and can appeal recommendations where inconsistencies exist).
5. We suggest that an economic perspective is an appropriate framework for guiding the pCODR's goals, decision rules and recommendations. However, regardless of which framework is ultimately used by the pCODR, we suggest it be clearly, transparently stated.

Finally, the paradox of relying on a centralized, national committee to make recommendations on the allocation of drug budget resources when the decision-making authority lies within the individual provinces, each of which has a different budget, different values and different opportunity costs needs to be addressed, either by the pCODR or by other stakeholders.

CONCLUSION:

Using an economic perspective, this paper identifies some key concerns regarding the transparency of and consistency among the JODR's resource allocation goals, decision-making criteria and decision rules. These concerns formed the basis for our (above-listed) recommendations to the newly established pCODR. It is our hope that these recommendations can be considered by the pCODR as it continues to evolve as Canada's national collaborative platform for cancer drug funding recommendations.

APPENDIX A: Summary Tables of Published CED-CCO Subcommittee Recommendations¹

Table A1: Recommendations that drug be funded [22]

Drug (generic name) and Indication	Recommendation	Bolded text from ‘Highlights of Recommendation’ section
<p>Abraxane (nab-paclitaxel)</p> <p>Treatment of metastatic breast cancer</p>	<p>“The CED recommended that nab-paclitaxel (Abraxane) be funded under Cancer Care Ontario’s New Drug Funding Program (NDFP), for the treatment of metastatic breast cancer, with specific criteria”</p>	<p>“Overall, the CED noted that when compared to standard paclitaxel and docetaxel, there is less risk that nab-paclitaxel will cause adverse reactions in patients. The CED concluded that nab-paclitaxel has a place in the treatment of patients who have had adverse or allergic reactions to taxanes or who cannot take the pre-medications used to lessen the adverse effective with the taxane class of drugs.”</p>
<p>Eloxatin (oxaliplatin)</p> <p>Adjuvant treatment of colorectal cancer</p>	<p>“The CED recommended that oxaliplatin (Eloxatin) be funded through CCO’s NDFP for the adjuvant treatment of colorectal cancer according to specific criteria. The CED’s recommendation was made on the basis that oxaliplatin has been demonstrated to provide both therapeutic benefit and value for money for this indication.”</p>	<p>“Overall, the Committee agreed that oxaliplatin (Eloxatin) in the FOLFOX regimen has been demonstrated to provide clinical benefit and value for money in the adjuvant treatment of colorectal cancer.”</p>
<p>Erbitux (cetuximab)</p> <p>Squamous cell carcinoma of the head and neck (SCCHN)</p>	<p>“The CED recommended that cetuximab (Erbitux®) be funded for the treatment of squamous cell carcinoma of the head and neck (SCCHN) according to specific criteria. The CED noted that in a small subgroup of patients who would otherwise receive radiation alone for treating their locally advanced SCCHN, the addition of cetuximab to radiation may provide added survival benefits.”</p>	<p>“In light of the clinical and cost- effectiveness data, the CED recommended that cetuximab be funded only for patients with locally advanced SCCHN who are over the age of 70 and have good performance status.”</p>

¹ The published recommendations refer to the “CED” instead of to the “CED-CCO subcommittee.” However, for cancer drugs (i.e. all of the drugs summarized in this Appendix), the recommendation and accompanying statements are from the CED-CCO subcommittee.

<p>Fludara (Fludarabine) 10mg tablets</p> <p>Chronic lymphocytic leukaemia</p>	<p>“The CED recommended that oral fludarabine (Fludara®) be funded when used in combination with rituximab for the first-line treatment of chronic lymphocytic leukemia (CLL), on the basis that this drug has been shown to provide efficacy and value for money in this clinical setting.”</p>	<p>“Overall, the CED noted that oral fludarabine, when used in combination with rituximab, has been shown to provide efficacy and value for money in the first-line treatment of CLL.”</p>
<p>Rituxin (rituximab) injection</p> <p>First-line treatment of chronic lymphocytic leukaemia</p>	<p>“The CED recommended rituximab (Rituxan®) be funded for the first line treatment of chronic lymphocytic leukemia (CLL) where fludarabine-based therapy is considered appropriate. The CED noted that the use of rituximab in this setting has been shown to improve survival and to provide value for money.”</p>	<p>“Overall, the committee noted that rituximab prolongs survival and is cost-effective in the first line treatment of CLL”</p>
<p>Vectibix (panitumumab)</p> <p>Treatment of metastatic colorectal cancer</p>	<p>“The CED recommended that panitumumab (Vectibix) be funded through Cancer Care Ontario's New Drug Funding Program for the treatment of metastatic colorectal cancer, according to specific criteria. The CED noted that panitumumab (Vectibix) has been shown to provide a clinical benefit and reasonable value for money in selected patients with metastatic colorectal cancer.”</p>	<p>“Overall, the committee noted that panitumumab (Vectibix) offers a treatment option for patients with metastatic colorectal cancer who have failed standard chemotherapies and whose tumours express the non-mutated (wild-type) KRAS gene.”</p>
<p>Vidaza (azacitidine)</p> <p>Myelodysplastic syndrome</p>	<p>“The CED recommended that azacitidine (Vidaza®) be funded for the treatment of myelodysplastic syndrome (MDS) according to specific criteria. The CED noted that this drug has been demonstrated to improve survival in MDS patients with a higher-risk form of the disease.”</p>	<p>“Overall, the CED acknowledged that azacitidine has been shown to provide survival benefits in patients with a higher-risk form of MDS, a condition with limited effective treatment alternatives. The CED was, however, concerned with the high costs associated with funding this drug.”</p>
<p>Xeloda (capecitabine)</p> <p>Treatment of metastatic colorectal cancer</p>	<p>“The CED recommended that capecitabine (Xeloda) be funded as a component of the CAPOX regimen for the first- and second-line treatment of metastatic colorectal cancer. The CED noted that the CAPOX regimen is similar in efficacy and safety to the FOLFOX regimen also used in this setting. Although the CAPOX regimen is more expensive, some of the additional drug cost is offset by efficiency gains in other parts of the healthcare system, as demonstrated by the cost-effectiveness analysis.”</p>	<p>“Overall, the committee noted that the CAPOX regimen is similar in efficacy and safety as the FOLFOX regimen in the treatment of metastatic colorectal cancer. Although the CAPOX regimen is more expensive, some of the added drug cost may be offset by efficiency gains in other parts of the healthcare system.”</p>

Table A2: Recommendations that drug be funded under Exceptional Access Program (EAP)[22]

Drug (generic name) and Indication	Recommendation	Bolded text from ‘Highlights of Recommendation’ section
<p>Eloxatin (oxaliplatin) First- and second-line treatment of metastatic colorectal cancer</p>	<p>“For the initial or first-line treatment of metastatic colorectal cancer, the CED recommended that oxaliplatin (Eloxatin) be funded only in patients who have a contraindication or intolerance to the FOLFIRI regimen, on the basis that oxaliplatin (Eloxatin) is similar in efficacy as this comparator regimen but is significantly more expensive.</p> <p>For the subsequent or second-line treatment of metastatic colorectal cancer in patients who have failed first- line therapy, the CED recommended that oxaliplatin (Eloxatin) not be funded, on the basis that value for money has not been demonstrated in this setting.”</p>	<p>“Overall, the Committee noted that, in the first-line treatment of metastatic colorectal cancer, the FOLFOX regimen is similar in efficacy as the FOLFIRI regimen but is much more expensive. Therefore, the Committee recommended that the FOLFOX regimen be funded for first-line treatment only in patients who have a contraindication or intolerance to the FOLFIRI regimen. The Committee recommended that the FOLFOX regimen not be funded in the second-line treatment of metastatic colorectal cancer because value for money has not been demonstrated.”</p>
<p>Gleevec (imatinib) Treatment of acute lymphoblastic leukemia</p>	<p>“The CED recommended that imatinib (Gleevec®) be funded through the Exceptional Access Program for the treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) according to specific criteria. The CED noted that Ph+ ALL has a poor prognosis and limited treatment options. While imatinib has not been proven to prolong survival, it has been shown to greatly improve remission rates, which is considered to be a meaningful patient health outcome for this disease.”</p>	<p>“Overall, the CED noted imatinib has been demonstrated to provide significant improvements in response rates for the treatment of Ph+ ALL. Given that this disease has a poor prognosis and limited treatment alternatives, the CED recommended that imatinib be funded.”</p>
<p>Gleevec (imatinib) Treatment of gastrointestinal stromal tumors</p>	<p>“CED recommended that imatinib (Gleevec) be funded through Individual Clinical Review/Exceptional Access Program for the treatment of inoperable and/or metastatic gastrointestinal stromal tumors.”</p>	<p>“Overall, the CED felt that the current evidence is not strong enough to support formulary listing of imatinib and consideration on a case-by-case basis is reasonable.”</p>

