

A Systematic Review of Common Drug Review Pharmacoeconomic Submissions and an  
Analysis of Emerging Trends

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Thesis submitted to the Faculty of Graduate and Postdoctoral Studies in partial fulfillment of  
the requirements for the MSc degree in Epidemiology

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## **Abstract**

Given financial constraints, drug manufacturers are required to provide pharmacoeconomic evaluations to demonstrate the value for money of their drug compared to current treatment when requesting reimbursement by publicly funded health care systems. This thesis is a retrospective examination of pharmacoeconomic evaluations submitted for review to the Common Drug Review process. Its purpose was to determine the pattern of adherence to guidelines, trends in methodological quality, and transparency, changes in the adoption and practice of sensitivity analysis and probabilistic methods, use of indirect treatment comparison, and identify methodological factors—determinants of recommendations. Using an instrument that was developed and tested, information from 201 pharmacoeconomic evaluations was collected and analysed. Pharmacoeconomic evaluations may have improved over time in terms of adherence, methodological quality, transparency, use of probabilistic sensitivity analysis and indirect treatment comparison. However, such improvements have been minimal and further efforts are needed to better improve pharmacoeconomic evaluations in the future.

## **Acronyms and Abbreviations**

CADTH	Canadian Agency for Drugs and Technologies in Health
CDEC	Canadian Drug Expert Committee
CDR	Common Drug Review
CEA/CUA	Cost-effectiveness analyses and/or cost-utility analyses
CMA	Cost-minimization analyses
the Guidelines	Guidelines for the Economic Evaluation of Health Technologies: Canada
PSA	Probabilistic sensitivity analysis

## **Acknowledgements**

First and foremost, I would like to express my sincere gratitude to my supervisor, Doug Coyle, and my thesis advisor, Karen Lee. Thank you for seeing the potential in me and investing your time and efforts in helping me complete my work. I have gained such a valuable learning experience working alongside you both.

I am forever grateful for the support of the Canadian Agency for Drugs and Technologies in Health. Thank you for granting me access to review the Common Drug Review pharmacoeconomic submissions, providing me with a wonderful workspace, and for funding my thesis.

I would like to thank Kathryn Coyle for her assistance in the development of the multivariable regression model.

Many thanks to the University of Ottawa Faculty of Graduate and Postdoctoral Studies and the Department of Epidemiology and Community Medicine for their financial support to present my work at the Canadian Society for Epidemiology and Biostatistics Biennial Conference.

I thank my family and friends for their love and support, especially to my parents, brother, grandparents and boyfriend.

## Table of Contents

Chapter 1 Introduction .....	1
1.1 Context: The Drug Reimbursement Process in Canada .....	1
1.2 Rationale for Thesis.....	3
1.3 Objectives of Thesis .....	4
1.4 Relevance of Thesis.....	4
1.5 Thesis Outline.....	5
1.6 Thesis Category .....	5
1.7 Context of Thesis.....	6
Pharmacoeconomic Evaluations .....	6
Guidelines for the Economic Evaluation of Health Technologies: Canada .....	6
Importance of Adherence to Guidelines, Methodological Quality and Transparency of Reporting .....	9
Importance of Sensitivity Analysis and Probabilistic Methods.....	10
Importance of Indirect Treatment Comparison.....	11
Importance of Determinants of Formulary Listing Recommendation.....	13
Chapter 2 A Brief Review of the Literature.....	14
2.1 Introduction .....	14
2.2 Methods .....	14
2.3 Literature Review .....	15
2.4 Summary.....	16
Chapter 3 Methods .....	18
3.1 Introduction .....	18
3.2 Study Characteristics and Context.....	18
3.3 Instrument Development Process .....	19
Existing Instrument.....	19
Validation Through Literature Review .....	21
Pilot Test.....	21
Inter-Rater Reliability Test #1 .....	23
Inter-Rater Reliability Test #2 .....	24
3.4 Instrument.....	24

3.5	Data Collection .....	25
3.6	Data Processing .....	26
3.7	Data Analysis.....	27
	Study Characteristics .....	27
	Adherence to Guidelines.....	27
	Methodological Quality .....	30
	Transparency.....	33
	Sensitivity Analysis .....	34
	Indirect Treatment Comparison .....	35
	Determinants of Formulary Listing Recommendation .....	37
3.8	Ethical Considerations.....	40
3.9	Summary.....	40
	Chapter 4 Results .....	41
4.1	Introduction .....	41
4.2	Study Characteristics .....	41
4.3	Adherence to Guidelines Analysis .....	44
4.4	Methodology Analysis.....	51
4.5	Sensitivity Analysis Analysis .....	59
4.6	Indirect Treatment Comparison.....	62
4.7	Determinants of Formulary Listing Recommendation .....	68
4.8	Summary.....	71
	Chapter 5 Discussion and Conclusion.....	72
5.1	Discussion.....	72
	Adherence to Guidelines for the Economic Evaluation of Health Technologies: Canada .....	72
	Methodological Quality .....	73
	Transparency of Reporting .....	75
	Adoption of Sensitivity Analysis .....	75
	Use of Indirect Treatment Comparison .....	76
	Determinants of Formulary Listing Recommendation .....	77
	Interpretations and Recommendations.....	78

Strengths and Limitations .....	81
Future Implications .....	82
5.2    Conclusion.....	83
References .....	84
Appendices .....	89
Appendix A - Example of Scenarios for Each Formulary Listing Recommendation.....	89
Appendix B - Guideline Statements.....	90
Appendix C - Literature Review Search Terms, Strategy and Flow Chart.....	101
Appendix D - Existing Instrument (Lee and Manns 2007).....	103
Appendix E - Initial Revised Instrument .....	108
Appendix F - Research Instrument .....	119
Appendix G - Guideline Statements Linked with Research Instrument .....	132
Appendix H - Additional Results from Fishers Exact Test.....	146
Appendix I - Additional CDR Reanalysis Analysis.....	147
Appendix J - Additional Analysis on Probabilistic Sensitivity Analysis.....	148

## List of Tables

Table 1 Criteria for adherence to guidelines .....	28
Table 2 Criteria for ranking adherence to guideline statements .....	29
Table 3 Appropriate functional forms for parameters in PSA .....	35
Table 4 Description of indirect treatment comparison reporting items .....	36
Table 5 List of selected variables .....	37
Table 6 Form of analysis used in pharmacoeconomic submission from 2003-2012 .....	41
Table 7 Drug characteristics .....	42
Table 8 Forms of analysis used in thesis analysis from 2003-2012 .....	43
Table 9 CDEC formulary listing recommendation from 2003-2012 .....	43
Table 10 Adherence to guideline statements .....	44
Table 11 Trends in adherence to guideline statements by grouped year .....	46
Table 12 Basic methodology by grouped year .....	52
Table 13 Efficacy data by grouped year .....	53
Table 14 Inclusion of quality of life by grouped year .....	54
Table 15 Model validation by grouped year .....	55
Table 16 CDR reanalysis by grouped year .....	56
Table 17 Model assumptions by grouped year .....	57
Table 18 Model inappropriate assumptions by grouped year .....	58
Table 19 Forms of deterministic sensitivity analysis from 2003-2011 .....	60
Table 20 Treatment of parameter uncertainty and reporting methods for PSA from 2004-2011 .....	61
Table 21 Use of indirect treatment comparison by grouped year .....	63
Table 22 Reporting items in indirect treatment comparisons by grouped year .....	64
Table 23 Quality of individual studies with respect to reporting of indirect treatment comparison .....	65
Table 24 Use of indirect treatment comparison in cost-minimization analysis by grouped year .....	66
Table 25 Comparison of reporting items in cost-effectiveness analysis/cost-utility analysis and cost-minimization analysis .....	67

Table 26 Comparison of adherence to reporting items in cost-effectiveness analysis/cost-utility analysis and cost-minimization analysis.....	67
Table 27 Candidate variables for regression analysis .....	68
Table 28 Odds ratio of candidate variables for multivariable regression analysis .....	70
Table 29 Key methodological factors .....	71
Table 30 Functional forms used for transition probabilities from 2004-2011 .....	148
Table 31 Functional forms used for utilities from 2004-2011 .....	149
Table 32 Functional forms used for costs from 2004-2011 .....	149
Table 33 Functional forms used for treatment effects from 2004-2011 .....	150

## List of Figures and Illustrations

Figure 1 Pharmacoeconomic submissions' adherence to Guidelines for Economic Evaluations for Health Technologies: Canada.....	46
Figure 2 Trends in guideline statements with very good/good adherence.....	48
Figure 3 Trends in guideline statements with fair adherence .....	49
Figure 4 Trends in guideline statements with poor adherence.....	50
Figure 5 Trends in average number of guideline statements adhered to.....	51
Figure 6 Trends in use of sensitivity analysis from 2003-2011 .....	59
Figure 7 Number of types of reporting methods in PSA from 2004-2011 .....	62
Figure 8 Trends in indirect treatment comparison and network meta-analysis from 2003-2011 .....	64

## **Chapter 1 Introduction**

### **1.1 Context: The Drug Reimbursement Process in Canada**

In Canada, the pharmaceutical sector has been argued to be one of the most innovative and profitable industries (Industry Canada, 2012). However, others question whether or not the pharmaceutical industry can truly be considered innovative (Morgan, Lopert, & Greyson, 2008). From 2001 to 2011, total pharmaceutical sales in Canada have doubled to \$22.3 billion (Industry Canada, 2012). However, increasing drug expenditure necessarily puts pressure on the publicly financed health care system. Pharmaceuticals have become the second largest component of healthcare expenditures in Canada, with a forecasted 16 percent of total health expenditures in 2012 (Industry Canada, 2012). Approximately 42 percent of drug expenditures are covered within the publicly funded health care system, that is, provincial/territorial and federal drug subsidy programs and social security funds, and 58 percent by individuals— partly through private health insurance (Industry Canada, 2012).

Cost reduction, cost-effectiveness and achieving the best value for each taxpayer dollar, has been in the fore-front across the public sector in recent years (Flaherty, 2012). Given financial constraints, drug manufacturers are required to provide pharmacoeconomic evaluations to demonstrate the value for money of their drug compared to current treatment when requesting reimbursement by publicly funded health care systems. In an attempt to control drug expenditures and to harmonise the reimbursement process across Canada, the Canadian Agency for Drugs and Technologies in Health (CADTH) was mandated in 2003 to establish a pan-Canadian review process, the Common Drug Review (CDR), which reviews the clinical, cost-effectiveness, and patient evidence of drugs relating to new pharmaceuticals for which the drug manufacturer is requesting reimbursement. As part of the drug review process the CDR has an expert committee called the Canadian Drug Expert Committee (CDEC) which provides a formulary listing recommendation to all publically funded drug plans (except Quebec) (Canadian Agency for Drugs and Technologies in Health, 2013).

When a drug manufacturer is requesting reimbursement for their drug, they are required to provide a drug submission to CADTH for review through the CDR process. This drug submission includes items such as: clinical evidence, a written report of the pharmacoeconomic evaluation along with an executable economic model, and budget impact information. The CDR review consists of a clinical systematic review conducted by CADTH and a critique of the drug manufacturer submitted pharmacoeconomic evaluation which summarizes the methods and limitations. Clinical and pharmacoeconomic reports are created and sent to the drug manufacturer for comments. The returned comments are then addressed by the clinical and economic reviewers. Afterwards, the clinical and pharmacoeconomic reports as well as the responses to the drug manufacturer's comments are provided to the CDEC and drug plans (Canadian Agency for Drugs and Technologies in Health, 2013; Canadian Agency for Drugs and Technologies in Health, 2011).

