COMMON DRUG REVIEW
CLINICAL REVIEW REPORT TEMPLATE

Annotated with Reviewer Guidelines

Note: This template is used by CDR clinical reviewers in the preparation of clinical review reports.

Drug Product (Brand name and generic name)	
Manufacturer	
Master File Number	

Reviewer | Signature | Date

TABLE OF CONTENTS

PART I. EXECUTIVE SUMMARY 3

PART II. SYSTEMATIC REVIEW OF CLINICAL TRIALS 5

A. Research Question(s) 5

B. Review Methods 5
1. Selection Criteria 5
   a. Types of Clinical Trials 5
   b. Types of Interventions 5
   c. Types of Patients 6
   d. Types of Outcome Measures 6
2. Literature Search 7
3. Data Analysis 7

C. Review Results 7
1. Findings from the Literature 7
2. Summary of Clinical Trial Data 8
   a. Methods 8
   b. Outcomes 9
   c. Quality 10
3. Analysis of Outcomes 11
   a. Primary Outcomes for this Review 11
   b. Secondary Outcomes for this Review 11

D. Discussion 12

E. Conclusions 12

PART III. REVIEW OF THERAPEUTICS 13

A. Disease Prevalence/Incidence 13
B. Standards of Therapy or Accepted Clinical Practice 13
C. Ease of Identifying Appropriate Patients to Receive Drug 13
D. Potential for Off-Label Use 13

PART IV. REFERENCES 14

APPENDICES

Appendix 1: Drug Profile 15
Appendix 2: Review Methods 16
Appendix 3: List of Included and Excluded Studies 17
Appendix 4: Reviewer Worksheets 18

PART I. EXECUTIVE SUMMARY (2 pages)

Reviewer's Specialty/Practice
Please indicate in point form.

Condition
This section should provide a brief description of the disease or condition to be treated.

Drug
This section should include the name of the drug, the drug class and a very brief description of the drug mechanism. Approved indications and dosing should also be indicated here. Reference should be made to Appendix 1 (abridged product monograph provided by the manufacturer) for further drug-related information.

Research Question(s)
Please list in point form.

Review Methods
A systematic review of clinical trials was performed (see Appendix 2 for methods).

Results and Discussion
In this section, primary and secondary outcomes for the review should be indicated and results should be stated (see Part II, Section C). The reviewer should provide a summary of the discussion (see Part II, Section D). Any important unavailable evidence should also be indicated.

Conclusions
Please present conclusions in point form. These conclusions should be identical to those listed in Part II, Section E.

Please 'check' the appropriate box

Therapeutic Assessment

☐ High quality, large, randomized clinical trials demonstrate a **clear therapeutic advantage** over appropriate comparators currently used in Canada (i.e. benefits in terms of reduced morbidity and mortality).

☐ Clinical trials demonstrate a **possible therapeutic advantage** over appropriate comparators currently used in Canada (i.e. questionable/marginal improvement in patient benefit, benefit based on surrogate markers/intermediate outcomes, no efficacy benefit but reduced risk of harm (side effects/drug interactions), efficacy benefit offset by potential for harm, limitations in trial design make any therapeutic advantage questionable).

☐ Clinical trials demonstrate **no therapeutic advantage** over appropriate comparators currently used in Canada but characteristics of the drug confer a **non-therapeutic advantage** (i.e. less frequent administration required, more convenient/easy to use dosage form, other pharmacokinetic advantage).

☐ Clinical trials demonstrate **no therapeutic or non-therapeutic advantages** over appropriate comparators currently used in Canada.

☐ Clinical trials demonstrate a **therapeutic disadvantage** compared to appropriate comparators currently used in Canada (i.e. reduced efficacy benefits, increased potential for harm with no efficacy benefit).

☐ Clinical trials provide **insufficient information** to assess the drug.

PART II. SYSTEMATIC REVIEW OF CLINICAL TRIALS

A. Research Question(s)

Please state the clinical research question(s) that is/are most relevant to the drug plans for evaluation of the drug.

Example:

Is there evidence from clinical trials that drug A has a therapeutic advantage over standard therapies in patients with disease/condition B?

Is there evidence from clinical trials that drug A has a therapeutic advantage over placebo in patients with disease/condition B?

The research question should specify an intervention (drug A vs. comparators), a study population (patients with disease B) and an outcome (therapeutic advantage). Details concerning each of these components should be contained in the selection criteria below.

