Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

CDA-AMC THERAPEUTIC REVIEW

Therapeutic Review Framework and Process

AUGUST 2024

VERSION 5.0

Revision History

From time to time, our organization may amend the therapeutic review process. The public drug programs are consulted as required. We will typically request partner feedback for therapeutic review procedural changes. Amendments to, and clarifications of, the procedure and all related documents may be effected by means of directives (called *CDA-AMC Pharmaceutical Reviews Updates*) issued by our organization on an as-needed basis, between revisions of these documents. Generally, changes that are corrections or clarifications become effective immediately.

The following version control table, as well as the version number and date on the cover page, are to be updated when any updates or revisions are made.

Version	Date	Summary of Revisions
1.0	January 2012	Original framework posted
2.0	June 2015	New version of the Therapeutic Review Framework updated to include: • changes to the definition and scope • addition of detailed processes • clarification of the type of evidence included in a therapeutic review.
2.5	November 2015	As a result of partner feedback received in June 2015, the following changes to the Therapeutic Review Framework were implemented: • The patient group input process has been revised to allow for more patient group response time (based on experiences with pilot process and stakeholder feedback). • We will typically request partner feedback for therapeutic review procedural changes. In consideration of the 2015 partner feedback, additional context has been added to ensure clarity with regard to the following: • when and how our organization will handle the inclusion of evidence-based expanded use of drugs off-label) within therapeutic review reports • partner feedback within the therapeutic review process • when observational data are considered for review within therapeutic review projects.
3.0	June 2018	The document was restructured, simplified, and the subsequent procedural changes were added following posting for feedback in 2017 (Common Drug Review Update, issues 124 and 125): • Canadian Drug Expert Committee (CDEC) will consider whether or not the results of a therapeutic review suggest that any existing recommendations from the Common Drug Review process should be revised. • Existing CDEC or CEDAC recommendations that could be revised will be identified and communicated to partners • Patient groups and manufacturers affected by revisions to existing CDEC or CEDAC recommendations have the opportunity to provide feedback on draft revisions.
3.5	November 2019	The following revision was made (Pharmaceutical Reviews Update, issue #11) • Document restructured to account for the expansion of the Therapeutic Review process to support new single drug review processes and expert committees.
4.0	October 2020	The document was revised to reflect the alignment and consolidation of the CDA-AMC's drug reimbursement review processes.
5.0	August 2024	• Updated with CDA-AMC branding • "Stakeholders" changed to "Partners" or specific group

Table of Contents

1. Introduction

The purpose of this document is to outline a framework and standardized process for therapeutic reviews that meets the needs of our customers. If possible, our organization may adapt or supplement an existing therapeutic review to shorten timelines.

1.1 About Therapeutic Reviews

A therapeutic review is an evidence-based review of publicly available sources regarding a therapeutic category of drugs (e.g., antihypertensive drugs) or a class of drugs (e.g., angiotensin-converting enzyme inhibitors) in order to support drug reimbursement decisions, drug policy decisions, and to encourage the optimization of drug therapy. The optimal use of drug therapy involves ensuring that the right drugs are prescribed and used appropriately to improve or maintain optimal health. This requires balancing maximized benefits with minimized risks to people's health based on best-quality evidence, taking into account the options, costs, available resources, patient preferences, and societal context.

Publicly funded drug programs evaluate and consider the addition of new drugs to their formularies. They do this based on favourable efficacy, safety, and cost-effectiveness analyses as reviewed by our pharmaceutical review programs. Therapeutic reviews may be useful in any scenario where there is uncertainty regarding the comparative clinical effectiveness and cost-effectiveness of drugs in a particular therapeutic category or drug class.

The primary outputs from a therapeutic review will typically include the *Therapeutic Review Science Report, Therapeutic Review Recommendations Report,* and knowledge mobilization tools. In addition, the therapeutic review process may involve a reassessment of recommendations that were issued through our drug reimbursement review processes (i.e., CDA-AMC Common Drug Review, pan-Canadian Oncology Drug Review, and the Interim Plasma-Related Product Review).

