# Guidance for Economic Evaluations of Tumour-Agnostic Products

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**About CADTH:** CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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# Acknowledgements


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# Abbreviations

**ICER** incremental cost-effectiveness ratio

**OS** overall survival

**PFS** progression-free survival

# Introduction

In recent years, several cancer drugs targeting genetic mutations or biomarkers have been developed. These mutations or biomarkers are present across many, if not all, tumour types with varying frequency. When these alterations are rare, regulatory agencies frequently approve a cancer drug based on a basket trial, a type of trial that tests a new drug across different types of cancer with the same mutation or biomarker.[1] The evidence generated by these basket trials is challenging when it comes to economic analyses. The sample size is often small, resulting in only a few patients per tumour type. These studies are often single-arm trials; therefore, the incremental effectiveness of the new therapy in comparison to the relevant comparator in patients with the target mutation or biomarker is often unknown. Specific guidance is required on how to best approach the economic analysis of tumour-agnostic treatments to ensure consistency with and adherence to CADTH's *Guidelines for the Economic Evaluation of Health Technologies: Canada, 4th Edition*.[2]

The intent of this document is to provide additional guidance that pertains specifically to the economic evaluation of tumour-agnostic products (i.e., drugs that target multiple cancer types that have the same genetic mutation or biomarker targeted by that drug).[3] The guidance in this document outlines the requirements for conducting economic evaluations when assessing these treatments. More detailed guidance may be available when considering specific decision problems (e.g., drug reimbursement reviews); readers should consult these documents if relevant.

# Specific Guidance

These topic areas require additional guidance:

- Target population
- Comparator
- Clinical effectiveness
- Costs and utilities
- Modelling
- Analysis and reporting
- Uncertainty

## Target Population

As per CADTH's economic guidelines:

> The economic evaluation should reflect the **entire target population** as defined by the decision problem. Researchers should, however, examine any **potential sources of heterogeneity** that may lead to differences in parameter-input values across distinct subgroups. Note that heterogeneity may result from differences in the natural history of the disease, effectiveness of the interventions, health state preferences, or costs of the interventions. Heterogeneity may result in different decisions with respect to cost-effectiveness among different subgroups. The responsibility of the researcher, therefore, is to establish whether important heterogeneity exits in parameter estimates. A **stratified analysis** will allow decision-makers to identify any differential results across subgroups.

To ensure adherence to CADTH's current economic guidelines, economic evaluations of tumour-agnostic products must satisfy the following:

- A stratified analysis must be conducted for all tumour types reflecting the entire target population. If a treatment is being considered at multiple different places in the treatment sequence for a specific tumour type, analysis should also be stratified by place in the treatment sequence and compared with appropriate alternatives at each place in the treatment sequence.
- The stratified analysis must be applied in the following situations (but not limited to these situations):
  - High-incidence cancer with a rare mutation
  - Low-incidence cancer with a mutation that has higher frequency or is characteristic for the cancer type
  - Tumours occurring most frequently in the study population
- Although an analysis may be difficult to perform in some instances (e.g., when there are limited data), the cost-effectiveness of therapy can only be inferred in those tumour types for which an analysis is performed.
- A scenario analysis should be conducted that includes all target indications, with results weighted by tumour prevalence, combining estimated outcomes for tumour types for which cost-effectiveness information has been provided, and assuming treatment costs but no incremental clinical benefit for those for which no information is provided (see Analysis and Reporting). This represents an optimistic scenario in the absence of comparative clinical evidence and the exclusion of any potential safety concerns.

## Comparator

As per CADTH's economic guidelines:

> All interventions currently used and potentially displaced should be identified in addition to interventions likely to be available in the near future.

To ensure adherence to CADTH's current economic guidelines:

- Comparators should be specific to the tumour site and line of treatment. Stratified scenario analyses at various lines of treatment may be necessary.
- The use of a single "pooled" comparator arm is not considered appropriate methodology because:
  - It violates the Markov assumption of homogeneity of population.
  - Each tumour type has a different set of comparators with varying efficacy outcomes (e.g., progression-free survival [PFS] and overall survival [OS]), different costs, and different utilities.
  - It neglects to consider potential changes in the population tumour mix with time.

