Canada's Drug and
Health Technology Agency

CADTH Procedures for Time-Limited Reimbursement Recommendations

September 2023

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Introduction

What Are Time-Limited Reimbursement Recommendations?

A time-limited recommendation is a recommendation to publicly fund a drug or drug regimen for a certain period of time based on the condition that the sponsor will conduct 1 or more clinical studies that address the uncertainty and that CADTH will conduct a reassessment of the additional evidence. CADTH's future reassessment will lead to a final reimbursement recommendation.

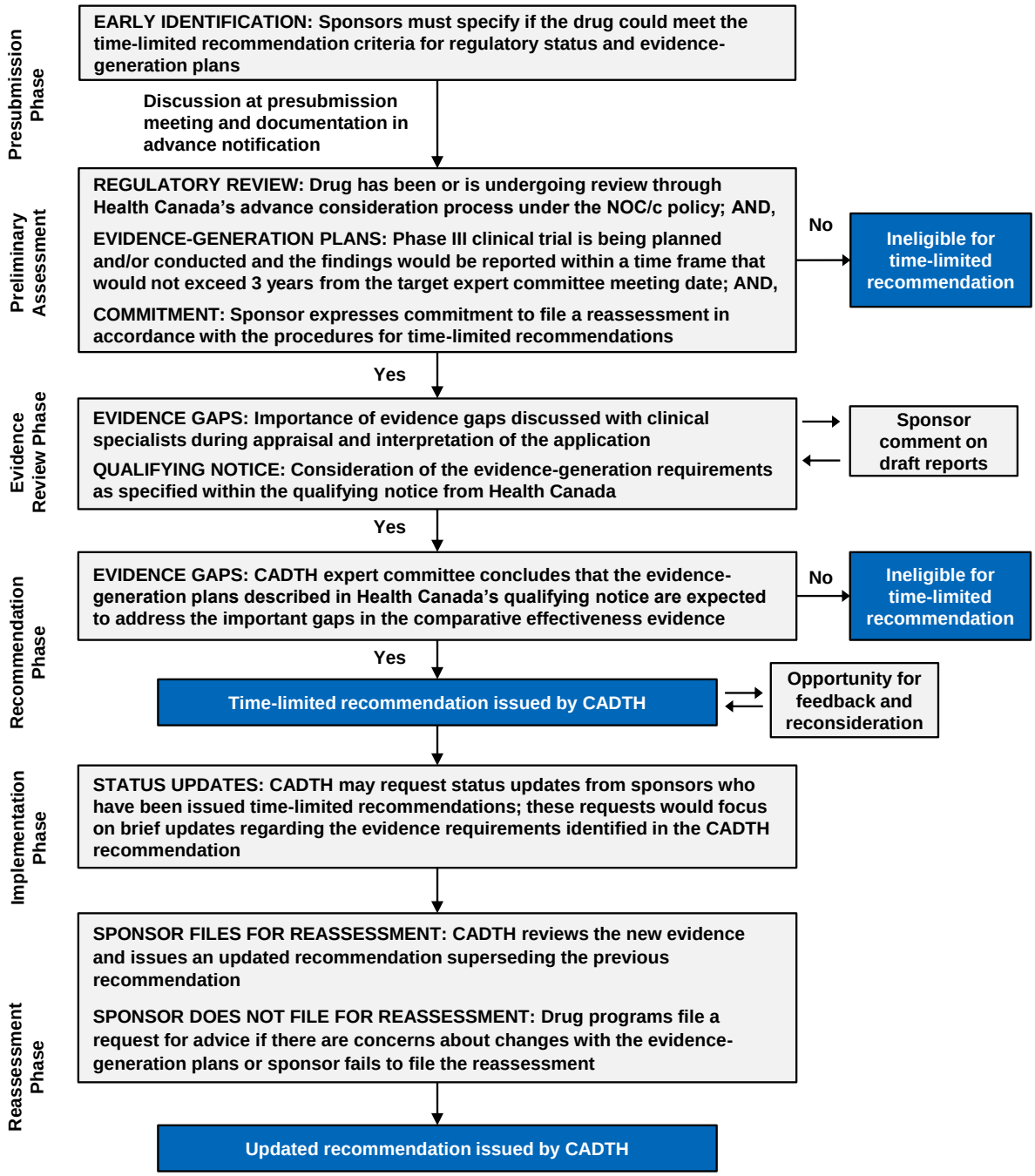
Evolving Regulatory Landscape

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.