Drug-related recommendations and/or advice from our drug reimbursement review processes and the therapeutic review program are provided by appointed, expert advisory committees to our organization

These expert committees are composed of individuals with expertise in drug therapy, drug evaluation, and drug utilization, and public/patient members who bring a lay perspective. The current committees and their members are listed on the CDA-AMC website.

1.2 Target Audience and Application for Decision-Making

Therapeutic review reports are produced for federal, provincial, and territorial government drug programs, including provincial cancer agencies, administrators and health policy-makers working at regional health authorities and hospitals in Canada who make decisions about the optimal use of, access to, or reimbursement of pharmaceuticals. Therapeutic review projects are not meant to replace professional medical advice. Readers are also cautioned that a lack of good-quality evidence does not necessarily mean a lack of effectiveness, particularly in the case of new health technologies for which little evidence is available, but that may in future prove to be effective.

2. Transparency and Partner Engagement

Our organization makes every attempt to be as transparent as reasonably possible in the therapeutic review process. The three principles of transparency, as defined by the CDA-AMC, are to:

1. solicit feedback from those affected by CDA-AMC reports (e.g., patient groups, health care providers, and pharmaceutical companies) whenever possible
2. facilitate the ability to reproduce or update CDA-AMC reports by reporting:
    a. methods used to create reports
    b. sources searched and/or provided
3. publish CDA-AMC reports in the public domain.

At the start of each project, a protocol that documents the methodology that will be used in the therapeutic review is drafted, posted, and registered with PROSPERO. In each *Therapeutic Review Science Report,* the policy questions, research questions, selection criteria, included studies, methodology, and search strategy are reported.

Therapeutic reviews are conducted in an open and transparent fashion with input from all interested partners (i.e., public, patient, health care providers, and pharmaceutical companies) solicited in order to facilitate a rigorous review (see Table 1 for details). Our organization notifies interested parties of partner feedback opportunities by posting a notice to the Calls for Feedback webpage and issuing an email to subscribers of the CDA-AMC E-Alert service. Instructions on providing feedback are included with every notification. In the therapeutic review process, partner feedback is solicited at the following stages:

- *Proposed project scope* (including existing CDA-AMC drug reimbursement recommendations for drugs to be included for review if applicable)
- List of included studies
- Draft *Therapeutic Review Science Report*
- Draft *Therapeutic Review Recommendations Report*
- Proposed revisions to existing CDA-AMC drug reimbursement recommendations (if applicable).

Therapeutic review reports are posted on the CDA-AMC website for anyone to access and review, although in exceptional circumstances, embargo periods may be considered. All drafts, search strategies, and working documents used to produce therapeutic review reports are archived for 15 years and may be requested if required, with the exception of copyright-protected documents or information provided in confidence by customers, manufacturers, or other agencies.

Table 1: Partners in CDA-AMC Therapeutic Reviews

Partner	What
All partners[a]	• Provide feedback on: ▪ proposed project scope ▪ draft list of included studies ▪ draft Therapeutic Review Science Report ▪ draft Therapeutic Review Recommendations Report ▪ Proposed revisions to existing CDA-AMC drug reimbursement recommendations
Pan-Canadian Customers	• Identify policy, reimbursement, practice issues, as well as implementation support activities for Canadian jurisdictions.
Patient groups	• Provide patient perspective on disease and impact on quality of life • Provide first-hand experiences with treatments included in the review • Identify therapeutic issues and controversies from a patient perspective • Comment on existing CDA-AMC drug reimbursement recommendations • Provide feedback at designated stages of the process
Expert committee	• Provide input into the development of research questions and guidance for evidence threshold, as well as populations identification, and outcomes • Identify information needed to make a recommendation • Identify any practice issues • Make recommendations
Clinical experts	• Provide context for developing research questions: ▪ understanding of current clinical approach and therapeutics, natural history of disease, comparators, outcomes, interpretation of evidence, populations, upcoming therapeutic, or diagnostic trends • Identify therapeutic issues and controversies • Identify clinical practice issues that are not captured by clinical evidence review
Manufacturer	• Confirm available evidence • Provide feedback at designated stages of the process

[a] Includes the public and all other partners mentioned in the table.