## Clinical Effectiveness

As per CADTH's economic guidelines:

> Decision-makers are generally concerned with the impact of interventions on patients treated in routine practice. In the reference case analysis, this would entail the need for clinically meaningful outcomes to inform the duration and quality of life.

> Researchers should evaluate and justify the validity of any surrogate end points used for parameter estimation. Uncertainty in the association of the surrogate to the final clinical outcome should be reflected in the reference case probabilistic analysis. This uncertainty can also be explored through appropriate scenario analyses. The existence of multiple potential surrogates should be reflected in the analysis of uncertainty. When considering the use of biomarkers as surrogate end points, the researcher should evaluate and justify the validity of the biomarker and the degree to which the biomarker satisfies the criteria of a surrogate end point.

To ensure adherence to CADTH's current economic guidelines:

- When direct comparator evidence is not available through clinical trial(s) and a comparator arm is modelled based on the medical literature, the effectiveness and safety must be supported by a comprehensive and replicable review of the literature and a clear and transparent assessment of fitness for purpose.
  - Ideally, the comparator arm evidence is based on a population with the same mutation as patients in the treatment arm.
  - If the comparator arm is based on a population not known to have the specific mutation, this additional uncertainty should be considered for both the mean estimates and variance (i.e., beyond what is illustrated in the trial evidence). This is to ensure that the prognosis that may be associated with specific mutations is captured. Therefore, comparator treatment effectiveness in a cohort of patients without the exact same mutation may differ from a comparator cohort with the mutation.
- The use of a single pooled PFS or OS curve to represent the efficacy of the tumour-agnostic product is not considered appropriate methodology. This violates the assumptions of Kaplan-Meier analysis because:
  - The trial population consists of patients with various types of tumours with varying prognoses. Trial participant outcomes are not independent observations; survival times for participants with the same tumour type may be correlated.
  - Patients with poor tumour prognoses die earlier in the observation window which, over time, increases the number of patients with favourable prognoses in the at-risk population.
- If the economic evaluation is based on surrogate outcomes, these must be validated and the uncertainty fully propagated. Evidence of the predictive nature of the surrogate must be considered in the model structure.

## Costs and Utilities

As per CADTH's economic guidelines:

> As part of conceptualizing the model (see Modelling section) researchers should identify health states for which utilities will be required.
>
> The researcher should identify all activities and resources that are likely to occur within the context of the decision problem (e.g., accounting for the target population, perspective, and time horizon). The conceptualization of the clinical or care pathway for the health condition will provide the basis for identifying relevant resources. The structure of the pathway will dictate how resource use and the associated costs are included in the model (e.g., whether they are determined by health state or event). Researchers must consider all resources that occur along the pathway and that are attributable to the interventions of interest.

To ensure adherence to CADTH's current economic guidelines:

- The use of single pooled pre-progression and post-progression costs and utilities data is not considered appropriate methodology because:
  - It violates the Markov assumption of homogeneity of population.
  - Each tumour type has a different set of comparators with varying efficacy outcomes, different costs, and different utilities.
  - It neglects to consider the potential changes in the population tumour mix over time.

### Companion Diagnostics

- The cost of any companion diagnostic must be incorporated as per CADTH's economic guidelines, specifically guidance on companion diagnostics.[4] Special care must be taken to incorporate:
  - The costs of testing in all patients who need to be tested to identify the target population if this is not standard of care at time the analysis is conducted
  - The specificity and sensitivity of the test(s) and any variation by tumour type
  - The variability in diagnostic costs across tumour types

## Modelling

As per CADTH's economic guidelines:

> Most decision problems can be addressed with a wide variety of modelling techniques. The choice of model type should be related to the characteristics of the decision problem, with justification provided regarding the choice of modelling approach. For any type of modelling approach chosen, the model must be methodologically sound and transparent, and researchers are encouraged to follow good modelling practice guidelines.