The reviewer may want to consider patient subgroups that may be likely to benefit more or less from the drug. If appropriate, a secondary research question relating specifically to these patients could be included.

The potential therapeutic advantage of a new drug will be judged by the demonstrated effects of the new drug vs. appropriate comparators on the outcome measures (beneficial and harmful) described in this section (see Part II, Section B1d).

B. Review Methods (see Appendix 2)

1. Selection Criteria

a. Types of Clinical Trials

The reviewer should specify the types of studies to be included in the review. Double-blind, randomized controlled trials are ideal; however, non-blinded, randomized controlled trials are also acceptable.

b. Types of Interventions

The reviewer should specify the interventions required for a study to be included in the review. Ideally, studies should compare the new drug to a standard therapy (head-to-head trial). However, data from studies comparing the new drug to placebo may also be relevant (placebo-controlled trials) in some cases.

Appropriate Comparators (Standard Therapies Available in Canada)

The reviewer should indicate all appropriate comparators for each approved indication of the drug. When relevant, the reviewer should indicate if comparators are pharmacologic comparators (similar mechanism of action) or clinical comparators (similar clinical outcome). If available, dose equivalencies should be included and justified. When possible, reviewers should indicate if dose equivalencies were derived from direct or indirect comparisons.

c. Types of Patients

The reviewer should specify characteristics of patients that are required for a study to be included in the review. Studies should include appropriate patients that reflect the population found under normal clinical conditions. If appropriate, criteria may specify distinct patient populations or severity of disease, etc.

d. Types of Outcome Measures

The reviewer should list the primary and secondary outcomes that will be considered in the review. Any methods of measurement of these outcomes that are likely to be unfamiliar should be explained in an additional appendix.

Emphasis should be placed on clinically relevant and valid outcomes of highest importance for the health of patients with the disease state (some examples for cardiovascular disease: all-cause mortality, cardiovascular-related mortality such as fatal MI or stroke, all-cause morbidity, cardiovascular-related morbidity such as non-fatal MI or stroke, etc.). Note that these outcomes encompass both benefit and harm, depending on whether the incidence is reduced or increased.

Intermediate or surrogate outcomes with less clinical relevance or less clear validation of clinical relevance for patients (example for cardiovascular disease: blood pressure or cholesterol level) should also be included if relevant. When relevant, the strength of evidence for extrapolation of the specific intermediate outcomes to clinically relevant patient outcomes should be discussed in the discussion (Part II, Section D).

Adverse events, serious adverse events and adverse drug reactions (also called adverse effects or side effects) may also be included as outcome measures. Please note the following definitions related to these terms.

Adverse Event

"Any untoward medical occurrence that may present itself during treatment or administration with a pharmaceutical product, and which may or may not have a causal relationship with the treatment" (see http://www.fda.gov/cder/guidance/iche3.pdf)

Serious Adverse Event

An adverse event that "results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, creates persistent or significant disability/incapacity, or a congenital anomaly/birth defect" (see http://www.fda.gov/cder/guidance/iche3.pdf)

Adverse Drug Reaction/Adverse Effect/Side Effect

The definition differs slightly depending on the status of the drug product (i.e. pre-approval vs. marketed products).

- "In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "response to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out" (see ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting and http://www.ncehr-cnerh.org/english/gcp/).

- "Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function" (see ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting and http://www.ncehr-cnerh.org/english/gcp/).

For further details on outcome measures, see Analysis of Outcomes (Part II, Section C3).

2. Literature Search (see Appendix 2)

3. Data Analysis (see Appendix 2)

C. Review Results

1. Findings from the Literature

The reviewer should give a brief overview of the evidence found (example: types of studies, patient population, outcome measures used) and any important unavailable evidence (example: no trials including relevant comparators or an important outcome).

Length: ½ page

C2. Summary of Clinical Trial Data

a. Methods

See reviewer worksheet in Appendix 4 (Data Extraction Worksheet) for a detailed listing of data extracted from each study.

Study Reference	Design	Participants	Interventions	Outcomes	Notes

C2. Summary of Clinical Trial Data
b. Outcomes

Study Reference	Outcome 1	Outcome 2	Outcome 3	Outcome 4	Outcome 5	Outcome 6	Outcome 7

C2. Summary of Clinical Trial Data

c. Quality See reviewer worksheets in Appendix 4 (Quality Assessment Worksheets) for detailed internal and external validity criteria.