Based on the information, CDEC provides one of three formulary listing recommendations: do not list, list with criteria and/or conditions and list. A do not list recommendation signifies not to include the drug in the list of publically funded drugs. A list with criteria and/or conditions recommendation means to include the drug in the list of publically funded drugs; however such a listing is conditional either on restricting use based on clinical criteria or on obtaining a price reduction. A recommendation to list signifies to include the drug in the list of publically funded drugs.

In September 2013, an additional recommendation was added – do not list at the submitted price, which meant not to include the drug in the list of publically funded drugs at the price submitted by the drug manufacturer (For examples of scenarios in each recommendation, refer to Appendix A - Example of Scenarios for Each Formulary Listing Recommendation)(Canadian Agency for Drugs and Technologies in Health, 2013).

The embargoed recommendation is then sent to the drug manufacturer and drug plans. At this time, the drug manufacturer may seek reconsideration or the drug plans may submit a request for clarification. In these cases, the drug submission will return to CDEC for further discussion and ultimately, a final formulary listing recommendation by CDEC is issued and posted on the CADTH website (Canadian Agency for Drugs and Technologies in Health, 2011).

The formulary listing recommendation given by CDEC is the product of the CDR process. However, the decision to reimburse the drug is made by the individual drug plans. Such decisions may differ from the CDEC recommendation and are based on factors such as the individual drug plan's mandate, jurisdictional priorities, and financial resources.

The above provides context to the rationale and objectives of this thesis as it outlines why drug manufacturers must provide pharmacoeconomic evaluations and how they are used in the reimbursement process through CDR.

## **1.2 Rationale for Thesis**

In general, since pharmacoeconomic evaluations are being used in the reimbursement process, pharmacoeconomic evaluations 1) should adhere to guidelines for economic evaluation established by CADTH, 2) should be of good quality in terms of methodology, 3) should be transparent in terms of reporting, 4) should adopt emerging methodology such as probabilistic sensitivity analysis (PSA) and indirect treatment comparison, and 5) should have an impact on CDEC formulary listing recommendation. However, the extent to which drug manufacturer pharmacoeconomic evaluations adhere to guidelines, use appropriate methodology, are transparent, adopt recent methods and impact formulary listing recommendation had never been done. It was therefore the rationale for this thesis.

Some studies have examined some aspects listed above; however, reports have not been extensive as that provided within this thesis. As it will be apparent below and in detail in Chapter 2 A Brief Review of the Literature, a formal literature review found few studies which examined the content and quality of drug manufacturer pharmacoeconomic evaluations. Studies tended to be of small sample size with short analytical timeframes (e.g.: 1996-1999- a three year period). Furthermore, studies were not specifically addressing issues relating to the drug manufacturers' pharmacoeconomic evaluations submitted to CADTH. The few Canadian studies relating to adherence to guidelines and methodological quality are dated – are not recent, and therefore do not reflect emerging methodologies: such as developments relating to probabilistic sensitivity analyses and indirect treatment comparisons. The adoption of these methodologies would be of major relevance to the pharmacoeconomic evaluations submitted for review. Finally, it is also unclear from the

published literature the extent to which information from pharmacoeconomic evaluations impact formulary listing recommendations.

### **1.3 Objectives of Thesis**

Given the use of drug manufacturer pharmacoeconomic evaluations in the reimbursement process and the notable knowledge gap listed above, the purpose of this thesis is to conduct a thorough review of drug manufacturer pharmacoeconomic evaluations submitted for review through the CDR process. Focus will be on assessing adherence to the Guidelines for the Economic Evaluation of Health Technologies: Canada and identifying trends in methodological quality and transparency of reporting. There will be detailed focus on two emerging issues: the adoption and practice of sensitivity analysis particularly probabilistic methods and the use of indirect treatment comparisons. Finally, statistical analysis will identify any methodological factors which are determinants of formulary listing recommendations.

### **1.4 Relevance of Thesis**

Findings from this thesis will help identify gaps in drug manufacturer pharmacoeconomic evaluations submitted as part of the drug reimbursement process, with the aim of improving future evaluations. From a policy perspective, it may assist drug manufacturers in providing more comprehensive and robust pharmacoeconomic submissions for review. Areas of pharmacoeconomic submissions that have improved across the years will serve as a positive reinforcement of good practice for drug manufacturers. Areas that require further improvement will inform drug manufacturers where to focus their efforts to improve their pharmacoeconomic evaluations.

Findings of this thesis will also help identify gaps in adherence, transparency and methodological quality of drug manufacturer pharmacoeconomic evaluations, which may inform any necessary changes to current CADTH guidelines for economic evaluation both to the benefit of industry and formulary recommendation committees such as CDEC. Changes may be as a result of the need for greater clarity and emphasis on existing guidance as well as identifying any gaps in current guidance relating to new methodological developments.

Finally, in identifying any methodological factors which are determinants of formulary listing recommendation, my thesis will discuss their impact on the recommendation and provide advice to drug manufacturers and CADTH. Such analysis will reinforce the relevance of the findings with respect to the need to both change current guidance and to encourage drug manufacturers to submit evaluations which more strongly adhere to the guidance available.

## **1.5 Thesis Outline**

The remainder of this chapter will provide context to the topics covered throughout the thesis. Topics covered will include discussion of what is a pharmacoeconomic evaluation, and what are the Guidelines for the Economic Evaluation of Health Technologies: Canada as well as greater context and rationale for the objectives of the thesis.

The following chapter will contain a brief literature review focusing on studies that have examined pharmacoeconomic evaluations submitted by manufacturers for recommendation. The third chapter will outline the methods used for reviewing and analyzing pharmacoeconomic evaluations. The fourth chapter will present the results of each analysis. The final chapter will discuss the results and end with some recommendations for change.

## **1.6 Thesis Category**

This thesis is a complete research project with components of a policy thesis. This thesis involves thorough instrument development and a comprehensive collection of data from pharmacoeconomic evaluations and accompanying material. Although this thesis builds from existing literature, the development of the instrument, collection of information, and analysis was conducted by myself, with input from my thesis advisory committee. As discussed earlier in the introduction, this thesis is relevant to public health policy as it examines pharmacoeconomic evaluations which are used for policy-making decisions and provides recommendations aimed to facilitate evidence based policy making.

## **1.7 Context of Thesis**

### Pharmacoeconomic Evaluations

A pharmacoeconomic evaluation is an economic evaluation that is specific to drugs. An economic evaluation is a comparative analysis of alternative courses of action in terms of costs and health outcomes (Drummond, 2005; Fox-Rushby & Cairns, 2005). Typically, the alternative courses of action are modelled using a decision analytic model which is a simplified real world situation of what would likely occur if a particular decision regarding a drug was made (Fox-Rushby & Cairns, 2005). Information such as clinical effects, resource use, costs, health state valuation, and epidemiological data are combined within the model to provide estimates of long term costs and outcomes associated with each treatment option. From these estimates, the cost effectiveness of alternative treatments are established with emphasis on the incremental cost per outcome obtained (Fox-Rushby & Cairns, 2005).

The value of conducting a pharmacoeconomic evaluation and model is that the information provided will allow the decision maker to identify the value for money of the drug submitted for consideration given the scarce health care resources available.

In this thesis, a pharmacoeconomic submission is the pharmacoeconomic evaluation submitted by the drug manufacturer for formulary listing recommendation and will be used synonymously with pharmacoeconomic evaluation and economic evaluation.

It is important to note that the primary focus of this thesis is the data submitted within the pharmacoeconomic submission by manufacturers, and not the clinical evidence submitted by manufacturers or the CDR review of clinical evidence.

### Guidelines for the Economic Evaluation of Health Technologies: Canada

Guidelines for the Economic Evaluation of Health Technologies: Canada were developed by CADTH in 2006 (Canadian Agency for Drugs and Technologies in Health, 2006). This version was preceded by editions in 1994 and 1997 (Canadian Coordinating Office for Health Technology Assessment, 1994; Canadian Coordinating Office for Health

Technology Assessment, 1997). These guidelines were developed with health economic experts and represented consensus of best practice.

In 1994, the first edition of the national guidelines for economic evaluations of pharmaceuticals was released in Canada; it was developed over an 18 month period by a committee of experts representing provincial and territorial ministries of health, the board that over-see pricing for all patented drugs in Canada, and pharmacoeconomic experts from academia (Menon, Schubert, & Torrance, 1996). Three years later, a guidelines review committee was established to update the guidelines based on the experiences gained since the release of the guidelines in 1994 and developments in methodology (Glennie et al., 1999). Then, in 2006 a third edition of the Guidelines for the Economic Evaluation of Health Technologies: Canada was released. This edition was updated to reflect the experiences gained since the release of the second edition in 1997 as well as developments in methodology (Canadian Agency for Drugs and Technologies in Health, 2006). Although an addendum for specific guidance for oncology products (Mittmann et al., 2009) to the third edition was made, overall, the methods and context of the third edition still applied to oncology products and therefore, could be applied universally since guidelines reflect best practice.

The purpose of the guidelines is to assist drug manufacturers in creating credible and standardized pharmacoeconomic evaluations, useful for decision making. The document outlines best practices for the conduct of pharmacoeconomic evaluations and highlights relevant and useful information needed for creating high quality and transparent pharmacoeconomic evaluations.

The Guidelines for the Economic Evaluation of Health Technologies: Canada contains a list of guideline statements which include details regarding the best practice for the following (for a complete details of each guideline statement mentioned above, refer to Appendix B - Guideline Statements):

- perspective: “viewpoint from which economic analysis is conducted (e.g., public payer, society, individual); defines which costs will be examined”

- types of evaluation: the type of evaluation used for the economic analysis (e.g., cost-utility analysis, cost-effectiveness analysis, cost-minimization analysis)
- discounting: “process by which streams of future costs and benefits occurring in future (typically beyond one year) are converted to equivalent present values using discount rate”
- time horizon: “period of time over which costs and outcomes are measured in economic evaluation”
- target population: “the patient population for the indication approved by Health Canada; may be defined using baseline demographic features that describe the type of patient (e.g., age, sex, socioeconomic status) with a specific condition, of a certain severity or stage, with or without co-morbidities or risk factors”
- comparators: “alternative to which the intervention is compared”
- variability and uncertainty : variability – “reflects known differences in parameter values associated with identifiable differences in circumstances; is represented by frequency distributions; variability can be attributed to diverse clinical practice patterns in different geographical areas or settings, or inherent.” Uncertainty – “a state in which true value of parameter or structure of process is unknown.” Stratified analysis is an example of an approach to handle variability, while sensitivity analysis is an example of an approach to handle uncertainty.
- resource use and costs: activities, resources, and costs “that are likely to occur in each alternative”
- effectiveness: “extent to which intervention produces benefit in defined population in routine or ‘real world’ circumstances”
- generalizability: “problem of whether one can apply or extrapolate results obtained in one setting or population to another; term may also be referred to as ‘transferability,’ ‘transportability,’ ‘external validity,’ ‘relevance,’ or ‘applicability’”

- reporting: “how each element of the economic evaluation, as outlined in the Economic Guidelines, has been handled”
- modelling: a synthesis of evidence and assumptions “from multiple sources to estimate the long-term incremental costs and outcomes of new therapies”
- valuing outcomes: “measure the outcome for a CUA [cost-utility analysis] in terms of the QALYs [quality-adjusted life years] gained using “preference-based measures to value meaningful differences between the intervention and alternatives in terms of HRQL [health-related quality of life]”
- study question: the question addressed in the economic evaluation
- equity: “as it relates to health, ‘fairness’ in allocation of resources, interventions, or outcomes among individuals or group”

The definitions above are taken directly from the Guidelines for the Economic Evaluation of Health Technologies: Canada (Canadian Agency for Drugs and Technologies in Health, 2006). For this thesis, the Guidelines for the Economic Evaluation of Health Technologies: Canada will be referred to as the Guidelines.

