Proposed Summary of Clinical Evidence and Economic Evaluation Template for Pharmaceuticals With Anticipated Comparator Efficacy and Safety Tailored Reviews

Instructions for Sponsors

Background

A pharmaceuticals with anticipated comparator efficacy and safety tailored review consists of CDA-AMC conducting an appraisal of the clinical evidence and economic evaluation submitted by the sponsor using this template. Information from the sponsor's submission will be validated and critically appraised by CDA-AMC.

Please read the instructions below and consult the recommended documentation before completing the template. If you have any questions regarding the application process, please email requests@cda-amc.ca with the complete details of your question(s).

Roles and Responsibilities for Publication

All Reimbursement Review reports are posted on the CDA-AMC website for anyone to access and review; although, in exceptional circumstances, embargo periods or redactions may be considered.

The sponsor is responsible for the quality, currency, propriety, and accuracy of the information provided to CDA-AMC for publication via this tailored review submission template, and that the content complies with both Canadian copyright law and current Ontario accessibility guidelines for posting information online (see section on accessibility below).

Should the tailored review submission be accepted for review and publication, the sponsor will have the opportunity to review the report for any inaccuracies or confidential information not in the public domain before posting on the CDA-AMC website.

Accessibility for Ontarians

In keeping with the *Accessibility for Ontarians with Disabilities Act* (AODA), all public documents must now be compliant with Ontario's accessibility guidelines to ensure access for people who experience disabilities. MS Word (and other Microsoft software) provides an Accessibility Checker for identifying and repairing accessibility issues, which is located under the **Review** tab and **Check Accessibility** sub-tab.

When completing your submission:

Reuse the existing AODA-compliant tables within this template if more tables are required. If using your own tables, ensure that all columns and rows have a header. Do not leave blank cells within tables.

Suggest 1 to 2 lines of alternative text (alt-text) to describe any figures or images included within this document.

When using figures and graphs, colour should not be used as the sole method for conveying content or distinguishing visual elements.

Before Completing the Template

Please review the following documents to ensure an understanding of our procedures and submission guidelines:

- Procedures for Reimbursement Reviews
- Pharmaceutical Review Updates for any applicable information.

Completing the Template

General Guidelines

Complete all sections of the template using 9-point Arial font type in text and 9-pont Arial font in tables. Do not alter the page margin settings. Include figure and table numbers and provide a list of figures and a list of tables after the table of contents. Data should reflect the results reported in the clinical study report(s) whenever possible. The total length of Sections 1 to 3 (excluding the tables of contents, abbreviations list, appendices, and reference list), cannot exceed 15 pages.

Provide clear references to source documentation used when completing the template. In-text citations to sponsor references must be referenced numerically in order of appearance using superscript numbers. The sponsor must provide an RIS file containing the references used in the report. An RIS file is a standardized bibliographic format that enables citation management programs to exchange documents.

When the template is complete, delete this cover page with the instructions, the record of updates section, and all red font instructions throughout the template. Please feel free to add company-specific elements such as a cover page, disclaimer, and/or footer as required. Save the completed template as a Word document.

Section 1

In this section the sponsor is required to summarize key background information regarding the drug under review and the condition for which the drug under review is indicated. Please ensure that statements are appropriately referenced.

Section 2

In this section the sponsor is required to summarize the results from a systematic literature review. The literature review must be conducted and reported in accordance with the instructions provided within this template. Appendices 1 to 5 accompany this section and must be completed.

Section 3

In this section the sponsor must summarize all indirect comparisons that have been included in the application (i.e., to support comparative efficacy or safety and/or the assumptions in the economic evaluation). In addition to this summary, the sponsor must provide the complete technical reports for the indirect comparisons as described in the Procedures for Reimbursement Reviews. Any sponsors who have not included one or more indirect comparisons in the application should explain within the template why an indirect comparison is not relevant for the review (i.e., do not delete the section if there are no data available). Appendix 6 accompanies this section and must be completed.

Section 4

This section is reserved for the CDA-AMC review of the sponsor's economic evaluation. In Appendix 7, which accompanies this section, the sponsor must summarize the treatment information, model information, data sources, and results of their cost minimization analysis. Please note that this appendix is to be completed in addition to the Technical Report and Excel workbook required per Section 5.6.2 of the Procedures for Reimbursement Reviews.

Record of Updates to Template

Version	Date	Summary of revisions
1	X	Original version posted

Table of Contents

Please update the Table of Contents prior to submitting the application.

List of Tables

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Abbreviations

Examples of commonly used abbreviations are provided below. Please add or remove from the list as needed.

AE	adverse event
CI	confidence interval
DB	double blind
EMA	European Medicines Agency
FAS	full analysis set
FDA	Food and Drug Administration
ITT	intention-to-treat population
PP	per-protocol
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SD	standard deviation
WDAE	withdrawal due to adverse event

Section 1. Introduction

Application Summary

Table 1: Application Submitted for Review

Item	Description
Drug (product)	Non-proprietary name (Brand Name), strength, dosage form(s), route of administration
Sponsor	
Health Canada indication	Health Canada indication as per product monograph (abbreviate if necessary); if pre-NOC submission state: Proposed:
Sponsor's reimbursement request	Ensure this is consistent throughout all components of the application If same as indication, state "As per indication."
Health Canada approval status	NOC, NOC/c, Under review (pre-NOC)
Health Canada review pathway	Standard, priority review, advance consideration under NOC/c, other (please specify)
NOC date	If NOC received, state: Month day, year If pre-NOC submission, state: anticipated Month day, year
Mechanism of action	State mechanism of action of the drug under review.
Recommended dosage	Recommended dose and dosage adjustments for notable subpopulations per the product monograph
Prescribing information	Please identify any confirmed or anticipated statements in the Canadian product monograph regarding restricting the prescribing and/or administration of the drug to certain health care professionals. If applicable, please provide details of any statements related to limiting the prescribing and/or administration of the drug to certain health care professionals. If there are no relevant statements, please state "Not applicable"

NOC = Notice of Compliance. Abbreviations must be listed under the table in alphabetical order.