Procedures for Issuing Time-Limited Recommendations

Figure 1: Summary of Process for Time-Limited Recommendations

Alt text: High-level summary of the process for issuing and reassessing time-limited recommendations starting from the presubmission phase to the reassessment phase.



NOC/c = Notice of Compliance with Conditions.

Eligibility Criteria for Time-Limited Recommendations

Drugs That Are Eligible for Time-Limited Recommendation

Drugs eligible for consideration for a time-limited recommendation are those with **all** 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).

2. **Evidence-generation plans:** A phase III clinical trial is planned and/or being conducted in a patient population that is reflective of the indication being reviewed by CADTH and the study completion date will not exceed 3 years from the target expert committee meeting date.

    - The phase III study must be conducted in the same patient population as the indication under review by CADTH (e.g., same line of therapy) using the same intervention being reviewed by CADTH (e.g., the same dosage regimen specified in the product monograph reviewed by CADTH). The final decision regarding the relevance of the population and the intervention will be determined by CADTH.

    - *Study completion* refers to the target date that will be publicly communicated through clinicaltrials.gov (i.e., the date the final study participant will be examined or have received an intervention for the purpose of the final collection of data for the primary and secondary outcome measures and adverse events).

    - If a sponsor anticipates interim study results will be available within the 3-year study period and expects these data to inform the removal of conditions associated with the regulatory approval, CADTH will discuss eligibility with the sponsor on a case-by-case basis.

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 (i.e., within 270 calendar days after the completion date of the phase III trial).

- If a drug meets the eligibility criteria based on the regulatory review status and the evidence-generation plans but the 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 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. In such cases, the drug will be reviewed in accordance with CADTH procedures for drugs that are ineligible for a time-limited recommendation.

- Sponsors must declare their willingness to participate in the time-limited recommendation when the application is initially filed with CADTH. Sponsors who do not consent from the outset of the process will not be permitted to request consideration for a time-limited recommendation in a request for reconsideration after a draft recommendation is issued.

- Any sponsors who initially decline to commit to the time-limited recommendation process at the time the application is filed, but subsequently wish to participate, will be required to withdraw the initial application and refile a new application.

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.

Drugs That Are Not Eligible for a Time-Limited Recommendation

Any drugs that do not meet all the eligibility criteria will not be considered for a time-limited recommendation. In addition, products that are reviewed through the Interim Plasma Protein and Related Products Process (i.e., those targeted for consideration by Canadian Blood Services) will not be eligible for time-limited recommendations at this time.

Rationale for Eligibility 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 criteria.

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. CADTH will conduct a preliminary screening of the information to evaluate eligibility for a time-limited recommendation. Screening will typically be conducted within 10 business days, and the outcome will be communicated to the sponsor.

For pending applications that meet the eligibility criteria, sponsors will be offered a 1.5-hour presubmission meeting (as opposed to the 1-hour meeting typically offered by CADTH). 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. Presubmission meetings will remain optional for sponsors with products that meet the eligibility criteria for a time-limited recommendation.

Advance Notification

Sponsors are 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 responses to the eligibility questions and conduct an initial assessment to determine if the eligibility criteria for a time-limited recommendation have been met; however, the decision regarding eligibility will be communicated when the application has been accepted for review. CADTH appreciates that complete details regarding the evidence-generation plans may not be available in the presubmission phase. In those cases, preliminary plans should still be communicated.

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.

All sponsors must complete the time-limited recommendation sections of the presubmission documentation regardless of whether they feel the pending application will meet the criteria. As stated in the advance notification form instructions, sponsors should indicate “not applicable” and provide the rationale for situations in which the drug does not meet the eligibility criteria.

Application and Screening Phase

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 for consideration as a time-limited recommendation 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. For drugs that are eligible for consideration through the time-limited recommendation process, the project webpage will be updated to state that the following: “Eligible for consideration as a time-limited recommendation.”

Drugs that are not eligible to be considered for a time-limited recommendation would be reviewed in accordance with the existing CADTH procedures and recommendation framework. Any sponsors who disagree with the eligibility decision should contact the project co-ordinator with complete details regarding why the sponsor believes the incorrect decision was made. CADTH will work with these sponsors on a case-by-case to clarify or revise the eligible decision as required.

Table 1: Screening Eligibility for Time-Limited Recommendations based on Regulatory Status, Conduct of a Phase III Trial, and Reassessment Commitment

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 phase III trial is being or will be conducted in a patient population that is reflective of the indication being reviewed by CADTH	☐	Yes
	☐	No
The phase III trial will be completed within a time frame that will not exceed 3 years from the target expert committee meeting date.	☐	Yes
	☐	No
	☐	N/A[a]
Target expert committee meeting date[b]	Month day, 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

[a] Please check N/A if the sponsor does not have a relevant phase III trial planned or ongoing for the indication of interest to the CADTH submission.