To ensure adherence to CADTH's current economic guidelines:

- The chosen modelling technique must address the decision problem and appropriately reflect the conceptualization of the clinical or care pathway for the health condition and the intervention being compared.
  - The assumption of independence between PFS and OS required for partitioned survival models is not consistent with the available evidence.
  - Markov state transition models using the clinical trial evidence to estimate the rate of transition from "pre-progressed" to "progressed" and from "progressed" to "dead" are more appropriate for tumour-agnostic technologies.
  - There may be additional information in the literature to support the calculation of transition rates across states (e.g., from "progressed" to "dead") which may serve as a larger base of knowledge than the small sample size in the clinical trial. This approach uses all clinical evidence available to inform the transitions in the decision model and not only the clinical trial data, which is often limited by short trial length and small sample sizes.
- As per CADTH's economic guidelines, researchers should report the percentage of the estimated incremental benefit that occurs beyond the observed data, preferably by tumour type. Researchers should also justify the assumptions that lead to any benefits accrued outside of the observed data, such as the length of treatment effect.

## Analysis and Reporting

As per CADTH's economic guidelines:

> **Analysis**
>
> All expected costs and expected outcomes should be reported separately for each subgroup identified within the target population, with sequential analyses conducted for each stratum. If the decision problem requires an overall estimate, researchers can provide an estimate for the entire target population through weighting the results by subgroup.
>
> **Reporting**
>
> When a stratified analysis is conducted, but a decision-maker cannot implement decisions by subgroups, rather than calculating the mean result (i.e., the ICER) over the entire population, the appropriate estimate of the overall result is determined by weighting the estimates for each subgroup by their respective prevalence.

To ensure adherence to CADTH's current economic guidelines:

- Each stratum of the stratified analysis must be reported as per CADTH's economic guidelines (including sensitivity analysis) and incremental cost-effectiveness ratios (ICERs) must be reported by tumour site.
- An overall ICER for the entire target population must be computed from the tumour-specific incremental costs and quality-adjusted life-years using the population prevalence of these tumours (as opposed to the prevalence from the trial population). This ICER must be calculated based on the weighting of costs and effects, and then aggregated for the overall ICER.
  - The analysis must be probabilistic, as stipulated in the CADTH economic guidelines. Uncertainty about prevalence estimates must be reflected within the probabilistic scenario analyses, on which the effect of extreme prevalence values on the overall ICER is assessed.
- Analysis must take into account all tumour types that may be influenced by the decision problem, not just select tumour types.
- For tumour types that are not modelled, the expected incremental cost compared with best supportive care should be the incremental costs of treatment. In addition, the expected incremental quality-adjusted life-years compared with best supportive care should be a point estimate of zero.
- As indicated in the CADTH economic guidelines, uncertainty must be fully propagated throughout the model.

## Uncertainty

As per CADTH's economic guidelines:

> Economic evaluations are undertaken to inform decision-makers about the expected costs and outcomes of alternative courses of action. It is important that decision-makers be provided with accessible information on any uncertainty regarding the results. As such, researchers should take a systematic and consistent approach to the specification and analysis of uncertainty in economic evaluations. Three categories of uncertainty need to be explicitly addressed: methodological, parameter, and structural.

Economic analyses need to account for the greater clinical uncertainty often associated with these treatments, both within the period for which there are observed data and with respect to extrapolation.

### Uncertainty Related to the Observed Data

- When sample size (n) per tumour type is less than 30, the underlying assumptions of survival (time to event) analysis (e.g., homogeneity in the survival function, independence of censoring, uniformity within a time interval) may not be met.[5]
- If these underlying assumptions cannot be met or demonstrated, researchers must consider methods to account for the increased uncertainty associated with the information.
- Researchers should adopt approaches that account for censoring and time to event.
- These can include:
    - Bayesian methods with appropriate selection of prior distribution[5,6]
    - Alternative approaches, such as those proposed by UK NICE DSU, are also acceptable as scenario analyses

### Uncertainty Related to the Extrapolation of Clinical Effects

- Assumptions about the duration of treatment effect must be addressed in scenario analyses as per CADTH's economic guidelines (e.g., no or waning treatment effect beyond the observed period).
- Greater uncertainty in the extrapolation period should be considered and, if possible, validated using external data. If data do not exist, conservative assumptions (e.g., no benefit beyond time points for which data are available) should be considered in exploratory analyses to allow scenarios based on the available evidence.
- Simply assuming the same degree of uncertainty during the observed period is not considered appropriate methodology.

# References


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