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HTA

Addendum to CADTH's Guidelines for the Economic Evaluation of Health Technologies: Specific Guidance for Oncology Products

December 2009

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Addendum to CADTH's Guidelines for the Economic Evaluation of Health Technologies: Specific Guidance for Oncology Products

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While the NCIC Clinical Trials Group provided support to facilitate the process of developing this guideline, the content of the guideline represents the opinions of the participating individuals. The NCIC Clinical Trials Group receives grant support from the Canadian Cancer Society Research Institute with funds provided through donations to the Canadian Cancer Society

Stakeholders

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Industry

AstraZeneca Canada Inc.
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Other

Canadian Partnership Against Cancer

Canadian Association of Provincial Cancer Agencies

Joint Oncology Drug Review

All comments that were received from reviewers and stakeholders were considered when preparing the final report.

This report is a review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") which are available to CADTH. The accuracy of the contents of the source documentation on which this report is based is not warranted, assured, or represented in any way by CADTH and CADTH does not assume responsibility for the quality, propriety, inaccuracies, or reasonableness of any statements, information, or conclusions contained in the source documentation.

CADTH takes sole responsibility for the final form and content of this report. The statements and conclusions in this report are those of CADTH and the Oncology Guidelines Working Group and not of its panel members or reviewers.

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Contributions

All contributors of the Oncology Guidelines Working Group (OGWG) were responsible for developing the concept, content, literature review, writing, manuscript review, editing of the document, and final approval of the document.

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Conflicts of Interest

All authors declared no perceived conflict of interest regarding the development of this document. Namely, none of the authors felt that their judgments regarding the appropriate use of methods were compromised by their financial interests elsewhere. Although not specifically declared as conflicts of interest, some contributors declared work conducted with the pharmaceutical industry, being aware of sensitivities regarding these relationships and in the interest of being completely transparent, and with the intent of contributing to the rigour of these guidelines, namely:

Nicole Mittmann declared educational programs, unrestricted funding, and consultancies through the Health Outcomes and PharmacoEconomic (HOPE) Research Centre, Sunnybrook Health Sciences Centre, a group that consults to the pharmaceutical industry.

William Evans declared educational programs on pharmacoeconomics for Pfizer and Boehringer Ingelheim.

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Deborah Marshall declared that until July 2008 she worked for i3 Innovus, a global health economics and outcomes research consulting company that provides research services to a range of pharmaceutical and medical devices companies. Since July 2008, she continued to provide ad hoc consulting for i3 Innovus.

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ABBREVIATIONS

CADTH	Canadian Agency for Drugs and Technologies in Health
CAPCA	Canadian Association of Provincial Cancer Agencies
CCO	Cancer Care Ontario
CPAC	Canadian Partnership Against Cancer
DFS	disease-free survival
DSA	deterministic sensitivity analysis
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
HRQL	health-related quality of life
HYE	healthy-year equivalents
JODR	Joint Oncology Drug Review
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LYG	life-years gained
NCIC	National Cancer Institute of Canada
NICE	National Institute for Health and Clinical Excellence
OGWG	Oncology Guidelines Working Group
OS	overall survival
PFS	progression-free survival
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QoL	quality of life
Q-TWIST	quality-adjusted time without symptoms of disease and toxicity
RCT	randomized controlled trial
SEER	Surveillance, Epidemiology and End Results Program
WGEA	Working Group on Economic Analysis

TABLE OF CONTENTS

1 INTRODUCTION

The purpose of an economic evaluation is to "identify, measure, value and compare the costs and consequences of alternatives being considered" to inform "value for money" judgments about an intervention or program.[1] A high-quality economic evaluation should provide decision-makers with useful, relevant, and timely information. Evaluations should be based on rigorous analytical methods, be impartial and credible in the use of data, and be transparent for and accessible by the reader.[2]

National guidance on the conduct of resource costing and economic evaluations has been available through the Canadian Agency for Drugs and Technologies in Health (CADTH) since 1994.[2-4] CADTH's guidelines are a resource for analysts who are undertaking health technology assessments of therapeutic products. The objective of CADTH's guidelines is "to assist the "doers" of economic evaluations (i.e., analysts) to produce credible and standardized economic information that is relevant and useful to decision-makers in Canada's publicly funded health care system."

CADTH's guidelines have been updated periodically. The third edition, which is the most recent version, was published in 2006. CADTH's *Guidelines for the Economic Evaluation of Health Technologies* sets the standards for the conduct and reporting of high-quality economic evaluations that can be used by decision-makers for public policy decisions.[2] For those performing economic analyses, CADTH's *Guidelines for the Economic Evaluation of Health Technologies* provide clear and practical guidance of a high standard on the preferred methods for the conduct of credible economic analyses. CADTH's guidelines also provide advice on how to resolve methodological issues while allowing sufficient flexibility in the application of methods given the variable quality of the clinical evidence.

The need for evidence about the value for money of new health technologies is not new or specific to any disease. In 1985, Ontario was among the first jurisdictions to require information on the cost-effectiveness of oral drugs in submissions to its Drug Benefit Program.[5]

More recently, this requirement for cost-effectiveness analysis has been extended to intravenous anticancer drugs, as a result of the integration of the Ontario Drug Benefit Program and Cancer Care Ontario (CCO) drug review and approval processes.[6] The Ontario approach combines a rigorous evaluation of the clinical evidence as synthesized by CCO's Program in Evidence-based Care, with the requirement for economic evaluation of the cost-effectiveness of the new anticancer agent. Building on this approach, the interim Joint Oncology Drug Review (JODR) process, an initiative to provide a common platform for oncology drug recommendations for all Canadian provinces except Québec, also requires an economic evaluation in addition to the evidence of clinical benefit.[6]

1.1 Cancer as "Special" Case

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.

Cancer is responsible for a large burden of illness in Canada and its incidence and prevalence continue to increase each year. In 2008, it was estimated that there were 166,400 Canadians newly diagnosed with cancer and approximately 73,800 related deaths.[7] The incidence of cancer in Canada has been increasing by approximately 2.5% per year, while prevalence has been rising at a faster rate, which is estimated to be 6% per year. The growing burden of cancer has stimulated research into the underlying causes of cancer and the biological changes associated with the malignant process. The increasing knowledge about the biology of cancer at the molecular level has led to the discovery of new therapeutic interventions and new drugs for the treatment of cancer. Most of these new drugs and therapies are very expensive and confer modest clinical benefits.

The burden of cancer, the cost of new anticancer therapies, or the magnitude of benefit that these new therapies confer do not justify a "special case" status for cancer. Similar arguments could be made for other common diseases that affect Canadians; for example, diabetes, cardiovascular disease, arthritis, and HIV infection.

Specific challenges are often encountered during a cancer-related health technology assessment. These challenges include the choice of what outcome to use (e.g., overall survival [OS] versus other measures of disease control, such as progression-free survival); the best method to estimate survival gain (e.g., mean survival, median survival, area under the curve); the time horizon to use, especially because most clinical trials report early results; what toxicities to include in the resource utilization data (e.g., mild versus severe); and what perspective to take (e.g., the perspective of the payer in a publicly funded federal/provincial/territorial health care system versus a societal perspective).

Furthermore, in oncology, the clinical evidence varies in type and in quality (e.g., randomized clinical trial, cross-over studies, non-comparative studies) depending on the type of cancer, stage, and prior therapies. This can introduce heterogeneity and uncertainty into subsequent health technology assessments.

Current general pharmacoeconomic guidelines do not provide sufficient direction to ensure a consistent approach to the conduct of economic analyses in oncology technology assessment. The decision to develop a guidance document was based on the observed heterogeneity and quality of the analyses in oncology submissions to decision-making bodies where some of these economic analyses have been conducted in an inappropriate or misleading fashion.

1.2 Addendum Goal

This oncology-specific guideline should be considered a companion document to CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition). Its goal is to provide more specific guidance to analysts on the methods for the conduct of high-quality economic evaluations in oncology using CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition)[2] as a frame of reference. CADTH's *Guidelines for the Economic Evaluation of Health Technologies* already defines the parameters that are required for good health technology assessments (e.g., time horizon, population, perspective, modelling).

Not only does this oncology-specific document focus on guidance for the conduct of technology assessment specific to cancer, it also provides guidance on what may be considered acceptable when gold standard methods cannot be used for justifiable reasons.

The oncology-specific guidance in this document is intended to promote the consistent conduct of health technology evaluations of new oncology products. This, in turn, is intended to assist decision-makers in their work. Performing analyses in a standard, clear manner that is useful to those who make recommendations on whether to approve public funding for new cancer therapies is also intended to assure Canadians that there is a fair, high-quality evidentiary basis for decision-making.

It is not the goal of this guideline document to update the methods and content of the current (third edition) of the CADTH guideline document. Any updates to that document will be addressed during the next revision of the CADTH document.

This guideline document also does not provide advice to decision-makers on such issues as threshold values or the decision-making framework (e.g., ethics, social values) that is needed to make drug approval decisions.

1.3 Addendum Audience

The primary audience for this oncology-specific document consists of economists and health service researchers in the public and private sectors who conduct economic evaluations.

A secondary audience consists of the consumers of economic evaluations. This audience includes Canadian decision- and policy-makers who make funding decisions about health technologies. This group includes health policy advisors in the federal/provincial/territorial Ministries of Health, members of the Common Drug Review and the interim JODR expert panels, and those working in jurisdictional drug plans, regional health authorities, hospitals, and other health care facilities. In addition, academics, medical specialist groups, health care providers, patients, patient advocacy groups, manufacturers, media, and the general public will also have an interest in these oncology-specific guidelines.[2]

2 METHODS

The work to produce this oncology-specific document was undertaken between 2006 and 2009. Members of the NCIC Clinical Trials Group (NCIC CTG) Working Group on Economic Analysis (WGEA) recognized the value of providing guidance on the conduct of high-quality economic evaluations. NCIC Clinical Trials Group facilitated and provided initial funding for the WGEA to develop an expanded committee to produce this oncology-specific document. A Memorandum of Understanding outlining a collaborative process to develop an oncology-specific document was established with CADTH. Subsequently, the oncology-specific guidelines were developed independently of the NCIC Clinical Trials Group WGEA by a working group of experts in health economics, oncology, and health care administration (15 members) or designated Oncology Guidelines Working Group (OGWG) members.