Disease Background

Provide a brief description of the disease. Please ensure the following information is reported with references (as applicable): incidence and prevalence, signs and symptoms, natural history, disease staging, survival/mortality, and relevant prognostic factors.

Diagnosis of the Condition

Briefly describe any diagnostic tests that would be required or recommended to identify the patient population that could be eligible for treatment with the drug under review. This should include the name, analyte, and rationale for each diagnostic test. Please note if there are any confirmed or anticipated statements in the Canadian product monograph regarding specific diagnostic technology that is recommended for the drug under review.

Please provide a brief overview of the following, if applicable:

- any provinces or territories where there is likely to be limited access to the diagnostic testing requirements for the indication(s) of interest at the time CDA-AMC's review is targeted to be completed
- any initiatives being undertaken by the sponsor and/or others to increase the availability of the diagnostic test in Canada

Place in Therapy and Comparators

Current Treatment Options

Describe current therapeutic approaches (including pharmacological and non-pharmacological interventions) in Canada for the condition of interest.

- Cite clinical practice guidelines as appropriate.
- Describe the treatment goals (such as prolonging life, delaying disease progression, improving symptoms, minimizing side effects, improving quality of life, increasing the patient's ability to maintain employment, maintain independence, reducing burden on caregivers, etc.).
- Identify all drug therapies that are currently available for the target population. If some drugs are not listed on public formularies, please describe how they can be accessed by the patient.

Impact of Drug Under Review on Treatment Options

Please briefly describe the potential impact (if any) of the indication of interest on currently reimbursed treatments, including which treatments are expected to be displaced.

Comparators

The comparators in the systematic review should align with those included in the economic evaluation. All relevant comparators should be included unless the sponsor has discussed with CDA-AMC and received formal notification that one or more relevant comparators may be excluded. Relevant comparators include the following:

- treatments currently reimbursed by at least 1 participating drug plan for the indication under review,
- reimbursed treatments that are currently used off-label in Canadian practice, or
- treatments that have previously received a recommendation in favour of reimbursement from CDA-AMC for the indication under review).

Table 2: Key Characteristics of Drug 1, Drug 2, etc.

Drug	Mechanism of action	Relevant indication(s)	Route of administration and dosage	Serious adverse effects or safety issues
Drug under review		State indication under review	State recommended regimen	State serious warnings and precautions and notable contraindications from the product monograph.
Comparator 1		State relevant indications approved by Health Canada or note 'not approved' if used off-label	State dosage regimen recommended in the product monograph. If the indication has not been approved by Health Canada, please state the dosage regimen that is used in clinical practice and provide supporting referencing.	
Comparator 2		As above	As above	
Add rows as needed		Add rows as needed	Add rows as needed	

[a] Clinical evidence has not been submitted for this comparator versus the drug under review. (Delete if not applicable)

Section 2. Systematic Review

Objectives and Methods

To perform a systematic review of the beneficial and harmful effects of [state non-proprietary drug name] for [state the indication of interest].

Review Protocol

Guidance for defining the population, intervention, comparators, outcomes, and study designs (PICOS) for the review protocol are provided below.

Population

For initial submissions and resubmissions, the population will be defined as the full population identified in the approved/proposed Health Canada indication for which the sponsor is submitting (unless otherwise decided upon in consultation with CDA-AMC). While a sponsor's reimbursement request may be specific to a subgroup or subpopulation of patients within the Health Canada indication, the population defined in the systematic review protocol will typically not be limited according to the reimbursement request. Subpopulations identified in the sponsor's reimbursement request should be pre-specified in the protocol as a subgroup(s) of interest and results reported where available. Other relevant subgroups that are likely to be of interest to clinicians, drug plans, patients, and those included in the sponsor's pharmacoeconomic submission should also be included in the protocol. These should be based on clinically important prognostic factors, confounders, or modifiers of treatment effects.

Intervention

The intervention will be specified as the drug, formulation, and route of administration under review, and within the Health Canada approved dosage range. For studies that include multiple intervention arms with differing dosages, only those arms with dosages within the Health Canada approved range should be included in the systematic review. For pre-NOC submissions, where there is uncertainty about which doses will be approved by Health Canada, all dosage arms may be included.

Comparator(s)

The comparator(s) in the systematic review should align with those included in the economic evaluation. All relevant comparators should be included unless the sponsor has discussed with CDA-AMC and received formal notification that one or more relevant comparators may be excluded. Relevant comparators include the following:

- treatments currently reimbursed by at least 1 participating drug plan for the indication under review,
- reimbursed treatments that are currently used off-label in Canadian practice, or
- treatments that have previously received a recommendation in favour of reimbursement from CDA-AMC for the indication under review.

The review will typically focus on drug comparators that are reimbursed by public drug plans. Though not typical, in some circumstances nondrug comparators (e.g., transfusion, plasmapheresis) may also be included as comparators. Comparators not approved by Health Canada for the indication under review may also be considered relevant if they are the standard of care and their use is reimbursed by drug programs for the indication of interest. Comparators available through Health Canada's Special Access Program for the indication under review may also be considered.

Outcomes

End points should reflect those studied in the clinical development program for the drug review. This includes, but is not limited to:

- all primary endpoints in the clinical studies
- all secondary endpoints in the clinical studies (for most reviews)

- any end points included in the economic evaluation
- health-related quality of life endpoints (irrespective of classification within the hierarchy of endpoints in the trial protocol)

Study design
In addition to the clinical trials submitted as pivotal studies to Health Canada, other phase 3 or 4 randomized controlled studies should be included in the systematic review. Consideration may be given to including other study designs in the protocol-selected studies on a case-by-case basis (e.g., if the pivotal trials are not Phase 3 randomized controlled trials).

