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Comparing assessment frameworks for cancer drugs between Canada and Europe: What can we learn from the differences?

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ABSTRACT

The increasing burden of costs associated with novel cancer therapies is becoming untenable. In Europe and Canada, assessment frameworks have been developed to attribute value to novel therapies and ultimately facilitate access to cancer drug funding. A review of the two frameworks has not previously been undertaken. This review provides insight into the relative strengths and benefits of each approach, the various perspectives of value (patient, physician and societal) and how the frameworks relate to their unique context and core principles. Both frameworks assess the clinical benefit of a new cancer therapy. The European framework considers effectiveness, quality of life, and toxicity in its determination of benefit and has the advantage of providing a simple summary score to facilitate priority setting. The Canadian framework considers other elements including cost-effectiveness, patient preferences and adoption feasibility; its deliberative framework precludes a simple summative presentation of value but can address complex and nuanced drug funding considerations with flexibility. Both frameworks have evolved to meet the needs unique to their jurisdictions and offer potentially complementary tools in the assessment of new cancer drugs. Lessons learnt in both systems can be applied to future iterations of the frameworks, which remain works in progress.

INTRODUCTION

The increasing burden of costs associated with novel cancer therapies is becoming untenable for patients and health systems alike. In Europe, the total estimated cost of cancer care reached €126 billion in 2009, with drug costs representing 27% of the total expenditure and drug costs continue to rise.¹ Moreover, the actual drug costs within European Union (EU) jurisdictions vary substantially due to differences in price setting and reimbursement mechanisms, variations in practice patterns and other factors.

In the USA, cancer drug prices have increased fivefold to 10-fold since 2000.² In

Canada, the purchase of cancer drugs has increased more than five times faster the growth in cancer incidence.³ High drug costs can limit access to novel anticancer therapies across countries,⁴ prevent individual patients from receiving effective options or only enable such access under significant financial stress or bankruptcy.⁵

The European Society of Medical Oncology (ESMO) is committed to facilitating high quality, responsible and affordable care for citizens within the EU. ESMO acknowledges that the landscape for drug access is highly variable across its 28 member countries (<http://www.esmo.org/Policy/Magnitude-of-Clinical-Benefit-Scale/Presentations>). With the aim of facilitating and potentially accelerating drug funding across EU nations, ESMO created and validated a tool to enable a relative scaling of clinical benefit associated with new cancer therapies—the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS).⁶ Understanding the degree of benefit of a new therapy, relative to other anticancer options would support discussions on the relative value of the new therapeutic options. Interventions with the highest rankings are endorsed by ESMO for accelerated access across Europe. The ESMO-MCBS is a dynamic tool, open to regular revision.

In Canada, the administration and delivery of healthcare services is the responsibility of each province or territory, guided by the provisions of the Canada Health Act⁷ and with funding assistance from the federal government in the form of fiscal transfer payments to the provinces. The Act mandates that therapies provided for patients in a hospital setting be provided free of charge. However, prior to the implementation of a pan-Canadian review process, each province undertook its own

review of the evidence, which frequently led to inequities of access. As well, there continues to be considerable regional variation in public coverage for oral therapies, including oral cancer drugs.

New cancer drugs are now reviewed initially by Health Canada for their safety and efficacy in order to obtain market authorisation. Either subsequent to, or concurrent with the Health Canada review, a new drug is reviewed by the pan-Canadian Oncology Drug Review (pCODR)-housed within the Canadian Agency for Drugs and Technologies in Health-where an expert review committee (pCODR Expert Review Committee or pERC) considers clinical effectiveness, patient values, cost and cost-effectiveness and the feasibility of adoption in its deliberations. Each of these domains is explicitly discussed in a deliberative framework in making a recommendation to the provinces for funding. The pCODR process is designed to bring consistency and clarity to the assessment of cancer drugs across the country. All provinces formally participate except for the province of Quebec. pCODR recommendations are used by the individual provinces and territories to guide their own cancer drug funding decisions.

Although the European and Canadian assessments were developed within and serve unique constituencies, both contribute to the assessment of benefits and values of novel therapies and ultimately facilitate access to cancer drug funding. A review of the relative roles and features of these two frameworks has not previously been undertaken. This review provides insight into the relative strengths and benefits of each approach, the various perspectives of value (patient, physician and societal), and how the frameworks relate to their unique context and core principles.