### Importance of Adherence to Guidelines, Methodological Quality and Transparency of Reporting

As mentioned above, the Guidelines outline best practices. Guidelines are only useful if they in turn influence practice such that studies follow the best practices outlined within guideline statements. In order to determine the extent to which pharmacoeconomic evaluations are reflective of best practices, adherence to guidelines is assessed. In this thesis, adherence is defined as the ability to satisfy the guideline contained within the Guidelines.

The methodological quality of pharmacoeconomic evaluations submitted for formulary listing recommendation is assessed by CDR pharmacoeconomic reviewers. A major focus of this thesis is to examine the methodological quality of pharmacoeconomic evaluation since the lack of methodological quality of the pharmacoeconomic evaluations

both limits the applicability of the submitted evaluations and may impact CDEC's decision to make a formulary listing recommendation (Anis & Gagnon, 2000). In this thesis, methodological quality relates to the choice of data and modelling techniques.

Finally, transparency in the reporting is important since lack of transparency may lead to improper interpretation of the results, and lead to doubts regarding the credibility of the pharmacoeconomic evaluation (McDaid, Mossialos, & Mrazek, 2002). For this thesis, transparency of reporting is defined as providing clear and transparent reporting of methods, reporting of analysis, and reporting of results.

Transparency in the reporting within pharmacoeconomic submissions has not been previously examined in published literature. Adherence to guidelines and the methodological quality of drug manufacturers' pharmacoeconomic evaluations submitted for formulary listing has been explored in Canada and internationally. However, previous reports do not have access to the pharmacoeconomic evaluations submitted for formulary listing recommendation and are, therefore, not as extensive as this thesis.

#### Importance of Sensitivity Analysis and Probabilistic Methods

As mentioned previously, the results of economic evaluation assist decision makers in identifying which drugs can be considered cost effective, however, as with all studies there will be a degree of uncertainty surrounding the results primarily due to uncertainty over parameters inputs within the economic model. Therefore, authors of economic evaluations use sensitivity analysis to address the impact of uncertainty on study results (A. H. Briggs & Gray, 1999; Fox-Rushby & Cairns, 2005).

The two approaches for dealing with parameter uncertainty are deterministic and probabilistic sensitivity analysis (PSA) (A. Briggs et al., 2012) In the deterministic approach to handling uncertainty, alternative values are assigned to parameter inputs (single or multiple parameters) and a revised estimate of outcomes associated with cost effectiveness are obtained. In PSA, distributions rather than fixed values are assigned to parameter inputs (A. Briggs et al., 2012). From this, multiple estimates of costs and outcomes can be obtained providing evidence on the uncertainty around the study results. PSA can be presented as a

scatter plot, where incremental cost-effectiveness ratio replicates are plotted on a cost-effectiveness plane, or as cost-effectiveness acceptability curve, where the probability that the drug is cost-effective at a given willingness to pay threshold is plotted (Canadian Agency for Drugs and Technologies in Health, 2006).

The assignment of the distribution to each parameter should be based on the nature of the parameter's statistical distribution (Andronis, Barton, & Bryan, 2009). For example, the natural statistical distribution of cost data is skewed and therefore, gamma and log normal distributions are best suited (A. Briggs, Claxton, & Schulpher, 2006; A. Briggs et al., 2012).

The use of PSA has been considered an emerging methodology within pharmacoeconomic evaluations (Sculpher, Claxton, & Akehurst, 2005). However, there are issues in the conduct of PSA that need to be considered. First, there are concerns that choice of parameter distribution used in the PSA is at times inappropriate (Claxton et al., 2005) which can affect the results of the sensitivity analysis. Second, in many PSAs not all relevant parameters are considered uncertain. Finally, the methods by which the results of PSA are presented have not previously been explored.

This thesis will assess the degree to which drug manufacturers within their pharmacoeconomic evaluations have adopted PSA, the degree to which they use appropriate parameter distributions, the degree to which they consider all relevant parameters and the methods of presenting the results of PSA.

### Importance of Indirect Treatment Comparison

As mentioned earlier, clinical effectiveness is a major input within a pharmacoeconomic evaluation. Within pharmacoeconomic submissions, this information is typically derived from the clinical trials conducted by drugs manufacturers. Often head-to-head randomized controlled trials – clinical trials comparing two drugs - are not available. Therefore, evaluations are often reliant in using results from placebo controlled trials – clinical trials comparing a drug to placebo.

The reimbursement requirement is to provide comparative effectiveness data – data that compares the effectiveness of all alternative drugs for the given condition. Therefore, if

only clinical trials comparing a drug versus placebo or no treatment are available, it is not possible to directly compare the effectiveness of two drugs. However, a recent development in comparative effectiveness data has emerged which allows the comparison of two drugs from different randomized controlled trials when direct comparison – comparing drugs within randomized controlled trials - is not available. This method is called indirect treatment comparison (Sculpher et al., 2005; Song, 2009).

There are various types of indirect treatment comparisons: naïve comparison, informal comparison, adjusted comparison, and network meta-analysis. A naïve comparison is a simple approach where the results from the individual arms of the two different randomized trials are compared to as if results from the individual arms are from the same trial (Glenny et al., 2005; Song, 2009). This approach is considered inappropriate since randomization within the trials is not conserved, and therefore the evidence is can be considered equivalent to observational evidence. As a result, there is an increase in possible bias and over or underestimation of the treatment effect (Donegan, Williamson, Gamble, & Tudor-Smith, 2010; Glenny et al., 2005; Song, 2009)

Another approach is an informal treatment comparison - a comparison of treatments with a common intervention using point estimates and confident intervals of two odds ratios. This type of comparison does not consider formal calculation of treatment effects or statistical significance testing (Song, 2009) and therefore, treatment effect estimates are subject to bias.

The methods of indirect comparison have matured and include more formal approaches such as the Bucher method (Bucher, Guyatt, Griffith, & Walter, 1997). More recently, network meta-analysis has emerged which is a complex method developed to allow consideration of both direct and indirect evidence (Lumley, 2002; Lu & Ades, 2004). This approach allows consideration of all available evidence rather than the restricted focus of conventional meta-analysis

This thesis will assess the degree to which drug manufacturers use indirect treatment comparisons to demonstrate comparative effectiveness data in their pharmacoeconomic

evaluations. Focus will be on whether the use of such methods has increased over time and whether such methods have been adopted appropriately.

### Importance of Determinants of Formulary Listing Recommendation

There are differing views on the importance of economic information, some authors have argued that cost-effectiveness information does little to influence decision makers (Brousselle & Lessard, 2011), while others argue that economic information does have an impact on the reimbursement decision of pharmaceuticals (Devlin & Parkin, 2004).

A recently published study focussed on identifying determinants of CDEC recommendations –specifically which factors were associated with a recommendation not to list a drug. This study examined 134 final recommendations and reasons for recommendations given by CDEC from 2003-2009 and found that clinical uncertainty and price considerations, rather than economic results, had a strong impact on formulary listing recommendation (Rocchi, Miller, Hopkins, & Goeree, 2012).

This study explored the determinants of formulary listing recommendation using reasons for recommendation available online rather than entire pharmacoeconomic submission and therefore is not comprehensive of the reimbursement process. Thus, the extent to which economic information from pharmacoeconomic evaluations impact the formulary listing recommendation in Canada is not well explored. Furthermore, there is limited evidence on whether methodological factors within pharmacoeconomic evaluations are determinants of formulary listing recommendation.

A positive listing recommendation can be considered a recommendation to list or list with criteria or condition (list with a reduced price, list with a clinical criteria, list in the similar manner as drug in class) and a negative listing recommendation can be considered a do not list recommendation. This thesis will include a statistical analysis designed to address which methodological factors are determinants of a positive listing recommendation.

## **Chapter 2 A Brief Review of the Literature**

### **2.1 Introduction**

The focus of this chapter is to highlight studies that examined the quality of drug manufacturers pharmacoeconomic evaluations submitted for formulary listing recommendation.

### **2.2 Methods**

The literature review focussed on studies which assessed the quality of pharmacoeconomic submissions for reimbursement as well as highlight methodological items used to assess the quality of pharmacoeconomic submissions. In addition to the work of Lee & Manns (2007) which was the impetus for this thesis, three databases: Medline, Pubmed and Embase as well as selected journals: Pharmacoeconomics and Value in Health were consulted. Canadian and international English studies which examined the quality of pharmacoeconomic evaluations for formulary listing and consulted a checklist, instrument, data extraction form, or itemized extracted data to guidelines for the assessment of methodological quality of pharmacoeconomic evaluations were included. Studies were broadened to include international studies to help inform changes to the initial instrument (Appendix E - Initial Revised Instrument). However, studies were restricted to English studies since the majority of the studies in this area are in English and it was assumed that non-English studies would provide little meaningful information to the context. Studies examining the quality of specific drugs or specific class of drugs were excluded since it was assumed that the methodological content of the instruments would be specific to the disease and would therefore not be applicable to many of the drug submissions As well, studies which evaluated the quality of pharmacoeconomic evaluations submitted to journals as opposed to drug plans or centralized drug review processes for formulary listing recommendation were excluded (For complete search terms, strategy and flow chart, refer to Appendix C - Literature Review Search Terms, Strategy and Flow Chart).

### **2.3 Literature Review**

In 2000, a Canadian study assessed the adherence to guidelines and the methodological quality of pharmacoeconomic evaluations submitted to the Pharmacoeconomic Initiative of British Columbia from 1996-1999. A total of 95 submissions were reviewed. The study discovered that pharmacoeconomic submissions had poor adherence to guidelines and methodological quality, particularly with respect to choice of comparator, sensitivity analysis, perspective, and long term time horizon (Anis & Gagnon, 2000).

In 2007, an American study investigated the quality and completeness of clinical and economic information within drug submissions to the Premera Blue Cross Health Plan from 2002-2005 with respect to the Academy of Managed Care Pharmacy guidelines for formulary submissions. A total of 53 submissions which contained economic information were reviewed. The study found poor adherence to guidelines with respect to conducting sensitivity analysis, stating perspective, including relevant comparators and clearly stating assumptions (Colmenero et al., 2007).