Table 3: Inclusion Criteria for the Systematic Review

Criteria	Description
Population	Specify population(s) Subgroups: List all relevant subgroups
Intervention	Drug, dose and route of administration, as applicable
Comparator	List all appropriate comparators
Outcomes	**Efficacy outcomes:** **Harms outcomes:** AEs, SAEs, WDAEs, Mortality, add AESI
Study designs	Pivotal trials, phase 3 RCTs

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Refer to Appendix 1 for details on the literature search strategy and study selection process and refer to Appendix 2 for the list of excluded studies.

Included Studies

Table 4: Details of Included Studies

Item	Study Name	Study Name
Study design and population		
Study design	Briefly describe (e.g., phase 3, double-blind, placebo-controlled RCT)	Briefly describe (e.g., phase 3, double-blind, placebo-controlled RCT)
Locations	List number of sites and state the countries/regions where the trial was conducted	List number of sites and state the countries/regions where the trial was conducted
Patient enrolment Dates:	**Start date:** State date **End date:** State date	**Start date:** State date **End date:** State date
Randomized (N)	State the total N and include the sample size in each treatment group.	State the total N and include the sample size in each treatment group.
Inclusion criteria	Please list key criteria only	Please list key criteria only
Exclusion criteria	Please list key criteria only	Please list key criteria only
Drugs		

Item	Study Name	Study Name
Intervention	State the drug, dosage, frequency of administration, route of administration, duration	State the drug, dosage, frequency of administration, route of administration, duration
Comparator(s)	For each comparator: state the drug, dosage, frequency of administration, route of administration, duration of treatment	For each comparator: state the drug, dosage, frequency of administration, route of administration, duration of treatment
Duration		
Screening phase	Specify duration	Specify duration
Run-in phase	Specify duration (delete if not applicable)	Specify duration (delete if not applicable)
Treatment phase	Specify duration	Specify duration
Follow-up phase	Specify duration	Specify duration
Outcomes		
Primary end point	State the primary endpoint including the timeframe (e.g., through 24 weeks)	State the primary endpoint including the timeframe (e.g., through 24 weeks)
Secondary and exploratory end points	**Secondary:** List the pre-specified secondary endpoints including the timeframe **Exploratory:** List the exploratory endpoints including the timeframe	**Secondary:** List the pre-specified secondary endpoints including the timeframe **Exploratory:** List the exploratory endpoints including the timeframe
Publication status		
Publications	State reference(s) to journal publications Author et al. Year[citation]	State reference(s) to journal publications Author et al. Year[citation]

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: For all tables reporting information from included studies, indicate data source including citation. Data should reflect the results reported in the clinical study report(s) whenever possible.

Description of Studies

For each study the following information should also be presented:

- Study objectives
- Randomization, whether randomization was stratified
- Data cut-off dates
- If applicable, briefly describe key design features (e.g., adaptive design, enrichment design, withdrawal design, cross-over design) and key points related to those features (e.g., duration of washout period between treatment periods in a cross-over study).
- For studies with a run-in/screening period, briefly describe its purpose.

Eligibility Criteria

Comment on criteria of note; there is no need to repeat all criteria listed in the summary table(s) provided above. Delete this section if not needed.

- Emphasize any key inclusion/exclusion criteria that are of importance to the condition or may identify a niche patient population
- Identify any important differences in inclusion and exclusion criteria between the studies.

Interventions

Briefly describe important details of the interventions employed in the included trials that are not already in the Details of Included Studies table (delete this section if not needed). This may include:

- A description of the titration schedule and the criteria used for determining the titration schedule should be included (e.g., fixed schedule or titration to target).
- For non-oral medications or medications requiring a device for administration (e.g., insulin pen, auto-injector, inhalation device), details related to the device, training, and administration should be included, examples of which are provided below:
    - For an injection, details may include whether the injection was self-administered or administered by study personnel at a study visit.
    - For an infusion, please include the infusion duration and indicate in what setting the infusion will be administered (i.e., hospital or infusion center).
    - If a device was used, please describe the training that was given initially and at each study visit. Please indicate if the device that was used is the same one that is or will be available in Canada.
- If the trial is blinded, indicate the use of placebos, double-dummy controls, and provide a brief description of the placebo including any methods to match administration and avoid unblinding.
- Include any criteria for rescue medication use where applicable, along with dosing schedules and maximum dosages permitted. Describe any stopping criteria for the intervention if relevant.
- Important permitted and/or prohibited concomitant medications and co-interventions.

Outcomes

Detailed descriptions of relevant outcome measures are presented in Appendix 3.

The summary table below is required for all applications. When identifying primary and secondary endpoints, include a superscript letter and footnote identifying which endpoints were adjusted for multiple comparisons in the statistical analyses.

Table 5: Summary of Outcomes Relevant to the Systematic Review

Outcome measure	Timepoint	Study 1	Study 2
List outcome 1	Please be specific (e.g., at 24 weeks; through 24 weeks)	Please state as: • Primary[a] • Key secondary[a] • Secondary • Tertiary • Exploratory • If the outcome listed in the row was used in some studies, but not others state 'not applicable' for those that did not include the outcome. Include a footnote to identify endpoints where statistical testing was adjusted for multiple comparisons	Please state as: • Primary[a] • Key secondary[a] • Secondary • Tertiary • Exploratory • If the outcome listed in the row used in some studies, but not others state 'not applicable' for those that did not include the outcome. Include a footnote to identify endpoints where statistical testing was adjusted for multiple comparisons
List outcome 2	As above	As above	As above
Add rows as necessary			

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: For all tables reporting information from included studies, indicate data source including citation. Data should reflect the results reported in the clinical study report(s) whenever possible.