A facilitated workshop was used to start the development of this oncology-specific document. During the workshop, OGWG members identified the chapters of CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) that could benefit from oncology-specific guidance or methods. These chapters included Target Population; Perspective; Time Horizon; Comparator; Effectiveness; Modelling; Valuing Outcomes; Costs and Resources; Variability/Uncertainty; and Equity.

OGWG members indicated that no oncology-specific guidance was needed for the following chapters: Study Question; Type of Evaluation; Reporting; Generalizability; and Discounting.

Literature searches were conducted by CADTH and OGWG members to find relevant articles on the topics that could be augmented by oncology-specific guidance, including surrogate and intermediate outcomes, oncology economic evaluations, equity issues, and sensitivity analyses. Search strategies were prepared and run by both CADTH Information Specialists with input from OGWG members and independently by OGWG membership. The results of the literature searches were used to inform the recommendations of the guideline document.

The following bibliographic databases were included in the search in Ovid: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, The Cochrane Library databases, and the NHS Economic Evaluation Database (NHS EED). OVID AutoAlerts were set up to send any new literature. Grey literature was identified by searching the websites of health technology assessment and related agencies, professional associations, and other specialized databases. Google and other internet search engines were used to search for additional information. Articles identified through the search strategies were reviewed by the health economist and oncologist leads for the assigned chapters of document. The literature search strategies are available upon request from CADTH.

The guideline document was created over 29 review cycles, two in-person meetings, and five teleconferences.

The oncology-specific document then entered CADTH's review cycle, which was conducted over four phases, as follows:

Phase 1

In phase 1, there was a one-week internal CADTH review.

Phase 2

In phase 2, there was a formal blinded review by academic Canadian and international experts in health economics and oncology from a technical perspective (e.g., internal validity and basis in theory) over two to three weeks. Reviewers' comments were discussed during a teleconference with working group members. Updated documents were distributed to working group members twice in one month. Reviewers' comments were addressed, and an updated version of the oncology-specific document was sent to CADTH in December of 2008.

Phase 3

In phase 3, there was a formal blinded review by government decision-makers (interim JODR, Canadian Association of Provincial Cancer Agencies [CAPCA]), pharmaceutical industry members, and the Canadian Partnership Against Cancer (CPAC) to assess relevance and feasibility of implementation over a four-week time horizon. Their comments were addressed over a month. The oncology-specific document was sent to CADTH in April of 2009. CADTH conducted an internal editorial and content review. Comments were distributed to the working group in May and June 2009 for feedback.

Phase 4

In phase 4, the oncology-specific document was sent to CADTH's quality advisors for review. During this process, the completeness of the responses to the reviewers' comments was examined. The document also underwent an editorial review.

3 DOCUMENT STRUCTURE

3.1 Hierarchical Approach to Evidence

A hierarchical approach to evidence was used in this oncology-specific document. This document recommends that the highest-quality evidence be used in the conduct of health technology assessments for oncology interventions in accordance with CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition). It is essential that the analyst use accepted methods in the conduct of technology assessments in oncology. Acceptable methods can be found in CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) and other sources.[8]

The OGWG understood that there are instances when ideal methods cannot be applied to economic evaluations of oncology treatments (e.g., when there is a lack of randomized clinical trial information), because the highest level of evidence is unavailable. This oncology-specific document provides guidance on exceptions and alternatives that may be considered when conducting economic evaluations under such circumstances. Justification for the use of these exceptions or alternative methods must be given. Examples of alternatives and exceptions are provided.

3.2 Presentation

This oncology-specific document is a companion to CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition). The aforementioned *Guidelines* document includes complete guidance in those chapters, with well-defined recommendations that are appropriate for oncology economic evaluations. These chapters are Study Question, Type of Evaluation, Reporting, Generalizability, and Discounting.

The remaining chapters of CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) provide general guidance for the conduct of health technology assessments. These chapters need additional specific commentary on the optimal conduct of cancer-related health technology assessments. For these chapters, the guideline statement from

CADTH's *Guidelines* document is presented first (grey text), followed by oncology-specific guidance. In some instances, oncology-specific examples are provided to clarify the oncology-specific guidance statement.

4 CADTH GUIDELINE STATEMENTS AND ONCOLOGY GUIDANCE

4.1 Study Question

4.1.1 State the study question to be addressed by the evaluation. The question should be well-defined, stated in an answerable form, and relevant to the decision facing the target audience. Relevant and related secondary questions should be included (e.g., the impact of the intervention on subgroups).

4.1.2 Define the patients or population, intervention, and comparators relevant to the study question. The primary perspective of the study may also be stated in the question.

4.1.3 Identify the target audience for the study. Secondary audiences may also be listed.

Oncology Guidance

The recommendations in CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) are sufficient for the conduct of oncology technology assessments. No further guidance is needed for oncology products. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement.

4.2 Types of Evaluations

4.2.1 State and justify the type(s) of economic evaluation chosen. Select the appropriate type of evaluation based on the nature of the research question, the condition of interest, and the availability of data on outcomes.

4.2.2 In the denominator of the incremental cost-effectiveness ratio (ICER), use a valid outcome measure that is most important to the health of the patient (i.e., important patient outcome).

4.2.3 Use a cost-utility analysis (CUA) as the Reference Case where meaningful differences in health-related quality of life (HRQL) between the intervention and comparators have been demonstrated.

4.2.4 Use a cost-effectiveness analysis (CEA) as the Reference Case when a CUA is an inappropriate choice. Use a final outcome (e.g., life-years gained), or if that is impossible, an important patient outcome. Only use a surrogate outcome if it has a well-established link (i.e., validated) with one of those outcomes. Consider a CEA as a secondary analysis when the use of one important patient outcome measure [other than a quality-adjusted life-year (QALY) gained] in the

denominator of the ICER can be justified, provided that there is a meaningful difference in such an outcome.

4.2.5 A cost-minimization analysis (CMA) is appropriate as the Reference Case when the evidence shows that the important patient outcomes of the intervention and comparators are essentially equivalent. Provide justification for conducting a CMA.

4.2.6 A cost-benefit analysis (CBA) may be useful in some situations, but generally, it should be considered as a secondary analysis. Explain all the steps taken to convert outcomes into monetary values, and analyze key assumptions using a sensitivity analysis.

4.2.7 A cost-consequence analysis (CCA) is generally not expected to be used as the Reference Case, unless a CEA or a CUA are inappropriate to use. To enhance reporting transparency, use a CCA as an intermediate step in reporting the other types of economic evaluations.

Oncology Guidance

The recommendations in CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) are sufficient for the conduct of oncology technology assessments. No further guidance is needed for oncology products. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement.

4.3 Target Population

4.3.1 Specify the target population(s) for the intervention and its expected use.

Oncology Guidance

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) provides sound and relevant recommendations on target populations in technology assessments. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement. The OGWG recommended that additional guidance on the details of the target populations for oncology-specific technology assessments be provided in this section.

In oncology, patients are characterized in several ways. Common population characteristics in oncology include tumour type (e.g., lung, breast), stage of disease (e.g., International Union Against Cancer/American Joint Committee on Cancer, stages I to IV), performance status (e.g., Eastern Cooperative Oncology Group [ECOG], Karnofsky),[9,10] relevant molecular markers (e.g., estrogen receptor, epidermal growth factor receptor [EGFR], V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog [KRAS]), prior treatments (e.g., surgery, radiotherapy, chemotherapy), line of chemotherapy (e.g., first-line, second-line), prior response to treatment (e.g., responder or non-responder), prior adjuvant therapy, risk classification schema of multiple variables, genomic markers, and genotype. The absence of a clear and detailed description of relevant patient characteristics in an oncology technology assessment would be unacceptable by this guideline's standards.

Recommendation

Provide all relevant oncology-specific patient characteristics with a clear and detailed description of the target population.

Examples:

- Women with operable axillary lymph-node-positive breast cancer who have undergone unilateral surgery.
- Patients with stage IV chemotherapy–refractory colorectal cancer going on to third-line or salvage treatment.

4.3.2 Perform the analysis for the entire target population that is specified in the study question. This may include the population representing the majority or all of its expected use. The efficacy-effectiveness data used in the analysis should be relevant to the target population in the analysis.

Oncology Guidance

The recommendations in CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) are sufficient for the conduct of oncology technology assessments. No further guidance is needed for oncology products. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement.

4.3.3 Conduct stratified analysis of smaller, more homogeneous subgroups, where appropriate, if there is variability (heterogeneity) in the target population.

Oncology Guidance

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) provides sound and relevant general recommendations on subgroups in technology assessments. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement. The OGWG recommended that additional guidance on the details of subgroups for oncology-specific technology assessments be provided in this section.

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) recommends the conduct of analyses for smaller, more homogeneous subgroups if there is variability or heterogeneity in the larger target population.

In oncology, there are subgroups associated with each disease site. Examples of common and relevant subgroup categories in oncology include stage of disease, performance status (e.g., ECOG, Karnofsky),[9,10] relevant molecular markers (e.g., estrogen receptor, human epidermal growth factor receptor 2 or Her2/neu, EGFR, KRAS), prior treatments (e.g., surgery, radiotherapy, chemotherapy), line of chemotherapy (e.g., first-line, second-line), prior response to treatment (e.g., responder or non-responder), prior adjunctive therapy, and risk classification schema of multiple variables.

Data sources for subgroup analyses may be subgroups that are specified in the trial *a priori*, or if the subgroup is of interest, via post hoc analyses.

Recommendation

Provide analyses for relevant subgroups that are specified a priori or for subgroups of interest, via post hoc analyses. Examples of common subgroup categories include tumour type, stage of disease, performance status, relevant molecular markers, prior treatments, line of chemotherapy, prior response to treatment, and prior adjuvant therapy.

Examples:

- Node-positive versus node-negative patients
- KRAS mutation status.