Study Reference	Internal Validity	External Validity
	Selection bias: **Performance bias:** **Detection bias**: **Attrition bias:**	
	Selection bias: **Performance bias:** **Detection bias:** **Attrition bias:**	
	Selection bias: **Performance bias:** **Detection bias:** **Attrition bias:**	
	Selection bias: **Performance bias**: **Detection bias:** **Attrition bias:**	

3. Analysis of Outcomes

Results of all the studies should be indicated for each outcome in this section. Avoid repeating numbers already presented in table format. Instead give an indication of the number and type of studies showing significant results. Also present results of any supplementary calculations performed.

For dichotomous outcome data, calculate odds ratio and/or absolute and relative risk reduction/risk increase and/or number needed to treat (NNT)/number needed to harm (NNH) with 95% confidence intervals as relevant.

For continuous outcome data, calculate mean difference with 95% confidence intervals as relevant.

a. Primary Outcomes for this Review

i. Outcome 1

For all diseases/conditions that result in death, reduction in the incidence of all-cause mortality and reduction in disease-specific mortality should be considered as primary outcomes of therapy with the intervention drug.

For all diseases/conditions resulting in disabling morbidity, reduction in the incidence of all-cause and disease-specific morbidity should be considered as primary outcomes of therapy with the intervention drug. For disease-specific morbidity, multiple outcomes may be appropriate.

Note: When reductions in all-cause morbidity and/or mortality are not assessed as outcomes in clinical trials for a disease/condition causing death and/or disabling morbidity, consider using serious adverse events (SAE) that result in death or disabling morbidity as indices. For diseases that do not result in death or disabling morbidity, consider including SAE as an additional primary outcome.

ii. Outcome 2, etc.

b. Secondary Outcomes for this Review

i. Outcome 1

Intermediate or surrogate outcomes should usually be included as secondary outcomes, when relevant.

ii. Outcome 2, etc.

iii. Patient Tolerance to the Drug

Patient tolerance should usually be included as a secondary outcome. Withdrawals due to Adverse Effects (WDAE) and number of patients requiring dose reductions due to drug intolerance should be considered as indices of patient tolerance to the drug. Reviewers should indicate total WDAE for all the studies with breakdown by reason.

D. Discussion

The reviewer should summarize the collective outcome results and the quality of the evidence supporting these outcome results, providing support for the specified conclusions. The clinical relevance of the outcome measures should be discussed and the clinical relevance of the size of treatment benefit/harm should be described. The strength of evidence linking any surrogate outcomes to patient benefits in terms of morbidity or mortality should be discussed. The reviewer should also indicate any information that is lacking.

Length: 1-2 pages

E. Conclusions

The conclusions should be based on analysis and interpretation of the literature presented in the discussion and should be presented in point form. They should be directly related to the research question and should provide the 'bottom line' as succinctly as possible.

If appropriate based on the evidence, conclusions should indicate any patient subgroups where evidence for therapeutic advantage differs from that of the general population.

PART III. REVIEW OF THERAPEUTICS

A. Disease Prevalence/Incidence

This section should include a description of the disease prevalence/incidence in the Canadian population with a breakdown by province/territory. This information and associated references are supplied by manufacturer in the submission. The reviewers and the internal information specialist will confirm this information.

Length: ½ page

B. Standards of Therapy or Accepted Clinical Practice

This section is not intended to be a full systematic review; however, it should be evidence-based and thoroughly referenced.

Describe all currently accepted therapeutic approaches (including pharmacological and non-pharmacological interventions) used to manage the medical conditions for which the drug under review has an approved indication. Include any limitations of the current treatment, if appropriate (i.e. effectiveness, adverse effects, administration).

Reviewers should also indicate the expected place in therapy of the new drug by indication (i.e. replacement for current therapy, use with current therapy, and/or only for non-responders, and/or only for those with contraindications or intolerance to current therapy, etc.)

It is acceptable to use clinical practice guidelines as references for this section. Evidence-based guidelines should be used whenever possible and levels of evidence should be indicated.

Length: 1-2 pages

C. Ease of Identifying Appropriate Patients to Receive Drug

Reviewers should indicate whether clinicians will be able to easily determine which patients would be appropriate candidates for treatment with the new drug.

Limitations of clinical trials that may impact on decision making, missing information that makes determination of appropriate candidates difficult and any ethical, social or patient implications associated with the use of the drug should be considered.

