Canada's Drug and
Health Technology Agency

CADTH Consultation: Proposed Process for Time-limited Reimbursement Recommendations

March 2023

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Introduction

Scope and Purpose of the Consultation

CADTH is inviting stakeholder feedback on a proposal to introduce time-limited reimbursement recommendations. We thank you in advance for your interest in CADTH's reimbursement review process.

What are time-limited reimbursement recommendations?

Time-limited reimbursement recommendations are recommendations that would be issued in favour of reimbursement in a manner that is time-limited and contingent on a future reassessment of additional evidence that addresses the uncertainty with the comparative clinical benefit and cost-effectiveness for the drug or drug regimen under review.

Why are time-limited recommendations a priority for CADTH?

CADTH is undertaking this initiative to:

- help ensure timely access to promising new therapies for serious conditions where there is unmet medical need
- ensure CADTH recommendations accurately reflect the currently available evidence when drugs have received conditional regulatory approval
- increase the confidence of CADTH recommendations and reports through improved reporting and consideration of evidentiary gaps and postmarket clinical studies designed to address uncertainty with the clinical evidence as reflected in the conditional regulatory approval.

Evolving Regulatory Landscape

Developments with global regulatory authorities are leading to faster and more agile review processes (e.g., conditional terms and conditions associated with approvals based on early-phase clinical data). These regulatory initiatives are an important consideration for CADTH and our expert committees as we seek to modernize our review processes to allow for greater confidence in CADTH recommendations where there is uncertainty in the clinical evidence. CADTH will continue to monitor Health Canada's initiatives on *Regulatory innovation for health products: Agile licensing for drugs* and would amend the procedures for time-limited recommendations to align with any confirmed revisions to the Health Canada processes for conditional regulatory approval in Canada.

How to Participate in the Consultation

To provide comments on the proposal, please use the feedback template. Feedback must be received by CADTH by **5:00 p.m. ET on May 1, 2023**. For feedback to be considered, you must identify yourself to CADTH. Only 1 response per organization will be considered. If you have any questions about the feedback process, please email CADTH.