4.3.4 Analysts are encouraged to analyze situations where it is anticipated that there will be inappropriate, suboptimal, or unintended use of the intervention.

Oncology Guidance

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) provides sound and relevant general recommendations on the differential utilization of new health technologies. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement. The OGWG recommended that additional guidance on the differential utilization of oncology-specific technologies and their assessment be provided in this section.

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) encourages analysts to analyze situations where it is anticipated that there will be inappropriate, suboptimal, or unintended use of the intervention.

In oncology, although current treatments are approved for specific indications through national or provincial mechanisms, there is off-label use of oncology agents.[11-13] Off-label use commonly refers to use for unapproved indications. It should be obvious that the clinical data from a trial in breast cancer cannot be used as a substitute for clinical data in a lung cancer population, nor can incremental cost-effectiveness ratios that are estimated for one indication (such as breast cancer) be directly applied to other indications (such as lung cancer). Off-label use can also mean the use of a product in a setting that may not match precisely the clinical trial setting. Off-label use in oncology typically refers to the use of the product in a different phase of treatment (the benefit is demonstrated as second-line therapy in a clinical trial, but the therapy is being offered as first-line therapy) or using comparator data that does not precisely match clinical trial comparators in the same disease site. Alternatively, clinical trial data may not align with the expected clinical use of the intervention in the real world in terms of comparators or combination therapy. An example might be erlotinib in advanced non-small cell lung cancer after failure of first- and second-line chemotherapy, which demonstrated benefit in a placebo-controlled trial. An analysis claiming that second-line chemotherapy is an appropriate comparator would be inappropriate.

Recommendation

In the Reference Case, analysts may be required to extrapolate beyond the randomized controlled trial (RCT) population to other indications or populations. This may be important when practice may include usage in other populations, in a different place in a sequence of therapy, or in combination with agents other than those studied in RCTs.

4.4 Comparators

4.4.1 Relate the choice of comparators to the study population, and the local context or practice in which the decision is being made. In principle, consider all technically feasible, acceptable, and relevant alternatives as potential comparators. Then, select the appropriate comparators. Describe and justify the comparators that are chosen for evaluation, and justify those that are not chosen.

4.4.2 In the Reference Case, use "usual care" (i.e., the most common or frequently used care) which the intervention is intended to replace. In some cases, "usual care" may include more than one relevant, widely used alternative for the same indication.

4.4.3 Consideration should be given to the following when choosing comparators:

- **a) Add "recommended care" as a comparator when usual care does not reflect appropriate (high-quality) care. It can be regarded as the first choice in practice or care, as recommended in clinical practice guidelines.**
- **b) Where the alternatives are different treatment strategies, distinguish between situations where the intervention is an additional element in the strategy, a different treatment sequence, or a distinct alternative that could replace another element in the treatment strategy. Comparators may be alternative packages of care that consist of many elements. Analyze each strategy separately and explain the alternatives.**
- **c) At times, it may be prudent to analyze the entry of future comparators, including the anticipated entry of lower cost technologies (e.g., generic drugs).**
- **d) For drugs, the alternative agents listed in a formulary may be the most relevant, although those that are not listed should not be excluded. The comparators should include the lowest cost available alternative that is often used for the same indication. Include the cost of the drug and any drug administration costs. Dosing regimens used in the analysis should reflect the dose and duration supporting the effectiveness data for the agent.**

Oncology Guidance

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) provides sound and relevant general recommendations on comparators in technology assessments. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement. The OGWG recommended that additional guidance on the details of comparators for oncology-specific technology assessments be provided in this section.

In oncology, the choice of a comparator is complex. As with other disease conditions, the OGWG members recognized that:

- In some cases, "usual" care may differ by provincial jurisdiction.
- The comparator that is used in a clinical study may not reflect the current commonly used provincial "standard."
- Several agents may be considered to be "usual" care.
- "Usual" care may include "off-label" use of an agent.

- In some circumstances, there may be multiple comparators.
- In some circumstances, there may be no comparator.

Analysts are encouraged not to rely solely on the comparators that are used in the clinical studies. It is recommended that analysts examine the environment across Canadian jurisdictions in order to help identify the feasible, relevant, appropriate, and practical comparators that are used in current clinical practice.

The analyst is encouraged to look beyond simple two-comparator comparisons in economic evaluations and consider the use of multiple comparators, where appropriate. In cases where there are multiple therapeutic options (e.g., multiple single agents, differences across jurisdictions), it is recommended that the economic evaluation use multiple comparators. For example, in certain jurisdictions, oral anti-cancer agents such as capecitabine are not covered by the provincial cancer agency, limiting the treatment options for patients if the drug is unaffordable, and thus having an impact on usual care.

If one comparator is chosen, this choice needs to be justified with reference to the therapeutic landscape.

In cases where the comparator that is used in the clinical study is not in line with the jurisdictional comparator(s), it is recommended that additional analyses (e.g., indirect comparisons, relational) be conducted to examine the differential economic value.[14-17]

The labeling of comparators as "usual care" should be justified with reference to provincial utilization or funding agency guidelines. Where "usual care" cannot be defined, it is recommended that the least expensive appropriate treatment option be used as the comparator. In cases where there is no standard therapy, "usual care" should be defined as no treatment or best supportive care. It is recommended that the least expensive appropriate treatment option be considered as one of the treatment comparators.

The quality of the evidence for each comparator must be examined and reported. Analysts are encouraged to use the highest-quality evidence available for the comparator.

An appropriate comparator may not be included in an economic evaluation because of the lack of sufficient quality evidence. Such an exclusion must be justified.

Recommendation

Analysts should not rely solely on the comparators that are used in clinical studies, and are encouraged to look beyond simple two-comparator comparisons in economic evaluations to consider the use of multiple comparators, where appropriate. Justification of the inclusion or exclusion of a comparator is required. As well, the quality of the comparators used in the analysis should be justified.

4.5 Perspective

4.5.1 State the perspective(s) of the study in terms of the costs included in the evaluation.

4.5.2 In the Reference Case, use the perspective of the publicly funded health care system.

4.5.3 Consider reporting separately the costs associated with adopting a wider perspective, where it is likely that they have a substantial impact on the results of the analysis. Quantify such costs separately, where possible, or at least discuss their likely magnitude and impact on the results of the analysis.

Oncology Guidance

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) provides sound and relevant general recommendations on perspective in technology assessments. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement. The OGWG recommended that additional guidance on perspective for oncology-specific technology assessments be provided in this section.

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) recommends using the perspective of a publicly funded health care system in the reference case. In oncology, provincial cancer agencies (e.g., CCO, British Columbia Cancer Agency) are nested in the broader health system. Reimbursement recommendations are often made at the provincial cancer agency level, but they fall within the scope of the provincial health ministries and departments for funding.

If the provincial cancer agency is used as the perspective for the reference case, then the analyst may only consider the drug cost and not all the direct health effects of the intervention. This is considered to be inadequate. Thus, the perspective must be based on that of a publicly funded health care system. Analysts are encouraged to review CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) for a list of resources that fall into the health care system perspective.

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) recommends adopting a wider perspective when there is likely to be an impact in cost for non-health system areas. A societal perspective may be considered if there are differences in the indirect resources (e.g., caregiver, family burden) and costs used outside the public payer system. Informal care and lost productivity for patients and families may be relevant in oncology. Because there is little research on any benefits beyond those to the individual in the health care system, researchers and economic analysts are encouraged to improve the robustness and quality of economic evaluations by recognizing the costs that are outside the health care system perspective.

Recommendation

The perspective of the analysis is the publicly funded health care system. It is also recommended that the analyst adopt a wider perspective (e.g., societal) if there is likely to be an impact on cost (lost productivity or caregiver burden).

Example:
The perspective of the economic analysis is the Ontario Ministry of Health and Long-Term Care, which provides funding to the CCO.

4.6 Effectiveness

4.6.1 Use a systematic review of the available literature to form the basis for evidence about the efficacy-effectiveness of the intervention. Justify failure to conduct a systematic review. Report the included studies and methods used to conduct the review and analyze or combine data.

Oncology Guidance

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) provides sound and relevant general recommendations on the source of efficacy-effectiveness information in technology assessments. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement. The OGWG recommended that additional guidance on the type and source of evidence for oncology-specific technology assessments be provided.

The OGWG recommended that systematic reviews be the basis of efficacy and effectiveness evidence for interventions. This recommendation for a systematic review of high-quality clinical evidence is in line with recommendations in other economic guidelines and guidelines on the level of evidence required for clinical data.[18,19]

If a systematic review is unavailable, it is recommended that the analyst conduct an original systematic review of all available peer-reviewed publications, with a focus on randomized controlled studies to establish the comparative efficacy and effectiveness between oncology interventions. The quality of the studies that are included in the systematic review should be evaluated using appropriate and validated instruments and inferences regarding the potential for bias should be drawn based on evidence-based approaches. The OGWG recognized that an ideal RCT would be one that is conducted in a blinded fashion; however, not all oncology trials can be blinded (e.g., studies comparing supportive care to interventional agents). Non-blinded trials are acceptable if blinded studies are not available or cannot be conducted.

Guidance on Using Evidence to Estimate Comparative Efficacy and Effectiveness

The OGWG recognized that not all comparative efficacy and effectiveness evidence for the primary outcome is available in published systematic reviews of well-conducted randomized controlled studies. When high-quality studies are not available, the analyst must consider the quality of the trial and whether or not the trial results have been peer-reviewed.

Special Guidance on Quality of Efficacy and Effectiveness Primary Outcomes Data

The highest quality of efficacy and effectiveness evidence should always be used for the primary outcome in health technology appraisals. The OGWG acknowledged that the highest quality efficacy and effectiveness data for the primary outcome is generally based on the results of research conducted in large, high-quality, comparative RCTs performed by established clinical trials groups across multiple centres. However, it also recognized that other study designs may be considered as the source of primary inputs for evidence of comparative efficacy and effectiveness in economic evaluations, particularly when high-quality trials cannot be conducted for ethical or other well-justified reasons. In these cases, data that are obtained from non-comparative studies (e.g., phase 2) may be used in an economic evaluation.