<p>Nexavar (sorafenib) Treatment of metastatic renal cell carcinoma</p>	<p>“The CED recommended that sorafenib (Nexavar) be funded through the Exceptional Access Program for the second-line treatment of metastatic renal cell carcinoma after failure of cytokine therapy, according to specific criteria. Although there were concerns regarding cost-effectiveness, the CED noted that sorafenib (Nexavar) has been shown to provide clinical efficacy.”</p>	<p>“Overall, the Committee noted that sorafenib provides clinical efficacy in the second-line treatment of mRCC after failure to cytokine therapy. Although there were concerns regarding cost-effectiveness, the Committee recognized that sorafenib offers a treatment option for a select number of patients who have failed cytokine therapy; therefore, it was recommended that funding be considered for these patients.”</p>
<p>Nexavar (sorafenib) Treatment of hepatocellular carcinoma</p>	<p>“The CED recommended that sorafenib (Nexavar) be funded through the Exceptional Access Program for the treatment of advanced hepatocellular carcinoma (HCC) according to specific criteria. The CED acknowledged that sorafenib (Nexavar) has been shown to provide a survival advantage in certain patients with HCC but noted that it is not cost-effective.”</p>	<p>“Overall, the committee noted that sorafenib has been shown to improve survival in patients with advanced HCC whose liver disease is of no worse severity than Child-Pugh Class A. The Committee also recognized that there are limited effective treatment options for advanced HCC. However, sorafenib is not cost-effective at the submitted price. In light of the above, the committee recommended that funding for this treatment be considered through the Exceptional Access Program (EAP).”</p>
<p>Sprycel (dasatinib) Treatment of chronic myeloid leukemia</p>	<p>“The CED recommended dasatinib (Sprycel) be funded through the Exceptional Access Program for adult patients with chronic myeloid leukemia according to specific criteria. The CED’s recommendation was made on the basis that evidence supports the use of dasatinib (Sprycel) in patients who do not respond to, or are intolerant of standard treatment.”</p>	<p>“Overall, the committee agreed that dasatinib (Sprycel) provides a treatment option for CML patients who do not respond or are intolerant to imatinib.”</p>
<p>Sprycel (dasatinib) Treatment of acute lymphoblastic leukemia</p>	<p>“The CED recommended that dasatinib (Sprycel®) be funded through the Exceptional Access Program for the treatment of Philadelphia chromosome- positive acute lymphoblastic leukemia (Ph+ ALL) according to specific criteria. The CED’s recommendation was made on the basis that dasatinib offers a treatment option in Ph+ ALL patients who do not respond to, or are intolerant of, standard treatment.”</p>	<p>“Overall, available evidence suggests that dasatinib provides clinical benefits in Ph+ ALL patients who cannot use imatinib, and it provides a treatment option to these patients who would otherwise have no other alternatives.”</p>

<p>Sutent (sunitinib)</p> <p>First-line and second-line treatment of metastatic renal cell carcinoma</p>	<p>“The CED recommended that sunitinib (Sutent) be funded through the Exceptional Access Program (EAP) for the first-line treatment of metastatic renal cell carcinoma (mRCC) if the price is reduced. The CED’s recommendation was made on the basis that the drug appears to be more effective and better tolerated than interferon-alpha for treating this disease, but is significantly more expensive.”</p>	<p>“Overall, the committee noted that 1st-line therapy with sunitinib appears to be more effective and better tolerated than interferon-alpha. However, sunitinib (Sutent) is not considered cost-effective when compared to interferon-alpha for treatment of mRCC.”</p>
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Table A3: Recommendations that drug not be funded [22]

Drug (generic name) and Indication	Recommendation	Bolded text from ‘Highlights of Recommendation’ section
<p>Afinitor (everolimus) Metastatic renal cell carcinoma</p>	<p>“The CED recommended that everolimus (Afinitor®) not be funded. The CED acknowledged that everolimus has been shown to reduce the risk of disease progression in patients with metastatic renal cell carcinoma whose disease has progressed on alternative therapies, but noted that this drug does not provide value for money at the submitted price.”</p>	<p>“Overall, the Committee acknowledged that everolimus has been shown to reduce the risk of disease progression in patient with metastatic renal cell carcinoma whose disease has progressed on alternative therapies, but noted that this drug is not cost-effective.”</p>
<p>Alimta (pemetrexed) Treatment of non-small cell lung cancer</p>	<p>“The CED recommended that pemetrexed (Alimta) not be funded through CCO’s New Drug Funding Program for the treatment of non-small cell lung cancer, on the basis that it’s price premium over the current alternative could not be justified.”</p>	<p>“Overall, the Committee acknowledged that pemetrexed (Alimta) has a more favourable side effect profile compared to docetaxel. However, the Committee indicated that the substantial price premium for pemetrexed (Alimta) could not be justified, given the absence of survival or quality of life advantage over docetaxel. The Committee indicated that funding of pemetrexed (Alimta) could be considered if the price was significantly reduced. “</p>
<p>Avastin (bevacizumab) Recurrent glioblastoma multiforme</p>	<p>“The CED recommended that bevacizumab (Avastin®) not be funded for the treatment of recurrent glioblastoma multiforme (GBM), on the basis that this treatment has not been proven to improve survival.”</p>	<p>“Overall, the CED recommended that bevacizumab not be funded because it has not been proven to prolong survival in comparison to other existing treatment options and its value for money is unknown.”</p>
<p>Erbix (cetuximab) Metastatic colorectal cancer</p>	<p>“The CED recommended that cetuximab (Erbix®) not be funded. The CED acknowledged that cetuximab provides clinical benefits in the treatment of metastatic colorectal cancer, but noted that a treatment alternative with similar benefits is available at a lower cost.”</p>	<p>“Overall, the CED acknowledged that cetuximab provides clinical benefits in the treatment of metastatic colorectal cancer but noted that this drug is not cost-effective and is more expensive than a comparator product.”</p>

<p>Faslodex (fulvestrant) Treatment of metastatic breast cancer</p>	<p>“The CED recommended that fulvestrant (Faslodex) 50mg/mL injection not be funded through the Ontario Drug Benefit Formulary, on the basis that there is no clinical evidence supporting its use as a last resort prior to chemotherapy, or that it increases survival rates.”</p>	<p>“Overall, the Committee noted that the current evidence supports using fulvestrant instead of anastrozole or exemestane for locally advanced or metastatic breast cancer as second- or third-line therapy. There is no currently available clinical trial evidence to support the manufacturer’s request to fund fulvestrant as the fourth or last resort before chemotherapy for the treatment of metastatic breast cancer.”</p>
<p>Gemzar (gemcitabine) Treatment of metastatic breast cancer</p>	<p>“The CED recommended not to fund gemcitabine (Gemzar) through Cancer Care Ontario’s New Drug Funding Program (NDFP) for the treatment of breast cancer, on the basis that efficacy and value-for- money could not be established with the appropriate drug comparator.”</p>	<p>“Overall, the committee noted that because an inappropriate comparison drug was used in the analyses the manufacturer provided, the comparative effectiveness and value-for-money cannot be determined. As such, the Committee recommended that gemcitabine not be funded through CCO’s NDFP for the treatment of patients with metastatis breast cancer.”</p>
<p>Hycamtin (topotecan) Treatment of small cell lung cancer</p>	<p>“The CED recommended that topotecan (Hycamtin) not be funded through Cancer Care Ontario’s New Drug Funding Program (NDFP) for the treatment of small cell lung cancer, on the basis that there are insufficient data to establish clinical benefit and value for money.”</p>	<p>“Overall, the committee concluded that there is insufficient data to establish the clinical benefit and cost-effectiveness of topotecan (Hycamtin) in the second-line treatment for SCLC.”</p>
<p>MabCampath (alemtuzumab) Treatment of chronic lymphocytic leukemia</p>	<p>“The CED recommended not to fund alemtuzumab (MabCampath) through Cancer Care Ontario’s New Drug Funding Program, on the basis that the evidence regarding its effectiveness is weak, and the value- for-money of the drug is unclear.”</p>	<p>“Overall, the CED noted that the evidence that supports the effectiveness of alemtuzumab (Mabcampath) in patients who do not respond to standard chemotherapy is weak, and this medication is associated with severe side effects. In addition, the value-for-money of using mabcampath for the treatment of this form of leukemia is unclear.”</p>
<p>Metvix (methyl aminolevulinate) Superficial basal cell carcinoma</p>	<p>“The CED recommended that methyl aminolevulinate (Metvix®) not be funded on the basis that this drug does not provide added clinical or economic advantages over existing comparators.”</p>	<p>“Overall, the committee noted that alternative therapies for the treatment of sBCC are available and methyl aminolevulinate provides no added therapeutic or economic value over these treatment options.”</p>

<p>Revlimid (lenalidomide)</p> <p>Treatment of anemia due to myelodysplastic syndrome</p>	<p>“The CED recommended that lenalidomide (Revlimid) not be funded unless the price was reduced. The CED noted that current evidence for the use of lenalidomide (Revlimid) in the treatment of myelodysplastic syndrome is promising but further data is required to fully determine its clinical benefit and value for money. The CED also indicated that if funding were to be considered, eligibility should be clearly limited to patients who will most likely benefit from treatment.”</p>	<p>“Overall, the committee noted that current evidence for the use of revlimid in patients with MDS is promising, but further data is required to fully determine its clinical benefit and value for money.”</p>
<p>Torisel (temsirolimus)</p> <p>Metastatic renal cell carcinoma</p>	<p>“The CED recommended that temsirolimus (Torisel®) not be funded. The CED noted that while temsirolimus may provide survival benefits in a subgroup of patients with metastatic renal cell carcinoma (mRCC), cost- effectiveness of this treatment has not been demonstrated.”</p>	<p>“Overall, the Committee acknowledged that temsirolimus provides survival benefits in patients with metastatic renal cell carcinoma and poor-risk disease. However, the high cost of treatment has not been shown to be cost-effective.”</p>
<p>Vantas (histrelin)</p> <p>Treatment of advanced prostate cancer</p>	<p>“The CED recommended that histrelin (Vantas) not be funded through Ontario Public Drug Programs, on the basis that the supporting clinical evidence for this drug is poor.”</p>	<p>“Overall, the committee indicated that evidence supporting the use of histrelin is of poor quality. Furthermore, this drug does not provide any therapeutic or economic advantages over existing formulary alternatives. For these reasons, the committee recommended that histrelin not be funded.”</p>
<p>Xeloda (capecitabine)</p> <p>Treatment of gastric Cancer</p> <p>(note: The JODR indicates that what was reviewed was Herceptin and Xeloda, but only a recommendation for Xeloda is published on the CED website.)</p>	<p>“The CED recommended that capecitabine (Xeloda) for the treatment of gastric cancer not be funded on the basis that efficacy and value for money are unconfirmed.”</p>	<p>“Overall, the Committee indicated that capecitabine (Xeloda) for gastric cancer should not be funded until its efficacy and value for money have been confirmed.”</p>

Appendix B: Summary of cost-effectiveness statements from published CED-CCO Subcommittee Recommendations

Table B1: Summary of cost-effectiveness statements from positive (published) CED-CCO subcommittee recommendations