In 2012, a Dutch study reviewed the methodological quality and adherence to guidelines of pharmacoeconomic evaluations submitted to the Dutch Health Care Insurance Board from 2005-2008. A total of 21 submissions were reviewed. This study found that 13 of the 21 pharmacoeconomic evaluations were not methodologically sound and that compliance to guidelines could be improved in terms of including deterministic sensitivity analysis, having less reliance on expert opinion, and including more details regarding the model (Hoomans, Severens, van der Roer, & Delwel, 2012).

In the same year, another study was published which reviewed the quality of pharmacoeconomic evaluations submitted to the Health Insurance Review and Assessment services in Korea from 2005-2009. A total of 47 submissions were reviewed. This study found overall fair quality of pharmacoeconomic submissions but low compliance rates with certain items in the guidelines such as including the appropriate target population that corresponded with the indication, including the appropriate data source for cost estimation, and including explicit and feasible model assumptions (Yim et al., 2012).

In 2007, another Canadian study, only available in abstract form, identified the methodological issues related to pharmacoeconomic evaluations submitted for review

through the CDR process from 2003-2005. A total of 19 submissions with economic analysis were reviewed. The study highlighted key findings with respect to the quality of pharmacoeconomic submissions such as inappropriate comparators, analyses based on inappropriate assumptions for key parameters, insufficient sensitivity analyses, and clinical and safety claims used as the basis for the pharmacoeconomic analyses which were not supported by the CDR (Lee & Manns, 2007). This study provided the impetus to this thesis to explore in more detail the methodological quality of all submissions through the CDR process.

## **2.4 Summary**

There were two studies that examined adherence to guidelines and/or methodological quality of pharmacoeconomic submissions in a Canadian setting, however, both studies were conducted over 5-10 years ago, which only included a small sample of pharmacoeconomic evaluations, and did not reflect updated guidelines and methodology of the 2006 edition of the Guidelines for Economic Evaluation of Health Technologies: Canada.

Three studies examined methodological quality and adherence to guidelines of more recent pharmacoeconomic submissions, however, none of which were from a Canadian setting, and its sample size and scope remained quite small. None of the latter studies examined the transparency of reporting, the appropriateness of sensitivity analysis and the use of indirect treatment comparisons. Furthermore, the studies provided little detail on the instrument used to extract data from the pharmacoeconomic submissions – only one stated having piloted the instrument, and none discussed the development process of the instrument.

The purpose of this chapter was to highlight previous studies that examined the quality of pharmacoeconomic submissions within a drug reimbursement process. The review highlights the paucity of available studies. Previous studies did not assess pharmacoeconomic submissions to the detail and in the extent that my thesis will. My thesis assesses pharmacoeconomic submissions in a longer time horizon (2003-2012), in greater detail including assessments on the adoption of sensitivity analysis and indirect treatment comparisons which previous studies did not explore, and my thesis provides a thorough

description of the development process of the instrument used for assessing pharmacoeconomic submissions.

The following chapter details the methods adopted within this thesis. It will describe how despite the weaknesses of previous studies, they have influenced the development of the instrument used to collect information from pharmacoeconomic submissions within this thesis.

## **Chapter 3 Methods**

### **3.1 Introduction**

This chapter will describe the methods used in the review of pharmacoeconomic submission to the CDR process. The chapter will highlight the study characteristics and context, the development of the instrument to abstract data, the data collected, the data collection process, and analysis of data.

### **3.2 Study Characteristics and Context**

At the end of June 2012, there were 234 manufacturer drug submissions submitted to CADTH for formulary listing recommendation. 32 submissions were withdrawn, suspended, stopped, rejected or ongoing and therefore, did not have a formulary listing recommendation. These were excluded from my thesis because these drug submissions did not complete the Common Drug Review process at the time of data collection.

A total of 202 manufacturer drug submissions received a formulary listing recommendation. All manufacturer drug submissions which received a formulary listing recommendation with the exception of one (the drug submission was not available for review) were reviewed in this thesis. The study population examined in this thesis are therefore the 201 pharmacoeconomic evaluations submitted by the drug manufacturer from 2003-2012 for which the CDR process was completed by the end of June 2012.

Of the 201 pharmacoeconomic evaluations, 111 were cost-effectiveness analyses and/or cost utility analyses (CEA/CUA) and 76 were cost-minimization analyses (CMA). In some cases (n=14), there was limited reporting; for instance, when a submission was analysed by CDR pharmacoeconomic reviewers as CMA but was not submitted as CMA or when an informal analysis (a cost-consequence analysis where costs and outcomes are analysed and presented separately and no economic model is provided) was submitted. These 14 pharmacoeconomic evaluations were excluded from the main analyses. For the majority of analyses in this thesis, only CEA/CUA were considered because of the nature of CMA – CMA typically do not include an economic model. However, for specific analyses such as analyses regarding indirect treatment comparison, CMA were considered.

### **3.3 Instrument Development Process**

#### **Background**

A research instrument is a tool such as a questionnaire or scale used to gather data for research purposes. An instrument is necessary to ensure systematic assessment of data and to standardize the data collection process. For this thesis, an instrument was designed to collect data regarding pharmacoeconomic evaluations submitted by the drug manufacturer for review through the CDR process. This instrument was developed through adapting and enhancing an existing instrument. The instrument was subject to pilot testing and inter-rater reliability testing prior to its application.

#### Existing Instrument

In 2007, an instrument in the form of a multiple choice questionnaire was created to review pharmacoeconomic evaluations and to provide a summary of methodological issues of pharmacoeconomic evaluation submitted for review through the CDR process from September 2003 until August 2005 (Lee & Manns, 2007) (Refer to Appendix D - Existing Instrument (Lee and Manns 2007)). This instrument was developed using existing published guidelines for conducting economic evaluations and was piloted for internal validity. To measure the level of agreement between two reviewers, a kappa statistic was calculated. The calculated kappa statistic was 0.992, which demonstrated excellent agreement (Lee & Manns, 2007).

Hence, this existing instrument became the starting point for the development of the thesis instrument. However, this existing instrument had limited methodological content and did not fully support the objectives of this thesis. For instance, it did not examining sensitivity analysis in detail and did not consider examining indirect treatment comparisons. Therefore, major modifications to the existing instrument were required to include sufficient methodology content to address the thesis objectives.

## Initial Revised Instrument

I created the research instrument with input from my thesis supervisor and thesis advisor who are content experts. All 22 multiple choice questions from the existing instrument were examined for content and clarity, and modifications were made accordingly. Additional methodology content was included and questions from the existing instrument deemed irrelevant were excluded. Changes to the existing instrument were made by consensus, therefore, agreement between my thesis advisory committee and I was required.

The revised instrument incorporated 63 short answer and multiple choice questions in 7 sections (Refer to Appendix E - Initial Revised Instrument). The first section, Submission Information, captured administrative information such as the brand name of the drug, the date of the submission, and the name of the manufacturer which submitted the drug submission. The second section, Economic Evaluation Details, gathered some basic methodology details such as the type of perspective and time horizon used in the analysis. The third section, General Information, collected details regarding the type of drug and the intended use of the drug. The fourth section captured information on the quality of the pharmacoeconomic submission. For instance, this section collected information on the appropriateness of the comparator used in the analysis, the appropriateness of the choice of economic analysis, the appropriateness of the model assumptions made, and the appropriateness of the clinical data used in the model. The Sensitivity Analysis section captured information on the details of the types of sensitivity analysis used to handle parameter uncertainty. For example, this section collected data regarding the type of deterministic sensitivity analysis used, and with respect to PSA, how uncertainty regarding transition probabilities, utilities, costs and treatment effects were handled - in other words, the functional distributions used to handle uncertainty was captured. The sixth section gathered information on indirect treatment comparison; the type of indirect treatment comparison conduct, if any, was captured as well as reporting methods of the indirect treatment comparison such as whether methods for study identification or methods of analysis were clearly presented. The final section gathered information from CDEC such as the type of formulary listing recommendation.

## Validation Through Literature Review

To validate the content of the instrument, the studies identified in the literature review detailed in Chapter 2 were examined to determine if any additional information should be collected.

In addition to the work conducted by Lee & Manns (2007), four studies which examined the methodological quality of pharmacoeconomic evaluations and adherence to guidelines were identified: Canadian, American, Dutch and Korean study. Within the four studies, 15 different methodological items were assessed. Type of economic analysis, perspective of analysis, treatment comparator, time horizon, and sensitivity analysis were assessed by all four studies. Three of the four studies examined: discounting, clinical data, resource use and costs, model assumptions, and results in terms of incremental analysis. Two studies captured whether the research question or objective was stated. One study assessed whether the economic model was validated as well as whether the measurement of quality of life was validated. Another study was the only one which examined whether data sources used in the model were generalizable to the target population as well as assessed whether the health outcome measure used in the model was validated.

The thesis instrument covered all the relevant items identified from the literature review. However, the published studies did not cover methodological content in detail; nor did they explore in detail the new methodological developments relating to economic evaluation: indirect treatment comparison and probabilistic sensitivity analysis. Therefore, it was agreed by the thesis advisory committee that it was unnecessary to expand on the 63 items of the instruments and that the proposed instrument would be more comprehensive and detailed than those previously adopted.

## Pilot Test

To ensure that the instrument captured the necessary information to answer the research questions, the instrument was piloted. Testing the instrument prior to data collection highlighted problems such as inappropriate questions or ambiguity of questions and

responses. As a result, pilot testing led to amendments to the instrument in order to capture recurrent and unexpected methodology items as well as removal of irrelevant items.

Prior to piloting the instrument, nine pharmacoeconomic submissions were hand selected by my thesis advisor, who is a content expert involved in the CDR process. These nine pharmacoeconomic submissions varied in the date of submission from 2004 to 2012 and in the type of economic analysis: those with an economic model such as CEA and CUA, and those without an economic model such as CMA. As well, these submissions were appropriate since they reflected various degrees of complexity and different issues relevant to the thesis and therefore, it was assumed that this would be helpful in testing the face validity and practicality of the instrument.

Also, prior to starting the pilot exercise, an annotated form of the instrument was created. This document served as a reference point for collecting data. It provided data abstractors with examples of responses, an indication of where information needed to answer each question could be found, and at times clarify the meaning of the question. Moreover, the annotated form ensured consistency of the use of the instrument, as it was consulted by abstractors throughout the pilot testing, inter-rater reliability testing and data collection.

The pilot exercise began with testing the instrument on the selected nine pharmacoeconomic submissions. I consulted the following material to respond to the multiple choice and short answer questions of the instrument: the manufacturer drug submission including the cover letter, pharmacoeconomic evaluation, clinical evidence, CDR Clinical and Pharmacoeconomic reports, and CADTH Website. Afterwards, discussion regarding the piloting exercise was held with the thesis committee. This then led to amendments to the instrument. For example, to facilitate data collection, rearrangement of the order of questions as well as instructions to disregard non-applicable questions were made. Additional methodology items were included to capture recurring methodology items that were not previously captured in the instrument. Also, modification of structure of the question and responses were made to improve clarity. Finally, the annotated instrument was altered to reflect the changes in the instrument.

### Inter-Rater Reliability Test #1

To validate the instrument in terms of reproducibility, an inter-rater reliability test was conducted. For this thesis, my supervisor and I independently examined five randomly selected pharmacoeconomic submissions and accompanying material using the instrument. The same process was repeated by my thesis advisor and me using a different set of five randomly selected pharmacoeconomic submission and accompanying material. The collected data was compared and tallied from agreement and disagreement. However, given the multiple choice questions and possible combination of responses, selected questions from the instrument were converted into yes/no response questions. For questions which may require more than one answer such as

“Within the CDR PE review for which of the following variables (efficacy, costs, resource use, etc.) were assumptions which were considered inappropriate?”