[b] Please refer to the *CADTH Expert Committee Meeting Schedule*.

Table 2: Screening Eligibility for Time-Limited Recommendations Based on Details of the Evidence Generation Plans

Evidence Generation Plans	Response
Summary of key evidentiary gap(s) and how it will be addressed through evidence generation	Clearly identify the gaps and/or limitations with the preliminary evidence that will be submitted to CADTH and briefly state how the forthcoming phase III trial will address the issues.
Confirmed or Anticipated Post-Market Study Requirements	
Population	Please state the patient populations where additional phase III evidence will be generated.

Intervention	Please state the intervention(s) that will be studied in the phase 3 trial, including all relevant background therapies, dosage strength(s), frequency of administration.
Comparator(s)	Please identify the comparator(s) that will be used in the phase 3 trial, including dosage strength and frequency of administration.
Outcome(s)	Please identify the outcomes that may be included to address the confirmed or anticipated regulatory conditions (e.g., as stated within the qualifying notice issued by Health Canada). Please include additional primary, secondary, or exploratory endpoints that are or will be investigated in the pending phase 3 trial. CADTH acknowledges that sponsors may not have all this information at the time of completing this form, particularly for files that will be filed prior to regulatory approval by Health Canada. Please provide as much detail as possible to help inform initial discussions regarding eligibility for consideration to receive a time-limited recommendation.
Timing (required follow-up)	Please state the required follow-up to address the conditional market authorization issued by Health Canada (please focus on the relevant phase III trial).
Study design	Please briefly state the design of the phase III trial.
Study protocol	If available, please provide a link to the study protocol (or indicate that it is not currently published). If a protocol is currently unavailable, please note this within this section.
Clinicaltrials.gov	Please provide the clinicaltrials.gov identification number (or indicate that it is not currently available).
Target dates for Phase III Study ***If dates are uncertain, please estimate to inform initial discussions regarding eligibility for consideration to receive a time-limited recommendation.***	
Start [a]	Month day, year
Primary completion [b]	Month day, year
Study completion [c]	Month day, year
Clinical Study Report completion [d]	Month day, year
Filing SNDS-c with Health Canada (if known)	Day, Month, Year (or state if unknown)

SNDS-c: Supplement to a New Drug Submission - Confirmatory

[a] Estimated date on which the clinical trial will be open for patient recruitment or the actual date on which the first patient was enrolled.

[b] Date that the final study participant was examined or received an intervention for the purpose of the final collection of data for the primary outcome.

[c] Date that the final study participant was examined or received an intervention for the purpose of the final collection of data for the primary and secondary outcome measures and adverse events.

[d] Estimate of the time required to finalize the Clinical Study Report after the study has been completed (CADTH appreciates this information may not be known. Please provide an estimate based on prior experience).

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*. There are no revisions 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 (and confirmed within the Qualifying Notice, once available), 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

In the case of an aligned review with Health Canada, both the sponsor and Health Canada may upload the draft Qualifying Notice to CADTH. To avoid any potential delays, the onus will always be on the sponsor to provide CADTH with the draft and final Qualifying Notice once available (i.e., Health Canada may provide this information to help accelerate the review, but they are not responsible for ensuring that CADTH receives the information).

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 3. This is required to ensure that all relevant information is available at the time of the committee's deliberations. If there is any uncertainty regarding the evidence-generation plans, the sponsor will be contacted by CADTH and requested to provide additional details.

As with all finalized information for an application filed on a pre-NOC basis, CADTH will assess the Qualifying Notice upon receipt. Depending on the nature and extent of changes to the information compared with what was originally filed and communicated to CADTH regarding the evidence-generation plans, CADTH will determine the timelines required to review it and incorporate it into the review report(s). This could result in the submission being considered at a later expert committee meeting.

Table 3: 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., CADTH Canadian Drug Expert Committee [CDEC] or the CADTH pan-Canadian Oncology Drug Review Expert Review Committee [pERC], as applicable).

Deliberative Process

For applications that may 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 a time-limited recommendation, but may issue an alternative recommendation as currently described in section 9.3.1 of the *Procedures for CADTH Reimbursement Reviews* (i.e., reimburse, reimburse with conditions [without a time-limited condition], or do not reimburse).

In accordance with the existing CADTH recommendation framework, 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.