Drug (indication)	Statements from ‘CED Recommendation’ section	Statements from ‘Highlights of Recommendation’ section
Oxaliplatin (adjuvant treatment of colorectal cancer)	“... has been demonstrated to provide both therapeutic benefit and value for money for this indication.”	<p>“The FOLFOX regimen costs approximately \$1,500 per treatment cycle. An economic evaluation demonstrated that this regimen provides value for money in the adjuvant treatment of colorectal cancer.”</p> <p>“...has been demonstrated to provide clinical benefit and value for money in the adjuvant treatment of colorectal cancer.”</p>
Fludarabine (chronic lymphocytic leukemia)	“...this drug has been shown to provide efficacy and value for money in this clinical setting.”	<p>“Oral fludarabine costs approximately \$5,000 per treatment course. When administration and other health care expense are factored in, the costs for oral and intravenous fludarabine are comparable.”</p> <p>“...has been shown to provide efficacy and value for money in the first-line treatment of CLL.”</p>
Rituximab (first line treatment of chronic lymphocytic leukemia)	“... the use of rituximab in this setting has been shown to improve survival and to provide value for money.”	<p>“Based on the list price, rituximab costs approximately \$25,000 per patient for a treatment course. The committee noted that this drug appears to provide reasonable value for money.”</p> <p>...” improves survival and is cost-effective...”</p>
Panitumumab (treatment of metastatic colorectal cancer)	“... has been shown to provide a clinical benefit and reasonable value for money in selected patients with metastatic colorectal cancer.”	"Panitumumab (Vectibix) costs approximately \$2,500-3,000 per treatment cycle. An economic analysis has shown that panitumumab (Vectibix) provides reasonable value for money.”

<p>Capecitabine (as part of the CAPOX regimen for 1st and 2nd-line treatment of metastatic colorectal cancer)</p>	<p>“Although the CAPOX regimen is more expensive, some of the additional drug cost is offset by efficiency gains in other parts of the healthcare system, as demonstrated by the cost-effectiveness analysis.”</p>	<p>“Based solely on drug costs, the CAPOX regimen costs significantly more than FOLFOX regimen. However, because capecitabine (Xeloda) is taken orally and does not require intravenous administration, hospital/clinic resources that would otherwise be utilized could be freed up and reallocated for other intravenous therapies.”</p> <p>“Although the CAPOX regimen is more expensive, some of the added drug cost may be offset by efficiency gains in other parts of the healthcare system.”</p>
<p>Cetuximab (squamous cell carcinoma of the head and neck (SCCHN))</p>	<p>No applicable statements</p>	<p>“Cetuximab costs approximately \$12,000 for a 7-week treatment course. In comparison, a course of platinum-based chemotherapy is \$80. Based on the Committee’s assessment, cetuximab is not a cost-effective treatment for patients in whom platinum-based chemotherapy could be used. However, this drug does provide reasonable value for money if it is used for treating patients over age 70 who would otherwise receive radiation alone.”</p> <p>“In light of the clinical and cost- effectiveness data, the CED recommended that cetuximab be funded only for patients with locally advanced SCCHN who are over the age of 70 and have good performance status.”</p>
<p>Azacitidine (treatment of myelodysplastic syndrome)</p>	<p>No applicable statements</p>	<p>“Azacitidine costs approximately \$6,000 for each 28-day treatment cycle. If on average each patient receives 10 cycles of azacitidine, the total cost amounts to \$60,000. Given the high drug cost and the substantial number of patients anticipated to require this treatment, the financial impact of funding azacitidine is significant.”</p> <p>“Overall, the CED acknowledged that azacitidine has been shown to provide survival benefits in patients with a higher-risk form of MDS, a condition with limited effective treatment alternatives. The CED was, however, concerned with the high costs associated with funding this drug.”</p>

Table B2: Summary of cost-effectiveness statements from (published) CED-CCO subcommittee EAP recommendations

Drug (indication)	Statements from ‘CED Recommendation’ section	Statements from ‘Highlights of Recommendation’ section
Oxaliplatin (Treatment of metastatic colorectal cancer)	<p>“...be funded only in patients who have a contraindication or intolerance to the FOLFIRI regimen, on the basis that oxaliplatin (Eloxatin) is similar in efficacy as this comparator regimen but is significantly more expensive.”</p> <p>“For the subsequent or second-line treatment of metastatic colorectal cancer in patients who have failed first- line therapy, the CED recommended that oxaliplatin (Eloxatin) not be funded, on the basis that value for money has not been demonstrated in this setting.”</p>	<p>“The FOLFOX regimen is approximately three times more expensive than the FOLFIRI regimen (\$1,492 per treatment cycle versus \$582 per treatment cycle). The Committee indicated that the price premium is not justified.”</p> <p>“In the subsequent or second-line treatment of metastatic colorectal cancer in patients who have failed first line treatment, data from one study reported that the FOLFOX regimen provided superior efficacy compared to oxaliplatin (Eloxatin) alone and 5- fluorouracil and leucovorin alone. However, a proper economic evaluation has not been conducted by the manufacturer to assess value for money in the second-line setting.”</p> <p>“...the FOLFOX regimen is similar in efficacy as the FOLFIRI regimen but is much more expensive.”</p> <p>“The Committee recommended that the FOLFOX regimen not be funded in the second-line treatment of metastatic colorectal cancer because value for money has not been demonstrated.”</p>
Sorefenib (renal cell carcinoma)	<p>“Although there were concerns regarding cost-effectiveness, the CED noted that sorafenib (Nexavar) has been shown to provide clinical efficacy.”</p>	<p>“Sorafenib (Nexavar) costs approximately \$5,200 for one month of therapy. An economic evaluation found that this treatment does not provide good value for money.”</p> <p>“Although there were concerns regarding cost-effectiveness, the Committee recognized that sorafenib offers a treatment option for a select number of patients who have failed cytokine therapy...”</p>
Sorafenib (treatment of hepatocellular carcinoma)	<p>“The CED acknowledged that sorafenib (Nexavar) has been shown to provide a survival advantage in certain patients with HCC but noted that it is not cost-effective.”</p>	<p>“Sorafenib (Nexavar) costs \$175 per day. An economic evaluation found that sorafenib (Nexavar) is not cost effective.”</p> <p>“However, sorafenib is not cost-effective at the submitted price.”</p>
Sunitinib (first line treatment of metastatic renal cell carcinoma)	<p>“... the drug appears to be more effective and better tolerated than interferon-alpha for treating this disease, but is significantly more expensive.”</p>	<p>“However, the high cost of sunitinib (Sutent) renders the therapy much less cost-effective when compared to interferon-alpha for the treatment of MRCC.”</p> <p>“However, sunitinib is not considered cost-effective when compared to interferon-alpha for treatment of mRCC”</p>

Table B3: Summary of cost-effectiveness statements from negative (published) CED-CCO subcommittee recommendations

Drug	Statements from ‘CED Recommendation’ section	Statements from ‘Highlights of Recommendation’ section
Everolimus (metastatic renal cell carcinoma)	“... this drug does not provide value for money at the submitted price.”	“Everolimus costs \$186 per day. Based on the CED’s assessment, this drug does not provide value for money at the submitted price.” “... this drug is not cost-effective.”
Cetuximab (metastatic colorectal cancer)	“... a treatment alternative with similar benefits is available at a lower cost.”	“Cetuximab costs approximately \$7,000 per month. Based on the CED’s assessment, this drug does not provide value for money. Moreover, a less expensive EGFR inhibitor for the treatment of metastatic colorectal cancer is already available.” “...this drug is not cost-effective and is more expensive than a comparator product.”
Temsirrolimus (metastatic renal cell carcinoma)	“...cost- effectiveness of this treatment has not been demonstrated.”	“Temsirrolimus costs approximately \$5,000 per month. This treatment has not been shown to provide value for money.” “...the high cost of treatment has not been shown to be cost-effective.”
Methyl aminolevulinate (superficial basal cell carcinoma)	“...this drug does not provide added clinical or economic advantages over existing comparators”	“Methyl aminolevulinate costs \$300 - \$600 per treatment course. Because methyl aminolevulinate must be used in combination with photodynamic therapy, additional costs to the health care system would be incurred. This makes the total cost of treatment much more expensive than imiquimod.” “... provides no added therapeutic or economic value over these treatment options.”
Histrelin acetate (metastatic prostate cancer)	No applicable statements	“Histrelin costs \$4,074 per year. This is comparable to some of the lower cost LHRH agonists currently listed on the Formulary.” “...drug does not provide any therapeutic or economic advantages over existing formulary alternatives.”

<p>Pemetrexed (treatment of non-small cell carcinoma)</p>	<p>“... price premium over the current alternative could not be justified.”</p>	<p>“Based on the manufacturer’s submitted price, the treatment cost of pemetrexed (Alimta) is approximately \$24,000 per patient. Docetaxel costs approximately \$16,000 - \$18,000 per patient.”</p> <p>“... the substantial price premium for pemetrexed (Alimta) could not be justified...”</p>
<p>Gemcitabine hydrochloride (treatment of metastatic breast cancer)</p>	<p>“... value-for- money could not be established with the appropriate drug comparator.”</p>	<p>“The cost of gemcitabine (Gemzar) therapy in combination with either docetaxel or paclitaxel to treat metastatic breast cancer ranges from \$1,900 to \$2,300 per cycle.”</p> <p>“... because an inappropriate comparison drug was used in the analyses the manufacturer provided, the comparative effectiveness and value-for-money cannot be determined.”</p>
<p>Alemtuzumab (treatment of chronic lymphocytic leukemia)</p>	<p>“...the value- for-money of the drug is unclear.”</p>	<p>“MabCampath costs approximately \$25,000 for one course of therapy. The next most expensive therapy is fludarabine, which costs approximately \$7,200 for each course of therapy.”</p> <p>“... the value-for-money of using mabcampath for the treatment of this form of leukemia is unclear.”</p>
<p>Topotecan (treatment of small cell lung cancer)</p>	<p>“... there are insufficient data to establish clinical benefit and value for money.”</p>	<p>“Topotecan (Hycamtin) costs approximately \$1,800 per treatment cycle. Value for money could not be determined because the manufacturer did not provide an economic model.”</p> <p>“... there is insufficient data to establish the clinical benefit and cost-effectiveness of Hycamtin in 2nd-line treatment for SCLC.”</p>
<p>Lenalinomide (treatment of anemia due to myelodysplastic syndrome)</p>	<p>“...further data is required to fully determine its clinical benefit and value for money.”</p>	<p>"Lenalidomide (Revlimid) costs \$361 per day, at a dose of 10mg daily. Because its clinical value has not been firmly established, the Committee indicated that the high cost of treatment could not be justified.”</p> <p>“...provides no added therapeutic or economic value over these treatment options.” (i.e. alternative therapies for the same indication”</p>