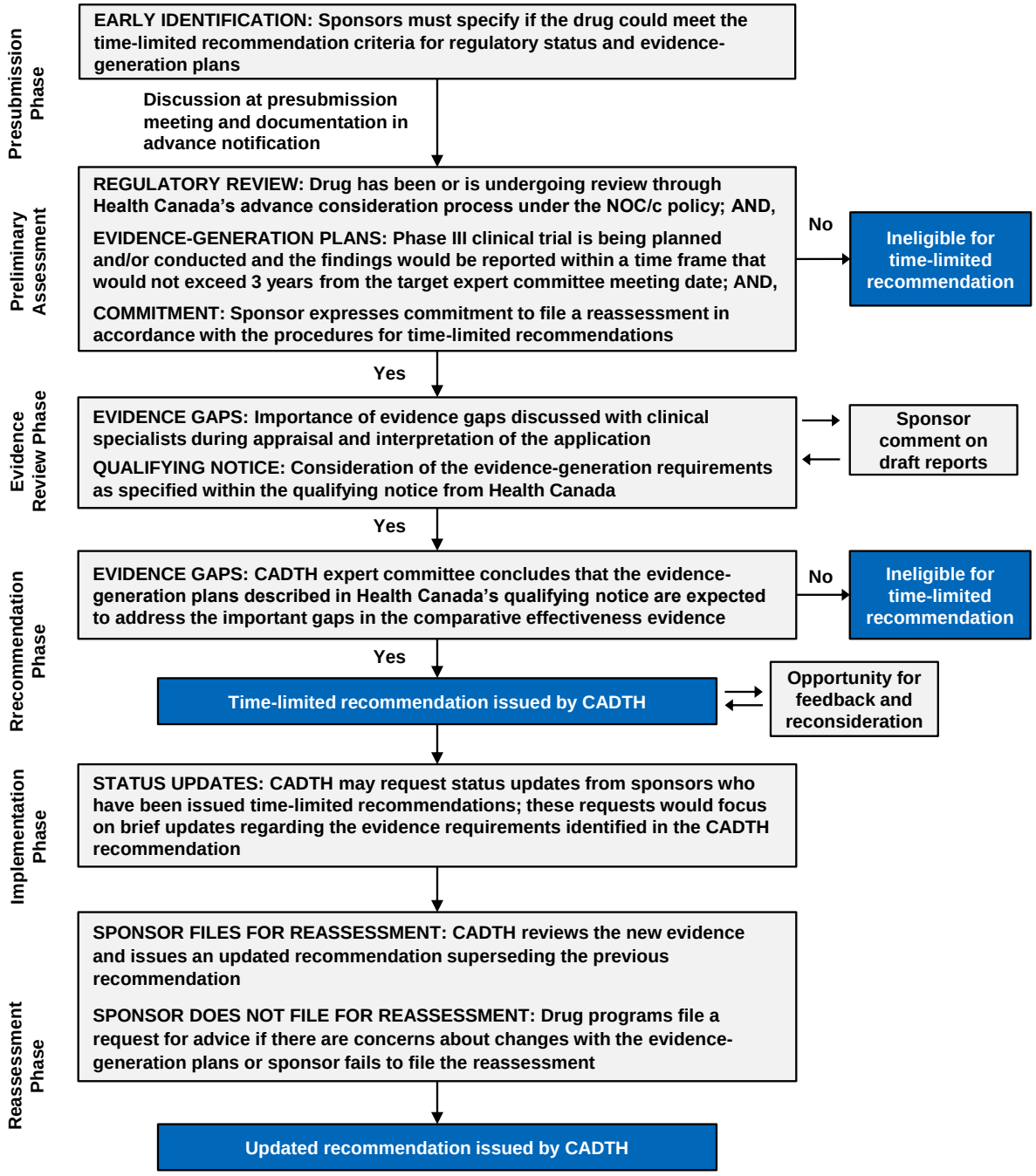
Consideration of Feedback

Following the consultation period, CADTH will carefully assess all stakeholder feedback before announcing the final details of the new time-limited reimbursement recommendation process. This will involve disclosing some or all comments or materials, or summaries of them, to CADTH's advisory bodies and the participating jurisdictions.

Proposal for Issuing Time-Limited Recommendations

Figure 1: Summary of Proposed Process for Time-Limited Recommendations

Alt text: Figure shows a high-level summary of the proposed process for issuing and reassessing time-limited recommendations.



NOC/c = Notice of Compliance with Conditions.

Eligibility Criteria for Time-Limited Recommendations

Proposed Eligibility Criteria

CADTH is proposing that eligibility for consideration for a time-limited recommendation initially be limited to files with the following characteristics:

1. **Regulatory review status:** The drug has been or is undergoing review through Health Canada's advance consideration process under the Notice of Compliance with Conditions (NOC/c) policy or the approval is accompanied by terms and conditions (CADTH will continue to monitor Health Canada's initiatives on *Regulatory innovation for health products: Agile licensing for drugs* and would amend the process align with any confirmed revisions to the NOC/c process in Canada); **AND,**
2. **Evidence-generation plans:** A phase III clinical trial is being planned and/or conducted in the relevant patient population at the time of the submission to CADTH and the study completion date will not exceed 3 years from the target expert committee meeting date; **AND,**
3. **Reassessment commitment:** The sponsor has expressed a commitment to file a reassessment application with CADTH in accordance with the time frames specified in the procedures for time-limited recommendations; **AND,**
4. **Evidentiary gaps:** The evidence-generation plans described in Health Canada's qualifying notice are expected to address the gaps in the evidence identified by CADTH's expert committee.

Rationale for Proposed Criteria

This initial subset of eligible files will provide a starting point for CADTH, the drug programs, and other stakeholders to establish and refine the implementation of these recommendations. Based on these initial experiences, the process may subsequently be expanded to include additional application types.

Presubmission Phase

In the presubmission phase, all sponsors will be required to specify whether or not the drug under review is expected to meet the time-limited recommendation eligibility criteria regarding the regulatory review status, the evidence-generation plans, and that the sponsor is willing to comply with the reassessment process for a time-limited recommendation.