[a] Statistical testing for these endpoints was adjusted for multiple comparisons (e.g., hierarchal testing)

Statistical Testing

Detailed descriptions of statistical analysis methods are presented in Appendix 3.

For multiple primary endpoints or analysis of the individual components of the composite endpoints, it should be specified if the analysis approach accounted for multiple testing with an appropriate control of the Type I error rate. For multi-arm trials, describe which arms were compared and whether a statistical adjustment was made for multiple testing with an appropriate control of the Type I error rate.

State whether the analyses presented in the report are the final analyses or interim analyses. If there were interim analyses, please state how these were accounted for in the statistical testing plan. For complex statistical testing structures (e.g., multiple endpoints) please ensure that the alpha level used for the endpoints is clearly stated in this section (please use a table to summarize if appropriate).

Subgroup Analyses

Key details of subgroup analyses should be reported, including whether they are pre-specified, whether the comparability of the treatment arms was checked, and whether multiplicity was taken into account.

Analysis Populations

Define analysis sets (e.g., FAS, PP, safety set) for each study included in the systematic review using text or a summary table.

Table 6: Analysis Populations of Study 1 and Study 2

Study	Population	Definition	Application
Study 1	e.g., Full analysis set	Add definition as per study protocol	State how the population was used in the analyses (e.g., all efficacy analyses)
	e.g., Safety analysis set	Add definition as per study protocol	State how the population was used in the analyses
	Add rows as required	Add rows as required	Add rows as required
Study 2	Add rows as required	Add rows as required	Add rows as required

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: For all tables reporting information from included studies, indicate data source including citation (and corresponding table number[s] in the clinical study report where applicable). Data should reflect the results reported in the clinical study report(s) whenever possible.

Patient Population

Baseline Characteristics

Summarize relevant baseline demographic and clinical characteristics of the population for each study using a table (example table below). Indicate in the table which analysis set the baseline characteristics have been summarized for (e.g., FAS set)

- for discrete data please report as n (%)
- for continuous data please report the mean (SD); where continuous data are skewed also report the median (IQR or range)

More than one table can be created if all studies do not fit in a single table. Additional text is not necessary for this section.

Table 7: Summary of Baseline Characteristics of Study 1 and Study 2

Characteristic	Study 1		Study 2	
	Treatment 1 (N =)	Treatment 2 (N =)	Treatment 1 (N =)	Treatment 2 (N =)
Study variable (units), measurement (% or variability of measurement) Example: Age (years), median (range)				

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: For all tables reporting information from included studies, indicate data source including citation (and corresponding table number[s] in the clinical study report where applicable). Data should reflect the results reported in the clinical study report(s) whenever possible.

Patient Disposition

Please summarize the patient disposition for each included study using a table. Additional text is not necessary for this section.

Table 8: Patient Disposition for Study 1 and Study 2

Patient disposition	Study 1		Study 2	
	Treatment 1 (N =)	Treatment 2 (N =)	Treatment 1 (N =)	Treatment 2 (N =)
Screened, N				
Reason for screening failure, N (%)				
State reason 1				
State reason 2				
Add/modify rows as required				
Randomized, N (%)				
Discontinued from study, N (%)				
Reason for discontinuation, N (%)				
Adverse events				
Lost to follow-up				
Add/modify rows as required				
FAS, N				
PP, N				
Safety, N				

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: For all tables reporting information from included studies, indicate data source including citation (and corresponding table number[s] in the clinical study report where applicable). Data should reflect the results reported in the clinical study report(s) whenever possible.

Exposure to Interventions

Study treatments

Summarize exposure using a table (example provided below) or paragraph text. Include information on adherence to treatment where relevant.

Table 9: Exposure to Study Treatment for Study 1 and Study 2 (Sample Table)

Exposure	Study 1		Study 2	
	Treatment 1 (N =)	Treatment 2 (N =)	Treatment 1 (N =)	Treatment 2 (N =)
Total, patient-weeks or patient-years				
Duration, mean (SD)				
Duration, median (IQR or range)				
Adherence, %				

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: For all tables reporting information from included studies, indicate data source including citation (and corresponding table number[s] in the clinical study report where applicable). Data should reflect the results reported in the clinical study report(s) whenever possible.

Concomitant Medications and Co-Interventions

Briefly describe concomitant medications or cointerventions required during the study. If concomitant medication doses were lowered or treatment stopped, describe the schedule as applicable (e.g., tapering corticosteroids). Additional information (i.e., a summary table) can be included in Appendix 4.

Subsequent Treatment (if applicable)

Please describe any protocols for managing cross-over to other treatment groups (e.g., placebo to active treatment) or the provision of additional therapies or interventions during the treatment period or follow-up phase (e.g., additional anticancer medication or surgery upon documented disease progression). If applicable, a table summarizing the overall use of subsequent treatments and breakdown of specific treatments and/or interventions can be included in Appendix 4.

Results

Efficacy

Summary of Key Efficacy Outcomes

Provide a table similar to the example below summarizing key efficacy outcomes for the studies (indicate the analysis population in the title or headings or by using footnotes). Results for other included efficacy outcomes can be reported in the text or in additional tables.

Table 10: Summary of Key Efficacy Results

Variable	Study 1 Treatment 1 N =	Study 1 Treatment 2 N =	Study 2 Treatment 1 N =	Study 2 Treatment 2 N =
Outcome 1				
Number of patients contributing to the analysis				
Baseline, mean (SD)				
Change from baseline, mean (SE)				
Treatment group difference versus control (95% CI)				
P value				
Outcome 2				
n (%)				

Variable	Study 1 Treatment 1 N =	Study 1 Treatment 2 N =	Study 2 Treatment 1 N =	Study 2 Treatment 2 N =
OR/RR (95% CI)				
RD (95% CI)				
P value				
Outcome 3				
Events, n (%)				
Overall survival (months), median (95% CI)				
HR (95% CI)				
P value				
Survival probability (%) at X months (95% CI)				
Difference in survival probability (%) (95% CI)				
Outcome 4				
As above				

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; FAS = full analysis set; RR = relative risk; OR = odds ratio.