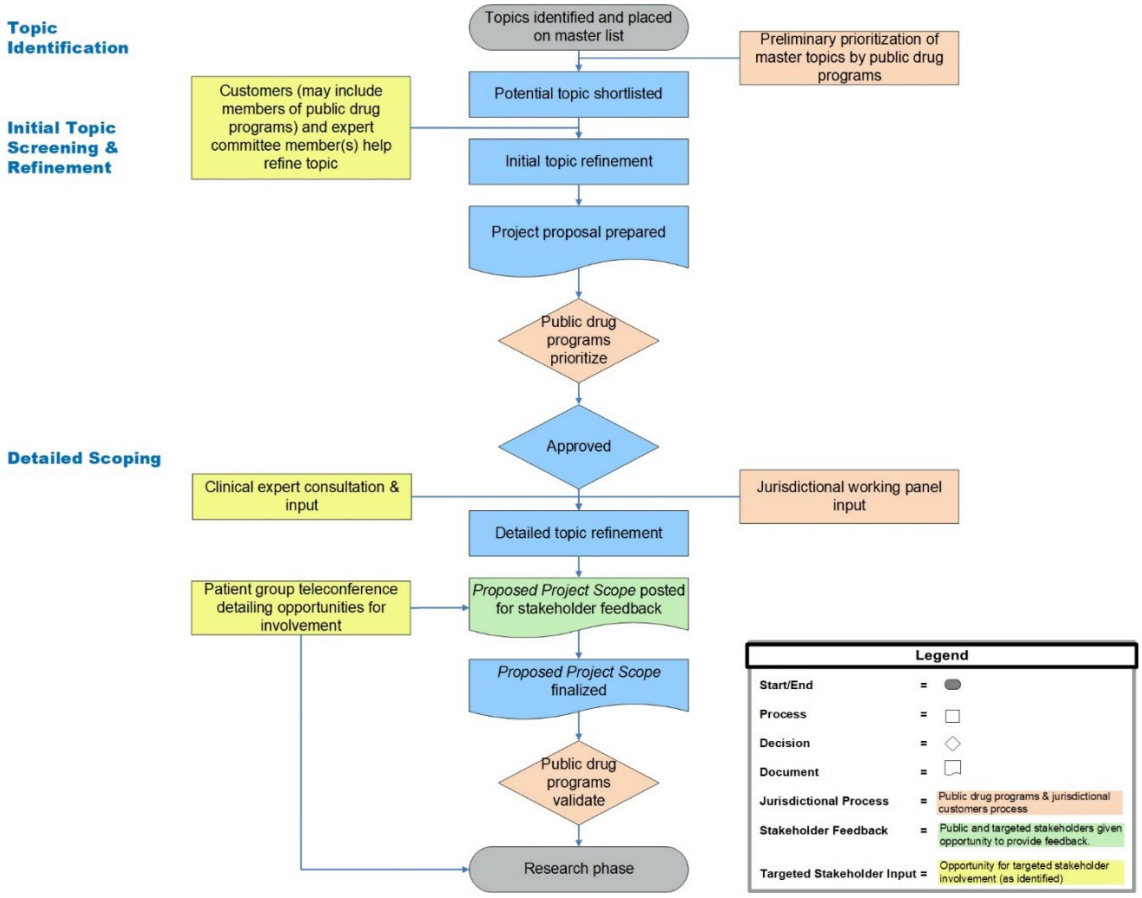
3. Target Timelines

After the project protocol and the list of included studies are finalized, the typical timeline to the expert committee recommendations is six to nine months. Exact timelines are determined by our organization in consultation with the jurisdictions. Throughout the therapeutic review project, we provide multiple opportunities for partner engagement, allowing 10 business days for feedback.