Presubmission Meetings

Sponsors must provide formal notification that a product may be eligible for a time-limited recommendation when filing presubmission meeting briefing materials. Sponsors will need to be prepared to discuss potential gaps in the evidence and their plans to address them through the conduct of a phase III trial. In accordance with CADTH's existing processes for presubmission meetings, the drug programs that participate in the reimbursement review process may observe and participate in the presubmission meeting.

Advance Notification

Sponsors will be required to complete specific advance notification forms to address the eligibility criteria regarding the regulatory review status and the evidence-generation plans. CADTH will document the sponsor's perspective and conduct an initial assessment to determine if the eligibility criteria have been met; however, the decision regarding eligibility will be communicated when the application has been accepted for review by CADTH. It is important to note that the final decision on whether a time-limited recommendation will be issued will be made by the CADTH expert committee after it concludes that there is sufficient evidence to issue an initial recommendation in favour of reimbursement based on the preliminary data that is available at the time of the review.

Application and Screening Phase

CADTH is proposing that within the application overview template, sponsors will be required to address the eligibility criteria regarding the regulatory review status, the evidence-generation plans, and their ability and willingness to file a reassessment application with CADTH in accordance with the time frames specified in the procedures for time-limited recommendations.

CADTH will examine the sponsor's application and confirm whether the drug under review meets the eligibility criteria based on regulatory review status and the proposed time frame for generating evidence. Sponsors will be notified regarding the decision on eligibility at the time the application has been accepted for review.

Table 1: Proposed Additions to the Application Overview Form for Screening Eligibility for Time-limited Recommendations

Eligibility for time-limited recommendations	Response
Regulatory status	
The drug has been issued an NOC/c by Health Canada or is undergoing review through Health Canada's advance consideration process under the NOC/c policy.	Yes No
Evidence generation	
A phase III clinical trial is being planned and/or conducted at the time of the submission to CADTH.	Yes No
The findings of the phase III trial will be reported within a time frame that will not exceed 3 years from the target expert committee meeting date.	Yes No NA
Target expert committee meeting date:	Day, Month, Year
Target primary complete date for the phase III trial:	Day, Month, Year
Commitment to file for reassessment (choose 1 of the following options)	
Sponsor is willing to commit to file a reassessment application with CADTH in accordance with the time frames specified in the procedures for time-limited recommendations.	Yes
Sponsor will not commit to filing a reassessment application with CADTH in accordance with the time frames specified in the procedures for time-limited recommendations. The sponsor acknowledges that the CADTH expert committee will be informed of the sponsor's decision and that a time-limited recommendation will not be an option for the drug under review.	Yes

NA = not applicable; NOC/c = Notice of Compliance with Conditions.

Stakeholder Engagement

Stakeholder Input

There will be no changes to the calls for patient group and clinician group input as part of the initiative to introduce time-limited recommendations. Calls for patient and clinician input will continue to be issued as described in section 6 of the *Procedures for CADTH Reimbursement Reviews*. Similarly, there are no revisions planned to the templates used for patient group input and clinician group input as a result of time-limited recommendations.

Stakeholder Feedback on Draft Recommendations

Time-limited recommendations will be issued in the same manner as standard reimbursement recommendations and stakeholders will have 10 business days to provide feedback to CADTH. Stakeholders will have the opportunity to provide

feedback on reimbursement conditions associated with time-limited recommendations. In accordance with the existing processes described in section 9 of the *Procedures for CADTH Reimbursement Reviews*, stakeholder feedback will be considered for editorial revisions to the CADTH recommendations and/or as part of a request for reconsideration.

Timelines for Drugs Eligible for a Time-limited Recommendation

Reviews will be conducted in accordance with the performance metrics outlined in the *Fee Schedule for CADTH Pharmaceutical Reviews* (i.e., 180 calendar days from the date the file is accepted for review by CADTH to the date the draft recommendation is issued to the sponsor and drug programs).

Review Phase

Consideration of Evidence Gaps

The CADTH reports will note the gaps in the evidence as identified by the sponsor within the evidence-generation plans, in addition to other gaps that may be identified during the review and recommendation phases. As part of the appraisal and interpretation of the evidentiary package filed by the sponsor, the potential importance of the gaps in the evidence will be discussed with clinical specialists who have experience treating and managing the condition in Canada.