Each response was converted into yes/no response question, for example:

“Did the CDR report recognize efficacy/ effectiveness as a limitation with methodology and/or inappropriate assumption?”

Two simple Cohen’s kappa statistics, its 95% confidence interval, and test of significance for two independent values of kappa were then calculated.

According to the literature, the results of the inter-rater reliability test suggested substantial agreement between my supervisor and me and between my thesis advisor and me (Viera & Garrett, 2005). The kappa values were 0.61(0.53-0.70) and 0.66(0.58-0.72) respectively. The results of the test of significance for two independent values of kappa, 0.71, suggested that data could be merged. As a result, all ten pharmacoeconomic submissions were then pooled and a new kappa statistic was calculated.

When pooling all ten pharmacoeconomic submissions, the kappa statistic of 0.64 (0.58-0.69) indicated a substantial strength of agreement, however the lower limit of its 95% confidence interval stretched into a moderate strength of agreement. As a result of the moderate agreement overlap, modifications to the multiple choice question response key and clarification of meaning of questions and responses were required.

Modifications to the instrument were necessary and required input and agreement from my supervisor and thesis advisor. For example, to facilitate the data collection process, the short answer question regarding perspective was converted into a multiple choice question. To incorporate a recurrent methodology item, a question regarding the appropriate choice of economic analysis was added. To improve clarity of questions and responses, changes to question and responses were made. Lastly, the annotated form was also altered to reflect any modifications to the instrument.

### Inter-Rater Reliability Test #2

As a result of the modifications to the instrument, another inter-rater reliability test was conducted with my supervisor, thesis advisor and I using a different set of randomly selected pharmaco-economic submissions.

The results of the second inter-rater reliability test suggested substantial agreement between my supervisor and I, 0.69(0.62-0.77), and substantial agreement between my thesis advisor and I, 0.74(0.67-0.81). The results of the significance test of two independent values of kappa (0.94) suggested that the two kappa values were equal and therefore all ten pharmaco-economic submissions were pooled to calculate a new kappa statistic, 0.72 (0.67-0.77).

The pooled kappa statistic #1 and #2 both suggested substantial agreement between reviewers. Furthermore, the upper and lower limit of the pooled kappa statistic #2 remained within a substantial strength of agreement. Therefore, considering the pooled kappa statistic was increased from 0.64 to 0.72 and the 95% confidence interval remained within the substantial strength of association boundaries, further validation of the instrument was not necessary and the instrument was finalized and ready for data collection.

### **3.4 Instrument**

The instrument development process described above resulted in a final instrument with 69 short answers and multiple choice questions encompassed in 7 sections (Refer to Appendix F - Research Instrument). The Submission Information Section collects administrative information such as brand and generic name, date of submission, and date of

final recommendation. The Economic Evaluation Details Section captures specific details regarding the economic evaluations such as time horizon and comparators as well as the perspective used in the economic analysis. Information collected in both sections are mostly in the form of short answers since the responses widely vary, whereas the information collected in the following sections are in the form of multiple choice questions. The General Information Section includes: type of drug and its intended use, information regarding results of clinical trials, type of analytic technique, and type of economic model. The Quality of Pharmacoeconomic Submissions Section focuses on the quality of methodology content which were items found in the literature review such as appropriateness of comparator, economic analysis, and model assumptions. The Sensitivity Analysis Section collects information on the type of sensitivity analysis, how uncertainty of parameters in PSA was handled, and information regarding additional analysis conducted by the CDR pharmacoeconomic reviewers. Indirect Treatment Comparison Section captures the type of indirect comparison and reporting methodology. The Use of Pharmacoeconomic Information Section serves to determine the reasons for recommendation and the type of formulary listing recommendation.

Each section of the instrument and its questions serve to answer the particular research questions of interest. However, some additional items from the instrument were collected for administrative purposes for CADTH and were not analyzed in this thesis.

### **3.5 Data Collection**

This thesis is a retrospective examination of pharmacoeconomic evaluations submitted by the drug manufacturer for review through the CDR process from 2003-2012. Starting from most recent formulary listing recommendation, I examined all 201 manufacturer drug submissions since 2003. Data were independently and directly extracted onto the developed instrument. Throughout the data collection process, biweekly discussions regarding uncertain responses with my thesis advisor were held to determine the correct response and to avoid coding error due to lack of expertise. Data abstraction took approximately 2 hours per study, highlighting the rationale for only one data abstractor. However, it is important to note that there are potential limitations to using only one

abstractor: data collection is subject to potential investigators bias and data may have been incorrectly coded due human error or lack of expertise.

The majority of the data collected was from the written pharmacoeconomic evaluation and the CDR pharmacoeconomic review report. In addition, the manufacturer's cover letter and the clinical review reports were consulted to answer questions relating to the General Information Section, Quality of Pharmacoeconomic Submissions Section and the Indirect Treatment Comparison Section. The CDR Recommendations and Reasons Reports found in the CADTH website was used to responded to the Use of Pharmacoeconomic Information Section.

### **3.6 Data Processing**

Since the collected information was extracted directly onto the research instrument, I created a database using Microsoft Excel for data processing before analysis. Each multiple choice question response that was noted on the research instrument was entered into the database as a numeric value and short answer responses were entered accordingly. As a form of verification, I cross-referenced each entry when inputting onto the database by comparing the database and the hardcopy of the coded instrument as well as I examined frequency counts to verify for any missing data. As a result, data entered incorrectly or missing were identified and added. The initial database using Microsoft Excel was meant to store information throughout data collection process, once data collection process was complete, data were transferred into SPSS where numeric values were then recoded to alphabetised responses.

After data processing, data analysis was divided into 6 sections according to the topic of the research question: adherence to guidelines, methodology, and transparency of reporting, sensitivity analysis, indirect treatment comparison, and determinants of formulary listing recommendation. An additional section was created to present study characteristics such as the form of analysis, the year of submission, and the listing recommendation. Data were analyzed using SPSS for the descriptive analysis and STATA for the analytic analysis.

### **3.7 Data Analysis**

The following sections describe in detail how data were analysed:

#### Study Characteristics

To provide an overview of the study characteristics, timeframe and outcome, data were analysed descriptively by form of analysis, year of submission, the type of drug and its intended use, and formulary listing recommendation.

Information analysed in this section included: the type of economic evaluation such as CEA/CUA; the year the review of the drug submission was initiated by CADTH; the classification given to the drug submission (for instance, the first treatment for disease/disorder); the intended use of the drug (i.e.: to increase the quality of life) and the CDEC recommendation (for example, positive recommendation, meaning CDEC recommend that the drug be publically funded).

#### Adherence to Guidelines

CADTH created the Guidelines for the Economic Evaluation of Health Technologies: Canada to assist makers of economic evaluations in producing credible and standardized economic information which is relevant and useful to decision makers. To determine the extent to which pharmacoeconomic evaluations are reflective of best practices, adherence to guidelines was measured. I conducted a descriptive analysis on the patterns of adherence to guidelines.

To determine adherence to guidelines, I created 14 guideline statements based on 13 guideline statements from the Guidelines for the Economic Evaluation of Health Technologies: Canada. The guideline statement relating to effectiveness and safety was separated into two separate statements – one for effectiveness and one for safety. Using the developed instrument, an algorithm was created to measure adherence to guideline statements (Refer to Appendix G - Guideline Statements Linked with Research Instrument). For example, a pharmacoeconomic evaluation was considered having adhered to Reporting guideline statements, if I coded ‘Yes’ to the following questions:

“Within the CDR PE Review, are the methods and analysis described as clear and transparent?”

“Within the CDR PE Review, were expected values for cost-outcomes and cost-effectiveness calculated properly?”

A summary of the criteria for adherence to guideline statements can be found in Table 1 which highlight the items used in Appendix G.

**Table 1 Criteria for adherence to guidelines**

<b>Guideline Statements</b>	<b>Description</b>
Types of Evaluation	Select the appropriate type of evaluation
Target Population	Specify the target population and the performed analysis for the entire specified target population
Comparators	Select the appropriate comparator which is the most common or frequently used care drug is intended to replace, also known as usual care
Perspective	Select the perspective of the publicly funded health care system, also known as the government perspective
Effectiveness	Include randomized controlled trial studies and appropriate effectiveness assumptions.
Safety	Include randomized controlled trial studies and appropriate safety assumptions.
Time horizon	Select the appropriate time horizon
Modelling	Include a clear and transparent model and formally validate the model
Valuing Outcomes	Select appropriate preference-based measures for valuing health related quality of life and appropriate quality of life assumptions.
Resource Use and Costs	Include Canadian resource use and costs and appropriate assumptions regarding resource use and costs
Discounting	Discount costs and health outcomes beyond one year to present

	values at 5% per year
Variability and Uncertainty	Assess uncertainty of key variables in sensitivity analysis
Generalizability	Include Canadian sources, not only Canadian costs being the only source of Canadian data
Reporting	Include a clear and transparent report and report final results as incremental cost-effectiveness ratios

Although certain guideline statements may be considered more important than other, given that no weighting factor exists, each guideline statement is weighted equally. With input from my thesis advisory committee, I established criteria for ranking adherence to guideline statements. These classifications were reflective of what CADTH reviewers would consider appropriate when reviewing pharmacoeconomic submissions.

To determine the relative adherence to each guideline statement, the percentage and frequency that each guideline statement was adhered to was calculated. Then, the extent to which individual pharmacoeconomic submissions adhered to guidelines was explored by calculating the number of guideline statements adhered to within each study. Given a relatively small number of submissions per year, to depict the trends in adherence to each guideline statements, data was analysed by grouped year of submission (2003-2005, 2006-2008, and 2009-2011). In this context, trends represent changes in a measure over time rather than the statistical measure relating to stability. To help illustrate the trends in average adherence to guideline statement ranks, a descriptive classification of adherence was developed (Table 2) through consultation with my thesis supervisory team and changes in such classifications over time were explored.

**Table 2 Criteria for ranking adherence to guideline statements**

<b>Adherence Rank</b>	<b>% Pharmacoeconomic Submissions</b>
Very Good Adherence	Greater than 90%
Good Adherence	75%-90%
Fair Adherence	50%-74%
Poor Adherence	Less than 50%

## Methodological Quality

A descriptive analysis on the trends of methodological quality of pharmacoeconomic submissions was conducted.

Methodological quality is related to the choice of data and modelling techniques. I examined five aspects of pharmacoeconomic evaluation: basic methodology, efficacy data, quality of life estimates, model validation, and model assumptions

### 1) Basic Methodology

When framing an economic evaluation, basic items should be considered (Fox-Rushby & Cairns, 2005). Therefore, to depict trends in basic methodology, form of analysis, perspective, time horizon, comparator and type of model were determined and analysed by grouped year of submission.

### 2) Efficacy Data

Efficacy data from various sources such as randomized controlled trials are used in an economic evaluation as an estimate of the clinical effectiveness of the intervention. Therefore, to illustrate trends in types of efficacy data used, highest quality of efficacy data, and whether CDR pharmacoeconomic reviewers had concerns over clinical effectiveness estimates were determined and analysed by grouped year of submission.