Length: ½ page

D. Potential for Off-Label Use

Based on the literature, approved indications in other countries or the pharmacology of the drug, the reviewer should identify other potential uses of the drug that may impact on its utilization. If possible, the reviewer should indicate how well established such off-label uses are.

Length: ½ page

PART IV. REFERENCES

The Reference Manager Identification Number will be indicated at the top right hand corner of each paper provided to reviewers. References for all sections of the report should be indicated by placing the Reference Manager Identification Number and the last name of the first author in brackets in the appropriate spot in the report. The information specialist and/or internal reviewer will insert the references into the report using the Reference Manager database. External reviewers will be requested to verify the references once they have been inserted into the report.

APPENDIX 1: Drug Profile

The information in this section is a summary of the information in the _____ product monograph. This information is supplied by the manufacturer and is not intended to be a complete summary of the evidence.

This information should be provided by the manufacturer in the described format and should not exceed 3 pages. The manufacturer extracts this information from the product monograph and includes it on a diskette in Word format as part of the submission. The reviewer should import this directly from the manufacturer's submission.

a. Product Information

Generic drug name		
Brand name and manufacturer		
Date of NOC		
AHFS classification & description ATC classification & description		
Dosage form(s) (this section may be expanded to include all dosage forms and strengths)	Dosage form & strength	DIN

b. Indication(s) (Approved by Health Canada)

c. Mechanism of Action

d. Pharmacokinetics and Pharmacodynamics (brief)

e. Dose, Treatment Duration and Dose Equivalency Estimates

f. Adverse Reactions & Frequency

g. Warnings and Precautions

h. Contraindications

i. Drug Interactions

APPENDIX 2: Review Methods

a. Overview of Review Methods

Research questions and selection criteria are developed jointly by two reviewers.

The literature search is carried out by an information specialist using a standardized search strategy (see below).

The two reviewers independently select studies for inclusion according to the predetermined selection criteria. Reviewers independently review citations and abstracts retrieved in the literature search and discard irrelevant articles. Case reports, review articles and studies unrelated to the use of the drug for the indication in question are discarded at this stage.

All articles considered potentially relevant by at least one reviewer are acquired from library sources. Reviewers independently make the final selection of studies to be included in the review and differences are resolved through discussion. A list of included studies as well as a list of excluded studies with reasons for exclusion is provided in Appendix 3.

The data extraction worksheet (see Appendix 4) is developed jointly by the reviewers. This worksheet is used to complete the summary tables in the report. Completed data extraction worksheets are kept on file at CDR.

Assessment of study quality involves independent assessment of the internal and external validity of the studies by each reviewer. These assessments are performed with the aid of worksheets listing specific criteria to be considered (see Appendix 4).

All independent assessments performed by the two reviewers are compared. When differences are found, consensus between reviewers is reached through discussion or with adjudication by a third reviewer.

The review report is prepared by one reviewer and reviewed by the second reviewer.

b. Literature Search Strategy

The literature search is performed by the internal information specialist. A summary write-up of the search strategy is given to the reviewer to be inserted in the report.

The summary write-up lists all sources searched, including the electronic databases, trial registries and sources which are used to identify grey literature such as posters, abstracts and unpublished data. No language limitations are used in the searches. The detailed search strategies are available upon request.

Note: If the reviewer hand searches reference lists and / or key journals, consults other references or requests information from the manufacturer, the reviewer should indicate this information here.

Length: ½ page

c. Data Analysis

The reviewer should describe the methods used to perform the data analysis for the review.

APPENDIX 3: List of Included and Excluded Studies

Once the final selection of studies has been completed, the internal reviewer will compile a list of the included and the excluded studies and forward this list to the external reviewer for review and insertion into the review report.

a. Included Studies

List the studies selected for inclusion in the review.

b. Excluded Studies

List the excluded studies under headings that explain the reasons for exclusion. The list of excluded studies only includes those studies excluded after initial selection of all potentially relevant studies.

APPENDIX 4: Reviewer Worksheets

a. Data Extraction Worksheet

Note: These worksheets will be used by reviewers to extract and tabulate data and assessment comments related to the clinical trials selected for inclusion in the review. Copies of the blank worksheets will be appended to each review for information purposes. The completed worksheets will be kept on file at CDR but will not be appended to the review since the relevant content is summarized in the Summary of Clinical Trial Data section.