Source: For all tables reporting information from included studies, indicate data source including citation (and corresponding table number[s] in the clinical study report where applicable). Data should reflect the results reported in the clinical study report(s) whenever possible.

Add footnotes (accompanied by superscript letters in the table) for the following:

- To specify (as applicable) model, adjustment factors, analysis population, and handling of missing data.
- To denote P values that have been adjusted for multiple testing.

Efficacy End Point 1

The text of the efficacy section should convey the main messages of the data that are presented in tables or graphs — please be concise and clear in the text.

Please avoid the following when presenting results:

- Interpreting the difference between two groups as being statistically significant based upon nonoverlapping confidence intervals for the individual within groups change (rather than a statistical test of the difference between groups).
- Focusing on the clinical relevance of within groups changes rather than the clinical relevance of the difference in the between groups change when there is a comparison group.

For time-to-event analyses overall frequency of events, number of patients censored, and time of follow-up (e.g., total days of follow-up, median or mean time of follow-up) for each stratum should be presented descriptively.

In addition to any relevant relative differences in effects (e.g., odds ratio, relative risk, hazard ratio), absolute differences in effects with confidence intervals should be presented in the data tables. These include mean difference for continuous outcomes, risk difference for dichotomous outcomes, and difference in survival probability for outcomes from time-to-event analyses. If data for these measures are unavailable, indicate this in the data table or text (e.g., not reported [NR] or not available [NA]).

Summarize the results from key sensitivity analyses and subgroup analyses under each of the outcomes. Subgroup analyses should reflect those that are specified within the systematic review protocol. If results for pre-specified subgroups for key end points notably differ from the main results, they may be reported in table format in an added appendix titled “Results of Subgroup Analyses for Studies in the Systematic Review”.

If data within the report are derived from different cut-off dates, please ensure that the dates are clearly specified when reporting the results.

Efficacy End Point 2

Please use a separate subheading for each endpoint.

Efficacy End Point 3

Please use a separate subheading for each endpoint.

Harms

In this space the sponsor must summarize key adverse event data for the drug under review. Do not report results of statistical analyses for safety outcomes.

Overview of Safety

Detailed results for harms are presented in Appendix 5.

Briefly summarize in text format (for treatment-emergent adverse events):

- Overall occurrence of AEs, SAEs, and deaths
- The most common AEs and SAEs
- If applicable, additional key takeaways

Withdrawals Due to Adverse Events

Summarize withdrawals due to adverse events and adverse events that resulted in an interruption of the study treatment(s). Clearly identify if the adverse events resulted in discontinuation of the study treatment and/or complete discontinuation from the study.

Adverse Events of Special Interest

Provide a brief summary of any adverse events of special interest. If relevant, provide a summary of how these events were managed in the clinical trial. Delete this section if not applicable.

Section 3. Indirect Evidence

In this section of the template the sponsor must summarize all indirect comparisons that have been included in the application (i.e., to support comparative efficacy or safety and/or the assumptions in the economic evaluation). If the application does not include one or more indirect comparisons, the sponsor should explain why an indirect comparison is not relevant for the review (i.e., do not delete this section if there are no data available).

Description of Indirect Comparison(s)

In this section the sponsor should summarize the methods and results of all indirect comparisons included in the application.

Objectives

Provide the objective of the indirect comparison focusing on the evidence gap it is aiming to address (e.g., absence of direct evidence for relevant comparators).

Study Selection and Review Methods

Details on study selection criteria and review methods are presented in Appendix 6.

Briefly state the scope (population, comparators, and outcomes) of the ITC(s).

Indirect Comparison Analysis Methods

Details on analysis methods for the indirect comparisons are presented in Appendix 6.

Briefly state the type of analysis performed.

Results

Summary of Included Studies

The table below is an example of what may be used to provide a description of important differences across trials for key characteristics. The list of characteristics are just examples; please delete or add rows as appropriate. No evidence of effect modification may be added as a comment, if appropriate.

Describe the trials included in the systematic review, and the indirect comparison analysis (including number of trials and patients), highlighting potential sources of heterogeneity (e.g., in the patients, interventions, outcomes, study design or follow up time). Please ensure that features that could lead to differences in treatment effect modifiers are addressed (e.g., patients recruited to studies of A versus B have less advanced disease than those in A versus C).

Consider: Dosage, treatment duration, route of administration, supportive care as well as information on treatment titration, induction or maintenance treatment. Highlight the differences between trials, if any.

Table 11: Assessment of Homogeneity (Sample Table)

Characteristics	Description and handling of potential effect modifiers
Disease severity	Comment on similarities and differences across studies and note if there were any relevant adjustments or sensitivity analyses.
Treatment history	As above
Trial eligibility criteria	As above
Dosing of comparators	As above
Placebo response	As above
Definitions of endpoints	As above
Timing of endpoint evaluation	As above
Withdrawal frequency	As above
Clinical trial setting	As above
Study design	As above

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: Indicate data source including citations.

Efficacy

Provide a summary of the indirect comparison results for efficacy outcomes, including point estimates and 95% confidence intervals and/or credible intervals (as appropriate for the method of analysis) for pairwise comparisons of interest to the review. Present a summary of the results for relevant comparators.

- Describe the results relating to how well the selected model(s) fits the data
- Provide a brief summary of the results of subgroup analyses and/or meta-regression, if relevant. If relevant/necessary, present the results of one or more sensitivity analyses. It is often sufficient to state that the results of all sensitivity analysis were consistent with the base case (if the methods used for the sensitivity analyses are appropriate and described adequately).

The table below is an example of a format that may be used to summarize results.