Types of efficacy data used in the economic model referred to the source of the efficacy data, whether information for example was taken from head-to-head randomized controlled trials or placebo controlled trials. Drugs submissions could have multiple sources of efficacy data; therefore the highest quality of efficacy data used was noted. Information regarding efficacy data came from the drug manufacturer pharmacoeconomic evaluation and the pharmacoeconomic report based on the CDR pharmacoeconomic reviewers.

Within the pharmacoeconomic report, pharmacoeconomic reviewers may report concerns over the clinical data used in the economic model; this information was used for the analysis of efficacy data.

### 3) Quality of Life Estimates

Quality of life estimates are a component required for cost-utility analysis and are typically taken from preference-based measures such as EQ-5D which measure health related quality of life. The Guidelines state that appropriate preference-based measures should be used (Canadian Agency for Drugs and Technologies in Health, 2006). Therefore, the trend in the inclusion and appropriateness of quality of life estimates was determined and analysed by grouped year.

Within the pharmacoeconomic report, pharmacoeconomic reviewers may report the appropriateness of the preference-based measure used to measure health related quality of life; this information was used in the analysis of quality of life estimates: for instance, an EQ-5Q may be used by the manufacture to measure health related quality of life, however, the reviewer felt that a different preference-based measure was more appropriate. This scenario is considered having included quality of life but not based on good information.

### 4) Model Validation

Another characteristic of methodological quality analysed in this thesis is model validation. According to many sources, a formal validation of the model should be conducted (Decision analytic modelling in the economic evaluation of health technologies: A consensus statement.2000; Brennan & Akehurst, 2000; Canadian Agency for Drugs and Technologies in Health, 2006; Weinstein et al., 2003). Therefore, to show trends in methods of model validation, type of model validation was determined and analysed by grouped year of submission.

Model validation is important because it involves testing the model to confirm that the model does what it is expected to do. There are two types of types of model validation: internal validation and external validation. “Internal validation confirms that the results generated by the model are internally consistent” while “external validation confirms that the

basic model structure, assumptions, and parameters are reasonable and accurately reflect the condition process, and the impact of the intervention and comparators.” (Canadian Agency for Drugs and Technologies in Health, 2006) One way of internally validating a model is to test the mathematical logic of the model or checking for errors in the mathematical code. A way of testing external validity is compare the health outcomes of the model against reliable independent data sets such as national cancer statistics (Canadian Agency for Drugs and Technologies in Health, 2006).

Within the pharmacoeconomic report, pharmacoeconomic reviewers report whether the model was validated, for instance, in terms of clinical relevance/logic, coding, and extrapolation techniques. For this thesis, a model was considered having face validity if the manufacturer reported having an expert or independent group validate the model. For example, a model was considered to have face validity if the completeness of the results, verification of the formulae and the codes, or verification of the basic model structure was reviewed by an expert or independent group. A model was considered having predictive/external validity if the manufacturer reported having compared predicted clinical outcomes resulting from extrapolation techniques against an independent data set.

##### 5) Model Assumptions

Within pharmacoeconomic evaluations assumptions are made relating to various data elements; therefore, an analysis on model assumptions, inappropriate model assumptions, and reanalysis based on alternative assumptions and data inputs was conducted. Within the pharmacoeconomic report, pharmacoeconomic reviewers may report assumptions made by the drug manufacturer relating to various data elements in the pharmacoeconomic evaluation such as efficacy/effectiveness, safety, cost, resource use, quality of life, and natural history of disease as well as comment on the appropriateness of assumptions made; this information was used in the analysis of model assumptions.

To illustrate the trends in types of assumptions, assumptions made relating to various data elements such as efficacy/effectiveness, safety, cost, resource use, quality of life, and natural history of disease were collected and analysed by grouped year of submission.

Afterwards, the total number of data elements with assumptions was collected and analysed by grouped year of submission.

As well, to illustrate the trends in average number of assumptions made, the mean and standard deviation were calculated and analysed by year of submission. Then, to illustrate the trends in inappropriate model assumptions, inappropriate assumptions made relating to various data elements were collected and analysed by grouped year of submission. Also, the total number of data elements with inappropriate assumptions was collected and analysed by grouped year of submission. Finally, to illustrate the trends in average number of inappropriate assumptions made, the mean and standard deviation were calculated and analysed by year of submission.

Within the pharmacoeconomic report, pharmacoeconomic reviewers may conduct a reanalysis based on alternative assumptions and data inputs; this information was used in the analysis of model assumptions. To show the trends in CDR pharmacoeconomic reviewer reanalysis based on alternative assumptions and data inputs, whether reanalysis was conducted, whether reanalysis led to significantly different results (defined as change to dominated, change to dominant, change from under 80 000 to over 100 000, change from over 100 000 to under 80 000, change from over 60 000 to under 40 000, change from under 40 000 to over 60 000), and the types of reanalysis were determined and analysed by grouped year of submission. The choice of values for significantly different results was based on perceived benchmarks for cost effectiveness. Finally, major drivers of the reanalysis were identified.

### Transparency

Transparency in the reporting of pharmacoeconomic evaluation is important for CDR reviewers because it facilitates the assessment of the methodological quality of the economic evaluation as well ensure credibility of the evaluation. None of the previous literature examined the transparency of reporting of pharmacoeconomic submissions. Therefore, I performed a descriptive analysis on the trends in transparency of reporting of pharmacoeconomic submissions.

Transparency of reporting referred to providing clear and transparency methods and analysis, and reporting results in incremental cost-effectiveness ratio. This information was derived directly from the CDR pharmacoeconomic report. Pharmacoeconomic submissions were considered to be transparent in reporting, if methods and analysis were clear and transparency methods and analysis, and if results were reported as incremental cost-effectiveness ratio. This is consistent with adherence to reporting guideline statement.

### Sensitivity Analysis

A descriptive analysis on the adoption of sensitivity analysis and probabilistic methods was performed. Information from this section was assessed by myself rather than the CDR pharmacoeconomic reviewer and was taken directly from the drug manufacturer's pharmacoeconomic evaluation.

First, to depict the trends in adoption of sensitivity analysis, the uptake of deterministic sensitivity analysis and PSA were determined and analysed by year of submission. Then, types of deterministic sensitivity analysis was determined and analysed by year of submission to depict trends over time.

Afterwards, an analysis of the completeness of PSA was conducted. PSA was considered to include all relevant parameters if uncertainty around transition probabilities, costs, and treatment effect were considered. Completeness of PSA was determined and analysed by year of submission.

In addition, an analysis on the appropriate functional forms for transition probabilities, utilities, costs and treatment effects was conducted. Appropriate functional forms were based on the theoretically correct distributions and the nature of the data; literature was consulted as well as discussion with my thesis supervisor and thesis advisor who are content experts led to the creation of the table below (Table 3). For instance, inputs for transition probabilities are usually binomial or multinomial. Binomial data share a relationship with beta distribution, while multinomial data have a relationship with Dirichlet distribution (A. Briggs et al., 2006; A. Briggs et al., 2012). Often times, cost data is skewed, and therefore, gamma and log normal distributions are best suited; however, theoretically cost data may also take form of a normal distribution (A. Briggs et al., 2006; A. Briggs et al.,

2012; Fox-Rushby & Cairns, 2005). The appropriate functional forms used in the pharmacoeconomic submissions were determined and analysed by year of submission.

**Table 3 Appropriate functional forms for parameters in PSA**

<b>Parameter</b>	<b>Appropriate functional form</b>
Transition probabilities	Beta Distribution, Dirichlet Distribution
Costs	Gamma Distribution, Log Normal Distribution, Normal Distribution
Utilities	Beta Distribution, Gamma Distribution, Log Normal Distribution, Normal Distribution
Treatment Effect	Normal Distribution (absolute effects) Log Normal Distribution (relative effects)

Finally, an analysis on how PSAs were reported was conducted. This analysis focussed on identifying the proportion of studies with PSA which PSA reported confidence intervals, scatter plots and/or cost-effectiveness acceptability curves. Proportions were examined by year of submission.

Indirect Treatment Comparison

In recent years, there has been development in indirect treatment comparison. However, none of the existing literature examined the use of indirect treatment comparison within pharmacoeconomic submissions. Therefore, I conducted a descriptive analysis on the use of indirect treatment comparison and the reporting methodology.

First, to determine the trends in use of indirect treatment comparison, the type of indirect treatment comparison such as naive, informal, adjusted and network meta-analysis were determined and analysed by grouped submission year. As well, to illustrate the proportion of network meta-analysis over time, use of indirect treatment comparison and network meta-analysis was also analysed by per year of submission.

Then, with respect to reporting methodology, whether clear methods for study identification, all relevant studies were included, clear methods for analysis, sufficient

information to replicate, the analysis included a meta-regression, and the analysis considered of sensitivity of result was determined and analysed by grouped year of submission. Afterwards, to determine whether pharmacoeconomic submissions with indirect treatment comparison adhered fully to the reporting methodology listed above, data were analysed by total number of reporting items adhered to.

In terms of reporting the methodology of indirect treatment comparisons, information was assessed by myself from what was reported by the manufacturer rather than by the CDR pharmacoeconomic reviewer as reviews tended not to focus in detail on this subject. Each reporting item was included for the following reasons. Including clear methods for study identification, clear methods for analysis and sufficient information to replicate are important for the reproducibility as well as the credibility of the indirect treatment comparison. Including all relevant studies is important because by not including all relevant studies, the clinical effectiveness estimates of the indirect treatment comparison may differ. Including a meta-regression when possible was important because it was a way to validate the indirect treatment comparison; however, it was noted that not all indirect treatment comparison can include a meta-regression. Considering the sensitivity of result is important because there is uncertainty regarding the clinical effectiveness estimates of the indirect treatment comparison (Table 4 Description of indirect treatment comparison reporting items).

**Table 4 Description of indirect treatment comparison reporting items**

<b>Reporting Items</b>	<b>Description</b>
Clear methods for study identification	Listed database, inclusion and exclusion criteria
All relevant studies included	Mentioned in the CDR report or relevant studies included in the CDR report were also included in the manufacturer’s submission
Clear methods for Analysis	Described methodology (i.e.: Bucher method)
Sufficient information to Replicate	Included programming language/code, equations)
Analysis included meta-regression	Included a meta-regression

Analysis considered sensitivity of results	Considered inclusion or exclusion of studies
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As with all other analyses detailed above, the primary analysis relating to indirect treatment comparisons focussed on studies which adopted CEA/CUA. As indirect treatment comparisons are often used to justify the adoption of CMA, a further analysis exploring the use and quality of such comparisons in submissions using CMA was conducted. This adopted the same methodology as above.

### Determinants of Formulary Listing Recommendation

The aim of this analysis was to identify methodological factors which are determinants for formulary listing recommendation. In order to identify determinants of formulary listing recommendation, statistical analysis was performed.

The dependent variable was the formulary listing recommendation, a dichotomous variable (positive formulary listing recommendation and negative formulary listing recommendation). The independent variables were taken from the previous analyses conducted in this thesis which related to adherence to guidelines, methodological quality, probabilistic sensitivity analysis and indirect treatment comparison.