DEVELOPMENT OF THE ESMO AND PCODR VALUE FRAMEWORKS AND DISTINGUISHING FEATURES

The ESMO-MCBS was designed to prioritise those anti-cancer therapies that offer the greatest benefit for adoption across the EU. The MCBS predominantly assesses value by determining the added benefit derived from a new therapy compared with the current standard of care. Given the tremendous variation in costs across European countries, cost considerations are not incorporated into the scale. The development of the scale was based on the premise that cure takes precedence over deferral of death, and greater value was placed on direct endpoints, such as survival and quality of life (QoL) (and disease-free survival in curable cancers) rather than on surrogate endpoints. The tool can be applied to comparative outcome studies-albeit only for patients with solid tumours. Drugs used with curative intent are evaluated separately from those used with non-curative (palliative) intent. The relative magnitude of benefit is assessed through consideration of hazard ratios for survival and progression-free survival, with threshold values for

improvement meant to reflect the views of the oncology community. Preliminary scores can be modified for major toxicity or QoL impact, leading to downgrades or upgrades.

The pCODR process is a multidimensional review of clinical benefit, patient values, cost-effectiveness and feasibility of adoption into the Canadian healthcare system. pCODR's guiding principles were developed with broad input from key stakeholders. Notably, input from the patient advocacy community was solicited and received. pCODR's mandate is to be evidence-based, ethical and considerate of the Canadian context with its multiple jurisdictions and drug funding structures.⁸ The creation of pCODR was a natural extension of pre-existing processes designed to rigorously evaluate evidence, to incorporate pharmacoeconomic evaluation and to include the patient perspective into the assessment of new cancer drugs. Cancer Care Ontario's Program in Evidence-based Care provided the model for the evidentiary review and Ontario's Ministry of Health was a leader in requiring cost-effectiveness evaluations in its evaluation of oral agents. The merger of these two processes was the foundation for the current pCODR review process that also explicitly seeks patient, care provider and payer perspectives during the review process. The intent of the pCODR process is to provide a consistent and fair review for all drug submissions received. Each drug submission follows a similar process whereby clinical and economic review teams critically appraise the medical literature and the pharmacoeconomic model provided by the submitter. The clinical review team also considers the patients' experiences with the disease and drug under review and the context in which the drug would be used within the Canadian healthcare system. Each clinical review team comprises oncologists with expertise in the specific disease site, supported by health research methodologists. Each economic review team comprises health economists, and interacts with the clinical review team to ground its analysis. To ensure the consistency and transparency of its cancer drug review process, the pCODR expert review committee applies a well-defined deliberative framework, which delineates all the elements that should be considered to formulate a funding recommendation (figure 1). The deliberative framework is used for all oncology drugs inclusive of therapies for rare (orphan) cancers or end-of-life care. In addition, the deliberative framework dictates that no single element overrides any other and that no threshold exists for any element in the review.

Both ESMO and pCODR processes assess the clinical benefit of a new cancer therapy (table 1). The ESMO-MCBS framework considers effectiveness, QoL and toxicity in its determination of benefit. The MCBS evaluation has the advantage of providing a simple summary score along a scale, which intrinsically facilitates communicating priorities to decision-makers. However, a true 'relative' value comparison between drugs may be limited

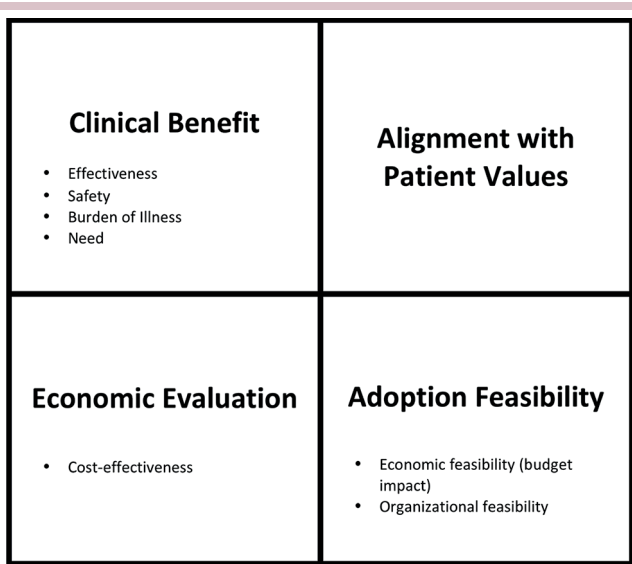


Figure 1 pan-Canadian Oncology Drug Review Expert Review Committee Deliberative Framework.

by the inability within the framework to compare the quality of studies underlying the evidence and the comparability of the study populations.