4. CDA-AMC Therapeutic Review Process

4.1 Topic Identification and Screening Phase

Figure 1: Topic Identification and Screening Phases Flow Chart



4.1.1 Topic Identification

Topic identification includes both reactive projects (i.e., for which a specific request was received from a CDA-AMC customer) and proactive projects (i.e., a project identified by our organization in anticipation that targeted technologies may have a significant impact on the Canadian publicly funded health system). Factors related to policy issues used to identify potential therapeutic review topics include, but are not limited to:

- when two or more drugs with similar indications are expected for future submissions to the CDA-AMC drug reimbursement review process
- when a CDA-AMC drug reimbursement recommendation triggers a coverage policy review of existing drugs (i.e., reimbursement policies)
- if a CADTH drug reimbursement recommendation suggests that a therapeutic review should be conducted to evaluate the comparative clinical effectiveness and cost-effectiveness of drugs in a particular therapeutic area.

4.1.2 Topic Screening and Refinement

Potential topics for therapeutic reviews are maintained in a master topic list. The aim of the therapeutic review topic submission and selection processes is to ensure that appropriate topics are identified and selected so that outputs are timely and relevant in addressing priority issues for public drug programs. The master topic list is reviewed and screened by our organization and the public drug programs to establish a short list of potential topics for therapeutic review projects. We refine these topics by setting up a jurisdictional working group comprised of representatives from the drug programs and clinical experts. The working group:

- provides input on jurisdictional interest in the topic and the potential impact of the therapeutic review
- assists in the development of policy and research questions
- establishes the timing of the project (i.e., when the information from the therapeutic review is required to most effectively support health care and policy decisions).

Information obtained from the jurisdictional working group is supplemented with a literature search to gain insight into the extent of evidence available on the topic and to determine if there has been previous work on the topic (to avoid duplication of effort and to assess potential opportunities for partnerships with other organizations).

4.1.3 Initial Project Proposal

We develop a project proposal that contains the results of the initial scoping search and the discussions with the jurisdictional working group. The proposal takes into account the factors, such as relevance, timeliness, and potential impact (Table 2). The public drug programs review the proposals and establishes the priority of the therapeutic review projects to be addressed by our organization.

Table 2: Key Factors Considered in Scoping Potential Therapeutic Review Projects

Relevance	• What are the policy and/or decision problems under consideration? • What are the reimbursement policies for the drug class targeted for assessment? • How are the drugs of interest currently being used in Canadian practice? • Is there evidence of suboptimal health policy or variation in clinical practice?
Timeliness	• When are the reports and recommendations required by the jurisdictions? • Are resources available to undertake the proposed therapeutic review? • Who are the knowledge partners that may assist with the development and dissemination of the report and recommendations?
Impact	• How could recommendations change clinical practice? • Who is the target population? • What is the Canadian prevalence of the condition(s)? • How could Canadians be affected by reimbursement, policy, or behavioural changes that may result from the therapeutic review? • What are the health care costs associated with the drugs of interest (e.g., direct, indirect, governmental, societal)? • How could the recommendations from the therapeutic review impact health care costs (e.g., change in purchasing decision, change in drug formulary policy)? • Is there similar work that has been recently published or undertaken by another organization? If so, are there opportunities for partnerships in research activities and/or the dissemination of the information? • Who are the target audiences for the therapeutic review (e.g., patients, policy-makers, clinicians, and/or health care practitioners)? • What is the possibility of changing policy and/or clinical practice?