<p>Bevacizumab (recurrent glioblastoma multiforme)</p>	<p>No applicable statements</p>	<p>“The average treatment cost for bevacizumab is approximately \$35,000 per patient (based on an estimate of 9 cycles of therapy). Value for money could not be established based on available information.”</p> <p>“...its value for money is unknown.”</p>
<p>Capecitabine (treatment of gastric cancer)</p>	<p>“... efficacy and value for money are unconfirmed.”</p>	<p>“Based solely on drug costs, capecitabine (Xeloda) is significantly more expensive than intravenous 5-FU. A comprehensive economic comparison between the two drugs is not available; therefore, it is unknown whether capecitabine (Xeloda) provides value of money when other costs associated with drug administration and monitoring are taken into consideration.”</p> <p>“... should not be funded until its efficacy and value for money have been confirmed.”</p>

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CHAPTER 4

Challenges in striving to simultaneously achieve multiple resource allocation goals: the pan-Canadian Oncology Drug Review (pCODR) example

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ABSTRACT: The pan-Canadian Oncology Drug Review (pCODR) makes recommendations to Canada’s provinces and territories (except Quebec) to guide their cancer drug funding decisions. The objective of this paper is to explore, using an economic perspective, the challenges associated with striving to simultaneously achieve the pCODR’s goals of maximizing health benefits with available resources and improving access to a more consistent standard of care across Canada. The first challenge concerns how to interpret the goals in order to determine how resources should be allocated to achieve each goal. The second challenge relates to whether, if pursued simultaneously, both goals can be achieved to the same extent that each goal could have been achieved alone with the same available resources. Regarding the first challenge we illustrate that, due to lack of definitional clarity, it is difficult to determine exactly how resources should be allocated in order to achieve the goal of improving access to a more consistent standard of care across Canada. Regarding the second challenge, we illustrate that choosing to strive for both of the pCODR goals simultaneously will likely be associated with tradeoffs in the extent to which one or both goals can be achieved (relative to what could have been achieved for each goal alone with the same available resources). We suggest that, if the pCODR and the provincial drug plan decision-makers it supports want to strive for both goals simultaneously, they need to prioritize the goals and explicitly identify the tradeoffs associated with the prioritization. This will ensure that the consequences of striving to simultaneously achieve both goals are made explicit, transparent and predictable for provincial drug plan decision-makers, physicians, patients, caregivers and society as a whole. **Word Count: 278**

1. INTRODUCTION:

Health care systems everywhere face the complex challenge of determining how to provide healthcare to best achieve their goals within an environment of scarce resources. The term resource scarcity (or affordability) means that, whatever resources are available, they are insufficient to support all possible activities. As a result of scarcity, healthcare systems are forced to make choices about how to allocate resources. They must decide what services to provide (and thus what not to provide), to whom, at what stage of a disease, and for how long in order to best achieve their goals.

Decision-makers responsible for drug coverage plans (e.g. government agencies) face the same resource allocation challenge as described above: given the budget allocated to them, they must decide which drugs to reimburse (and which not to reimburse), for whom, at what stage of a disease, and for how long. In Canada, organizations such as the pan-Canadian Oncology Drug Review (pCODR) have been developed to make drug reimbursement recommendations to Canada's provincial and territorial Ministries of Health. Established in 2010 by Canada's provincial and territorial Ministries of Health, the pCODR assesses the clinical evidence and cost-effectiveness of new cancer drugs and uses this information to make recommendations to the provinces and territories (except Quebec) to guide their drug funding decisions.¹ Each province is ultimately responsible for funding, administering and governing its own drug budget. Thus, after the pCODR

¹ From this point forward, we refer to provinces and territories as "provinces" for simplicity.

makes a recommendation for a new cancer drug, each pCODR-participating drug plan then makes a decision on whether or not to accept the pCODR recommendation.

Because the pCODR is making recommendations to guide the allocation of publicly funded drug budget dollars, it is important that the pCODR's resource allocation goals, or objectives, (we use these terms synonymously in this paper) are clearly understood by stakeholders (which include the pCODR-participating drug plans, physicians, patients, caregivers and the general public). This will enable stakeholders to judge whether and to what extent these goals have been achieved. A commonly referred-to, although not always explicitly stated, resource allocation goal for health care systems is to maximize health benefits (aggregated across a population) through the allocation of available resources. While the pCODR does not explicitly state that this is its resource allocation goal, the pCODR uses cost-effectiveness analysis (CEA) to guide its reimbursement decision-making. The underlying premise of CEA is that the goal of society or decision-makers is to maximize the total aggregate health benefit conferred for a given level of resources.[1,2,3,4] Therefore, the maximization of health benefits with available resources is an implied resource allocation goal of the pCODR. In addition to this implied goal, the pCODR states that its objective is “to build the foundation for a streamlined, national cancer drug review process that supports evidence-based decision-making”, which will ultimately “improve access to a more consistent standard of care across Canada, and bring clarity for patients, health professionals and industry about how, when and why drug funding decisions are made.”[5] Improving access to a more

consistent standard of care across Canada is an equity (fairness) goal that will require resources to be allocated in a particular way in order to be achieved. Therefore, the pCODR appears to have two separate goals that, if they are to be achieved, will influence the allocation of scarce resources.

The objective of this paper is to explore, using an economic perspective, the challenges associated with striving to simultaneously achieve the pCODR's two resource allocation goals. In doing so, we first explain why an economic perspective is used (Section 2). We then describe the nature of the challenges associated with striving to simultaneously achieve the two pCODR goals (Section 3). The challenges fall into two categories. The first challenge concerns how to interpret the goals in order to determine how resources should be allocated to achieve each goal. To address this challenge we explore whether the goals are clearly and transparently defined and operationalized by the pCODR (Section 3A). The second challenge relates to whether, if pursued simultaneously, both goals can be achieved to the same extent that each goal could have been achieved alone with the same available resources. To address this challenge we explore whether, with the same available resources, the activities (e.g. the drugs) to which resources should be allocated in order to achieve the goal of maximizing health benefits with available resources alone is the same as the drugs to which resources should be allocated in order to achieve the goal of improving access to a more consistent standard of care across Canada alone (Section 3B). The pCODR states that its national cancer drug review process will bring clarity about how, when and why drug funding decisions are made.[5] Therefore,

in Section 3C we discuss whether the pCODR transparently states how its two resource allocation goals are integrated in order to reach reimbursement recommendations.

Finally, in Section 4 we illustrate one of the consequences of the above challenges, namely the tradeoffs in goal achievement that may be involved in striving to simultaneously maximize health benefits with available resources and improve access to a more consistent standard of care across Canada. Our use of the term ‘tradeoff’ refers to a reduction in the extent to which a particular goal can be achieved when multiple goals are simultaneously pursued relative to when that single goal is pursued alone with the same available resources.

2. USING AN ECONOMIC PERSPECTIVE TO EXPLORE THE CHALLENGES OF STRIVING TO SIMULTANEOUSLY ACHIEVE THE pCODR’S TWO GOALS

Economics is just one perspective that could be used to explore the challenges of striving to simultaneously achieve both of the pCODR’s goals. However, we suggest that it is an appropriate perspective for several reasons. Economics is a discipline that studies how to allocate scarce resources in order to best achieve the goals stated by decision makers.

Economics is based on three fundamental concepts: scarcity (whatever resources are available, they are insufficient to support all possible activities); choices (because resources are scarce, we must choose between different ways of using them) and opportunity cost (by choosing to use resources in one particular way, we forego opportunities to use these same resources in any other way). These three fundamental

concepts are relevant to the provincial drug budget resource allocation task that the pCODR recommendations are intended to guide. Due to resource scarcity (i.e. because there are a limited number of dollars available in the drug budgets), provinces must make choices regarding which drugs to publicly reimburse. Furthermore, these choices are associated with opportunity costs: by choosing to spend drug budget dollars on reimbursing certain drugs, the provinces forego the opportunity to use these drug budget dollars to reimburse any other drugs.

Scarcity, choices and opportunity costs are also relevant to the challenge of striving to simultaneously achieve both of the pCODR's goals. If there was no resource scarcity, then Canada's provinces could simultaneously achieve both goals (unless contradictory) to the same extent that each could be achieved alone. However, resources are scarce. Consequently, if the type and mix of drugs that should be reimbursed in order to achieve each of the pCODR goals alone differ, then choosing to allocate resources in order to achieve one of the goals to its maximum extent with the available resources will have opportunity costs. These opportunity costs manifest as tradeoffs in the extent to which the other goal can be achieved.

3. CHALLENGES TO ACHIEVING THE pCODR'S GOALS

SIMULTANEOUSLY

3A. Definitional Clarity of the Goals

To determine how resources should be allocated in order to best achieve a given goal it is critical that the goal be clearly defined and operationalized. Below we explore the pCODR's two goals to determine whether each is clearly defined and operationalized.

Goal 1: Maximizing Health Benefits With Available Resources

A clear definition of the goal of maximizing health benefits with available resources is not provided by the pCODR. Indeed, the goal itself is not explicitly stated and instead has been inferred by us based on the pCODR's use of CEA to guide reimbursement recommendations. The CEA literature, however, clearly states that the goal of CEA is to maximize the health of the population.[1,2,3,4] While the measure that should be used to quantify health gains under a CEA analysis is not explicitly defined in the literature, most people use quality-adjusted-life-years (QALYs). A QALY is a year of life that has been adjusted for quality of life. With QALYs, an individual's health is measured as the product of a person's total years of life adjusted for quality, and a population's health is measured as the sum of QALYs for all individuals in the population. Though the way QALYs should be valued is also not explicitly defined in the literature, most people value them in the manner described by Wagstaff.[6] That is all QALYs are valued equally regardless of who gains or loses them.