In accordance with existing CADTH procedures, the sponsor will have the opportunity to review and comment on the draft CADTH reports, including commentary related to evidence gaps, before the expert committee meeting.

Qualifying Notice

For applications filed on a pre-Notice of Compliance (NOC) basis, the clinical review reports will not be completed until the details of the qualifying notice for the NOC/c have been provided to CADTH, as described in Table 2. This is required to ensure that all relevant information is available at the time of the committee's deliberations.

Table 2: Requirements for Qualifying Notice

Regulatory status at filing	Aligned review participation[a]	Documentation required by CADTH
Application filed on a post-NOC/c basis	Not applicable	• The final qualifying notice issued by Health Canada must be included in the application package.
Application filed on a pre-NOC basis	Sponsors who opt into the information-sharing process between CADTH and Health Canada	• CADTH receives confirmation from Health Canada and the sponsor that the content of the qualifying notice has been determined. • A draft of the qualifying notice is provided to CADTH as soon as content has been determined.
	Sponsors who do not opt into the information-sharing process between CADTH and Health Canada	• The final qualifying notice issued by Health Canada must be submitted to CADTH by the sponsor.

NOC = Notice of Compliance; NOC/c = Notice of Compliance with Conditions.
[a] As described in section 4.2.3 of the *Procedures for CADTH Reimbursement Reviews*, an optional information-sharing process for submissions filed with CADTH on a pre-NOC basis has been established to permit Health Canada and CADTH to exchange information related to the drug under review.

Recommendation Phase

Placement on the Expert Committee Agenda

Drugs that satisfy the preliminary eligibility criteria for a time-limited recommendation (i.e., based on regulatory review pathway and timelines for evidence generation) will only be placed on the agenda when the information noted in the qualifying notice has been provided to CADTH. The recommendation will be issued by the existing CADTH drug expert committees (i.e., Canadian Drug Expert Committee [CDEC] or the pan-Canadian Oncology Drug Review Expert Review Committee [pERC], as applicable).

Deliberative Process

For applications that may be eligible to receive a time-limited recommendation, the committee will be provided with the evidence-generation plans specified within the qualifying notice for consideration during the deliberations. The committee will consider all recommendation options as currently described in section 9.3.1 of the *Procedures for CADTH Reimbursement Reviews*, including a do not reimburse recommendation.

To receive a recommendation in favour of reimbursement when there is uncertainty with the clinical evidence at the time of the CADTH review, the available evidence must reasonably suggest that the drug under review could substantially reduce morbidity and/or mortality associated with the disease versus comparators identified within the

CADTH review. In situations where the gaps in the evidence identified by the expert committee align with those identified in the qualifying notice for the NOC/c, the committee may issue a time-limited recommendation.

CADTH Recommendation

The recommendation document will state that the reimbursement recommendation is being issued in a manner that is time-limited and contingent on further evidence generation to address the uncertainty in the evidence. CADTH will notify stakeholders that the recommendation is time-limited by including the following:

- **Recommendation category:** CADTH will introduce "time-limited recommendation" as a new recommendation category within our procedures. The recommendation category will be clearly communicated on the CADTH website and on the cover page of the recommendation document.
- **Cover page:** The cover page of the recommendation document will note that the category of decision is a "time-limited recommendation." In addition, the following statement will be included on the cover page: *This recommendation is time-limited and contingent on a future reassessment of additional evidence that addresses the uncertainty with the comparative clinical benefit and cost-effectiveness.*
- **Recommendation statement:** The reimbursement recommendation statements will be structured in the following format: *The CADTH expert committee recommends that [DRUG] be reimbursed for the treatment of [INDICATION] for a time-limited period while additional evidence is generated…*
- **Reimbursement condition:** The table of reimbursement conditions will include an additional category for "time-limited reimbursement." The condition will state: *The recommendation in favour of reimbursement is time-limited and contingent on a future reassessment of additional evidence that addresses the uncertainty with the comparative clinical benefit and cost-effectiveness.*
- **Reason for condition:** The reason for the time-limited reimbursement condition will be stated. The CADTH expert committee will describe the key factors that contribute to uncertainty with the clinical evidence that must be addressed through the completion of the pending phase III study being conducted by the sponsor.
- **Implementation guidance:** The CADTH expert committees will note in the recommendation the anticipated timelines for primary completion of the required study.