Based on discussion with the thesis advisory committee, independent variables were selected with respect to adherence to guidelines, methodological quality, clinical scenarios, probabilistic sensitivity analysis and indirect treatment comparison (Refer to Table 5) and were considered in the creation of the multivariable regression model.

**Table 5 List of selected variables**

<b>Outcome</b>	<b>Description</b>
Formulary Listing Recommendation	A recommendation given by the Canadian Drug Expert Committee
<b>Candidate Variables</b>	<b>Description</b>
<b>Clinical scenarios</b>	

Type of Drug	Comparison of drug submission to other drugs in terms of formulary listing status
Highest Level of Clinical Outcome As Model Input	The highest level of evidence used for the effectiveness of the drug in model
<b>Methodological Quality</b>	
Population	Comparison of population modelled to the reimbursement population sought by manufacturer
Clinical Concerns	Comparison of clinical studies used in model and studies identified in Common Drug Review Clinical report.
Time Horizon	Appropriateness of time horizon used in model
Quality of Life	Inclusion and appropriateness of quality of life estimate in model
Computational Errors	Computational errors discovered by the Common Drug Review in the Economic evaluation
Transparency	Economic evaluation presented clear and transparent methods and analysis
Significantly Different Reanalysis Results	Comparison of the manufacturer's base-case results and the results of the Common Drug Review Reanalysis
<b>Probabilistic Sensitivity Analysis</b>	Manufacturer conducted a probabilistic sensitivity analysis
<b>Indirect Treatment Comparison</b>	Manufacturer conducted an indirect treatment comparison
<b>Adherence to Guidelines</b>	
Adherence to Types of Evaluation	Adhered to Types of Evaluation Guideline Statement
Adherence to Target Population	Adhered to Target Population Guideline Statement
Adherence to Comparators	Adhered to Comparators Guideline Statement
Adherence to Perspective	Adhered to Perspective Guideline Statement
Adherence to Effectiveness	Adhered to Effectiveness Guideline Statement

Adherence to Safety	Adhered to Safety Guideline Statement
Adherence to Time Horizon	Adhered to Time Horizon Guideline Statement
Adherence to Modelling	Adhered to Modelling Guideline Statement
Adherence to Valuing Outcomes	Adhered to Valuing Outcomes Guideline Statement
Adherence to Resource Use and Costs	Adhered to Resource Use and Costs Guideline Statement
Adherence to Discounting	Adhered to Discounting Guideline Statement
Adherence to Variability and Uncertainty	Adhered to Variability and Uncertainty Guideline Statement
Adherence to Generalizability	Adhered to Generalizability Guideline Statement
Adherence to Reporting	Adhered to Reporting Guideline Statement
<b>Miscellaneous</b>	
Year of Drug Submission	The grouped year of drug submission (2003-2005; 2006-2008; 2009-2011)

The following are the steps taken to create the multivariable regression model.

First, to determine if a relationship existed between the selected variables and formulary listing recommendation, a Fisher's exact test was conducted. Variables were considered to have a relationship if the p value of the Fisher's exact test was  $\leq 0.20$ . This step served to identify candidate variables for the regression model (Refer to Results Table 27 and Appendix H - Additional Results from Fishers Exact Test).

Then, in order to measure the relationship between the candidate variables and formulary listing recommendation as well as confirm the findings of the Fisher's exact test, a univariate logistic regression was performed (Refer for Results Table 28).

Afterwards, correlation between the candidate variables was assessed. If the correlation coefficient between two variables was  $> 0.70$ , one of two variables was removed - the variable with the greater magnitude of association with the dependent variable remained

(University of Sydney Faculty of Veterinary Science, 2010). Collinearity diagnostics were conducted to determine if variables had high collinearity.

Then, a multivariable logistic regression was performed on the remaining variables using a stepwise method; variables were entered into the model if the p value of the z test was  $\leq 0.05$  and retained if the p value of the z test was  $\leq 0.20$ .

Possible interactions were considered and the fit of model was assessed as well as possible outliers.

The variables in the multivariable regression model were considered key methodological factors which were determinants for formulary listing recommendations and its relationship was measured using odds ratio.

### **3.8 Ethical Considerations**

In terms of ethical consideration, pharmacoeconomic submissions are owned by CADTH. Therefore, prior to commencing the study, the approval for the use and analysis of pharmacoeconomic submissions was sought and granted by CADTH. The approval by the Ottawa Hospital Research Ethics Board was not required since pharmacoeconomic submissions are synthesis of existing data and do not involve individual patient data. However, to ensure privacy and confidentiality of collected data, data were stored in CADTH facilities and results of the analysis are presented at an aggregated level, therefore, the identity of the each drug submission is not revealed.

### **3.9 Summary**

This chapter described the development of the instrument used to assess the study population of this thesis and the methods of analysis. The following chapter will present the results of the various analyses.

## Chapter 4 Results

### 4.1 Introduction

This chapter will begin by presenting study characteristics; then, describing the results from the adherence to guidelines, trends in methodological quality, and transparency of reporting analysis. Afterwards, findings regarding the adoption of sensitivity analysis and probabilistic methods as well as the use of indirect treatment comparison will be described. Lastly, the key methodological factors which are determinants of formulary listing recommendation will be presented.

### 4.2 Study Characteristics

A total 201 pharmacoeconomic submissions were examined; the most prevalent being CMA. Of the 201 pharmacoeconomic submissions, 111 were CEA/CUA. Ten submissions were considered informal analyses – cost-consequence analyses, four submissions were labelled as a cost-effectiveness analysis but were analysed as a CMA. These latter 14 submissions were not included in further analysis due to their limited reporting. Thus, the analysis includes a total of 111 CEA/CUA and 76 CMA (Table 6).

**Table 6 Form of analysis used in pharmacoeconomic submission from 2003-2012**

	<b>n</b>	<b>%</b>
<b>Total Pharmacoeconomic Submissions</b>	<b>201</b>	
<b>Form of Analysis</b>		
Cost-Effectiveness Analysis Only	16	8%
Cost-Utility Analysis Only	52	26%
Both Cost-Effectiveness Analysis & Cost-Utility Analysis	43	21%
Cost-Minimization Analysis	76	38%
Informal Analysis <sup>a</sup>	10	5%
Analysed as Cost-Minimization Analysis	4	2%

<sup>a</sup> A cost-consequence analysis where costs and outcomes are analysed and presented separately and no economic model is provided.

The majority of pharmacoeconomic submissions are for drugs with other treatments in its class that are currently listed – publically funded. Few pharmacoeconomic submissions

are for drugs that are novel treatments and even fewer are for drugs where other treatment for the disease/disorder is available but was not publically funded at the time of the submission. Most pharmacoeconomic submissions are for drugs with the intention to increase the quality of life, almost 30% of pharmacoeconomic submissions are for drugs with the intended use of increasing survival. Some submissions are intended to reduce burdens such as pill burden (Table 7).

**Table 7 Drug characteristics**

	<b>n</b>	<b>%</b>
<b>Total Pharmacoeconomic Submissions</b>	201	
<b>Type of Drug</b>		
First Treatment for Disease/Disorder <sup>a</sup>	8	4%
Not First Type But First Drug in Class That Could be Listed for Disease/Disorder <sup>b</sup>	6	3%
Other Drugs In Class Currently Listed	187	93%
<b>Drug is intended to increase: <sup>d</sup></b>		
Quality of Life	167	83%
Length of Life	59	29%
Convenience <sup>e</sup>	35	17%

<sup>a</sup> A novel drug, no other drug exists for the disease/disorder

<sup>b</sup> There are other drugs that exist for the disease, but are not publically funded

<sup>c</sup> There are other drugs that exist for the disease that are publically funded

<sup>d</sup> Total exceed 100%; some drugs have more than one intended use

<sup>e</sup> Reduces burden - in the form of a fixed dose combination, or oral medication as opposed to injection, or administration once per year as opposed to weekly, or reduced pill burden, or no patient monitoring

Overall, there is a slighter greater proportion of CEA/CUA compared to CMA. In general, the proportion of CEA/CUA is larger than CMA each year. Since very few were submitted in 2003, further analyses by year of submission pooled submissions for 2003 and

2004. As none of the submissions in 2012 were completed by June 2012, analyses by year do not include 2012 (Table 8).

**Table 8 Forms of analysis used in thesis analysis from 2003-2012**

	CEA/CUA		CMA		CEA/CUA & CMA	
	n	%	n	%	n	%
<b>Total</b>	<b>111</b>	<b>59%</b>	<b>76</b>	<b>41%</b>	<b>187</b>	<b>100%</b>
<b>Year of Submission to CADTH</b>						
2003	1	33%	2	67%	3	100%
2004	8	53%	7	47%	15	100%
2005	10	67%	5	33%	15	100%
2006	20	63%	12	38%	32	100%
2007	15	68%	7	32%	22	100%
2008	16	57%	12	43%	28	100%
2009	13	46%	15	54%	28	100%
2010	11	69%	5	31%	16	100%
2011	17	61%	11	39%	28	100%
2012	0	0%	0	0%	0	0%

More than half the drug submissions received a Do Not List listing recommendation, whereas 45% of drug submissions with CEA/CUA and 41% of drug submissions CMA received a positive recommendation such as List, List with Price Criteria, List with Clinical Criteria and List in Similar Manner as Other Drug in Class (Table 9).

**Table 9 CDEC formulary listing recommendation from 2003-2012**

	CEA/CUA		CMA	
	n	%	n	%
<b>Total</b>	<b>111</b>		<b>76</b>	
<b>Listing Recommendation</b>				
Negative <sup>a</sup>	61	55%	45	59%

Positive <sup>b</sup>	50	45%	31	41%
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<sup>a</sup> Do not list

<sup>b</sup> List or list with criteria or conditions

### 4.3 Adherence to Guidelines Analysis

Not all pharmacoeconomic submissions adhered to guideline statements; this is apparent in the wide range of percentage of guideline statements that were adhered to (25%-97%). The most commonly adhered to guideline statement was Perspective, while Valuing Outcomes was the guideline statements adhered to the least. As mentioned earlier, a descriptive classification of adherence was created: very good adherence (greater than 90% of pharmacoeconomic submission), good adherence (75%-90% of pharmacoeconomic submissions), fair adherence (50%-74% of pharmacoeconomic submissions), and poor adherence (less than 50% of pharmacoeconomic submissions). Guideline statements ranged from very good to poor adherence. Perspective and Types of Evaluations scored very good adherence, whereas Discounting, Time Horizon, and Target Population received good adherence. Guideline statements with fair adherence were Comparators, Safety, Variability and Uncertainty, Resource Use and Cost, Effectiveness, while Guideline statements scoring poor adherence were Generalizability, Reporting, Modelling and Valuing Outcomes. None of the statements had perfect adherence (Table 10).