While the valuation of benefits for the health benefit maximization goal is typically operationalized using QALYs in the manner we describe above, the goal could also be operationalized in other ways. For example, the assumption that all QALYs should be valued equally may not accurately capture important equity considerations related to health benefits gained. Quality adjusted life-years could thus be valued in other ways, with health gains realized in certain disease areas or by certain populations being weighted more heavily than health gains in other areas. Of note, the National Institute for Health and Clinical Excellence (NICE) is presently exploring this issue, reviewing the concept of QALY weighting as part of their 2011/12 update to their guide for methods of technology appraisal.[7] Although there are different ways that the goal of maximizing health benefits with available resources could be operationalized, we assume for the remainder of the paper that the operationalization is as we described above: via the use of QALYs in the manner described by Wagstaff.[6]

Goal 2. Improving Access to a More Consistent Standard of Care Across Canada

The pCODR notes that its national, evidence-based drug review process will ultimately improve access to a more consistent standard of care across Canada.[5] However, the phrases “access”, “more consistent” and “standard of care” are not defined, discussed, or operationalized any further. Consequently, numerous questions arise, some of which are outlined below.

First, what is the definition of the term “standard of care”, and by whom is the standard of care determined? Is the standard of care determined by what is recommended in clinical

guidelines? For some types of cancer, there might be more than one clinical guideline describing how the disease should be managed once diagnosed, while for other types of cancer there might not be any guidelines. If there are multiple guidelines, which guidelines should be referenced and based on what criteria is the guideline of choice selected? Alternatively, does the pCODR intend to determine the standard of care itself? Although the pCODR refers to itself as an evidence-based drug review process, its mandate does not include the development of clinical guidelines. Therefore, it is not clear how a pCODR-determined standard of care would align with other guidelines developed by the medical community. Furthermore, while the standard of care is often interpreted to mean the best possible care, this may not be possible in the case of the pCODR. Because resources are scarce and the level of scarcity varies across provinces, and if the pCODR's goal is aimed at having the same cancer drugs reimbursed in all provinces, then the standard of care might be the least costly cancer drug(s) (which are often less effective or worse in some manner relative to more costly drugs for the same disease) that can be afforded by all provinces. As such, achieving the goal of "improving access to a more consistent standard of care across Canada" may actually mean that the cancer drugs that get reimbursed across provinces are worse than currently available cancer drug options.

Second, what is meant by the phrase "more consistent"? To illustrate the challenges associated with interpreting this phrase, we assume that "standard of care" means "the drugs recommended by the pCODR", and that pCODR goal is related only to the reimbursement (i.e. drugs are free of charge for beneficiaries at the point of consumption)

of the drugs recommended as the standard of care on the provincial drug plans. Based on these assumptions, what has to happen in order for the standard of care to be considered “more consistent”? The word “more” implies a level of gradation in terms of having consistency in the standard of care across Canada. Therefore, do only certain cancer drugs, but more than currently are, need to be reimbursed across all provinces in order for the standard of care to be “more consistent”? If so, which drugs? Or, do all (or certain) cancer drugs need to be reimbursed in a certain number of provinces instead of in all provinces in order for the standard of care to be “more consistent”? Alternatively, instead of looking at the number of provinces in which cancer drugs are reimbursed, is the standard of care “more consistent” if the total number of cancer patients in Canada for whom certain (or all) cancer drugs are publicly reimbursed increases?

Third, what is meant by the term “access”? Is the pCODR referring to the public reimbursement (i.e. the drug is free of charge at the point of care for drug plan beneficiaries) of cancer drugs, patients’ ability to physically access drugs, both or something else? For a variety of reasons, such as proximity to a medical center that can administer a given drug or patient-related financial constraints such as transportation and accommodation costs associated with treatment (if for example a patient needs to reside near a cancer center over the course of their treatment), there may be differences in patients’ ability to access a given drug even if it is publicly reimbursed across all provinces. This has recently been observed by Chafe et al who noted that, “While there is moderate consistency in the selection of cancer drugs that account for the highest

provincial expenditures, considerable differences were found in the rates at which some drugs are accessed across provincial programs.”[8]

In summary, the phrases “standard of care”, “more consistent” and “access” can, as we have illustrated above, have multiple interpretations. This creates uncertainty for drug plan decision-makers because different interpretations of these phrases can have different implications in terms how resources should be allocated in order to achieve the pCODR’s equity goal of improving access to a more consistent standard of care across Canada. It also creates challenges related to the transparency and accountability of the pCODR’s recommendations: from a transparency perspective, the exact goal that the pCODR is trying to accomplish (as relates to consistency in standard of care) is unclear; from an accountability perspective, the multiple possible interpretations of the consistency goal make it difficult to determine whether the pCODR’s recommendations and the provincial drug plan reimbursement decisions are consistent with the goal. Thus, while striving to improve access to a more consistent standard of care across Canada may seem like a benign and possibly beneficial goal, it is in reality a highly complex objective that requires further clarification before it can be incorporated into the resource allocation decision-making task in a meaningful way.

3B: Striving to Simultaneously Achieve Both pCODR Goals

Even if both pCODR goals were clearly defined and operationalized, we still need to determine whether they can be simultaneously achieved to the same extent that each

single goal could have been achieved alone with the same available resources. To address this question we first describe the resource allocation considerations associated with achieving each single goal alone.

i) Resource Allocation Considerations for Achieving a Single Goal of Maximizing Health Benefits with Available Resources

A goal of maximizing health benefits with available resources is based on striving to ensure that the available resources are spent on the activities that confer the maximum aggregate health benefits for the population. Typically, when considering whether to reimburse a new drug, drug plan decision-makers are working in an environment where resources are already fully allocated (i.e. where the drug budget is already fully spent). Thus, in order to reimburse a new drug, resources have to be transferred away from activities that are currently receiving resources (i.e. currently being funded). Resources could come from elsewhere in the drug budget (by discontinuing or restricting the reimbursement of other drugs), from the overall healthcare budget (by discontinuing or restricting other healthcare activities), or from outside of healthcare (by discontinuing or restricting activities in other provincial ministries such as education or transportation). Reimbursing a new drug (for the typical case of a new drug that is more effective and more costly than what is currently reimbursed) will achieve the goal of maximizing health benefits with available resources if:

- a) There is an activity or combination of activities currently being funded that, if discontinued or restricted (in terms of funding), would free up enough resources to reimburse the new drug

AND

- b) The total benefits that would be foregone by discontinuing or restricting the funding of these activities is less than the total health benefits that would be gained by reimbursing the new drug²

Whether there is an activity or combination of activities from which resources can be transferred in order to reimburse a new drug and whether more health benefits will be gained than lost as a result depends on two factors: a population's medical needs and a decision-maker's total available resources. These factors, which are described below, vary across provinces. Consequently, whether a given new drug can be reimbursed in a way that maximizes health benefits with available resources is also likely to vary across provinces.

² Even if the drug budget can be increased in order to reimburse new drugs (such that resources do not have to be transferred away from other activities), the (cancer) drugs will still be competing for more resources than there are resources available because of resource scarcity. Therefore, if the goal is to maximize health benefits with available resources, then decision-makers must still consider what is foregone by using the available resources to reimburse a new drug instead of using the same resources in any other way.

Medical Needs: The medical need for a new drug depends on a population's underlying demographics, socioeconomics and epidemiology.[9,10] These factors, which vary across provinces, will drive the prevalence of the disease that the drug is intended to treat, which will in turn determine: a) the total amount of resources required to provide (i.e., reimburse) a new drug needed to treat that disease (and thus, the total amount of resources that need to be freed up) and b) the total aggregate health benefits that will be gained by reimbursing that drug for those in need within the population. A population's other medical needs (which are based on the prevalence of other diseases), if met, will determine the total resources presently allocated towards other healthcare activities (and thus, whether existing healthcare resources are already fully allocated), along with the total health benefits gained from those activities. Because a population's medical needs affect the total resources required to reimburse a new drug and the net gain (or loss) of aggregate health benefits that result from allocating resources away from currently funded activities (when necessary) and towards a new drug, these medical needs must be factored in when trying to allocate resources in a way that will maximize health benefits.

Total Available Resources: A decision-maker's total available resources (i.e. the total available dollars) will determine which and how many activities can be funded. In the case of the provincial drug plan decision-makers, the total available resources (i.e. the total drug budget dollars) will determine which and how many drugs can be reimbursed. The total resources available to a drug plan decision-maker typically vary across provinces due to differences in the size of each provincial drug budget and the size and

characteristics of the population served. Furthermore, whatever resources are available, they will be insufficient to pay for all possible activities, due to resource scarcity.

To illustrate how a decision-maker's total available resources determine whether reimbursing a new drug maximizes health benefits with available resources, we use an example based on two hypothetical provinces: 'Province A' and 'Province B'. Province A has a larger drug budget than Province B, but the two provinces are identical in all other variables (e.g. disease prevalence, size of population). Because of its larger drug budget, Province A can reimburse more drugs than province B. As a result, when a new and more costly drug is being considered for reimbursement it is more likely that, amongst the current drugs that are being reimbursed, one can find a candidate for dis-reimbursement (i.e., a drug or combination of drugs that, when dis-reimbursed, will free up enough resources to pay for the new drug and where the health benefits lost as a result of the dis-reimbursement are less than the health benefits gained from the new drug) in province A than in province B.

ii) Resource Allocation Considerations for Achieving a Single Goal of Improving Access to a More Consistent Standard of Care Across Canada

The different interpretations of the pCODR's goal of improving access to a more consistent standard of care across Canada can, as we highlighted in Section 3A, have different implications in terms how resources should be allocated. However, we make some simplifying assumptions in this section in order to provide some examples of how

resources might have to be allocated in order to achieve this goal. In our first example, we assume that the goal of improving access to a more consistent standard of care across Canada is aimed at having all of the pCODR-recommended drugs reimbursed in all provinces for provincial drug plan beneficiaries with the same medical need. We further assume that there are sufficient resources in all provinces to achieve this goal (i.e., resources that can be freed up by discontinuing currently funded activities). Based on these assumptions, and regardless of the impact that freeing up resources has on other currently-funded activities, the consistency goal would be achieved if all provincial drug plans reimburse all of the pCODR-recommended drugs for drug plan beneficiaries with the same medical need.