An example of how the time-limited reimbursement condition will be presented within the recommendation is provided in Table 3.

Table 3: Sample Time-Limited Reimbursement Condition

Reimbursement condition	Reason	Implementation guidance
Time-limited reimbursement		
A recommendation in favour of reimbursement is time-limited and contingent on a future reassessment of additional evidence that addresses the uncertainty with the comparative clinical benefit and cost-effectiveness.	The CADTH expert committee will describe the key limitations of the clinical evidence that must be addressed through the completion of the pending phase III study being conducted by the sponsor.	The CADTH expert committee will note the anticipated timelines for primary completion of the required study.

It is important to note that the purpose of a time-limited recommendation is to ensure that recommendations based on preliminary data can subsequently be reviewed and confirmed or revised when confirmatory phase III data are made available. These recommendations should not be interpreted as CADTH's expert committees advocating for a outcomes-based agreement or other form of managed entry agreement.

Request for Reconsideration

Sponsors will be permitted to file a request for reconsideration regarding time-limited recommendations in the same manner as described in section 9.5 of the *Procedures for CADTH Reimbursement Reviews* (e.g., requesting revisions to the reimbursement conditions). Reconsiderations requesting the removal or modification of condition(s) specifying that the recommendation is time-limited and contingent on evidence generation and reassessment will typically be managed in accordance with the existing processes for requests based on major revisions.

Implementation Phase

Status Updates

CADTH may request status updates from sponsors who have been issued time-limited recommendations. These requests will be brief updates regarding the evidence requirements identified in the CADTH recommendation and Health Canada qualifying notice. For example:

- Has the status of the phase III clinical study changed (e.g., ongoing, cancelled, terminated early)?
- Have the timelines for completing and reporting the phase III study been revised?
- Have there been amendments to the study protocol that will impact the patient population(s) being studied, outcomes being assessed, dosage or frequency of the drug being administered, and/or revisions to the comparator drug(s).

This information will be shared with the participating drug programs but will not otherwise be disclosed by CADTH.

Additional Implementation Support From CADTH
CADTH, along with the pan-Canadian Pharmaceutical Alliance (pCPA) and drug programs, could determine if there is a need for greater implementation support from CADTH for time-limited recommendations.

Reassessment of a Time-Limited Recommendation

Proposed Timelines for Reassessment

In accordance with the conditions stated within the CADTH recommendation, sponsors of drugs that are issued time-limited recommendations will be required to file for reassessment once the phase III evidence has been generated. Failure to file the required reassessment will mean that the sponsor has not satisfied the conditions of the time-limited recommendation. In these cases, the participating drug programs may file a request for advice, as described in the section on *Drug Program–Initiated Reassessment*. This may result in CADTH issuing a revised recommendation that the drug not be reimbursed by the drug programs.

CADTH appreciates that sponsors will require time after the phase III study has been completed to evaluate the clinical data, update the required pharmacoeconomic analyses, and revise the budget impact analysis (as required). For the purposes of consultation, CADTH is proposing the timelines described in Table 4. Sponsors are encouraged to provide feedback on these proposed timelines.