The pCODR deliberative framework explicitly elaborates on the components that represent benefit, including not only the traditional 'pillars' of effectiveness and QoL,

but also safety, burden of illness borne by society and the availability of effective alternatives. In an example of the latter consideration, the lack of alternatives for multiply-relapsed patients with acute lymphoblastic leukemia was pivotal in pCODR's recommendation to fund the monoclonal antibody, blinatumomab (https://www.cadth.ca/sites/default/files/pcodr/blinatumomab_blinicyto_all_fn_rec.pdf). Of note, the ESMO framework would not have been used to consider blinatumomab at all, as haematological malignancies are excluded from the current iteration of the framework. The reason for this exclusion of drugs for haematological conditions is presumably because the ESMO prioritisation of outcomes is not applicable or validated in the malignant haematology context.

The blinatumomab example does illustrate a degree of flexibility in the pCODR evaluation process. The framework relies on deliberative democracy to assess net clinical benefit by reviewing the clinical evidence in its totality.⁹ The evaluation of haematological-specific outcomes, the analysis of non-comparative (phase II) studies, the use of data from meta-analyses and the evaluation of multiple randomised trials are readily addressed using the pCODR deliberative process. In another example, pCODR simultaneously deliberated on both the AVEX¹⁰ and MAX¹¹ randomised trials in making its recommendation to fund the addition of bevacizumab to capecitabine for first-line

Table 1 A review of the relative roles and constructs of the pCODR and the ESMO-MCBS frameworks

Factor	pERC deliberative framework	ESMO-MCBS
Objective	To provide an outline of all the elements that should be considered by pERC during its review. pERC uses the sum of all elements to formulate a funding recommendation	To provide an objective and reproducible approach that allows comparisons of the magnitude of benefit
Sources of input	-Systematic review of clinical literature -Economic evaluation -Patient input -Jurisdictional input	-Randomised or comparative trials, meta-analyses
Target audience	-Ministries of health/cancer agencies -Clinicians -Public	-Policy-makers -Clinicians -Patients and their families
Eligible indications	Solid tumours, haematological malignancies	Solid tumours
Elements considered:		
Clinical effectiveness (including QoL)		
Safety		
Burden of illness		
Need		
Economic evaluation		
Patient values		
Implementation feasibility		X
Outcome of framework	Qualitative recommendation	Score out of 4 or 5

ESMO-MCBS, European Society of Medical Oncology-Magnitude of Clinical Benefit Scale; pCODR, pan-Canadian Oncology Drug Review; QoL, quality of life.

metastatic or advanced colorectal cancer (https://www.cadth.ca/sites/default/files/pcodr/pcodr_avastin_capecitabine_mrcr_fn_rec.pdf). In contrast, the subtle differences in the progression-free survival benefit associated with bevacizumab in the two trials and the lack of a statistically significant benefit in QoL reported in the MAX trial, resulted in the ESMO-MCBS scoring the AVEX trial at 3 and the MAX trial at 1, raising uncertainty about which score should be applied to guide a funding decision for bevacizumab.

The deliberative framework of pCODR also may allow for more detailed consideration of the clinical context of the disease. For example, the ESMO scores for the clinical benefit of nab-paclitaxel in first-line metastatic pancreatic cancer (MPACT)¹² and regorafenib for refractory metastatic colorectal cancer (CONCUR)¹³ were both 3, and the HRs for overall survival in both trials were similar (HR 0.72 and 0.55, respectively). For regorafenib in colorectal cancer, there was also a second randomised trial (CORRECT)¹⁴ with a HR of 0.77 and an ESMO score of 1. QoL was not reported for nab-paclitaxel in MPACT and was not improved with regorafenib in the CONCUR or CORRECT studies. Overall, the absolute magnitude of the overall survival benefit with both treatments was relatively small (<3 months). During pERC deliberations, the clinical contexts of both diseases were taken into consideration. Metastatic pancreatic cancer has a very poor prognosis with limited treatment options even in the first line setting, whereas metastatic colorectal cancer generally has multiple treatment options available until it becomes refractory to therapy. Considering these two different contexts, pERC concluded that it was justified to recommend funding nab-paclitaxel, conditional on cost-effectiveness being improved to an acceptable level. However, pERC did not recommend funding regorafenib.