However, it must be recognized that non-randomized, non-comparative trials in oncology have specific problems (e.g., bias, lack of comparability). The use of lower-quality evidence in economic assessments increases the level of uncertainty about the results. Technology assessments using this type of evidence must acknowledge these limitations and be accompanied by sensitivity analyses. Analysts can read further about the pitfalls of interpreting oncology outcomes from non-randomized trials.[20]

Peer-Reviewed Efficacy and Effectiveness Data

The OGWG recognized that mature primary outcome data from high-quality studies may not be available in peer-reviewed publications when an economic analysis is conducted. If that is the case, then other sources of data may be acceptable as inputs for economic evaluations. Other recommended sources of outcome data include: peer-reviewed data that have been accepted for publication and in press, but not yet published; or additional data from published trials (which are acceptable because they are based on peer-reviewed trials, and the fact that there are often space or word count constraints in published studies so that outcomes data ─ e.g., for sub-groups or secondary clinical outcomes ─ may not be available in their entirety). Here the quality of the data is based on the design of the original trial.

While the potential for bias from lack of peer review has not been firmly established, the OGWG felt that studies that are not published or peer-reviewed are of questionable quality, as they have not undergone independent scrutiny and are typically unavailable to the public.

Published Abstracts of Efficacy and Effectiveness Data

Efficacy and effectiveness information in oncology may first become available as an abstract presented at a scientific meeting, which is then presented in poster or oral format (e.g., American Society of Clinical Oncology, American Society of Hematology). In general, there are concerns about the use of information from abstracts from meetings. Some of these concerns include:

- Inadequate information on patient characteristics and outcomes because of space and word count constraints.
- Results without appropriate statistical analysis.
- Preliminary information that may not address the study's primary end point.
- Data that differs from the results found in the final publication.

Data in abstracts are typically based on early interim analyses. These data have limitations (e.g., lack of detail, incomplete analyses). For these reasons, the use of data from abstracts increases

the uncertainty of an economic model and the use of abstract data should only be considered if the study has been presented in a peer-reviewed publication.

The consistency and quality of abstracts and publications have been studied.[21-25] Tam and colleagues examined the consistency between phase 3 clinical trial abstracts and the subsequent publications. The authors concluded that American Society of Clinical Oncology abstracts were reliable as a source of data for practice guidelines, but should be used cautiously because discrepancies with the final publications occasionally occurred. [26]

Hopewell and Clarke examined the completeness of clinical trial abstracts presented at scientific meetings. The authors concluded that the criteria for trial abstracts that are presented at meetings should be revised to improve the completeness of data reporting.[27]

Based on these comments about the uncertainty of results that are presented in abstract form and variance in the final publication, the OGWG recommends that published abstracts should not be used as the only source of data on clinical effectiveness, but may be acceptable if there is a corresponding published or "in press" peer-reviewed manuscript.

Guidance on Efficacy and Effectiveness Data for Non-Primary Clinical Parameters

When undertaking an economic evaluation, clinical parameters other than the primary outcome must be considered. The source of other clinical outcomes may be practice patterns, administrative databases, and reviews of medical records and non-randomized clinical trials.

Long-term clinical practice data can provide useful population data to estimate clinical probabilities and define the effectiveness of therapy in practice. Such information may be available in unpublished formats (e.g., locally derived data). The analyst is encouraged to justify the use of such unpublished sources and discuss the potential for bias from the data.

The OGWG recognized that there is often limited effectiveness data available for oncology agents at the time a drug has received marketing approval. The OGWG highlighted the fact that, post-launch, there is an opportunity to examine the effectiveness of new therapeutic agents in the real world. Consequently, the analyst is encouraged to consider evaluating and incorporating effectiveness data and to incorporate this data into the economic submission. Real world overall survival (OS) rates from administrative databases might be used as a comparator in an economic evaluation.

Recommendation

Systematic reviews of large, peer-reviewed, published, blinded, randomized controlled trials are recommended for establishing comparative estimates of efficacy and effectiveness. The highest level of evidence for efficacy and effectiveness is recommended for the primary outcome of health technology appraisals. The accepted and recommended basis for technology assessment is peer-reviewed data from high-quality randomized controlled trials. The uncertainty about effectiveness and efficacy evidence increases when alternative levels of evidence are used in economic evaluations. Data presented in abstract formats are not recommended unless they have been presented in a peer-reviewed format (e.g., abstract based on a sub-population of a study that has been peer-reviewed).

The use of alternative sources of data and study designs must be justified and referenced. The use of lower quality efficacy and effectiveness evidence in economic assessments increases the level of uncertainty about the results. Evaluations that use this lower quality evidence must acknowledge the limitations of the available evidence and sensitivity analyses should be conducted to test the robustness of the conclusions. The analyst is encouraged to consider incorporating effectiveness data into economic evaluations.

4.6.2 Where feasible and scientifically credible, translate efficacy data into the best quantitative estimate of effectiveness in the Reference Case, using the best available evidence and appropriate modelling techniques. This may involve linking surrogate outcomes to important patient outcomes or extrapolating data beyond the duration of the trial.

Oncology Guidance

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) provides sound and relevant general recommendations on surrogate outcomes in technology assessments. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement. The OGWG recommended that additional guidance on the linkage of surrogate outcomes to important patient outcomes for oncology-specific technology assessments be provided in this section.

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) recommends that analysts use final outcomes in health technology assessments. In oncology, the ultimate goal of a therapeutic intervention is to cure disease. Failing that, the goal is to prolong OS rates or to improve patients' symptoms and quality of life.

In oncology, the clinical outcomes of importance depend on the therapeutic intent, which may be curative, adjuvant, or palliative. The goal for the adjuvant or curative group is to cure the disease. The goal for the palliative group is to help improve the symptoms associated with terminal cancer and prolong survival.

Curative treatment is treatment that is intended to cure patients of their cancer.[28]
Adjuvant treatment is a curative-intent treatment that is administered with the primary therapy; for example, chemotherapy is the adjuvant treatment when surgical resection of a primary colon cancer tumour is followed by chemotherapy for possible residual micro-metastatic disease.[28]

Palliative treatment is treatment that is given in a non-curative setting. It is specifically directed to help improve cancer-related symptoms (e.g., pain due to metastatic bone disease), to improve the quality of the remainder of a patient's life, and to possibly prolong survival. Several treatment modalities can be administered with palliative intent; for example, surgery, radiation therapy, and systemic therapy that are not considered to be curative cancer treatment.[28]

Curative or Adjuvant Setting

In curative or adjuvant clinical studies, OS has been the gold standard and preferred treatment end point. OS is a clinical outcome that is used to directly measure substantial clinical benefit to cancer patients. As a result, OS is the most commonly used objective clinical parameter for determining the benefit of an anti-cancer intervention.

The impact of toxicity on the patient is not captured when OS is used alone. Consequently, for economic analyses, disease burden measures that capture health-related quality of life, such as the quality-adjusted life-year (QALY), are considered to be a more relevant end point because they combine OS and the impact of the toxicity of the treatment on quality of life in one measure.

OS is the recommended outcome only when there are no anticipated differences in HRQL for the different comparators of curative or adjuvant interventions. The lack of difference in toxicity must be justified by using data. The use of OS as a final outcome measure may be justified if there are no concerns about disutility between therapies. There is evidence that adjusting OS for HRQL during cancer treatment may not change the interpretation of the results for the reimbursement decision because cost per OS and cost per QALY have been shown to be highly correlated.[29]

Surrogate Outcomes

Economic literature is concerned with intermediate and surrogate outcomes versus final outcomes. According to CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition), "final outcomes are directly related to the length and quality of life."[2] Surrogate outcomes have been characterized as response variables that are able to replace the true end point for the purpose of testing the null hypothesis.[30,31]

Intermediate outcomes may be clinically meaningful on their own (e.g., reduction in local or metastatic recurrence), or they may be linked to a final outcome (e.g., mortality). Intermediate outcomes and final outcomes are collectively "important patient outcomes" in CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition).

Economic textbooks state that "Although intermediate outcomes may themselves have some value (or clinical meaning), the economic analyst should ideally choose an effectiveness measure relating to a final outcome."[8] CADTH's guidelines are more flexible, stating that "analysts are encouraged to select an outcome indicator that is most appropriate for the relevant condition, and most feasible, given the available data on outcomes for each alternative."

In common parlance, surrogate and intermediate outcomes are used as interchangeable terms, but they are not. Surrogate outcomes are a subset of intermediate outcomes and are defined as "a laboratory measurement or a physical sign used as a substitute for a clinically meaningful end point that measures directly how a patient feels, functions, or survives."[32] Unlike intermediate outcomes, a surrogate outcome is not used to measure directly how a patient feels or functions, and it does not have independent clinical value. Furthermore, validated and unvalidated surrogate outcomes should be distinct, where validated surrogate outcomes are proven to be predictive of an important patient outcome. Similarly, intermediate outcomes may have validated links to final outcomes. A non-cancer example would be blood pressure as a validated surrogate outcome and myocardial infarction as an intermediate outcome, with independent clinical meaning and a validated link to mortality. Therefore, important non-final patient outcomes constitute intermediate outcomes with clinical value or validated links to final outcomes, and validated surrogate outcomes. To be consistent with CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) terminology, the term "surrogate outcome" is used in this oncology-specific document.

Surrogate outcomes are clinical outcomes of importance for the health of patients. These outcomes are valid predictors of final outcomes. In oncology, clinical outcomes that may be valid surrogate outcomes and that have been used in trials include progression-free survival (PFS), time to progression, and response rate (overall response, complete response, or partial response). Recent literature discusses benefits and limitations of surrogate outcomes in the field of oncology.[31,33-36]

The decision to use a surrogate outcome in an oncology economic evaluation must be justified. Surrogate outcome validation must make statistical, clinical, and biological sense.[37] The following questions about the possible use of a surrogate outcome should be considered by the analyst:[38]

- Is there a strong, independent, consistent association between the surrogate outcome and the final clinical end point?
- Is there evidence from randomized trials that improvement in the surrogate has consistently led to improvement in the final outcome in the same disease setting and in the same drug class?
- Is there evidence from randomized trials that improvement in the surrogate outcome has consistently led to improvement in the final outcome in the same disease setting in other drug classes?
- What were the results?
- How large, precise, and lasting was the treatment effect?