Table 12: ITC Sample Data Table (e.g., Summary of NMA Results for Efficacy Results, [Treatment] Versus Comparators)

Comparator	Outcome 1 (units) at time point, mean difference and/or OR (95% CrI)	Outcome 2 (units) at time point, mean difference and/or OR (95% CrI)
[Comparator 1]		
[Comparator 2]		
[Comparator 3]		

Abbreviations must be listed under the table in alphabetical order. For example, CrI =, credible interval; FE = fixed effects; OR = odds ratio; RE = random effects; NA = not applicable; NMA = network meta-analysis.

Source: Indicate data source including citation.

Efficacy End Point 1

Please use a separate subheading for each endpoint.

Efficacy End Point 2

Please use a separate subheading for each endpoint.

Efficacy End Point 3

Please use a separate subheading for each endpoint.

Harms

Provide a summary of the indirect comparison results for harms outcomes using the guidance provided above. If no harms endpoints were evaluated in the indirect comparison, please state this within this section (i.e., do not delete the section heading in the absence of comparative harms data).

Section 4. Economic Evaluation

This section is reserved for the CDA-AMC review of the sponsor's economic evaluation and is to be left blank by the sponsor.

Appendix 1: Literature Search Strategy

Literature Search and Study Selection

Literature Search Methodology

Literature searches must be developed following internationally accepted standards for systematic reviews. Examples of search guidance documents include:

- European Network for Health Technology Assessment. Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness. Methodological Guidelines. Diemen (The Netherlands): EUnetHTA; 2019.
- Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021.

Searching bibliographic databases

MEDLINE and Embase must be searched as these are the major biomedical bibliographic databases that concern pharmaceuticals. Other databases may be included as relevant, for example: (Cochrane, CENTRAL, PsycINFO, CINAHL, Scopus, Web of Science). Use a sensitive database search strategy, employing:

- controlled vocabulary (e.g., MeSH, Emtree terms, etc.)
- text words (e.g., synonyms)
- registry numbers
- chemical drug names
- trade drug names
- generic drug names

Follow field codes and syntax correctly for each database (platform) searched, for example:

- Ovid MEDLINE: (trade drug name or generic drug name or developmental drug name).ti,ab,kf,ot,hw,rn,nm.
- Ovid Embase: Generic drug name/ or (trade drug name or generic drug name or developmental drug name).ti,ab,kf,ot,rn,dq.

In some instances, it may be necessary to apply a search concept for the indication/condition. Similar principles to search strategy design apply: controlled vocabulary (e.g., MeSH, Emtree terms, etc.); text words (e.g., synonyms).
If applying study design filters to the search, consult available search filters as outlined by these resources:

- CDA-AMC's database search filters
- Glanville J, Lefebvre C, Manson P, Robinson S and Shaw N, editors. ISSG Search Filter Resource. York (UK): The InterTASC Information Specialists' Sub-Group; 2006 [updated 9 Nov. 2021; cited 9 Nov. 2021].

Peer review is strongly recommended, using the *PRESS Peer Review of Electronic Search Strategies*

Searching clinical trial registries

Multiple trial registries should be searched and reported on in the literature search appendix section, including:

- ClinicalTrials.gov: Produced by the U.S. National Library of Medicine
- WHO ICTRP: International Clinical Trials Registry Platform, produced by the World Health Organization
- Health Canada's Clinical Trials Database
- EU Clinical Trials Register: European Union Clinical Trials Register, produced by the European Union

Reporting of the literature search

Systematic literature searches must be reproducible. The search strategy should be reported in the literature search appendix section. Elements presented should follow the *PRISMA-S extension checklist*.

Example of Reporting Clinical Literature Search Methods

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist. Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid; Embase (1974–) via Ovid; Cochrane Central Register of Controlled Trials (CCTR) via Ovid; and Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO. All Ovid searches were run simultaneously as a multi-file search. Duplicates were removed using Ovid deduplication for multi-file searches, followed by manual deduplication in Endnote. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were [intervention] and [indication/population]. Clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. See Appendix 1 for the detailed search strategies. The initial search was completed on MONTH DAY, YEAR.

Example of Literature Search Strategy Reporting

Databases

- Ovid – MEDLINE All (1946-present)
- Ovid – Embase (1974-present)
- Ovid – Cochrane Central Register of Controlled Trials (CCTR)
- EBSCO – CINAHL
- Scopus
- Web of Science

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid. Other duplicates were removed using bibliographic management software.

Date of searches: [Provide search date. If dates vary, provide search date for each database]

Search filters applied: Systematic reviews; meta-analyses; network meta-analyses; health technology assessments; guidelines; overview of reviews; randomized controlled trials; controlled clinical trials; qualitative studies; observational studies; economic evaluations; costs and cost analysis studies, and quality of life studies.

Limits

- Publication date limit: none
- Language limit: none
- Humans

Database Search Strategies
Provide search strategies

Clinical Trials Registries

ClinicalTrials.gov
Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials. [Search terms – List search terms]

WHO ICTRP
International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. [Search terms – List search terms]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials. [Search terms – List search terms]

EU Clinical Trials Register
European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials. [Search terms – List search terms]

Study Selection

Figure [Number]: PRISMA Flow Diagram

In this space the sponsor should provide a PRISMA diagram depicting the flow of information through the different phases of the systematic review. For additional information, including examples and templates for PRISMA diagrams, please see: http://prisma-statement.org/prismastatement/flowdiagram.aspx

Appendix 2: List of Excluded Studies

Table 13: Excluded Studies

Reference	Reason for Exclusion
Add reference	When identifying the reason for exclusion, please use a similar format as the following examples: • Study design • Intervention (if the intervention in the study does not meet that identified in the systematic review protocol, for example, different dose, formulation, etc.) • Comparator • Study population • Duplicate study
As above	As above
Add rows as necessary	

Appendix 3: Outcome Measures and Statistical Analysis for Studies in the Systematic Review

Description of Outcome Measures

Describe each of the outcome measures reported in the systematic review and provide information on minimal important differences (MID).