4.1.4 Detailed Scoping

Following prioritization and approval, we conduct detailed scoping on the therapeutic review topics and create a proposed project scope document. The scope is determined by the needs of our jurisdictional customers. In exceptional circumstances, the project scope may include drugs with evidence-based expanded use (i.e., for a clinical indication for which a pharmaceutical manufacturer has not applied to Health Canada and that is not included in an approved Health Canada product monograph, sometimes referred to by partners as off-label use). Key considerations used when determining whether to include a comparator that does not have regulatory approval from Health Canada for that indication are:

- evidence of use of the drug for the condition of interest in Canadian clinical practice (e.g., integration of the drug into clinical practice guidelines, consultations with clinical specialists)
- availability of data evaluating the efficacy and safety of the drug in an indication for which the manufacturer has not applied or received approval from Health Canada
- evidence of health technology assessment organizations and/or payers having made recommendations or decisions to fund the drug, despite lack of regulatory approval
- approval for use of the drug for the indication of interest has been issued by other regulatory authorities (e.g., US FDA or the European Medicines Agency).

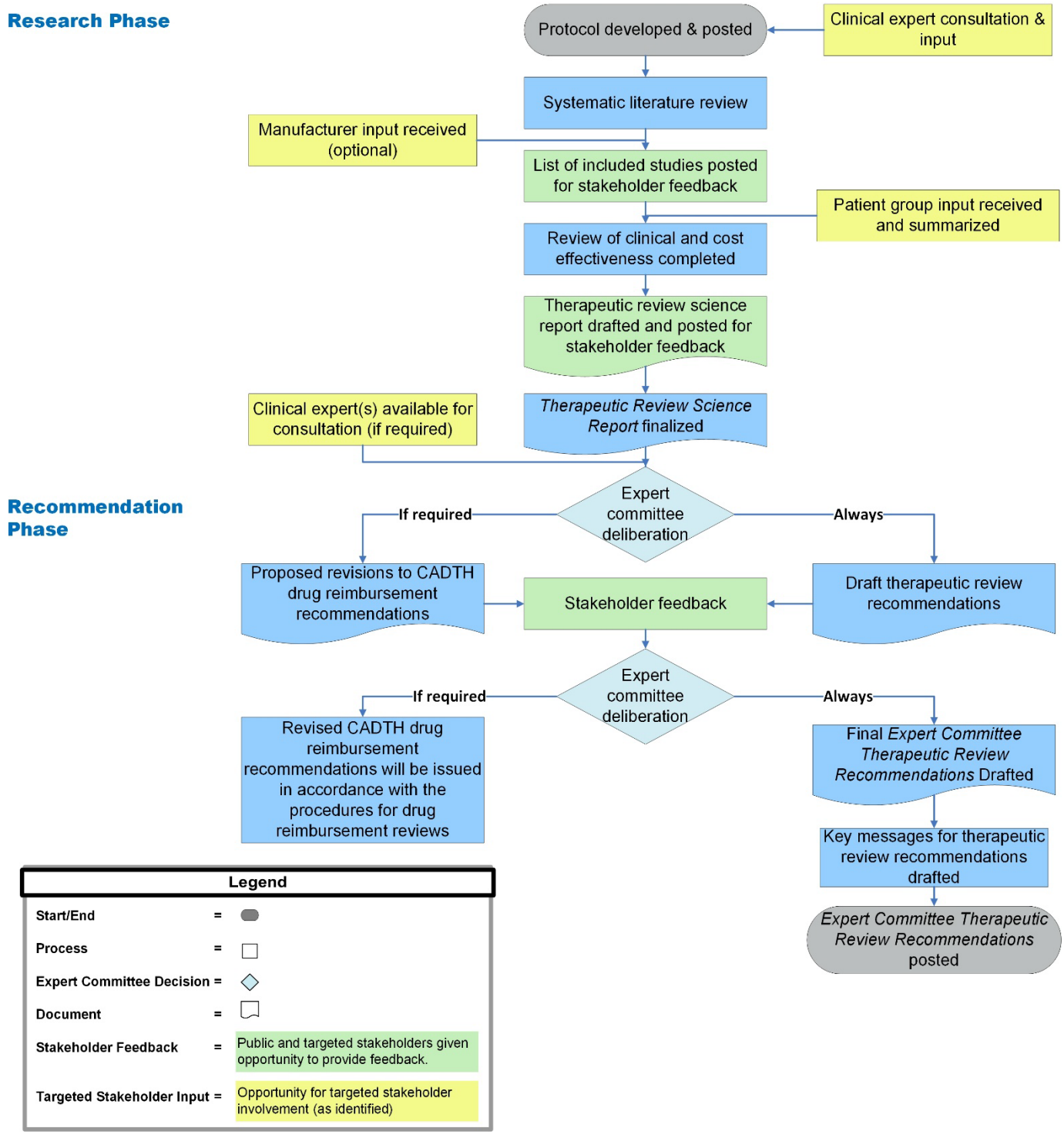
The project scoping document is posted on the CDA-AMC website for partner feedback (typically for a period of 10 business days). Any partners may comment on the proposed project scope. Our organization especially welcomes feedback on the population, comparators, and outcomes described in the scope as this is used to inform protocol development. All feedback is reviewed by the CDA-AMC and is used to finalize the scope of the therapeutic review project. Based on partner feedback, our organization refines the proposed project scope document and obtains final advice from the public drug programs on whether or not to proceed.