Surrogate Outcomes in the Curative or Adjuvant Setting

Final outcomes, such as deaths prevented and serious morbidity avoided, which translate into life-years gained (LYG), healthy-year equivalents, or QALYs, are preferred outcomes for health economic evaluation. Survival and HRQL data may not always be available from oncology studies when economic analyses need to be conducted. Analysts should not assume that the use of surrogate clinical outcomes in clinical studies is an endorsement of their validity as predictors of mortality or burden of illness. Analysts are often required to use data from proposed surrogate measures to represent final outcomes.[39] For example, PFS may be the primary outcome in a study and not OS. If OS data are unavailable, then intermediate outcomes may need to be considered.

The use of surrogate outcomes in economic analyses for oncology agents has received attention.[40-42] Appropriate methods to establish relationships between these surrogate outcomes and final outcomes include single-trial analysis, meta-analysis, and hybrid approaches.[37,43] In general, surrogate end points may be used as valid outcome measures provided that there are empirical data showing that they are reliable predictors of OS, and that there is a biological rationale. There are examples of links between surrogate markers and final outcomes for colorectal cancer,[44-46] and breast cancer.[42,47] It is recommended that the analyst determine the quality of the relationship between surrogate outcome and final outcome, and justify the use of the surrogate outcome as the outcome of interest in the economic evaluation.

The use of a surrogate outcome in health technology assessments must be accompanied by extrapolations to OS. Three types of relationships are possible:

- The surrogate outcome is entirely predictive of OS.
- The surrogate outcome is somewhat predictive of OS.
- The surrogate outcome has no proven relationship with OS.

Which of these relationships might apply depends on the best available evidence in a given scenario and must be accompanied by appropriate justification.

There are instances when OS may not be different between therapeutic options. For example, in breast cancer, multiple studies comparing mastectomy to breast conserving surgery with radiation therapy have shown OS to be equivalent. The toxicities and delivery issues differ, however, when these treatments are compared, and the efficacy outcome of choice for such an economic analysis would be QALY. OS or a justified PFS would be used to weigh health preference values by time.

The relationship between a proposed surrogate measure and final outcomes will have an impact on the uncertainty analyses. The analyst needs to recognize that uncertainty about the transformation of surrogate measures may be statistical or structural. In the uncertainty analysis, the analyst will need to consider the uncertainty of the comparative effect of treatment and the uncertainty about the extrapolation of this effect. If little is known about the extrapolative relationship between the proposed surrogate measure and final outcomes, a scenario analysis or weighted scenario analysis that examines a plausible spectrum of predicted events, including the possibility of a negatively correlated relationship, needs to be considered.

Palliative Setting

Medications for palliation are intended to help improve the symptoms associated with terminal cancer and ideally to prolong survival. Consequently, the QALY is the recommended outcome for palliative care economic analyses. Other outcome measures, such as quality-adjusted time without symptoms of disease and toxicity (Q-TWIST) and healthy year equivalent (HYE), may be equally suitable, but should be considered to be lower levels of economic evidence because they do not allow for comparisons across health programs.

Surrogate Outcomes in Palliative Setting

PFS is an outcome in the palliative setting. PFS may be considered an option as an outcome provided that there is a validated relationship between OS and PFS. The same caveats about surrogate outcomes that were noted for curative and adjuvant treatments also apply for palliative treatments.

Recommendation

In the Reference Case, QALY and LYG are the recommended outcomes for oncology economic evaluations in the curative or adjuvant, and palliative settings. Extrapolation from surrogate outcomes to QALY and LYG must be accompanied by appropriate justification based on the best available evidence. Surrogate outcomes can be used as supplementary outcomes or as the main outcome when there is clear and strong justification for why QALY and LYG cannot be used.

4.6.3 Where feasible in the Reference Case, incorporate "real world" factors that modify the effect of the intervention, where there are established links to important patient outcomes based on the best available evidence. These factors include patients' adherence to treatment, screening and diagnostic accuracy, and health care providers' compliance and skill. State the nature of the factor, measures used to quantify the effect, and the methods and assumptions used for modelling.

Oncology Guidance

The recommendations in CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) are sufficient for the conduct of oncology technology assessments. No further guidance is required for oncology products. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement.

4.6.4 The evaluation of medical devices should focus more broadly on the entire episode of care rather than on only the technical performance of the device. The outcomes of medical and surgical procedures, and diagnostic technologies may depend on the operator's skill and experience. The extensive use of sensitivity analysis may be required to properly evaluate situations where the evidence of efficacy-effectiveness is weak.

Oncology Guidance

The recommendations in CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) are sufficient for the conduct of oncology technology assessments. No further guidance is required for oncology products. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement.

4.6.5 Where feasible, include the impact of adverse events associated with the intervention if they are clinically or economically important, and analyze them appropriately. Depending on the nature, frequency, duration, and severity, adverse events may have an impact on patients' adherence, mortality, morbidity, HRQL (utilities), or resource use. Value these in a manner that is consistent with the principles outlined in the Economic Guidelines.

Oncology Guidance

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) provides sound and relevant general recommendations on adverse events in technology assessments. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement. The OGWG recommended that additional guidance on the details of adverse events for oncology-specific technology assessments be provided in this section.

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) recommends that analysts include the impact of adverse events that are associated with the intervention if they are clinically (e.g., efficacy, safety, QoL) or economically important. Clinically and economically important adverse events in oncology typically are, but are not limited to, grade III, IV, and V adverse events. Grade I and II adverse events should also be considered in the economic evaluation if they are categorized as clinically or economically important. In oncology, adverse events are defined using one of several similar grading systems:

The definitions of adverse events (AE) in oncology include:[48]

Grade I: Mild AE (e.g., mild rash)
Grade II: Moderate AE (e.g., nausea and vomiting)
Grade III: Severe AE (e.g., neutropenia),
Grade IV: Life-threatening or disabling AE (e.g., febrile neutropenia)
Grade V: Death related to AE

Regarding quality of evidence for adverse events, those analysts doing meta-analyses who are used to deriving risks of AEs should consider valid statistical methods for pooling data based on rare events.[49,50]

Recommendation

The analyst must include clinically and economically important adverse events in the economic evaluation. Justify and reference the exclusion of any adverse events that are not considered in the economic evaluation.

4.6.6 In the Reference Case, extrapolate data based on the best quantitative estimate of the relevant parameters, using the best available evidence and appropriate modelling techniques. Describe the strength of the evidence for extrapolating data and assess uncertainty through a sensitivity analysis. Unless such an analysis is based on high-quality evidence, identify it as speculative, and give appropriate caveats in the report.

Oncology Guidance

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) provides sound and relevant general recommendations on extrapolation in technology assessments. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement. The OGWG recommended that additional guidance on the details of outcomes values for oncology-specific technology assessments be provided in this section.

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) recommends that analysts use the best quantitative estimate of the relevant parameter. The mean value for outcomes is used in preference to the median value because the mean value is a parametric estimate of the data set. Finding the mean survival based on raw clinical data is the preferred method of determining the mean.

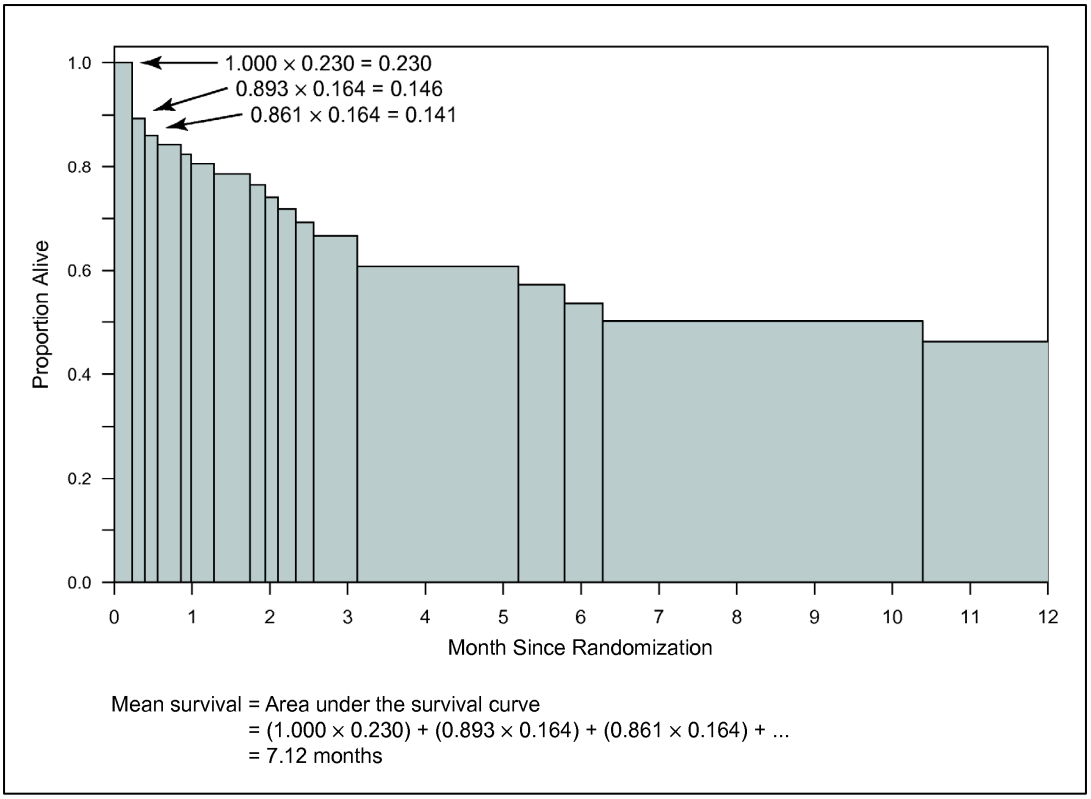
If raw clinical data are unavailable, the mean value may be estimated from the survival curve. Different methods are available for the determination of mean values. One method is the calculation of the area under the survival curve (Figure 1). Other validated methods, such as methods that transform median to mean (e.g., under specific assumptions, such as constant rate), are also available. All methods must be justified and explained. The extrapolation of clinical data is discussed in the modelling section.