- Briefly describe the relevant efficacy outcomes for the included studies (i.e., all outcomes included in the protocol) in sufficient detail for the reader to be able to understand and interpret the outcome data (definitions and measurement).
- Descriptions of scale measures should include a brief overview of the scale including:
  - Construct(s) or domain(s) measured
  - Structure of the scale (i.e., is there one single overall score or individual domain scores or both)
  - Range of scores.
  - Direction of the scale (e.g., do higher scores indicate greater impairment? Better HRQoL?)
  - Whether or not an estimated MID was identified (for overall and individual domain scores). Please clearly state the source of the MID (e.g., reference to publication, regulatory opinion, clinical expert opinion) and the method used for estimation (e.g., anchor-based) and whether the MID refers to within-group or between group differences (or both). Identify the population in which the MID was estimated (e.g., patients with severe COPD; general population estimate). If multiple estimates of the MID are identified, the full range of MIDs should be reported. If no MID has been identified, this should be explicitly stated.
- Describe how outcomes are adjudicated (centrally adjudicated, or investigator adjudicated, or both).
- Responder definitions, cut points and rationale for cut point selection should be described and referenced.

Statistical Analysis

Clinical Trial Endpoints

Provide a brief description of the statistical analysis for each outcome reported in the systematic review.

- The covariates and/or baseline values that were included in the statistical models should be specified. It should be stated that the analysis was unadjusted if no covariates and/or baseline values were included in the analysis.
- If a historical control was used, the source of the data and method for statistical comparison to the active treatment arm should be reported.
- Data imputation and other missing data methods (e.g., LOCF, statistical models such as MMRM, non-responder imputation) and the associated assumptions should be reported.
- The main sensitivity analyses, if any, and the rationale for the analysis (e.g., alternate analyses that use different imputation techniques) should be described.
- Repetition within the description and the information provided in the summary table(s) should be avoided where possible. If methods for the secondary outcomes are similar to those for the primary outcome, simply state this and highlight any differences.
- Items should be summarized in a table where appropriate (see example below). Paragraph text is not needed if all details are in the table.

Table 14: Statistical Analysis of Efficacy End Points

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity analyses
Study 1				
List endpoint 1	e.g., MMRM	Please list the factors which were adjusted (e.g., baseline values, age, etc.)	Please state how missing data were addressed	Please list all sensitivity analyses (e.g., multiple imputation)
Add rows as required	As above	As above	As above	As above
Study 2				
As above	As above	As above		As above

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: For all tables reporting information from included studies, indicate data source including citation.

Sample Size and Power Calculation

Report assumptions regarding expected differences in treatment effect and variation (e.g., SD), as well as the rationale for selecting the parameters used in the calculation. Other potentially relevant information (e.g., whether loss to follow-up was accounted for, if there were power calculations for secondary endpoints) should be reported as applicable.

Appendix 4: Exposure to Other Treatments for Studies in the Systematic Review

If there is no relevant information to present in this appendix, include a statement to that effect.

Table 15: Sample Table for Subsequent Treatment

Exposure	Study 1		Study 2	
	Treatment 1 (N =)	Treatment 2 (N =)	Treatment 1 (N =)	Treatment 2 (N =)
Received subsequent therapy, n (%)				
State therapy, n (%)				
State therapy, n (%)				
Add rows as required				

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: For all tables reporting information from included studies, indicate data source including citation (and corresponding table number[s] in the clinical study report where applicable). Data should reflect the results reported in the clinical study report(s) whenever possible.

Appendix 5: Detailed Harms Results for the Studies in the Systematic Review

Provide an overall summary table of key harms data (example shown below). Please note the following:

- Thresholds for common events may vary across development programs. Please ensure that the threshold for inclusion in the table is clearly reported (e.g., ≥ 5% of patients). The threshold should generally align with what has been included in the draft or final product monograph.
- Please report individual events at the preferred term level.

Table 16: Summary of Key Harms Results

Adverse events	Study 1		Study 2	
	Treatment 1 (N =)	Treatment 2 (N =)	Treatment 1 (N =)	Treatment 2 (N =)
Most common adverse events, n (%)				
≥ 1 adverse event				
State adverse event				
State adverse event				
Add rows as required				
Serious adverse events, n (%)				
Patients with ≥ 1 SAE				
State SAE				
State SAE				
Add rows as required				
Patients who stopped treatment due to adverse events, n (%)				
Patients who stopped				
State adverse event				
State adverse event				
Add rows as required				
Deaths, n (%)				
Patients who died				
Add description of events or list of common causes of death				
Add rows as required				
Adverse events of special interest, n (%)				
Specify events based on those listed in the safety evaluation plan, n (%)				
Add rows as required				

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: For all tables reporting information from included studies, indicate data source including citation (and corresponding table number[s] in the clinical study report where applicable). Data should reflect the results reported in the clinical study report(s) whenever possible.

Appendix 6: Detailed Methods for the Indirect Comparisons

If no indirect treatment comparisons are included in the application include a statement to that effect.

Study Selection and Review Methods

Summarize each included ITC in text or one or more tables similar to the one below. Do not repeat information in the text that is presented in the tables.

- Describe the methods used to conduct the systematic review and to select studies for inclusion in the indirect comparison.
- Describe the methods used to extract data (e.g., duplicate extraction, or single reviewer extraction with check).
- Describe how the authors assessed study quality, and how this information was used (e.g., to exclude certain studies).