Table 4: Proposed Timelines for Filing Reassessment Applications

Milestone	Time frame	Description
Initial notification	≤ 90 calendar days after the primary completion date of the phase III trial	• Sponsors must provide notification to CADTH of their intent to file the new evidence for reassessment. • If a sponsor indicates that they are declining to file for reassessment, the participating drug programs can file a request for advice.
Formal advance notification of pending reassessment	≥ 30 business days before filing the application	• Sponsors must provide formal advance notification to CADTH regarding the pending reassessment application. • This time frame for advance notification is in accordance with existing CADTH procedures for reimbursement reviews.
Call for stakeholder input regarding the pending reassessment	29 business days before filing the application	• CADTH issues a call for stakeholder input. • This time frame for issuing the call for stakeholder input is in accordance with existing CADTH procedures for reimbursement reviews. • Stakeholders will be notified that the pending application is for a reassessment of a previously issued CADTH recommendation.
Reassessment application filed by sponsor	≤ 180 calendar days after the primary completion date of the phase III trial[a]	• Sponsors must file the reassessment application in accordance with the CADTH requirements. • In the event a sponsor fails to file the reassessment application by the deadline, the participating drug programs can file a request for advice and CADTH will determine if the initial time-limited recommendation should be revised.
Updated draft recommendation issued by CADTH	≤ 180 calendar days after the reassessment application is accepted for review by CADTH	• CADTH will issue a revised draft recommendation in accordance with the existing performance metrics stated within the *Fee Schedule for CADTH Pharmaceutical Reviews* (i.e., within ≤ 180 calendar days after the reassessment application has been accepted for review by CADTH). • The recommendation will be posted for stakeholder feedback, and sponsors, or the participating drug programs, will have the opportunity to file a request for reconsideration.

[a] This time frame has been selected to provide industry with sufficient time to prepare the reassessment application and to provide the participating drug programs with a clear time frame for when the time-limited recommendation will be reassessed by CADTH.

Initiating the Reassessment Process

Sponsor-Initiated Reassessment

Eligible sponsors will typically be the Drug Identification Number (DIN) holders for the drug and indication that received the time-limited recommendation from CADTH; however, it could be another manufacturer, supplier, distributor, or other entity that has been recruited by the DIN holder.

Drug Program–Initiated Reassessment

The participating drug programs can file a request for advice at any time if there are concerns about changes with the evidence-generation plans that were filed at the time of the CADTH review. This may include, but is not limited to:

- cancellation or postponement of the phase III confirmatory trial
- amendments to the protocol of the phase III confirmatory trial that could impact the ability of the study to address uncertainty identified by the CADTH expert committee
- failure of the sponsor to file a reassessment application with CADTH.

In these cases, CADTH may determine that the sponsor has not satisfied the terms of the time-limited reimbursement recommendation and the previous recommendation may be revised. This may include issuing a “do not reimburse” recommendation that will supersede the previous recommendation.

Application Requirements for Reassessment

Scope of the Application

Population

CADTH is proposing that the reassessment be “fit-for-purpose,” with applications tailored to address the decision problem, as shown in Table 5. The scope of the population addressed within the reassessment will not exceed the population that was evaluated in the initial CADTH review. This is typically the full population identified in the Health Canada–approved indication, unless the sponsor received approval to file for a more restrictive population or an unlabelled indication.

Table 5: Proposed Scope of Clinical and Economic Review

Sponsor request	Clinical review	Economic review
Sponsor is not seeking any revisions to the existing reimbursement criteria for the drug	Review of clinical evidence will be focused on the new evidence generated to address the gaps that were identified in the initial recommendation	Updated pharmacoeconomic evaluation that addresses the currently reimbursed population
Sponsor is seeking revisions to the existing reimbursement criteria for the drug (e.g., expansion of the patient population)	Updated systematic literature review and indirect comparisons (if applicable)	Updated pharmacoeconomic evaluation that addresses both: • the currently reimbursed population; **AND,** • the population that is relevant to the sponsor's request for revised reimbursement criteria

Intervention

The intervention should be the dosage strength(s), formulation(s), and route(s) of administration that were the subject of the initial CADTH recommendation. If new strengths or formulations have been marketed since the initial CADTH recommendation, these should be included in the reassessment (if relevant to the indication of interest).

Comparator(s)

All relevant comparators should be included unless the sponsor has discussed with CADTH and received formal notification that 1 or more relevant comparators may be excluded. Relevant comparators include any of 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
- treatments that have previously received a recommendation in favour of reimbursement from CADTH for the indication under review.

The relevant comparators must reflect the treatment landscape at the time of filing the reassessment with CADTH and cannot be limited to those that were relevant at the time of the initial submission.