Recommendation

The arithmetic mean is the preferred statistical measure. The use of raw clinical data is the preferred method of determining the mean. In cases where the raw clinical data are unavailable

or incomplete, other methods may be used. Means should be calculated using acceptable methods, which must be justified and referenced.

Figure 1: Area Under the Survival Curve



4.7 Time Horizon

4.7.1 Base the time horizon on the natural course of the condition and the likely impact that the intervention will have on it. State and justify the time horizon(s) of the evaluation.

4.7.2 In the Reference Case, ensure that the time horizon is long enough to capture all relevant differences in future costs and outcomes of the alternatives being analyzed. Apply the same time horizon to costs and outcomes. Consider using a lifetime time horizon, and justify where a shorter time horizon is used.

4.7.3 If the long-term costs and outcomes are modelled, it may be appropriate to present the shorter-term analysis based on primary data, and the longer-term analysis using the extrapolated or modelled data. Multiple time horizons might be appropriate for exploring alternative scenarios in some cases. Explain the causal relationships and techniques that are used to extrapolate or model the data.

Oncology Guidance

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) provides sound and relevant general recommendations on time horizons for technology assessments. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement. The OGWG recommended that additional guidance on the details of time horizons for oncology-specific technology assessments be provided in this section.

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) recommends using the time horizon for the natural course of the condition and the likely impact that the intervention will have on it. The analyst must ensure that in the Reference Case, the time horizon is long enough to capture all relevant differences in future outcomes and costs. Many oncology interventions affect survival. As a result, the treatment benefit will be underestimated if any time horizon that is shorter than lifetime is used. The use of many interventions also can lead to sustained effects on QoL. Therefore, the recommended Reference Case for technology assessments in oncology has the lifetime time horizon.

Lifetime efficacy data may be unavailable from clinical studies. Early benefits in the form of PFS may be seen, and long-term OS may not be measured. Therefore, attempts to project the effects of treatment over a lifetime time horizon will involve extrapolation. The uncertainty that is inherent in extrapolation must be set against the bias that is introduced by using a time horizon that does not fully capture all treatment benefits.

It is recommended that for the Reference Case, the analyst extrapolate to lifetime using acceptable modelling techniques to provide a complete picture of outcomes, resources, costs, and health preference. The analyst is encouraged to refer to CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) for references.

Extrapolation beyond the clinical study time horizon, using acceptable modelling techniques, should be considered. Uncertainty about the extrapolation and specific assumptions about the duration of treatment effectiveness must be explored.

The duration of the effect or how long the effects of the intervention are sustained plays a role in determining the time horizon. The analyst must justify a non-lifetime time horizon and discuss the impact of the shorter time horizon on the overall incremental ratio in terms of costs and outcomes. See further comments on the relationship between time horizon and modelling in the Modelling Section 4.8.

Recommendation

A lifetime analysis is recommended in the Reference Case to capture the efficacy, safety, costs, and health preference values of patients receiving an intervention for a specific cancer. When lifetime data are unavailable from a clinical study, acceptable modelling techniques must be used. Shorter time horizons are acceptable in specific circumstances but must be justified.

4.8 Modelling

4.8.1 Modelling considerations:

a) **Follow good modelling practices when constructing the model used to conduct the evaluation. Analysts are encouraged to consult good modelling practice guidelines as required.**
b) **Describe the model, including its scope, structure, and assumptions. Provide justification for assumptions and choices.**
c) **Use a model structure that is appropriate for addressing the study question. Build the model in such a way as to permit updating of results as more data become available.**
d) **Explain and justify any causal relationships and extrapolation techniques used in the model. Base the extrapolation of data on valid techniques that reflect reasonable scientific evidence, and test through sensitivity analysis.**
e) **Formally validate the model, and state how this was done.**

4.8.2 Data considerations

a) **Systematically identify, collect, and assess the data used in the model.**
b) **Report and identify all data sources. Explain and justify all parameter choices and assumptions.**
c) **Describe the quality (e.g., strength of evidence) of the data used in the model. Be explicit about data limitations and how they were dealt with. Try to quantify the impact of the limitations on the uncertainty of the evaluation results.**
d) **Gather the best available evidence on key model parameters for which the model results are most sensitive. Justify any failure to gather the best available evidence of such parameters.**
e) **Use caution when expert opinion is used to establish parameter values. Justify its use; and describe the source of the opinion, the method of elicitation, and the results of the exercise. Assess such estimates through a sensitivity analysis.**
f) **Use appropriate methods to analyze or combine data from different sources. Explain and justify the methods used, and report the results of the analysis. Report limitations in the methods or data used, and where feasible, test through a sensitivity analysis.**
g) **Incorporate data into the model using appropriate techniques, and explain the methods used. If data are incorporated as point estimates, use mean estimates of parameters in the base case. If estimates are incorporated as probability distributions, state and justify the form of the distributions.**

Oncology Guidance

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) provides sound and relevant general recommendations on modelling in technology assessments. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement.[2] The OGWG recommended that additional guidance on the use of modelling in oncology-specific technology assessments be provided in this section.

There are recommendations in CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) for the conduct of modelling. These recommendations also hold true

for oncology. In oncology, treatment intent can be curative, adjuvant, or palliative. Thus, appropriate modelling techniques for each treatment type are needed. Appropriate modelling techniques are outlined in CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition).

Curative or Adjuvant Treatment

It is recommended that accepted modelling techniques as described in CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) be used in any extrapolation beyond clinical trial data. The analyst must justify and reference the modelling technique that is used.

Palliative Treatment

In a high-quality economic evaluation, there will be extrapolation beyond clinical trial data using accepted modelling techniques as described in CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition). It is necessary to justify the modelling technique that is used. Extrapolation may be unnecessary when the end points that are collected during the study occur in patients who have a poor prognosis. Thus, the lifetime horizon is captured in the study for most (e.g., 90%) of the patients.

Recommendation

It is recommended that the analyst extrapolate beyond the clinical trial to capture the lifetime horizon using acceptable modelling techniques.

Additional Guidance for Duration of Effect

The duration of the effect or how long the effects of the intervention are sustained plays a role in determining the time horizon and how to extrapolate. All survival curves eventually converge; the challenge is to determine when they converge. Truncating an analysis at the end of the study may introduce bias in favour of survivorship or may prevent the consideration of long-term benefits. A truncated time horizon may be acceptable if justification can be provided, or if the magnitude of the bias can be estimated (e.g., if the bias is likely to affect the outcome by less than 5%).

More commonly, it will be necessary to extrapolate beyond observed clinical trial data to populate a lifetime horizon model. It is recommended that the analyst consider the following analyses to examine the duration of benefit:

- Decrease in the treatment effect after the clinical study until survival curves converge. This option is the most relevant for the base case in an economic evaluation. The value of the decrease and the duration of the decrease must be justified.
- Immediate loss of treatment effect or survival curves converge after the end of the clinical study. This is the most conservative option of the three listed for an economic analysis. This option may not be clinically relevant, because the clinical effect of an outcome (final or surrogate) may not stop immediately after the end of a trial. If chosen as the base case, the clinical relevance must be justified.
- Maintain the clinical study treatment effect based on the study effect until the survival curves converge. This is the least conservative option of the three listed for an economic analysis. This option may not be clinically relevant, because the clinical effect of a surrogate outcome

may not match the final outcome after the end of a trial until death. If chosen as the base case, the clinical relevance must be justified.

The choice of which of these three scenarios to apply to the economic analysis depends on the best available evidence in a given scenario and must be accompanied by appropriate justification.

4.9 Valuing Outcomes

4.9.1 Use appropriate preference-based measures to value meaningful differences between the intervention and alternatives in terms of HRQL.

4.9.2 Measure the outcome for a CUA in terms of the QALYs gained. Report changes in the length of life and quality-weight separately, and report the procedure for combining them. State the assumptions and methods used to estimate QALYs. Justify using alternative outcome measures in a CUA.

4.9.3 Preferences (utilities) can be measured directly or indirectly. Study the alternative methods a priori and select, in advance the one that is most appropriate for the condition and study question. Justify the selection and method, report on the validity and reliability of the method selected, and explain the steps undertaken to measure preferences.

4.9.4 Where preferences are measured directly, use the standard gamble or time trade-off approaches. To avoid double-counting, subjects in exercises measuring preferences should be asked to value lost leisure time in terms of changes in preferences, and to assume that health care costs and income losses are fully reimbursed.

4.9.5 A representative sample of the general public, suitably informed, is the preferred source for preferences. Patients who have direct experience of the relevant health states may be an acceptable source. Describe the population from which the preferences were derived, and their relevance to the Canadian population.

4.9.6 Willingness-to-pay methods for valuing outcomes in a CBA are regarded as a secondary type of analysis. Explain the steps to convert outcomes into monetary terms. Validate key assumptions, and test through a sensitivity analysis.

Oncology Guidance

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) is sufficient for the conduct of oncology technology assessments. No further guidance is required for oncology products. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement.

4.10 Resource Use and Costs

4.10.1 General

a) **Systematically identify, measure, and value resources that are relevant to the study perspective(s). Classify resources in categories that are appropriate to the relevant decision-maker (e.g., primary care, drug plan, hospitals).**

4.10.2 Resource identification

a) **Exclude protocol-driven costs taken from clinical trials. Transfer payments should be excluded from the public payer and societal perspectives.**
b) **Unrelated costs that are incurred during normal life-years should be excluded from the evaluation. Unrelated costs that are incurred during life-years gained from the intervention may be included at the analyst's discretion in a sensitivity analysis.**

4.10.3 Resource measurement

a) **Report quantities of resources in physical units.**
b) **Report the costing method used and justify the approach taken. Measure and value with greater precision those resources that contribute most to total and incremental costs. Where lower quality cost estimates are used, use a sensitivity analysis to determine the impact of cost assumptions.**
c) **Where feasible, base resource use estimates on data for Canadian routine practice. Where resource use data are from international sources, clinical trials, or non-observational sources (clinical practice guidelines), validate or adjust them for Canadian routine practice, using appropriate methods.**

Oncology Guidance

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) provides sound and relevant general recommendations on resource identification and measurement in technology assessments. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement. The OGWG recommended that additional guidance for resources in oncology-specific technology assessments be provided in this section.