Table 17: Study Selection Criteria and Methods for Indirect Comparisons

Item	Description
Criteria	
Population	Briefly state the population(s) of interest for the indirect comparison
Intervention	List intervention including dosing information
Comparator	List comparators including dosing information
Outcome	List outcomes including time points
Study designs	Briefly describe the study designs included in the indirect comparison
Publication characteristics	Specify inclusion of published and/or unpublished studies
Exclusion criteria	Briefly describe the exclusion criteria used for selecting studies
Methods	
Databases searched	Briefly list databases included in the literature search
Selection process	Briefly describe the review methods (e.g., articles screened independently by 2 researchers)
Data extraction process	Briefly describe the review methods
Quality assessment	Briefly describe the methods used to assess the quality of studies (e.g., appraisal tools)

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: Indicate data source including citation.

Indirect Comparison Analysis Methods

- Briefly describe the following (where applicable), either in text or table format:
  - The statistical model
  - How model fit was assessed. If multiple models were run, describe how the model selected as the primary analysis was chosen. If only 1 model was used, please provide the reason(s).
  - Please note the following for Bayesian models:
    - Describe prior distributions for modeling parameters.
    - Describe justification for use of informative priors, and whether sensitivity analyses were done to assess the impact of the priors selected.
    - Convergence diagnostics, burn-in period, number of iterations and number of chains should also be described.
  - How homogeneity was assessed. Please address clinical, methodological, and statistical heterogeneity.

  - Steps taken to address potential sources of heterogeneity (e.g., excluding studies, doses, or timepoints from the analysis) or meta-regression analyses.
  - Rationale for sensitivity analysis with description of methods used.
  - Rationale for subgroup analysis with description of methods used.
  - How consistency between direct and indirect comparisons were evaluated (if relevant e.g., inconsistency modelling, simple direct versus indirect, or if it was not possible to assess consistency due to the lack of a closed loops)
  - Methods used to conduct standard pairwise meta-analysis (if conducted).
  - For Network Meta-Analyses, how nodes in the network were constructed, how different doses, different routes of administration, different drugs within the same class, and comparators were handled (separate nodes or pooled analysis).
  - Methods used for rescaling or conversion of results to a common scale, in cases where studies reported different scales or measures. Discuss appropriateness of any methods for reconstructing individual patient data from summary data.
  - Which set of analysis results have been used where studies have conducted multiple analyses of a given endpoint (e.g., multiple approaches to dealing with missing data).
  - The outcomes were analyzed and the rationale for excluding any of those that were pre-planned for analyses.

- The table below provides an example of how the key data elements may be described using a table format. Add or delete rows as appropriate. As methods may vary for different types of outcomes (continuous, dichotomous) or by network or population, additional columns may be added as needed.

Table 18: Indirect Comparison Analysis Methods

Methods	Description
Analysis methods	Briefly describe the methods
Priors	As above
Assessment of Model fit	As above
Assessment of Consistency	As above
Assessment of Convergence	As above
Outcomes	As above
Follow-up timepoints	As above
Construction of nodes	As above
Sensitivity analyses	As above
Subgroup analysis	As above
Methods for pairwise meta-analysis	As above

Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio

Source: Indicate data source including citation.

Appendix 7: Summary of Sponsor's Economic Evaluation

Please note that this appendix is to be completed in addition to the Technical Report and Excel workbook required per Section 5.6.2 of the Procedures for Reimbursement Reviews.

Table 19: Key Components of the Sponsor's Economic Evaluation

Component	Description
Treatment information	
Drug under review	Generic name (Brand). Note if DUR is used in addition to other treatment(s). Summarize the recommended dosage as per the product monograph
Submitted price of Drug Under Review	Generic name (Brand): Price per lowest dispensable unit (e.g., per tablet, vial, prefilled syringe) to 4 decimal places as per Pricing and Distribution document for each form/strength
[Annual or per-course costs] of [Drug Under Review]	State the assumed/calculated treatment cost (annual or per course [e.g., 28-day course]) including full regimen cost if drug under review is part of a regimen If any modifying assumptions are made (e.g., weight-based dose, relative dose intensity, different costs in first course vs. subsequent course) please describe them here
Model information	
Type of economic evaluation	Cost-minimization analysis
Treatment assessed	State the drug or regimen under review
Included comparator(s)	Generic name. Note if comparator is used in addition to other treatment(s). If one of the comparators is best supportive care, standard of care, etc., define what it is comprised of. If multiple comparators, use an alphabetized, bulleted list
Perspective	State the perspective, i.e., Publicly funded health care payer
Time horizon	State the time horizon, e.g., # years
Modelled population(s)	Briefly describe the modelled population
Characteristics of modelled population	State the mean starting age of patients in the population, along with any other relevant characteristics (e.g., sex, weight, BMI/BSA)
Model health states	If needed, describe the model's health states and how transitions are assumed to occur between them. If there are no modelled health states, please state "Not applicable".
Data sources	
Comparative efficacy	Describe the sources inputs, and assumptions made that inform the comparative efficacy of the drug or regimen under review relative to the included comparator(s).
Resource use and other costs	Briefly describe the sources, inputs, and assumptions pertaining to additional resource use costs (e.g., hospital and laboratory services, specialist visits)
Summary of the submitted results	
Base case	State the base case results
Scenario analysis	Present influential scenario analyses as required

Abbreviations must be listed under the table in alphabetical order.

References

References must be provided in this section and should adhere to standard citation practices for publication, as per the following examples:

1. Murray CJL. Maximizing antiretroviral therapy in developing countries: the dual challenge of efficiency and quality [published online December 1, 2014]. *JAMA*. doi:10.1001/jama.2014.16376
2. Centers for Medicare & Medicaid Services. CMS proposals to implement certain disclosure provisions of the Affordable Care Act. http://www.cms.gov/apps/media/press/factsheet.asp?Counter=4221. Accessed January 30, 2012.
3. McPhee SJ, Winker MA, Rabow MW, Pantilat SZ, Markowitz AJ, eds. *Care at the Close of Life: Evidence and Experience*. New York, NY: McGraw Hill Medical; 2011.