Note: The data extraction worksheet should be modified by reviewers for review of specific drugs.

Study title		
Reference		
Methods		
Study design		
Study duration		
Diagnosis		
Eligibility criteria (inclusion and exclusion criteria)		
Country of origin		
Industry sponsorship	☐ Yes ☐ No ☐ Unknown	
	Intervention (_____)	**Comparator** (_____)
Dose and duration of treatment		
Sample size		
Baseline Characteristics Of Study Participants		

Outcomes	Intervention (_____)	Comparator (_____)

b. Quality Assessment Worksheet: Internal Validity of Randomized Controlled Trials

Study Title	
Reference	
Internal Validity Criteria	Details and Comments
Selection Bias **Was patient entry to the trial biased towards those more likely to have favourable results?** ☐ Were eligibility requirements predefined and appropriate? ☐ Were baseline characteristics between groups comparable? If not, was adjustment done? ☐ Were recruitment processes specified and appropriate? ☐ Were all potentially eligible patients invited to participate or did investigator discretion affect those included (#screened vs. #enrolled)? ☐ Did authors account for all eligible patients who did not enter the trial? ☐ Were allocation strategies, appropriate (randomized and concealed) Appropriate: central randomization, numbered or coded containers, drugs prepared by pharmacy, serially numbered, opaque, sealed envelopes, etc. Inappropriate: alternation, reference to case record# or date of birth.	
Performance Bias **Did the treatment given, including concomitant treatments, allow an unbiased estimate of the effect of the drug under investigation?** ☐ Were concurrent therapies equivalent for both groups? ☐ Was the procedure for drug dosage adjustment handled similarly between groups (procedure for dose escalation/reduction and interruption)? ☐ Were the numbers of patients requiring dose adjustment and/or concomitant therapy similar between groups? ☐ Was patient compliance considered? ☐ To what degree was discretion available to physicians to move patients between study arms and use additional drugs?	
Detection Bias **Was assessment of outcomes performed in a way that minimised bias? Were groups treated equally, apart from the experimental therapy?** ☐ Were blinding procedures performed for patients, care providers and those assessing response? ☐ Was the method of double blinding appropriate (placebo and active treatment were identical forms) Note: an example of inappropriate blinding would be comparison of tablets vs. injection with no double dummy ☐ Could the side effect profile of one of the drugs have resulted in unblinding?	
Attrition Bias **Was patient follow-up and handling of protocol deviations adequate to prevent bias** ☐ Was intention-to-treat (ITT) analysis performed (Were all patients analyzed in the groups to which they were randomized)? ☐ Were all patients entered in the trial properly accounted for and attributed at its conclusion? ☐ Were the number and reasons for withdrawals and dropouts reported? ☐ Did the number of withdrawals and dropouts compromise randomization?	

c. Quality Assessment Worksheet: External Validity of Randomized Controlled Trials

Study Title	
Reference	
External Validity Criteria	Details and Comments
Study Participants ☐ Are patient characteristics (age, sex, disease severity, risk factors, co-morbidities) representative of patients that will be treated with the drug in the community? ☐ Are patients we are concerned with so different that the results do not apply?	
Sample Size ☐ Were power calculations performed at the design stage of the study? ☐ Were the numbers recruited sufficient to detect the outcomes specified?	
Usual Care Setting ☐ Does the study protocol and setting represent the usual care patients will receive in the community? ☐ Was the level of care (primary to tertiary) and experience/specialization of the care providers representative of usual care? ☐ Is the treatment feasible in our setting?	
Standard Treatment Regimens ☐ Are drug dosage, timing, route of administration, duration of treatment, types of treatment and concomitant therapies appropriate? ☐ Did dosing favour or hinder the intervention drug or comparator in any way (i.e. was dose of intervention or comparator drug suboptimal/ in excess of recommended dosing guidelines?)	
Standard Treatment Outcomes Measured ☐ Were outcome measures appropriate? ☐ Were outcomes measured appropriately (methods of measurement, appropriate time intervals)? ☐ Were all clinically relevant outcomes reported? ☐ What is the magnitude of the effect? Were both statistical and clinical significance considered?	
Length of Follow-Up ☐ Defined? ☐ Appropriate length? ☐ Complete (80% is absolute minimum)? ☐ Representative?	
Other ☐ Were sub-group analyses specified *a priori* in the study protocol?	