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) provides guidance about the appropriate resources based on the perspective of the assessment. In oncology, it is recommended that the analyst use "real-world" utilization and evidence-based treatment guidelines (e.g., CCO-Program in Evidence Based Care) to gather information about resource utilization of such items as chemotherapy administration, pharmacy preparation, pre-medication drug costs, and adverse event-related resources.

There are differences in the use of resources among jurisdictions across Canada. Consequently, it is recommended that analysts include all appropriate resources in the main economic analysis. Resources must be presented in a disaggregated format to allow provincial agencies to extract data that are pertinent to a specific jurisdiction.

The inclusion of utilization data based on protocols and guidelines may not represent "real world" utilization. Real world utilization data can be obtained from several sources, including claims data, hospital admissions data, review of medical records, and electronic health registry data.

In some cases, "real world" utilization or evidence-based treatment guidelines are unavailable for a given treatment or for specific disease sites. Consequently, resources that are collected from a clinical study or trial may be considered only when resource utilization information is unavailable from guidelines or protocols.

Additional Guidance on Sources of Resource Utilization Data

Some resource utilization and patient epidemiology data can be obtained from unpublished sources. Examples of clinical practice information that can be used to support clinical data for economic evaluations include:

Administrative Datasets: OS rates for best supportive care, when supportive care is considered to be an appropriate comparator for an intervention and where efficacy information is available only from non-comparative studies (e.g., annual survival rates for women with metastatic breast cancer from British Columbia Cancer Agency); adverse event type and rates (e.g., febrile neutropenia rates for a specific treatment from the Surveillance, Epidemiology and End Results [SEER] program).

Medical Records: proportion of patients receiving transfusions (e.g., review of charts for diagnosis of anemia).

This information may provide the analyst with the "real life" outcomes that are important for the development of the economic argument. This clinical practice information can include relevant population data to use in determining clinical probabilities and representing the effectiveness of therapy in practice. Such information, however, may only be available in abstract form or in unpublished formats because it is locally relevant, but does not necessarily generate enough general scientific interest for publication. The analyst is encouraged to justify the use of such unpublished sources and to discuss the quality of the data.

Recommendation

Data from unpublished sources (e.g., administrative data, patient registries, medical records) from "real life" practice may be used to provide resource utilization information for economic evaluations.

4.10.4 Resource valuation

a) **Conceptually, use economic (opportunity) costs as the basis for valuing resources. In principle, use the total average cost (including capital and allocated overhead costs) as the unit cost measure.**
b) **Report the valuation methods used, and justify the approach where appropriate. Use market prices, where available. Standard costs can be used, where available and appropriate. Where costs are directly calculated or imputed, they should reflect the full economic cost of all relevant resources at normal operating levels.**

c) **When evaluating the public payer perspective, use the full cost (i.e., contributions paid by the public payer, private insurers, and patients) of the intervention and comparators in the Reference Case. For interventions involving cost-sharing arrangements with patients who are likely to have a noticeable impact on the results, use a sensitivity analysis to assess the implications of variations in the proportion of the cost of the intervention and comparator paid by the public payer. Use the same proportions for the intervention and comparators, unless there is a reason to do otherwise.**
d) **Adjust any cost obtained from earlier times to the current period. Use appropriate methods, and provide justification when converting costs (i.e., resource quantities and unit costs) from another country to Canadian currency.**
e) **Consider a separate analysis of the impact of the intervention on lost time by patients and informal caregivers, where it is likely to have a substantial impact on the results.**
f) **Use the friction cost approach to value lost time from paid work. Report the friction period and unit cost used to value lost productivity. Gross wage rates plus the costs associated with recruiting and training replacement workers can be used to value long-term absences from work. Exclude the lost time from paid work due to premature death that occurs beyond the friction period.**
g) **There are several acceptable methods for valuing lost time by patients and informal care-givers, but there is no preferred alternative.**
h) **Describe the methods, data, and assumptions used to measure and value lost time by patients and informal caregivers. Present quantities and unit costs of lost time separately before combining them. Conduct a sensitivity analysis using alternative methods and assumptions.**

Oncology Guidance

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) provides sound and relevant general recommendations on resource valuation in technology assessments. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement. The OGWG recommended that additional guidance on the use of costs in oncology-specific technology assessments be provided in this section.

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) provides guidance on resource valuation. A reference for the determination of costs is included in the aforementioned document.[2,51] For oncology, costs vary across the jurisdictions in Canada.

It is recommended that the analyst present the costs from one base-case jurisdiction. This will improve the consistency of cost data and sources. It is recommended that analysts include all appropriate costs in the analysis. These costs must be presented in a disaggregated format to allow provincial agencies to extract data that are pertinent to a specific jurisdiction.

Some provincial cancer agencies include different costs as part of their perspective (e.g., radiotherapy, but not surgery in one province, but both in another). Analysts are encouraged to include all clinically appropriate costs in the analysis. This will allow provincial agencies to extract data that are pertinent to a jurisdiction.

A high-quality technology assessment will include direct medical and non-medical costs in keeping with the perspective of the economic evaluation (the publicly funded health care system). Direct costs should include costs of drugs, concomitant medications, adverse drug reactions, surgery, radiation therapy, administration (e.g., chemotherapy preparation, chemotherapy chair time), health care personnel (e.g., pharmacists, technicians), laboratory tests, and diagnostic examinations. Analysts must justify the inclusion of the costs that are used in the economic evaluation and the exclusion of others.

Non-medical costs (e.g., costs of transportation, parking, child care, elder care) and indirect costs (e.g., costs of lost productivity, unpaid caregiver burden) as defined by CADTH are not relevant for the recommended oncology perspective (the publicly funded health care system). A societal perspective may be considered for oncology if the burden is perceived to be great and falls outside the publicly funded system perspective, when indirect resources (e.g., caregiver, family burden) and costs need to be considered.

Recommendation

It is recommended that the analyst present the costs from one base-case jurisdiction. This will improve the consistency of cost data and sources. Included and excluded costs must be justified.

4.11 Discounting

4.11.1 In the Reference Case, discount the costs and health outcomes that occur beyond one year to present values at the (real) rate of 5% per year.

4.11.2 Conduct sensitivity analyses using (real) discount rates of 0% and 3%.

4.11.3 When different discount rates are used from those recommended, present results in a sensitivity analysis, and justify the relevance.

Oncology Guidance

The recommendations in CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) are sufficient for the conduct of oncology technology assessments. No further guidance is required for oncology products. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement.

4.12 Variability and Uncertainty

4.12.1 Handling variability

a) **Variability can be attributed to diverse clinical practice patterns in different geographical areas or settings, or to inherent variability in the patient population (i.e., patient heterogeneity). Handle variability in practice patterns through further analysis.**
b) **Deal with variability in the population by stratifying the target population into smaller, more homogeneous groups. Identify the basis for the stratification. Define subgroups preferably at the planning stage, because post-hoc analysis may be unacceptable, unless a strong justification is given.**

4.12.2 Handling uncertainty

a) **Uncertainty can be attributed to two types of model inputs: parameter and model (structure, methods, and assumptions). Deal with both types of uncertainty systematically and thoroughly, and fully assess the impact on the results and conclusions.**
b) **In the Reference Case, at a minimum, conduct a deterministic sensitivity analysis (DSA).**
   - **Perform the analysis for all model inputs to determine the impact on the results. Justify the omission of any model input from the sensitivity analysis.**
   - **Identify and fully assess the key model inputs contributing most to uncertainty. The choice of analysis should involve more than a one-way sensitivity analysis. Perform a multi-way sensitivity analysis, threshold analysis, and analysis of extremes (e.g., best- and worst-case scenarios) for key model inputs.**
   - **Assess the full range of plausible values for each parameter, and plausible alternatives for each assumption. State and justify the ranges of values selected, and the alternative assumptions used. Alternative assumptions should take into account the variability between the jurisdictions or settings of the target audience.**
c) **A probabilistic sensitivity analysis (PSA) of parameter values that can be defined probabilistically is encouraged to more appropriately assess parameter uncertainty.**
- **The analysis should take the form of a Monte Carlo simulation. State and justify any assumptions regarding the range of values for key parameters, the form of probability distributions, and the number of Monte Carlo iterations.**
- **Model uncertainty should be accessed through a DSA and model validation methods, with separate (probabilistic) results shown for each alternative analysis.**
- **Parameter uncertainty can be assessed using a DSA and a PSA.**

d) **Where a PSA has been used, quantify the contribution of each parameter to decision uncertainty. Value-of-information methods can be used to indicate where the collection of additional information may be helpful for making decisions.**

Oncology Guidance

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) provides sound and relevant general recommendations on sensitivity analysis for technology assessments. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement. The OGWG recommended that additional guidance on the use of sensitivity analyses in oncology-specific technology assessments be provided in this section.

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) provides guidance on handling the variability and uncertainty of model parameters. The document, at minimum, recommends DSA for all model inputs and PSA of parameter values that can be defined probabilistically.

In oncology, there is agreement with CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) in terms of sensitivity analyses of parameters. The following parameters should be included in the sensitivity analysis: efficacy (e.g., final or surrogate

outcomes); adverse events (e.g., grade III or IV or V, at a minimum); resource utilization (e.g., guideline and trial); utilities (e.g., direct, indirect); and costs (e.g., intervention, comparator). The ranges for sensitivity analyses should encompass 95% confidence intervals or plausible parameter ranges (e.g., clinically plausible). A combination of 95% confidence intervals and plausible parameter ranges may be used in the sensitivity analysis. All ranges that are used in the sensitivity analysis should be justified.