The example above interprets the pCODR goal as an “all or none” proposition (i.e. the only way to achieve the goal is for all provinces to reimburse all pCODR-recommended drugs for eligible beneficiaries). However, depending on how the word “more” in the pCODR’s goal is defined, there may be yet other ways for resources to be allocated in order to achieve the goal. This is particularly relevant in the event that there are insufficient resources to accomplish the “all or none” version of the goal that we used in our first example. To illustrate our point, we assume again that the goal is related to the reimbursement of pCODR-recommended drugs on the provincial drug plans. However, instead of assuming that all pCODR-recommended drugs have to be reimbursed in all provinces, we assume that the standard of care is considered to be “more consistent” if each of the pCODR-recommended new drugs is reimbursed in at least 3 provinces for

patients with the same medical need. In this case, only three provinces would have to allocate resources towards reimbursing each pCODR-recommended drug for eligible beneficiaries with the same medical need in order for the goal to be achieved. This is just one way that resources might have to be allocated in order to achieve the pCODR's consistency goal, depending on how "more consistent" is defined and operationalized.

iii) Combining the two pCODR Goals

The sections above describe how resources should be allocated in order to achieve the goal of maximizing health benefits with available resources alone or the goal of improving access to a more consistent standard of care alone. However, because both of these are pCODR goals, the question becomes whether the two goals can be simultaneously achieved to the same extent that each could have been achieved alone with the same available resources. To address this question, we again make some simplifying assumptions. First, we assume that the goal of improving access to a more consistent standard of care across Canada is aimed at having all of the pCODR-recommended drugs reimbursed in all provinces for provincial drug plan beneficiaries with the same medical need. We next assume, as an example, that the pCODR recommends Drug A to be reimbursed for patients with Cancer X. In this example, the pCODR's consistency goal will be achieved if all provinces reimburse Drug A for patients with Cancer X (assuming they have sufficient resources to do so and regardless of the impact this has on other currently-funded activities). The health benefit maximization goal, on the other hand, will be achieved if resources are allocated using the approach described in section 3Bi. That is, reimbursing Drug A for patients with Cancer

X will only maximize health benefits with available resources in a province if: a) there is an activity or combination of activities currently receiving resources that, if discontinued or restricted (funding-wise), would free up enough resources to reimburse the new drug and b) the benefits that would be given up by discontinuing or restricting these activities are less than the health benefits that will be gained by reimbursing the new drug. It is possible that, in some provinces (say, for example, in ‘Province C’ and ‘Province D’), reimbursing Drug A for patients with Cancer X will maximize health benefits with available resources. If all of the provinces reimbursed Drug A for Cancer X for patients with the same medical need, then both of the pCODR goals will have been achieved to the same extent that each goal could have been achieved alone with the same available resources in Provinces C and D (as long as the drugs for which reimbursement must be discontinued in order to pay for Drug A are not other pCODR-recommended drugs or are the same pCODR- recommended drugs). However, because of differences in medical needs and total available resources, the mix and type of drugs that will maximize health benefits with available resources is expected to vary across provinces. Therefore, while health benefits may be maximized in Provinces C and D by reimbursing Drug A for patients with Cancer X, reimbursing Drug A for patients with Cancer X in the other provinces may lead to a loss of total health benefits. In the latter provinces, the health benefit maximization goal will not have been achieved to the same extent that it could have been achieved alone with the same available resources. Furthermore, due again to different medical needs and total available resources, while Provinces C and D may be able to achieve both pCODR goals to the same extent that each goal could have been

achieved alone by reimbursing Drug A for Cancer X, reimbursing other pCODR-recommended drugs may not result in a net gain of aggregate health benefits in these same provinces. Therefore, for any given pCODR-recommended drug, it will likely not be possible to simultaneously achieve both of the pCODR goals across all provinces to the same extent that each goal could have been achieved alone with the same available resources.

3C: Does the pCODR Transparently Describe how it Integrates its two Goals?

If the two pCODR goals cannot be simultaneously achieved to the same extent that each could have been achieved alone with the same available resources (a likely scenario, as we suggest above), then the goals will need to be prioritized. In other words, decisions have to be made regarding which goal is more important to achieve. At this point it is not clear how the pCODR integrates the two goals in order to make reimbursement recommendations because there are no explicit, public statements from the pCODR regarding the relative importance of each goal.

4. POSSIBLE TRADEOFFS ASSOCIATED WITH STRIVING TO SIMULTANEOUSLY ACHIEVE THE pCODR'S TWO GOALS

Because it will not always (and we think, in most cases) be possible to simultaneously achieve both of the pCODR goals to the same extent that each could have been achieved alone with the same available resources, tradeoffs will be incurred. The nature and magnitude of the tradeoffs will vary depending on a) how each goal is defined and

operationalized and b) how the goals are prioritized. Due to the lack of definitional clarity regarding the consistency goal and because the pCODR has not indicated any prioritization of the goals, the exact tradeoffs associated with striving to simultaneously achieve the two pCODR goals are difficult to fully delineate. However, it is still important to understand what some of these tradeoffs could be. In order to illustrate some of the possible tradeoffs we make the simplifying, hypothetical assumptions outlined below.

1. The pCODR's consistency goal is prioritized over the goal of maximizing health benefits with available resources and is treated as a constraint (i.e. resources must be allocated to achieve the consistency goal in full as we define it in assumption # 2 below), assuming that there are sufficient resources to do so and regardless of where the resources come from to satisfy this constraint.
2. The pCODR's goal of improving access to a more consistent standard of care across Canada is aimed at having all of the pCODR-recommended cancer drugs publicly reimbursed (i.e. the drug is free of charge at the point of consumption) in all provinces for all provincial drug plan beneficiaries with the same medical need.
3. The provincial drug budgets are fixed and fully allocated, and the resources required to reimburse a new drug will have to come from these budgets (i.e.

they will not be taken from other budgets within the Ministries of Health or from other Ministries).

NOTE: In some provinces there are separate budgets for cancer vs. non-cancer drugs. We assume that, even in provinces with a separate cancer drug budget, the resources required to reimburse a new drug have to come from within the combined budgets for cancer and non-cancer drugs.

We acknowledge that the assumptions above may not always be applicable in reality. However, we make them to illustrate some of the tradeoffs associated with trying to simultaneously achieve the two pCODR goals. Even with these simplifying assumptions, the factors that must be taken into account in order to determine the tradeoffs are highly complex. In (perhaps more realistic) situations that stray from these basic assumptions, determining the tradeoffs becomes even more complex.

For our illustration we assume again that the pCODR recommends Drug A be reimbursed for patients with Cancer X. Based on the assumptions above all provinces will have to reimburse Drug A for patients with Cancer X in order to achieve the consistency goal. To do this, resources will have to be transferred away from currently reimbursed drugs. However, as described in Section 3Biii, discontinuing or restricting the reimbursement of currently-funded drugs in order to reimburse Drug A may result in more health benefits being lost than are gained in at least some provinces. In these instances the health benefit

maximization goal cannot be simultaneously achieved alongside the consistency goal to the same extent that it could have been achieved alone with the same available resources. Furthermore, the specific drugs for which reimbursement is discontinued or restricted and the associated total health benefits that have to be foregone in order to reimburse Drug A are likely to vary across provinces due to differences in medical need and total available resources. Therefore, the degree to which the health benefit maximization goal is impeded will also be different across provinces. Finally, depending on what is currently reimbursed in a province and on how many resources need to be freed up, the resources required to reimburse Drug A may have to come from discontinuing or restricting the reimbursement of cancer drugs that are presently reimbursed in the provinces (e.g., cancer drugs that were reimbursed in the provinces before the establishment of the pCODR). Thus, unless discontinuing the reimbursement of currently funded cancer drugs is specifically prohibited in the definition and operationalization of the pCODR goals, achieving the pCODR's consistency goal may have the unintended consequence of creating new inequalities across Canada in the public reimbursement of currently funded cancer drugs.

In making the assumption for illustrative purposes that the pCODR's consistency goal is a constraint, we demonstrate in the above scenarios that the health benefit maximization goal is achieved to a lesser extent than it could have been achieved alone with the same available resources. This is one example of how the pCODR goals can be integrated but there are also other ways of integrating the goals. For example, each goal could have a

weighting in terms of relative importance instead of one goal fully trumping the other. This type of integration would result in different types of tradeoffs relative to what we have described in our example above (e.g. instead of only one goal being achieved to a lesser extent, both goals might be achieved to a lesser extent than each goal could have been achieved alone with the same available resources). In order to determine, in these cases, the exact degree to which each goal is traded off against achievement of the other goal, the weighting of each goal would have to be transparently described by the pCODR.

5. DISCUSSION

This paper highlights challenges associated with striving to simultaneously achieve the pCODR's goals of maximizing health benefits with available resources and improving access to a more consistent standard of care across Canada. First, due to lack of definitional clarity, it is difficult to determine exactly how resources should be allocated in order to achieve the pCODR's goal of improving access to a more consistent standard of care across Canada. Second, due to differences across provinces in medical needs and the total available resources per beneficiary, it is likely that the mix and type of drugs that should be reimbursed in order to maximize health benefits with available resources will vary across provinces whereas the same cancer drugs would have to be reimbursed across all provinces in order to achieve the goal of improving access to a more consistent standard of care across Canada (if this latter goal is defined as we suggested in section 4). Consequently, choosing to strive for both of these goals simultaneously will likely be associated with tradeoffs in at least some provinces in the extent to which one or both of

the goals can be achieved (relative to what could have been achieved for each goal alone with the same available resources).