Our partners are apprised of the proposed therapeutic review and the target dates for providing input. While notice of the proposed therapeutic review is posted on the CDA-AMC website, affected manufacturers and partners, including patient groups, may be notified directly by our organization. To support and encourage patient groups to participate, groups are invited to a teleconference with CDA-AMC staff early in the process. During the teleconference, the project is described, expectations are identified, and possibilities for involvement in the project are discussed.

4.2 Research Phase

Our therapeutic review processes reflect nationally and internationally recognized standards and methodologies. New methodologies for assessing drugs are continuously monitored and evaluated, and those that are found to enhance current CDA-AMC processes are incorporated. Therapeutic reviews are based on the best available evidence for addressing the relevant policy questions.

Figure 2: Research and Recommendation Phases Flow Chart



4.2.1 Research Protocol

We draft the project protocol using the scoping documents and scoping search. The project protocol addresses the scope of the project and the methodologies to be used. Input on the draft project protocol is obtained from expert committee discussants and clinical experts. Input includes, but is not limited to, assisting in the development of research questions, identifying relevant outcomes, and identifying subgroups of potential interest. Once finalized, the project protocol is posted on the CDA-AMC website for information purposes only, and registered in the PROSPERO international database.

4.2.2 Included Studies

The list of studies that have been selected as relevant for the clinical report are posted for partner feedback. The list of included studies may be revised depending on the feedback received. The primary evidence evaluated for possible inclusion in a therapeutic review is from the public domain. Sources of evidence are described as follows:

- Published literature is identified by searching major biomedical bibliographic databases using an internally peer-reviewed search strategy. Biweekly search updates are run for the duration of the review.
- Grey literature (literature that is not commercially published) is identified by searching relevant sections of the *CDA-AMC Grey Matters* checklist. Internet search engines are used to identify additional Web-based materials.
- Clinical experts are engaged and given the opportunity to suggest evidence to be reviewed.
- Manufacturers affected by the review are contacted to confirm the available evidence.
- Authors may hand search the references of included studies.

Partners are given the option of identifying and providing unpublished data for consideration in the therapeutic review on the condition that, if used, it will be included in publicly available reports and documents related to the therapeutic review.

4.2.3 Patient Group Input

Interested patient groups are asked to complete a patient group template, available on the CDA-AMC website. The template prompts patient groups to comment on the range of patients' first-hand experiences with the treatments under review; what is important to individuals with the condition and to their families; and specific prompts related to the policy or research questions being addressed by the therapeutic review. Patient groups will have approximately 50 business days to be able to contact their membership and complete the template prompts. Groups can contact our organization's Patient Engagement Officers with questions or to seek advice.

To encourage diversity of voices and experiences, we accept patient group input from organized patient groups, but not from individual patients or caregivers. Interested individuals should either contact a relevant patient group, contact the CDA-AMC to be connected with a relevant patient group, or consider alternative feedback opportunities (see Table 1).

