Guidance Document on Reporting Indirect Comparisons

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CADTH

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Authorship

Trevor Richter, BSc, MSc, PhD
CADTH

Karen M. Lee, MA
CADTH

Industry Liaison Forum Science Working Group Contributors

Robert Tam, BSc (Hons), MHA
Director, Government Affairs and Market Access
Genzyme

Christine Chin, BSc, MSc
Director, Value and Access
Sanofi Canada

Farzad Ali, BPharm, MSc
Director, Access – Health Economics and Outcomes Research for Oncology and Innovative Portfolio
Pfizer

This document underwent peer review by:

Brian Hutton, MSc, PhD
Ottawa Hospital Research Institute

Sheri Pohar, BScPharm, MSc, PhD
CADTH

Andrea Tricco, MSc, PhD
Li Ka Shing Knowledge Institute of St. Michael's Hospital

The CADTH Pharmaceutical Industry Liaison Forum (ILF) was established in November 2009 as a vehicle for information-sharing between CADTH and associations representing pharmaceutical industry stakeholders. The forum is not a decision-making body. Its discussions help to inform CADTH's policy development and approaches to broad consultation with pharmaceutical industry stakeholders.

The ILF has two working groups:

- The Working Group on Engagement Issues: Its purpose is to identify, assess, and develop, where possible, joint approaches on issues relating to CADTH-industry interaction.
- The Working Group on Technical and Scientific Issues: Its purpose is to identify, assess, and develop, where possible, joint approaches and standards on scientific and methodological issues.

The Working Group on Technical and Scientific Issues identified the reporting of indirect comparisons (IDCs) as a topic of interest to enhance transparency and promote standardized reporting.

Rationale

The goal of this document is to provide guidance on reporting IDCs. While the use of IDCs is increasing, reporting often lacks adequate description of methodology. Researchers have identified clarity on appropriate methods and reporting of Bayesian mixed treatment comparisons (MTCs) as a priority.[1]

The purpose of this document is to provide a standard reporting structure for IDCs to establish transparency. With transparent reporting, the rigour of the approach and results of the analysis can be assessed.

The document borrows from the growing literature on IDCs and network meta-analyses (NMAs), as identified in the literature search conducted through the ILF Working Group on Technical and Scientific Issues.[2-4] IDC reporting best practices were gathered and incorporated into these reporting guidelines.

This document represents the third draft of reporting guidelines for IDC by the ILF Working Group on Technical and Scientific Issues, and has been reviewed by CADTH staff and members of Canada's Research-Based Pharmaceutical Companies (Rx&D) and BIOTECanada.

Note that this is not a technical guidance document (nor a methodological "how to"), but is limited to providing guidance on reporting the *methods* and *results* of IDCs. For guidance on IDC methodology, please see the reference documents cited.

Structure for Reporting Indirect Comparisons

The structure for IDC reporting follows a typical layout with the following sections: Executive Summary, Introduction, Methods, Results, and Discussion. This document examines each section; for more detailed explanations of many of the concepts presented here, please refer to the sources noted in the References section of these guidelines.

1. Executive Summary

1.1 Provide a summary of Sections 2 (Introduction) to 5 (Discussion):

- State the study rationale/objective(s), methods (inclusion criteria and model framework), results (effect sizes for major outcome[s], major sensitivity analysis results), major limitations, and conclusion.
- Capture key points in each section, e.g., the number of studies included in the model.

2. Introduction

2.1 State the rationale for the IDC:

- Specify why the IDC is required.
- If there is direct evidence versus appropriate comparators, state the added value of conducting an IDC.

2.2 State the IDC objectives:

- Specify the study question that the IDC should address.
- Outline end points of interest.

3. Methods

3.1 Describe the methodology used for a systematic review:

- Follow standard guidelines for systematic reviews, including providing the protocol (ideally published publicly, e.g., PROSPERO[5]).
- Provide literature search strategy, including publication dates for inclusion, databases used, keywords, and relevant Medical Subject Headings (MeSH) terms.

For more information, see guidelines available from the Cochrane Collaboration[6] and the U.S. Agency for Healthcare Research and Quality (ARHQ).[7]

3.2 Describe and justify the inclusion/exclusion criteria for the IDC (including a PICOS table: P = populations; I = interventions; C = comparators; O = outcomes; S = study type).

3.3 Describe and justify the population(s) used in the analysis:

- Include details such as, for example, full population as per the Health Canada indication versus population(s) defined by specific lines of treatment.

3.4 Describe selection and choice of comparator(s):

- A comparator refers to current routine care, the most used treatment, or what would be replaced by the introduction of the new intervention.
- Include all relevant comparators and justify handling of comparators available and not available in Canada.
- Specify doses included for each treatment.
- Report and justify how different doses were handled for individual treatment or classes (e.g., combination or collapsing of different doses/classes).

3.5 Report all sources of information, including databases:

- Include references to publications, as well as database sources.

3.6 Describe study selection process:
- Report this using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.[8]

3.7 Describe validity/quality assessment of individual studies:
- Describe and justify trial characteristics for individual treatment groups (ideally in tabular form), such as baseline population characteristics, concomitant medications, and dosing regimens as well as trial duration (e.g., including duration for the assessment of primary end point).
- Outline methods of quality assessment of literature that met the inclusion criteria.

3.8 Describe outcome measures:
- Justify outcome measures selected for analysis.
- If efficacy-based outcome measures, justify omission of safety/adverse event outcomes in analysis.