Striving to simultaneously achieve the pCODR's two resource allocation goals and incurring tradeoffs in the extent to which the goals can be achieved might not necessarily be considered a bad thing. It is possible that these tradeoffs are acceptable to the pCODR and to provincial drug plan decision-makers. The pCODR and the provincial drug plan decision-makers may decide, for example, that improving access to a more consistent standard of care across Canada is an important goal and that some reduction in the ability to maximize health benefits with available resources is acceptable in order to achieve this consistency (or vice versa). However, there are no explicit statements from the pCODR about such tradeoffs and thus it is not clear that the pCODR (or, in turn, the provincial drug plan decision-makers) are presently aware that tradeoffs will likely be incurred in striving to simultaneously achieve these two goals. If the pCODR is aware of these tradeoffs, we suggest that it is incumbent on them to clearly and transparently specify the nature and magnitude of the tradeoffs so that they are transparent for drug plan decision-makers, physicians, patients, caregivers and the general public.

There is yet another challenge with striving to simultaneously achieve both of the pCODR goals. Because achievement of the consistency goal, if defined as we suggested in Section 4, must be effected nationally, then all of the pCODR-participating provinces would have to agree to: a) the existence of and b) the definition of the consistency goal.

Furthermore, they would all have to accept the tradeoffs associated with striving to simultaneously achieve both of the pCODR goals, even though the magnitude and nature of the tradeoffs are likely to vary across provinces (in addition to varying depending on the cancer drug under consideration). Presently, it is not clear that all pCODR-participating provinces have agreed to a consistency goal that requires all provinces to reimburse the same cancer drugs or to the tradeoffs associated with striving to simultaneously achieve both pCODR goals. Underscoring this point is the fact that some provinces maintain their own cancer advisory bodies to provide province-specific cancer drug reimbursement advice. For example, Ontario has recently established the Ontario Steering Committee for Cancer Drug Programs. Noting that “there remains a need to obtain arms-length cancer-specific policy and program advice to support Ontario’s cancer drug reimbursement programs and processes”, this steering committee will, among other things, provide guidance on Ontario-specific cancer drug funding policies and decisions.[11] Finally, there is a fundamental paradox associated with striving for consistency across Canada in the public reimbursement of cancer drugs given that Quebec, which represents approximately 24% of the Canadian population, does not participate in the pCODR process.[12]

A potential criticism of our arguments may be that we have misinterpreted the goal of improving access to a more consistent standard of care across Canada.[5] However, we suggest that our interpretation (i.e. that the goal is aimed at having the same cancer drugs reimbursed across Canadian provinces) is not outside the realm of what might be intended

by the pCODR (or outside the realm of how drug plan decision-makers might interpret this goal) for two reasons. First, the pCODR is responsible for making recommendations regarding which drugs should be reimbursed on the provincial drug plans (which supports our illustrative assumption that the goal is related to drugs and not other treatment modalities). Second, variation across provinces in cancer drug reimbursement was cited as a reason for the establishment of the JODR (which ultimately evolved into the pCODR), supporting our illustrative assumption that the pCODR's goal is aimed at having the same drugs reimbursed across all provinces.[13] Our assumptions notwithstanding, if there is another intended definition and operationalization of this goal, it is incumbent upon the pCODR to state this clearly and transparently. Arguments that we have misinterpreted the goal simply serve to underscore the challenges we have highlighted in this paper about how to interpret the goal in order to allocate resources in a way that best achieves the goal.

Another possible criticism of the arguments we have laid out in this paper may be that we are incorrect in inferring that the pCODR has an underlying goal of maximizing health benefits with available resources. We suggest that, even without this goal being explicitly stated, maximizing health benefits with available resources is an implied goal that underpins the pCODR's work. This is because the pCODR uses CEA as a key component of its reimbursement review process and, as noted in the CEA methodology literature, the underlying premise of CEA is that the goal of society or society's decision-

makers is to maximize the total aggregate health benefit conferred to the population for a given level of resources.[1,2,3,4]

Although we use the pCODR as a reference point in this paper, the pCODR is not the first or only agency to have a goal related to having a more consistent standard of care nationally alongside a goal of maximizing health benefits with available resources. For example, when NICE first started conducting assessments (called ‘technology appraisals’) to guide the National Health Service (NHS) and local health authorities on which medicines and treatments should be publicly reimbursed its goals included “...maximizing the health gain from the use of NHS resources...” and “...to remove unfairness in the availability of technologies in different localities and to minimize the possibility of further examples of unfairness or inequity being introduced.”[15] The NHS also notes that “NICE's technology appraisals programme is designed to ensure that people across England and Wales have equal access to new and existing medicines that are deemed clinically and cost effective, reducing the risk of a postcode lottery of care.”[16] Therefore, the challenges we highlight in this paper are relevant not only for the pCODR but also for other drug reimbursement review agencies (and their respective stakeholders) that are (or are considering) striving to achieve both of these goals simultaneously. There may also be healthcare initiatives outside the realm of drug reimbursement where a goal of achieving national consistency is sought. Given that maximizing health benefits with available resources is a frequently cited goal for healthcare systems, the challenges of striving to simultaneously achieve both goals would

similarly apply. Finally, these challenges would be even more complex in scenarios where decision-makers try to simultaneously achieve more than two goals that, if they are to be achieved, influence the allocation of scarce resources.

6. CONCLUSION

In this paper we highlight some of the challenges associated with striving to simultaneously achieve the pCODR's goals of maximizing health benefits with available resources and improving access to a more consistent standard of care across Canada. In addition to the challenges related to the definitional clarity of the consistency goal, we suggest that it will likely not be possible to simultaneously achieve both goals across all provinces to the same extent that each goal can be achieved alone with the same available resources. Therefore, if the pCODR and the provincial drug plan decision-makers it supports want to strive for both of these goals simultaneously, they need to prioritize the goals and explicitly identify the tradeoffs associated with the prioritization. This will ensure that the consequences of striving to simultaneously achieve both goals are made explicit, transparent and predictable for provincial drug plan decision-makers, physicians, patients, caregivers and society as a whole.

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CHAPTER 5

CONCLUSION

Reimbursement of pharmaceuticals is a subject of increasing interest and controversy, both in Canada and in other countries around the world. One of the more controversial topics within this area is the reimbursement of cancer drugs. As noted by Mittmann et al (2009), “there has been a great deal of discussion within the health technology assessment community about whether cancer should be treated as a special case, which implies that the agents used to treat cancer need to be evaluated differently from other health care technologies.” In Canada, cancer drugs are now treated separately from drugs in other disease areas for resource allocation purposes. This separate treatment occurred through the creation of the Joint Oncology Drug Review (JODR), which ultimately evolved into what is now known as the pan-Canadian Oncology Drug Review (pCODR). The pCODR assesses the clinical evidence and cost-effectiveness of new cancer drugs and uses this information to make recommendations to the provinces and territories (referred to from this point on as “provinces” for simplicity) to guide their cancer drug funding decisions (pCODR, n.d.a).

This thesis, composed of three separate papers, appraised: the rationale for the JODR/pCODR’s establishment, the JODR/pCODR’s resource allocation goals, and the JODR/pCODR’s decision-making criteria (i.e. the specific criteria used to evaluate a drug) and decision rules (i.e. the how the decision-making criteria are combined in order

to make a reimbursement recommendation). The overarching theme linking my three thesis papers is whether the JODR/pCODR facilitates achievement of a goal of maximizing health benefits with available resources at the Canadian provincial drug plan level.

The first paper in this thesis (Paper 1) investigated whether a justification that is derived from an economic perspective has been provided for cancer drugs to be treated separately from drugs in other disease areas for resource allocation purposes. As explained in the Introduction section of this thesis, Paper 1 focused on the JODR because the pCODR was not yet in existence when Paper 1 was written. Furthermore, while the JODR ultimately evolved into the pCODR, I expected that a rationale for the separation of cancer drugs (even if not derived from an economic perspective¹) would have been provided by the JODR since it was the first incarnation of a national, cancer specific drug reimbursement review body in Canada. I demonstrated in Paper 1 that, while some reasons were given by the JODR for its establishment (such as “differences in structures and processes for the review and approval of oncology drugs” (Koester, 2008) and “variation in pharmaco-economic submission requirements and expectations for manufacturers” (Koester, 2008) the JODR did not provide a rationale for the separate treatment of cancer drugs that is derived from an economic perspective. Similarly, an economically derived rationale for the separation of cancer drugs from drugs in other disease areas for resource

¹ In Paper 1 I included all rationales given for cancer drugs to be treated separately from drugs in other disease areas for resource allocation purposes and then appraised whether any were consistent with an economic perspective.

allocation purposes was not provided in the peer-reviewed literature or by another country. I then highlighted that, from an economic perspective, separating cancer drugs from drugs in all other disease areas for resource allocation purposes is likely to impede Canada's provincial drug plans' ability to achieve a goal of maximizing health benefits with available resources. This is because separating cancer drugs prevents drug reimbursement review committees from evaluating cancer drugs within the context of all possible uses of the available drug budget. Consequently, it interferes with decision-makers' ability to determine what drugs (from among all possible drug options) will, if reimbursed, confer the maximum aggregate health benefits for the population. This is discussed in further detail in Paper 1.

Even if separating cancer drugs from drugs in all other disease areas didn't interfere with provinces' ability to achieve a goal of maximizing health benefits with available resources, there are factors related to the functioning of the JODR/pCODR itself (i.e. decision-making criteria and decision rules; the existence of additional, simultaneous goals) that will influence whether the JODR/pCODR can facilitate achievement of this goal. These factors are addressed in Papers 2 and 3.