If the expert committee identifies additional important gaps in the clinical evidence that are outside the scope of the phase III clinical trial described within the Qualifying Notice, this may result in a recommendation that the drug not be reimbursed or a recommendation that the drug be reimbursed only for a subset of the population in

which there is sufficient evidence to draw conclusions regarding the comparative clinical benefit (with or without a time-limited reimbursement condition).

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 reassessment of additional evidence that addresses the uncertainty."
- **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."
- **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 completion of the required study. As with the exiting CADTH process, implementation guidance will typically reflect the issues identified within the clinical review report, but the committee may raise additional issues that arise during the deliberations. Stakeholders

would have the opportunity to review and provided feedback on these issues within the draft recommendation documents.

An example of how the time-limited reimbursement condition will be presented within the recommendation is provided in Table 4.

Table 4: 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.	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 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 will require status updates from sponsors who have been issued time-limited recommendations. These will consist of brief updates from sponsors regarding the evidence requirements identified in the CADTH recommendation and Health Canada

Qualifying Notice. To streamline this process for industry CADTH will align these requests with the format currently described in *Health Canada's Guidance Document: Notice of Compliance with Conditions (NOC/c)* (refer to Appendix 4: Progress of Ongoing Confirmatory Trials Report). An example of the request is provided in Table 5.

Table 5: Status Update Request from CADTH

Sponsor:	*State company name*
Product:	*Brand (non-proprietary name); dosage form and strength*
CADTH Project number:	*Please add CADTH project number*
Letter of Undertaking Date:	*Month Day, Year*
Description of Trial:	*Please provide a brief description of the relevant trial*
Trial Schedule:	*Protocol approval date; Trial enrollment start date and conclusion date; Last patient evaluation date; Health Canada submission date.*
Current Status:	*Pending, Ongoing, Delayed, Terminated, or Submitted*
Explanation of the Status:	*Please provide a brief description of the current status. Please highlight important protocol amendments.* • *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).*

CADTH will issue these requests for status updates using standardized forms sent to the sponsor twice per year (at the beginning of April and October). Sponsors will be asked to complete the update within 10 business days and inform CADTH if an extension is required.

Sponsors are also encouraged to proactively inform CADTH regarding any updates to the conduct of the phase III clinical study. To ensure appropriate tracking and triage, please send these updates to requests@cadth.ca and CADTH will subsequently contact the sponsor (if required).

This information will be shared with the authorized recipients described within the Reimbursement Review confidentiality guidelines (refer to Appendix 1 of the *Procedures for CADTH Reimbursement Reviews*) and may be discussed with CADTH's

expert committees, but will not otherwise be disclosed by CADTH. The expert committees may be asked to evaluate the importance of protocol amendments and their impact on the ability of the phase III study to address the uncertainty with the clinical evidence that was reviewed by the committee (this would be of particular importance in a situation in which the study population, intervention, or outcomes have been revised by the sponsor).

Reassessment of a Time-Limited Recommendation

CADTH and Health Canada Reviews

As with the existing Reimbursement Review processes, the CADTH reassessment process will occur independently of the review by Health Canada (i.e., Supplement to a New Drug Submission – Confirmatory [SNDS-c] review). Although the initial time-limited recommendation process is only for drugs that have received an NOC/c from Health Canada, the CADTH review process will continue to focus on issues related to comparative clinical effectiveness and cost-effectiveness. It is not intended to duplicate Health Canada's review of the new evidence.

The CADTH reassessment process for a time-limited recommendation may occur in parallel with the sponsor's submission of an SNDS-c to Health Canada as part of the requirements to address the conditional regulatory approval. In these cases, sponsors are encouraged to participate in the aligned reviews process between Health Canada and CADTH for these SNDS-c applications.

If the regulatory review results in withdrawal of the drug and/or indication of interest from the Canadian market, any ongoing CADTH reassessment would immediately be stopped in accordance with section 11 of the *Procedures for CADTH Reimbursement Reviews*. Any applicable CADTH recommendations would be updated with a disclaimer that the drug and/or indication has been withdrawn.

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 should 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). CADTH will apply the timelines described in Table 6 for the reassessment of drugs that are issued a time-limited recommendation.

Unanticipated Delays With Phase III Study

During stakeholder consultations, CADTH heard clearly from industry that unanticipated delays can occur during the conduct of a phase III clinical trial. In these cases, CADTH will work with sponsors and the public drug programs on a case-by-case basis to determine if the conditions of the time-limited recommendation can be addressed within an acceptable time frame and, if so, the revised required timelines for the reassessment.

Table 6: Target Timelines for Filing Reassessment Applications

Milestone	Time frame	Description
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	≤ 270 calendar days[a] after the completion date of the phase III trial[b]	• 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.