3.9 Describe methods for analysis/synthesis of evidence/models:
- Describe choice of framework (frequentist and/or Bayesian).
- State and justify the reference treatment selected.
- Specify the type of analysis used, e.g., Bucher method versus MTC, random versus fixed effects model, etc.
- Justify the analysis used.
- State the algebraic model used for parameter estimation (e.g., in regression or Bayesian analysis).
- Explain how model fit and model selection were assessed.
- Justify the inclusion of trials in light of the consistency and similarity assumptions:
  - Clearly identify studies excluded from the analysis due to heterogeneity of populations, study design, etc.
- Provide sufficient information that would allow reproduction of the analyses, including code (if applicable). If lengthy and/or complex, the code could be provided in an appendix.
- Describe selection of covariates for meta-regressions.
- List all assumptions including details on prior information used (if applicable) (e.g., choice of prior for Bayesian methods).
- Describe handling of potential bias/inconsistency (e.g., deviance information criterion [DIC] for Bayesian analysis).
- Describe assessments of model convergence.
- Describe assessment and handling of transitivity.
- Describe approach(es) to handling heterogeneity.
- Describe the summary measures used (e.g., odds ratios, mean difference, treatments rankings, etc.).

3.10 Describe selection and choice of sensitivity analyses (e.g., priors, exclusion of outliers):
- Include description and justification for subgroup analyses.

4. Results

4.1 For a more detailed explanation of reporting the results of an IDC, refer to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines.[9]

4.2 Summarize studies included in the network of evidence:
- All trials in the target patient population that compare two or more of the treatments included in the analysis should be included.
- Present study network (network diagram) when there are more than two treatments included in the analysis.

4.3 Describe risk of bias assessment for included studies.

4.4 Report individual study data:
- If appropriate, present results (raw outcome data) in a table (see Table 1).

4.5 Present results of the evidence synthesis:
- Present the relative treatment effects (outputs from the evidence synthesis) in a table (see Table 2) and/or a figure (if appropriate):
  - Report estimates of relative treatment effects (e.g., odds ratios, hazard ratios, differences in means) along with 95% confidence interval (CI) or credible intervals (depending on the framework of analysis) compared with a common reference treatment or anchor (see Table 2).
    - Report results of all (relevant) pairwise comparisons:
      - Summarize these results in a table (see Table 3).
- Forest plots should be used to present a summary of the results.

4.6 Describe assessment of model fit (if applicable):
- Examples include the DIC and residual variance.
- Describe approach used to address inconsistencies where present.

4.7 Report sensitivity/scenario analyses results including different model types (e.g., random versus fixed effects), inclusion/exclusion criteria (e.g., placebo-controlled versus active-controlled), and subgroup analyses (e.g., studies completed prior to 2004 versus all studies).

5. Discussion

5.1 Describe/summarize main findings:
- Include major sensitivity analyses.

5.2 Justify model results:
- A clear discussion of the underlying statistical and clinical assumptions implied by the model, and their impact on the final decision, should be provided.

5.3 Assess internal validity of findings:
- Focus on the quality of the individual studies and differences across trials that might violate similarity and consistency assumptions (confounding bias).

5.4 Assess external validity of findings:
- Focus on comparisons between the IDC and direct evidence or other similar IDCs.

5.5 Describe major limitations:
- Examples include (but are not limited to): limitations of the systematic review, heterogeneity between results of pairwise comparisons, inconsistencies between the direct and indirect evidence, inappropriate outcomes, lack of data for specific comparators, etc.

5.6 Report the implications of the results for target audience:
- Present a conclusion based on the results.
- Address the level of uncertainty associated with any conclusions.

Examples of Presentation of Information[1]

TABLE 1: FORMAT FOR PRESENTING SOURCE DATA FOR STUDIES INCLUDED IN THE INDIRECT COMPARISON

(Include data for all treatment groups for all included studies.)

Study Reference	Treatment A		Treatment B		Treatment X	
	n	N	n	N	n	N
Williams, 1993	23	221			21	221
Jones, 2002	43	122	44	122	44	122
…						
Kimura, 2011	12	111	11	113		

n = number of patients who met criteria for Outcome 1 (e.g., complete response); N = total number of patients.

TABLE 2: FORMAT FOR PRESENTING TREATMENT EFFECT SIZES FOR EACH INDIVIDUAL TREATMENT INCLUDED IN THE INDIRECT COMPARISON ANALYSIS

(Treatment effect size should be presented for each treatment versus the same common comparator or anchor.)

Treatment	OR (95% CI)	NNT/NNH (95% CI)	Probability of Being Best of All Compared, %	Rank
A	1.00 (Reference)	1 (0.3 to 1.6)	45	2
B	0.99 (0.10)	1 (0.9 to 1.1)	50	1
X	1.21 (0.71)	2 (0.7 to 4.3)	5	3

CI = confidence interval; NNT/NNH = number needed to treat/number needed to harm; OR = odds ratio; Rank = rank of treatment based on probability of being best in multiple probabilistic trials.

TABLE 3: FORMAT FOR PRESENTING PAIRWISE COMPARISONS

(All pairwise combinations of treatments should be presented.)

Intervention	Comparator		
	A	B	X
A	1		
B	0.99 (CI)	1	
X	1.21 (CI)	1.11 (CI)	1

CI = confidence interval.

[1]Tables can be modified if the suggested format is inappropriate to capture essential information, but should ideally conform to the standards for consistency, rather than being made overtly complex by including excessive (non-essential) information.

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