Outcomes

The outcomes of interest in the sponsor's application should reflect those that were studied in the phase III clinical trial and identified as important gaps in the evidence by the CADTH expert committee.

Study Design

The focus of the reassessment application must be on the updated data from the phase III trial. Consideration may be given to including other study designs on a case-by-case basis (e.g., real-world evidence generated to address additional gaps in the evidence).

Application Requirements

The submission requirements for reassessment of a time-limited recommendation will be the same as those currently described in section 5 of the *Procedures for CADTH Reimbursement Reviews*.

Review Phase

CADTH will re-review the product with the new evidence and determine if it has addressed the previously identified gaps. The review will be conducted in accordance with the standard reassessment process described in section 8.2 of the *Procedures for CADTH Reimbursement Reviews*.

Recommendation Phase

Deliberative Process and Recommendations

A CADTH expert review committee will deliberate on the new evidence and stakeholder feedback for the reassessment. Outcomes of the reassessment deliberation could include:

- **Removal of the time-limited condition:** A recommendation that the drug or drug regimen continue to be reimbursed by the participating drug programs in accordance with the reimbursement criteria previously recommended by the CADTH committee (or those criteria that are currently being used by the drug programs at the time of deliberation). In this case, the recommendation will note that the sponsor has satisfied the reassessment requirements and the time-limited condition will be removed from the recommendation.
- **Revised reimbursement conditions:** A recommendation that the drug or drug regimen continue to be reimbursed by the participating drug programs, but with revised reimbursement criteria. In this case, the expert review committee may recommend updated reimbursement conditions to reflect the new evidence and/or advances in the therapeutic space. The recommendation may be updated to reflect

the revised pharmacoeconomic economic analysis for the drug or drug regimen. The updated recommendation will note that the sponsor has satisfied the reassessment requirements and the time-limited condition will be removed from the recommendation.

- **The drug or drug regimen should not be reimbursed:** This recommendation will be issued if the expert committee concludes that the new evidence is insufficient to address the previously identified uncertainty with the clinical benefit. As always, CADTH could provide implementation advice and/or guidance for a recommendation if requested by the public drug programs.

Updated CADTH Recommendation

CADTH will issue an updated recommendation that will supersede the previously issued time-limited recommendation. In accordance with existing CADTH procedures, a final recommendation will only be issued after stakeholder feedback has been provided on a draft recommendation and any requests for reconsideration and/or editorial revisions have been considered and resolved.

Request for Reconsideration

Sponsors will be permitted to file a request for reconsideration regarding an updated draft recommendation in the same manner as currently described in section 9.5 of the *Procedures for CADTH Reimbursement Reviews.*

Transparency

Confidentiality Guidelines

To ensure transparency for stakeholders in this initiative, sponsors must consent that all information related to the evidence-generation plans will be disclosable when the CADTH recommendations and reports are posted on the CADTH website. This will be reflected in revisions to the CADTH confidentiality guidelines (as shown in Table 6).

Table 6: Proposed Revisions to CADTH Confidentiality Guidelines

Item	Redactable	Rationale
All information related to the evidence-generation requirements for conditional regulatory approvals (i.e., NOC/c)	Not redacted	This information is required to ensure that stakeholders, including patients, understand: • the rationale for the time-limited recommendation • the type of evidence that will be generated to address the uncertainty • the time frame for generating and submitted the evidence.

NOC/c = Notice of Compliance with Conditions.

Application Fees

Initial submissions for applications that are eligible to receive a time-limited recommendation will be subject to a schedule A or schedule E fee in accordance with the *Fee Schedule for CADTH Pharmaceutical Reviews*. Reassessments filed to address time-limited reimbursement conditions will typically be subject to a schedule A fee (a schedule E fee could be applied on a case-by-case basis depending on the complexity of the reassessment application).

Evaluation of Time-limited Recommendations

To ensure that issuance of time-limited recommendations has the intended impact and is meeting the needs of stakeholders, CADTH is proposing that a formal evaluation be conducted after 3 to 5 time-limited recommendations have been issued. As part of this evaluation, CADTH will seek feedback from industry and the drug programs that participate in the CADTH reimbursement review process regarding their experience with the time-limited recommendations.