Once patient group input has been received, it may be summarized by our organization and sent back to the patient group(s) for comments on accuracy and completeness. The summary is incorporated into the *Therapeutic Review Science Report*, with perspectives and

shared experiences discussed, when relevant. The completed patient group input template, as provided to the CDA-AMC, is posted on the our website.

4.2.4 Review of Clinical Evidence

Once the results of the clinical literature search have been received, the two authors independently screen retrieved titles and abstracts and come to a consensus on what literature to order. Both authors independently review the full-text articles selected, as well as any unique information received from partners. Following this, they come to a consensus on which studies meet the inclusion criteria for the project (as documented in the project protocol). If there is disagreement on the findings, a third clinical researcher is engaged in the analysis. Unique studies identified are added to the project's list of included studies for review.

If sufficient studies are found that meet inclusion criteria with similar populations and outcomes, data are extracted from the included studies to conduct a meta-analysis. The meta-analysis is a statistical summary of the selected studies that tests the pooled data for statistical significance. Both authors critically appraise, analyze, and interpret the clinical data to generate a reproducible, transparent, and rigorous review of the available clinical evidence. The clinical draft is internally reviewed.

4.2.5 Review of Economic Evidence

Once the results of the focused economic literature search and (if sent) unique information from partners have been received, our organization determines whether a new economic model is required to provide information on cost-effectiveness. We then assess the feasibility of undertaking a full economic analysis. Where a model is developed, it will adhere to the Guidelines for the Economic Evaluation of Health Technologies: Canada and be based on input from the clinical experts and project team. Data inputs for the model are sought from the published literature or based on available data. If a full economic analysis is not feasible, we will explore other options to assess the economic or financial implications.

4.2.6 Drafting the Science Report

The review team prepares a draft report that combines both the clinical and economic drafts. The draft *Therapeutic Review Science Report* is posted for feedback and partners are invited to provide comments. The draft report is posted on the CDA-AMC website and also forwarded to targeted partners (e.g., affected manufacturers and patient groups). The time allotted for comments is 10 business days. Partner feedback is then reviewed and the report is revised based on the feedback (as required).

4.3 Recommendations Phase

4.3.1 Draft Therapeutic Review Recommendations

At this first meeting, the expert committee discusses the *Therapeutic Review Science Report* and whether any changes are necessary. The committee hears presentations of the input from patients and caregivers, clinical and economic evidence, input from clinical experts, and implementation considerations at the jurisdictional level. All committee members have the opportunity to ask questions or make comments. Partner feedback on the draft *Therapeutic Review Science Report* is shared and discussed. Clinical experts involved in the therapeutic review are available to answer questions and comment on the evidence presented. There are two primary objectives of this meeting:

- to develop draft recommendations or advice to address the policy and research questions that were raised by the public drug programs at the outset of the therapeutic review process
- to propose revisions to existing CDA-AMC drug reimbursement recommendations (if applicable, based on the outcome of the therapeutic review)

The *Therapeutic Review Recommendations Report* summarizes the recommendations and/or advice, reasons for recommendations, values and preferences of the committee members, patient preferences, the clinical and economic evidence that was discussed, and the research gaps that were identified by the committee. The draft *Therapeutic Review Recommendations Report* and a document summarizing the committee's proposed revisions to any existing CDA-AMC drug reimbursement recommendations (if applicable) are posted on the CDA-AMC website for partner feedback for a period of 10 business days. At this time, the final *Therapeutic Review Science Report* is also posted for informational purposes.

4.3.2 Final Therapeutic Review Recommendations

Our organization and the expert committee discussants meet to discuss partner feedback. The discussants prepare a report that includes responses to partner feedback on the recommendations and/or advice statement, and the proposed final statement. The discussants' report and partner feedback are presented to the expert committee along with a revised statement, and a discussion is held on feedback and revisions. The expert committee then finalizes the recommendations and/or advice statements. A summary of the feedback considered is included within the final *Therapeutic Review Recommendations Report*.