Additional Guidance on Modelling Uncertainty

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) provides little guidance on uncertainty related to modelling. Typically, parameter and model uncertainty are treated similarly in the aforementioned document, despite the fact that there have been methodological advances in modelling uncertainty and variability since its publication.

This issue is not specific to oncology. Analysts are encouraged to consider model uncertainty with parameter uncertainty when conducting sensitivity analyses.

Recommendation

It is recommended that the analyst examine parameter and modelling uncertainty when conducting the sensitivity analyses.

4.13 Equity

4.13.1 State the implicit and explicit equity assumptions made in the evaluation. If possible, state the implications of the assumptions on the results of the analysis.

4.13.2 Identify the equity-relevant characteristics of the subgroups that may benefit from, or be adversely affected by, the intervention. Population characteristics such as age, sex, ethnicity, geographical area, socioeconomic group, or health status may be relevant for equity purposes.

4.13.3 Analysts are encouraged to provide information on the distributional impact (e.g., benefits, harms, and costs) and cost-effectiveness of the intervention for those subgroups predetermined to be relevant for equity purposes.

4.13.4 Use equal equity weights for all outcomes in the Reference Case. Present the analysis in a disaggregated and transparent manner to allow decision-makers to assess the distributional impacts and the trade-offs between equity and the efficient allocation of resources.

Oncology Guidance

Equity in decision-making about drugs that are used to treat rare diseases has been a topic of recent discussions.[52,53] In Canada, there is no clear definition of an orphan disease (http://www.raredisorders.ca).

The decision-making framework for rare diseases may be poorly served by the current guidance for the conduct of economic evaluations.[54] Decision-makers, however, may need to consider other factors that fall outside the usual economic framework.

Recommendation

Analysts are encouraged to construct economic evaluations for rare diseases and orphan drugs using the proposed guidelines. At this time, there is no specific guidance available on the conduct of economic evaluations for orphan drugs that might be used in oncology.

4.14 Generalizability

4.14.1 Address generalizability in the design of the evaluation and in the interpretation of its findings. There are three aspects of generalizability to be addressed:

- **distinction between efficacy and effectiveness of the intervention**
- **handling of data on costs and preferences (utilities) that are derived from another setting**
- **handling of data from trials involving several countries, including that of the decision-maker.**

4.14.2 Justify any data derived from outside Canada and verify for the Canadian setting. If data are adjusted for the Canadian setting, describe and justify the methods used. Report, analyze, and justify the use of cost data from multinational trials.

4.14.3 Where there is local variation in clinical practice or other model parameters, the Reference Case can be performed at a national (or aggregate) level using the most widespread or best available practice or data. A sensitivity analysis can be performed using regional or local practice and data. If a DSA is used, test the key model parameters throughout the range of values that apply in the jurisdictions representing the target audience.

4.14.4 Present the results in a disaggregated manner to facilitate the interpretation of results for different settings. Report the quantities of resources consumed and unit costs separately.

4.14.5 State the extent to which the findings of the evaluation can be generalized to the jurisdiction(s) or setting(s) of the target audience, including any study limitations that affect the generalizability of the evaluation findings.

Oncology Guidance

CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) is sufficient for the conduct of oncology technology assessments. No further guidance is required for oncology products. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement.

4.15 Reporting

4.15.1 Report the evaluation in a transparent and detailed manner. Provide enough information to enable the audience to critically evaluate the validity of the analysis. Use a well-structured report format (Appendix 3).

4.15.2 Include a summary and a conclusion of the evaluation that are written in non-technical language and that are accessible to the target audience.

4.15.3 Present the analysis in disaggregated detail first, showing total, undiscounted costs and outcomes separately for the intervention and each comparator. Introduce aggregations, incremental results, and value judgments as late as possible.

4.15.4 Report final results as incremental cost-effectiveness ratios (ICERs), based on incremental differences of expected costs and expected outcomes of the alternatives. Follow standard decision rules for estimating ICERs, including the exclusion of dominated alternatives. To aid understanding, analysts are encouraged to present the results of the analysis in graphical or visual form, in addition to tabular presentation.

4.15.5 Describe funding and reporting relationships of the evaluation, and disclose any conflicts of interest.

4.15.6 Make documents demonstrating quality assurance in the conduct of the evaluation available to decision-makers. If requested, make a copy of the model available to decision-makers for review.

Oncology Guidance

The recommendations in CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) are sufficient for the conduct of oncology technology assessments. No further guidance is required for oncology products. The analyst is encouraged to refer to the aforementioned document for more information on this guideline statement.

5 DISCUSSION

The OGWG discussed several concepts that are related to the variables of economic evaluations for oncology interventions, including valuing outcomes, and equity.

5.1 Efficacy and Effectiveness

In oncology, OS has been the gold standard and preferred treatment end point in cancer treatment intervention studies. The impact of the toxicity of treatment on the patient, however, is not captured when OS is used alone. In health economics, the QALY is a more relevant end point because mortality and morbidity are combined in one measure. OS is the recommended outcome only when there are no differences in HRQL between treatment interventions. The lack of any difference in toxicity between two regimens, however, must be empirically justified. If there are no underlying concerns about disutility from therapy, the use of OS as a final outcome measure

may be justified. There is evidence that adjusting OS for HRQL in oncology treatment may not change the results because cost per life-year and cost per QALY are highly correlated.[29]

5.2 Quality of Evidence

Even valid justification does not improve the quality of data that has design limitations. A lack of "perfect information" (high-quality data that are needed to fully populate a lifetime horizon model) results in a need for alternative methods in a technology assessment and is accompanied by inherent uncertainty. The results should be interpreted with caution. Less confidence about the economic results where larger information gaps exist should be discussed. There will be information gaps, but these may not be critical gaps.

5.3 Surrogate Outcomes in Oncology

Some surrogate parameters are clinically approved (e.g., DFS in breast cancer) because they are recognized as appropriate end points by regulatory agencies for decisions about marketing approval, and by clinicians for decisions about individual patient care. Reimbursement decision-makers, however, have been reluctant to label surrogate outcomes as approved outcomes. This results in a problematic environment where clinical trials are designed to generate data that are sufficient for regulatory and clinical decision-making, but that inadequately address the requirements for information in reimbursement decision-making. There is a need for more examination of clinical trial design, extrapolation and modelling techniques and a need for more research to validate surrogate outcomes and provide links to final outcomes.

5.4 Valuing Outcomes

The National Institute for Health and Clinical Excellence (NICE) has favoured the EQ-5D for all technology assessment evaluations.[55] In Canada, CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) does not recommend a health preference instrument in general or oncology-specific health technology assessments. Some groups have begun to explore the relationships between HRQL and health preference instruments in oncology.[56,57] The analyst is encouraged to explore these relationships for oncology products.

5.5 Equity

Equity is "fairness" in the allocation of resources, treatments, or outcomes among individuals or groups.[58] The discussions on equity in CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) focus on the benefits, harms, and costs that are associated with a technology. These are often unevenly distributed across the population. In these situations, equity concerns that can arise are often defined as horizontal equity. Horizontal equity issues apply equally to products that are used in oncology as they would to any other treatment. The analyst is encouraged to make a reasonable effort to address issues of horizontal equity.

Other forms of equity that are not addressed in CADTH's *Guidelines for the Economic Evaluation of Health Technologies* (third edition) may apply to treatments in oncology. One example is vertical equity, which suggests that analysts examine equity issues that occur when

looking across technologies. One illustration is the fact that treatments for many rare cancers (e.g., renal cell carcinoma, follicular thyroid cancer) are more expensive than those for common disease sites (e.g., breast, lung) and may have different effectiveness outcomes. A recent editorial asked whether or not Canadian patients should be denied access to potentially effective new treatments for formerly untreatable and serious diseases only because it is virtually impossible to evaluate the cost-effectiveness of these treatments using conventional criteria.[59] In addition, if we use the same effectiveness criteria as with common disease sites, it is likely that many of these treatments will be associated with higher incremental cost-effectiveness ratios than suggested thresholds for reimbursement. Arguments that seek to ensure that access to treatment is equal regardless of whether a disease is classified as rare or not may be justified on equity grounds and, therefore, can be included in analyses under equity. The drugs that are used to treat these rare conditions are typically labeled as orphan drugs. The European Union considers orphan medicinal products to be products that are used in the diagnosis, prevention, or treatment of life-threatening or very serious conditions that occur in fewer than five in 10,000 people.[60] In Canada, there is no clear definition of an orphan disease (http://www.raredisorders.ca).

The province of Alberta has recently implemented a Rare Diseases Dug Program. However, this program uses a strict definition of a rare disease as a genetic disorder that occurs in fewer than one in 50,000 Canadians or fewer than 50 Albertans. Diseases currently eligible for coverage consideration include: Gaucher disease; Fabry disease; mucopolysaccharidosis I (Hurler/Hurler Scheie syndrome); Hunter syndrome; and Pompe disease.[61] There is no corresponding definition for oncology rare diseases.

5.6 Costs and Resources

Because there is little research on any benefits beyond those to the individual in the health care system, researchers and economic analysts are encouraged to improve the robustness and quality of economic evaluations in the future by recognizing costs outside the health care system perspective.

6 CONCLUSION

This document provides guidance on methods that are used to conduct high-quality economic evaluations in the area of oncology. To ensure that health technology evaluations of new oncology products are conducted consistently, there is a need to increase the precision in describing what analytic methods are appropriate for a cancer-related health technology evaluation.

Adherence to the recommendations in this document should improve the quality and validity of oncology technology assessments. The use of these recommendations does not guarantee or entitle those who submit these analyses to receive funding through cancer agencies. Nor does the document provide guidance for decision-makers in terms of thresholds or how to make decisions on rare diseases.
These oncology guidelines should aid in creating transparency, consistency, and quality in economic evaluations of oncology interventions for the analyst and the reviewer. A dialogue between analysts and decision-makers should be encouraged.

Finally, this document is the first phase in the evolution of economic guidelines for oncology products. This document will be updated as more evidence on economic evaluation methods becomes available and as economic evaluations of oncology products mature. We encourage researchers to improve the methods that are used to conduct economic evaluations of oncology products.

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