In Paper 2 I appraised the transparency of and consistency among the JODR's resource allocation goals, decision-making criteria and decision rules, using an economic perspective. I first demonstrated in this paper that one of the JODR's goals appeared to be clearly stated (i.e. supporting a more consistent standard of therapy), but this goal was

not clearly defined or operationalized. Another JODR goal (i.e. maximizing health benefits with available resources) was not clearly stated but could be clearly inferred based on the JODR's use of cost-effectiveness analysis (CEA). Because the JODR's consistency goal was not clearly defined or operationalized, I focused for the remainder of Paper 2 on the JODR's decision-making criteria, decision rules and recommendations as they related to the goal of maximizing health benefits with available resources. As relates to this goal, the JODR did not clearly state, define or operationalize its decision-making criteria or decision rules and, even after a review of all of the JODR's published recommendations, I was not able to clearly infer them. Nonetheless, I was still able to deduce (based on the information that the JODR used when making a reimbursement recommendation) that the JODR had insufficient information to make reimbursement recommendations that were consistent with achieving a goal of maximizing health benefits with available resources. There are two reasons for this. First, the JODR used incremental cost-effectiveness ratios (ICERs) to guide its reimbursement recommendations. However, there are a number of limitations to using ICERs to determine which drugs should be reimbursed in order to maximize health benefits with available resources. For example, the conditions that must be met in order to use ICERs in a way that will lead to maximization of health benefits with available resources (i.e. conditions of perfect divisibility and constant returns to scale²) are in fact not met in most

² Under a scenario of constant returns to scale, the benefit derived from an intervention per dollar spent is constant, regardless of how many units are purchased. For example, if one mammogram test provides 10 units of benefit, then one-tenth of a mammogram test will provide 1 unit of benefit and 10 tests will provide 100 units of benefit. The condition of perfect divisibility requires that it be possible to purchase all interventions in incremental units (e.g. that it be possible to purchase one-tenth of a mammogram test).

(if not all) decision-making settings (including the JODR/pCODR setting) (Birch & Gafni, 2006; Birch & Gafni, 1993). A full description of the limitations of using ICERs to achieve a goal of maximizing health benefits with available resources is provided in Paper 2. Second, the JODR did not appear to consider the opportunity cost of reimbursing a new drug when making their reimbursement recommendations. However, if the goal is to maximize health benefits with available resources, then a new drug should only be reimbursed if the total health benefits that are gained in reimbursing the new drug exceed the total health benefits that will be foregone (i.e. the opportunity cost) as a result of discontinuing currently-funded activities in order to pay for the new drug. As described in my thesis Introduction, the pCODR's role, guiding principles, and goals are identical to those of the JODR. Therefore, appraising the JODR using the questions posed in Paper 2 provided an opportunity to offer recommendations to the newly formed pCODR.

The third paper in this thesis (Paper 3) explored, using an economic perspective, the challenges associated with striving to simultaneously achieve the pCODR's goals of maximizing health benefits with available resources and improving access to a more consistent standard of care across Canada. The first challenge for Canada's drug plan decision-makers (i.e. the provincial drug plans) concerns how to interpret the goals in order to determine how resources should be allocated to achieve each goal. As discussed in Paper 3, there are a number of questions that can be raised about the meaning of the pCODR's goal of striving to improve access to a more consistent standard of care across

Canada. This creates uncertainty for drug plan decision-makers because different interpretations of the goal can have different implications in terms how resources should be allocated in order to achieve the goal. The second challenge for provincial drug plan decision-makers is that, for any given pCODR-recommended drug, it will likely not be possible to simultaneously achieve both of the pCODR goals across all provinces to the same extent that each goal could have been achieved alone with the same available resources. I suggested in this paper that, if the pCODR and the provincial drug plan decision-makers it supports want to strive to achieve both of these goals simultaneously, they need to prioritise the goals and explicitly identify the tradeoffs associated with the prioritization (i.e. the reduction in the extent to which one or both goals can be achieved relative to what could have been achieved for each goal alone with the same available resources). This will ensure that the consequences of striving to simultaneously achieve both goals are made explicit, transparent and predictable for provincial drug plan decision-makers, physicians, patients, caregivers and society as a whole.

The various issues identified in this thesis suggest that the pCODR is unlikely to facilitate Canada's provincial drug plans' ability to achieve a goal of maximizing health benefits with available resources (a goal derived from an economic perspective) for several reasons. First, the very existence of the pCODR prevents decision-makers from evaluating cancer drugs within the context of all possible uses of available drug budget resources. This separation of one disease area from all others for resource allocation purposes is likely to compromise drug plan decision-makers' ability to achieve a goal of

maximizing health benefits with available resources. Second, the information that is used by the pCODR to make reimbursement recommendations (i.e. the ICERs for new drugs, but not the opportunity cost of reimbursing new drugs) is insufficient for the purposes of achieving this same goal. Third, the pCODR's adoption of a second resource allocation goal (i.e. improving access to a more consistent standard of care across Canada) adds another potential impediment to Canada's provincial drug plans' ability to maximize health benefits with available resources (if both of these goals are striven for simultaneously and depending on how the goals are prioritized).

Some may argue that an economic perspective is not an appropriate perspective through which to address the questions and issues raised in this thesis. However, as described in the Introduction to this thesis, I suggest that an economic perspective is an appropriate perspective to use. First, the very nature of the task with which the JODR/pCODR and provincial drug plan decision-makers are involved (i.e. determining which drugs to fund with the available provincial drug budget dollars) is one of allocating scarce resources, and economics is a discipline that studies how to allocate scarce resources in order to best achieve the goals stated by decision makers. Second, the three fundamental concepts upon which economics is based - scarcity, choices and opportunity cost - are relevant to the provincial resource allocation task that the JODR/pCODR recommendations are intended to guide. Due to resource scarcity (i.e. because there are a limited number of drug budget dollars available), provinces must make choices regarding which drugs to publicly reimburse. These choices are associated with opportunity costs: by choosing to

spend drug budget dollars on reimbursing certain drugs, the provinces forego the opportunity to use these drug budget dollars to reimburse any other drugs. Third, the JODR (initially) and pCODR (presently) use cost-effectiveness analyses (CEA) to guide drug reimbursement recommendations. Cost effectiveness analysis is an economic tool that can be used to determine whether allocating resources in a particular way advances the goal of maximizing health benefits with available resources. By using CEA as a key component of its reimbursement review, the JODR/pCODR has implicitly embraced an economic approach to guiding its resource allocation recommendations. Fourth, in the ‘Frequently Asked Questions’ section of the pCODR website, it is stated that: “The pCODR process also ensures that scarce health-care resources are used to fund the most effective cancer drugs” (pCODR, n.d.b). This statement is consistent with the economic perspective, because it recognizes that resources are scarce and that choices need to be made regarding how to allocate resources (i.e. regarding which drugs to fund). As such, I suggest that an economic perspective is an appropriate lens through which to investigate the JODR/pCODR.

Another possible criticism of this thesis is that I have incorrectly assumed that the JODR/pCODR has an underlying goal of maximizing health benefits with available resources. I suggest that, even without this goal being explicitly stated, maximizing health benefits with available resources is an implied goal that underpins the work of the JODR/pCODR. This is because, as noted above, the JODR/pCODR uses CEA as a key component of its reimbursement review process, and the underlying premise of CEA is

that the goal of society or society's decision-makers is to maximize the total aggregate health benefit conferred to the population for a given level of resources (Gafni & Birch, 2006; Gold et al, 1996; NICE, 2004; Weinstein & Stason, 1977).

Some might also argue that the pCODR has additional goals that I have not taken into consideration in this thesis. However, if there are other goals, it is incumbent upon the pCODR to be specific and transparent about what these goals are and how they are to be operationalized. Furthermore, the existence of any additional pCODR goals would make the challenges I described in Paper 3 regarding simultaneously striving to achieve multiple resource allocation goals even more complex, and would further strengthen the argument that the pCODR is unlikely to facilitate provincial drug plans' ability to achieve a goal of maximizing health benefits with available resources.

Based on the issues laid out in this thesis I make a number of recommendations below.

These recommendations are relevant not only for the pCODR, but also for other publicly funded organizations (referred to as 'agencies' below) responsible for making drug funding recommendations and/or decisions. My recommendations are as follows:

1. If maximizing health benefits with available resources is the goal, then separate treatment should not be given to drugs in any particular disease area.

2. Regarding the information used to determine whether a drug should be reimbursed, and if the goal is to maximize health benefits with available resources:
 - a. The practice of using ICERs to guide resource allocation decision-making should be re-evaluated given the theoretical and practical limitations of this approach.
 - b. What payers have to give up in order to reimburse a new drug (i.e. the opportunity cost of reimbursing a new drug) needs to be incorporated into the agency's evaluation framework in order to determine whether the health benefits that will be gained by reimbursing a new drug will exceed the health benefits that have to be foregone in order to free up enough resources to reimburse the new drug.

3. In most cases it will not be possible to simultaneously achieve the goals of maximizing health benefits with available resources and improving access to a more consistent standard of care nationally to the same extent that each goal could have been achieved alone with the same available resources (i.e. tradeoffs will be incurred in the extent to which one or both of the goals can be achieved). Therefore, if an agency is striving for these two goals simultaneously, then they need to prioritize the goals and clearly identify the tradeoffs associated with this prioritization. This will ensure that the consequences of striving to

simultaneously achieve both goals are made explicit, transparent and predictable for stakeholders.

I recognize that there may have been historical reasons for the establishment in Canada of a separate organization to make resource allocation recommendations solely for cancer drugs. The reimbursement of cancer drugs admittedly poses significant challenges for drug plans, both in Canada and internationally. This is because there has been a rapid emergence of new drugs to treat various forms of cancer, many of these drugs are associated with a high cost and there is a high prevalence of cancer in Canada and around the world. In addition, due to the increase in early detection for some forms of cancer, cancer is increasingly becoming a chronic disease. While proposing a solution to the challenges described above is beyond the scope of this thesis, all of these factors create the potential for cancer drugs to pose a significant financial burden to public drug budgets. In my thesis I have illustrated some of the problems associated with Canada's current approach to helping provinces manage the cancer drug reimbursement challenges described above (i.e. the approach of having the pCODR make reimbursement recommendations for cancer drugs). I hope that the points raised in my thesis will encourage further debate regarding the strengths and limitations of the pCODR and of other possible approaches for managing the public reimbursement of cancer drugs.

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