4.3.4 Revised Drug Reimbursement Recommendations

If required, revised recommendations will be issued in accordance with the *Procedures for CDA-AMC Drug Reimbursement Reviews*..

4.4 Knowledge Mobilization Phase

We develop a brief, plain-language summary for all therapeutic review projects. Additional knowledge mobilization tools may be developed to support implementation and outreach. Our organization considers the following factors when determining the appropriate approach for knowledge mobilization:

- customer requests
- large deviations from optimal utilization (overuse or underuse)
- a new intervention becomes available
- size of patient populations
- impact on health outcomes and/or cost-effectiveness or budgets
- benefits to multiple jurisdictions
- measurable outcomes
- potential to effect change in prescribing and use (to the extent that evidence is available).

Discussions are held with the jurisdictions to obtain feedback on the tools developed.

Appendix 1: Definitions

Advice: Advice consists of a statement(s) provided by the our expert committees that provides direction regarding a policy decision or course of action related to the optimal use of a health technology, but does not make a recommendation. Advice is issued based on an assessment of supporting evidence.

Business Day: Any day (other than a Saturday, Sunday, statutory holiday, or company holiday) on which the CDA-AMC office is open for business during normal business hours.

CDA-AMC: Our organization is an independent, not-for-profit agency funded by Canada's federal, provincial, and territorial governments. Our role is to deliver reliable, timely, and credible evidence-based information and impartial advice to Canada's health care leaders and decision-makers through a variety of customized products and services.

Customer: A CDA-AMC customer is an entity or organization that requests our products or engages our services. (The customer is most often the first point of contact and requests knowledge from CDA-AMC. Customer needs may vary with specific topics, and they may request or choose between different products, services, and suppliers. By expressing their needs, customers drive the knowledge that our organization produces.)

Discussants: Two technical expert members and one public member act as discussants for CDA-AMC drug projects that contain recommendations or advice statements.

Expert Committee A CDA-AMC advisory body composed of individuals with expertise in therapy and evaluation, and public members. For drugs reviewed through the Therapeutic Review or Drug Reimbursement Review process, an expert committee makes formulary reimbursement recommendations for use by the participating federal, provincial, and territorial publicly funded drug programs. Expert committees also provide other drug-related recommendations or advice based on CDA-AMC reviews, to inform decisions and strategies including optimal drug use in Canada.

Jurisdictions: These include the federal, provincial, and territorial health ministries from across Canada.

Meta-Analysis: A quantitative statistical analysis that is applied to separate but similar experiments of different and usually independent researchers, and that involves pooling the data and using these pooled data to test the effectiveness of the results.

Optimal Use: Use of a drug or health technology that balances maximized benefits with minimized risks for people's health based on quality evidence, taking into account the options, costs, available resources, and societal context.

Patient Group: For the purpose of CDA-AMC therapeutic reviews, a patient group is defined as an organized group that represents patients with a specific disease or condition, or collection of diseases or conditions. A group will typically have members who are patients, and/or patients' family members, and have a public face, such as a website or Facebook page.

Recommendations: One or more statements issued by our organization on behalf of an expert committee that provides specific counsel to support the optimal use of a drug or health technology on the basis of the assessment of the supporting evidence.

Science Report: The systematic evaluation of the properties and effects of a health technology that addresses a technology's direct and intended effects, as well as its indirect and unintended consequences. HTAs are primarily aimed at informing decision-making regarding health technologies.

Partners: Partners for the therapeutic review process are organizations, institutions, or individuals who have a strong and vested interest in specific optimal use projects and their outcomes. Stakeholders may include (but are not limited to):

- federal, provincial, and territorial ministries of health
- hospitals and health institutions
- health regions
- individual patients, consumers, and caregivers
- patient groups
- health professionals
- industry.

Tools: These are knowledge mobilization tools used to enable health care decision-makers to use the guidance and/or recommendations that are developed. Tools may include summaries, presentations, conference or workshop materials, continuing education content, and interactive tools (i.e., electronic tools) that allow decision-makers to customize the guidance provided with their own information.