pCODR also considers the relative gain in clinical benefit in relation to the new drug's cost based on a formal cost-effectiveness analysis. To date, numerous funding recommendations from pCODR have been contingent on the cost-effectiveness of the new agent being improved to a more acceptable level within the Canadian context. Thus, the Canadian framework is an approach to health technology assessment and value judgement. Although ESMO-MCBS highlights that the determination of value is predicated on an understanding of the magnitude of clinical benefit,⁶ its omission of drug cost and cost-effectiveness within the score emphasises that it is not on its own a 'value' framework. The value of any intervention is an implicit judgement of the trade-off in treatment choices in relation to the cost consequences of each of those choices. As a consequence, any 'value' determination in the absence of a consideration of cost may not fully assess a patient's or society's willingness-to-pay to receive the anticipated outcomes.

Patient values represent a key dimension within the Canadian framework. A formal and engaged patient input process is part of all drug evaluations. Input submitted by

patient advocacy groups (or individual patients and caregivers if an advocacy group does not exist) is presented by one of the patient members of pERC to ensure that patients' and families' real-world experiences with the cancer and its treatment are routinely considered as part of the drug review process. For example, in making a positive recommendation for the funding of ruxolitinib in myelofibrosis, (https://www.cadth.ca/sites/default/files/pcodr/pcodr_ruxolitinib_jakavi_pv_fn_rec.pdf) the committee noted that improvement in QoL and relief from splenic pain were important factors to patients.

Finally, the feasibility of drug adoption into the health system, including issues such as budget impact and drug wastage, is considered in all reviews. pCODR recommendations explicitly address issues raised by provincial representatives concerning the feasibility of implementing a positive recommendation. Recommendations are also paired with suggested 'next steps for stakeholders', wherein guidance is provided on pricing negotiations to improve cost-effectiveness, sequencing of therapies and the potential need to collect population-based evidence to guide optimal use of new therapies. Typically, when these implementation factors are not sufficiently addressed in advance of technology diffusion, the easiest approach for a health system administrator is either not to fund or to delay the implementation of the decision to fund the treatment.

DISCUSSION

The pCODR deliberative framework has evolved out of best practices from within the Canadian clinical oncology, health technology assessment and patient advocacy communities. Although it lacks the simplicity of a single summative score to represent 'value', its recommendations more closely mirror the complex and nuanced factors that contribute to drug funding considerations within Canada. In a similar way, the ESMO-MCBS has evolved to meet the needs of its own unique context serving multiple European jurisdictions, which warrants a simpler quantitative expression of benefit without consideration of costs.

Both ESMO and pCODR processes are considered works in progress. At present, pCODR seeks to further increase opportunities for feedback, in particular enhancing physician engagement by soliciting comments from the wider community of practising oncologists prior to deliberation and seeking feedback following initial recommendations. pERC has also made recommendations on occasion to collect prospective real-world data following funding. As a result, provincial cancer agencies, such as Cancer Care Ontario, are starting to develop proof-of-concept pilots to generate real-world evidence from routinely collected health administrative databases. Potential collaborations with the Canadian Centre for Applied Research in Cancer Control and the Canadian Clinical Trials Group could be leveraged for this purpose, to ensure that pCODR's recommendations, and the data on which they are based, remain sound and relevant over time. Finally, pCODR

strives to maintain consistency in its recommendations by maintaining a database of its decisions and referencing the database during its deliberations.

ESMO-MCBS could potentially assign importance to patient and physician input, burden of illness and lack of alternative therapies, to its assessment of value while maintaining a user-friendly numerical output. It currently omits drugs for haematological malignancies and it cannot be used to score value when drugs are assessed in non-randomised trials or when multi-trial comparisons are warranted. Although cost-effectiveness is not considered, the ESMO score does allow for an assessment of cost considerations at the jurisdictional level, without impacting the assessment of clinical benefit, which would remain relevant across all EU member countries. We understand that a second version of the ESMO-MCBS is forthcoming.

Though both pCODR and ESMO-MCBS frameworks were created to meet the unique needs of their constituents, lessons can be learnt from each to improve the ultimate goal of providing value and benefit to patients with cancer. In reality, the two systems are complementary, with the ESMO-MCBS providing quantitative assessments of benefit observed in individual clinical trials while the Canadian framework provides a deliberative and multi-faceted approach to health technology assessment.

Competing interests None declared.

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