[b] Study completion date: Date final study participant was examined or received an intervention for the final collection of data for the primary and secondary outcome measures and adverse events.

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.

Similar to the existing request for advice process, the manufacturer(s) of the drug(s) (i.e., DIN holder) in question will be apprised regarding the drug program–initiated

reassessment and the reasons for the review. The DIN holder will be invited to comment or provide information within 10 business days of receiving the notification from CADTH.

Stakeholder Engagement

All eligible stakeholders may participate in the reassessment process irrespective of their prior participation with the initial assessment.

Application Requirements for Reassessment

Preparing for the Reassessment

As with the current reimbursement review process, sponsors who have questions about the scope of the application and/or any of the application requirements are encouraged to contact CADTH (requests@cadth.ca) well in advance of the target filing date to seek clarification. Sponsors can provide written questions to CADTH and participate in a presubmission meeting to have a detailed discussion about the pending reassessment. Deviations from any of the requirements within the economic evaluation section must be discussed with, and accepted by, CADTH in advance of filing the reassessment application. Please submit the following template to requests@cadth.ca with complete details of the deviations from these requirements.

Scope of the Application Population

The reassessment will be conducted in a manner that is “fit for purpose” with applications tailored to address the decision problem, as shown in Table 7. The reassessment will focus on the indication that was previously reviewed by CADTH 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.

As outlined in Table 7, sponsors may request revised reimbursement criteria as part of the reassessment process (e.g., modifications to initiation, renewal, discontinuation, or prescribing criteria). Sponsors that want to have additional populations addressed within the reassessment should contact CADTH (requests@cadth.ca). These requests will be addressed on a case-by-case basis and may require the sponsor to file multiple applications and/or be subject to multiple application fees.

Table 7: Scope of Clinical and Economic Review for a Reassessment

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 • 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. The relevant comparators must reflect the treatment paradigm and reimbursement status at the time of filing the reassessment application and cannot be limited only to those that were relevant at the time of the initial submission to CADTH.

Relevant comparators are defined in accordance with the *Procedures for CADTH Reimbursement Reviews* and 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.

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. This may include surrogate end points if CADTH's expert committee concluded that additional surrogate data would address uncertainty with the clinical evidence in the initial recommendation.

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); however, this evidence must be provided in addition to the phase III trial data and will not be accepted as a substitute for the phase III trial 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

Placement on Expert Committee Meeting Agenda

The target expert committee meeting for a reassessment will be established based on the target timelines currently used for all applications (refer to the *CADTH Expert Committee Meeting Schedule*).

Deliberative Process and Recommendations

A CADTH expert 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 reimbursement condition only:** 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.

- **Removal of time-limited reimbursement and 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. 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*.

Implementation Phase

As with the existing reimbursement review process, CADTH's recommendations are nonbinding to the drug programs. Each drug program makes its own reimbursement decisions based on the CADTH's recommendation, in addition to other factors, including the plan's mandate, jurisdictional priorities, and financial resources.

CADTH will provide the participating drug programs and the pan-Canadian Pharmaceutical Alliance (pCPA) with implementation support following the issuance of an updated reimbursement recommendation. This may include updates to provisional funding algorithms for oncology drugs (refer to section 13 of the *Procedures for CADTH Reimbursement Reviews* for details on this process).

Confidentiality Guidelines

Initial Application

To ensure transparency for stakeholders in this initiative, sponsors must consent that the evidence-generation requirements for conditional regulatory approvals (i.e., NOC/c) described within the Qualifying Notice from Health Canada 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 8).

Table 8: Revisions to CADTH Confidentiality Guidelines for Time-Limited Recommendations

Item	Redactable	Rationale
Evidence-generation requirements for conditional regulatory approvals (i.e., NOC/c) described within the Qualifying Notice from Health Canada.	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.

Status Updates

This information may be shared with the authorized recipients described within the reimbursement review confidentiality guidelines (refer to Appendix 1 of the *Procedures for CADTH Reimbursement Reviews*) and may be discussed with CADTH's expert committees but will not otherwise be disclosed by CADTH.

Reassessment Application

All sponsor-supplied information filed with CADTH as part of a reassessment application will be managed in accordance with the reimbursement review confidentiality guidelines (refer to Appendix 1 of the *Procedures for CADTH*

Reimbursement Reviews). There are no changes to the management of confidential clinical or economic information as part of the time-limited recommendation process.

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

CADTH will evaluate time-limited recommendations after the first 3 to 5 recommendations have been issued or after 18 months to ensure they are having the intended impact and meeting the needs of stakeholders.