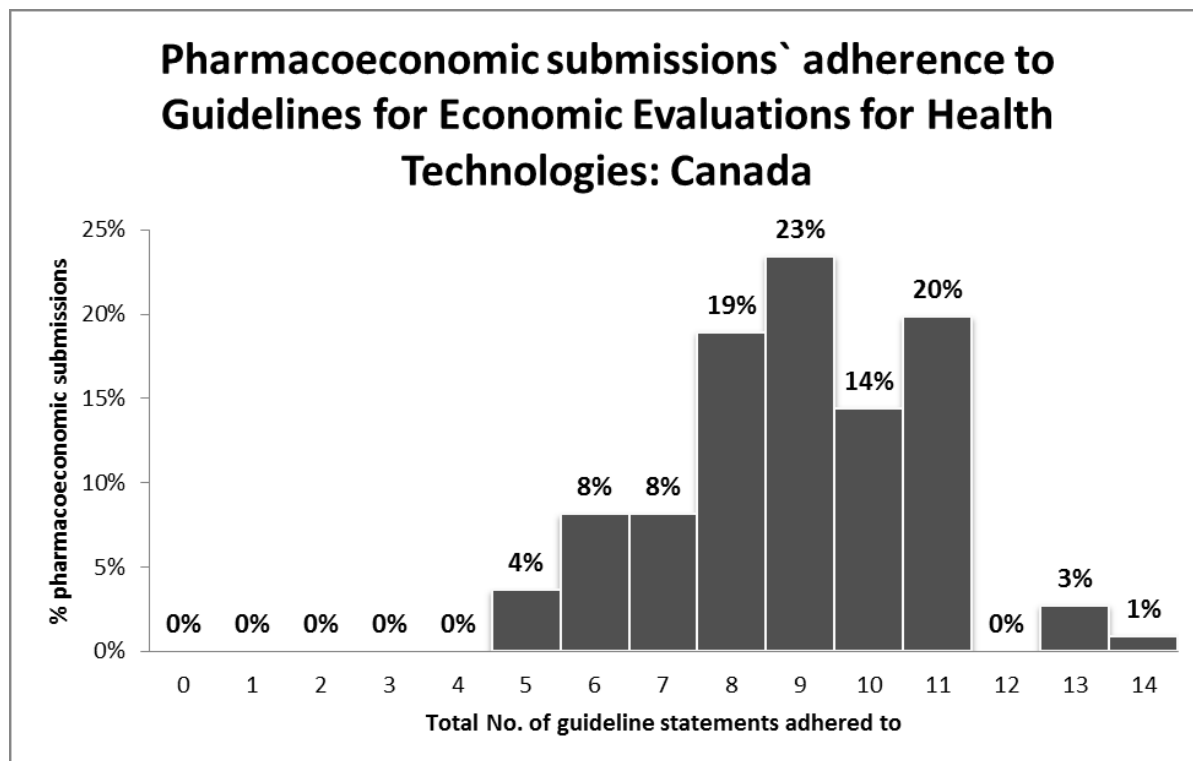
**Table 10 Adherence to guideline statements**

Guideline Statement	Adhered to Guideline Statement		Rank
	n	%	
Perspective	108	97%	Very Good
Types of Evaluations	102	92%	Very Good
Discounting	98	88%	Good
Time Horizon	88	79%	Good
Target Population	87	78%	Good
Comparators	78	70%	Fair
Safety	78	70%	Fair

Variability and Uncertainty	69	62%	Fair
Resource Use and Costs	60	54%	Poor
Effectiveness	58	52%	Poor
Generalizability	52	47%	Poor
Reporting	46	41%	Poor
Modelling	42	38%	Poor
Valuing Outcomes	28	25%	Poor

The majority of pharmacoeconomic submissions adhered to at least half of the guideline statements with a range of total number of guideline statements adhered to of 5 to 14. More than half of pharmacoeconomic submissions adhered to 8-11 guideline statements; the most prevalent being 9 (23%). Only 1 pharmacoeconomic submission adhered to all 14 guideline statements, whilst 3 submissions adhered to all but 1 guideline statement. These latter three submissions did not adhere to Effectiveness, Modelling, and Comparators respectively (Figure 1 Pharmacoeconomic submissions' adherence to Guidelines for Economic Evaluations for Health Technologies: Canada).

**Figure 1 Pharmacoeconomic submissions` adherence to Guidelines for Economic Evaluations for Health Technologies: Canada**



When considering trends in adherence to guidelines, for two guideline statements, adherence was very good throughout – Perspective and Type of Evaluation. For two more guideline statements, adherence improved from good to very good - Time Horizon and Discounting. In addition, there is a significant improvement for Target Population and Safety from fair to very good adherence. There is improvement in Effectiveness, Reporting and Modelling, however, adherence is still considered poor or fair. There were no improvements in other guideline statements such as Resource Use and Cost, Comparators, Variability and Uncertainty, Generalizability, and Valuing Outcomes (Table 11).

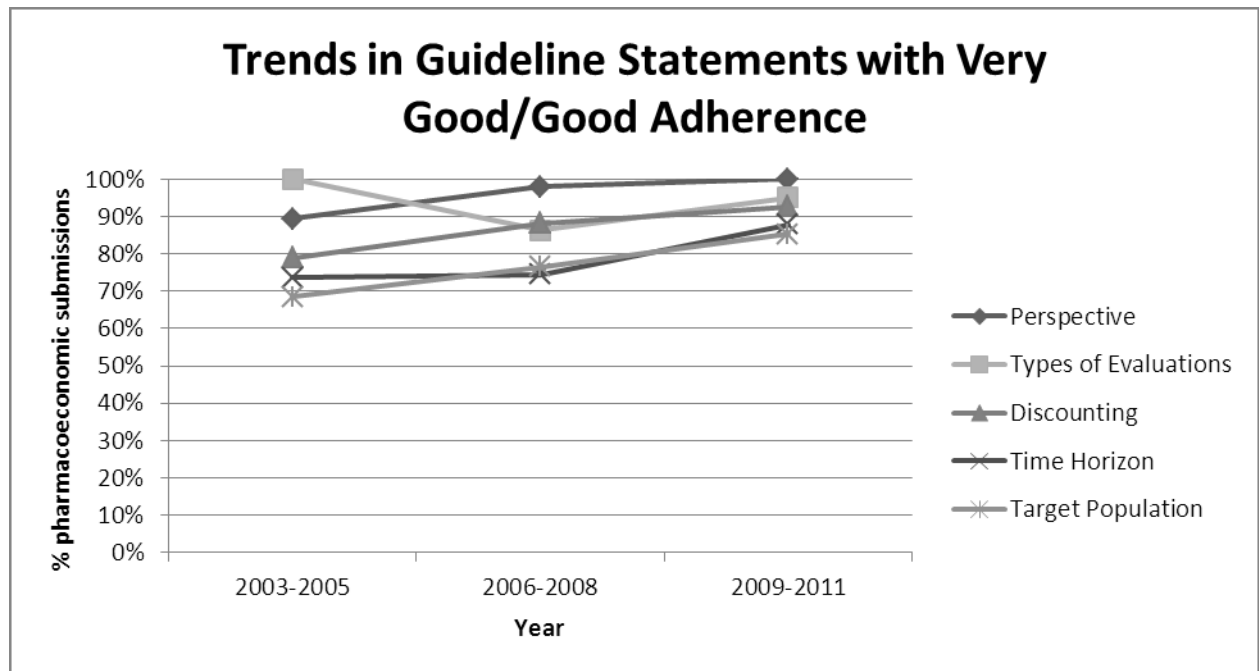
**Table 11 Trends in adherence to guideline statements by grouped year**

	<b>2003-2005</b> n= 19	<b>2006-2008</b> n= 51	<b>2009-2011</b> n= 41
<b>Guideline Statement</b>			
Perspective	17 (89%)	50 (98%)	41 (100%)

Types of Evaluation	19 (100%)	44 (86%)	39 (95%)
Discounting	15 (79%)	45 (88%)	38 (93%)
Time Horizon	14 (74%)	38 (75%)	36 (88%)
Target Population	13 (68%)	39 (76%)	35 (85%)
Comparators	12 (63%)	39 (76%)	27 (66%)
Safety	10 (58%)	34 (67%)	33 (80%)
Variability and Uncertainty	13 (68%)	28 (55%)	28 (68%)
Resource Use and Costs	11 (58%)	29 (57%)	20 (49%)
Effectiveness	8 (42%)	26 (51%)	24 (59%)
Generalizability	12 (63%)	19 (37%)	21 (51%)
Reporting	6 (32%)	20 (39%)	20 (49%)
Modelling	4 (21%)	20 (39%)	18 (44%)
Valuing Outcomes	4 (21%)	16 (31%)	8 (20%)

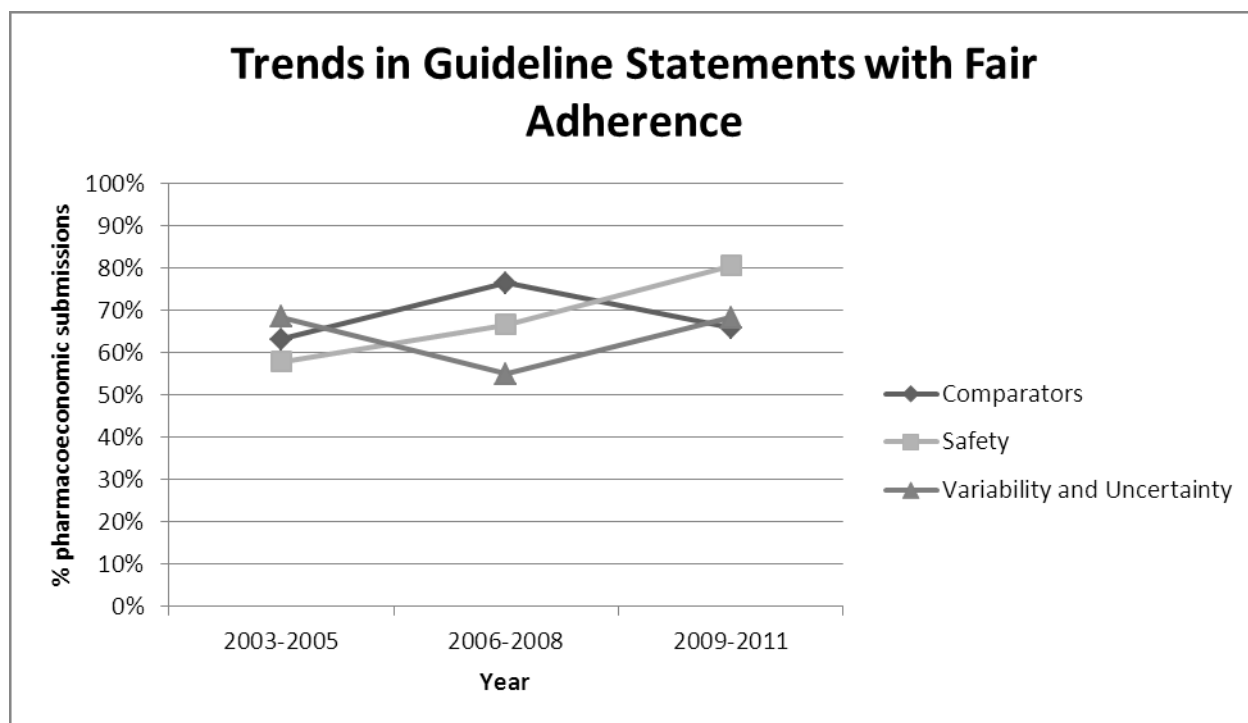
Of the five guideline statements that scored very good and good adherence, there is an increase trend in adherence to all except Types of Evaluations. Moreover, the range in % of guideline statements scoring very good and good adherence narrowed over time (Figure 2).

**Figure 2 Trends in guideline statements with very good/good adherence**



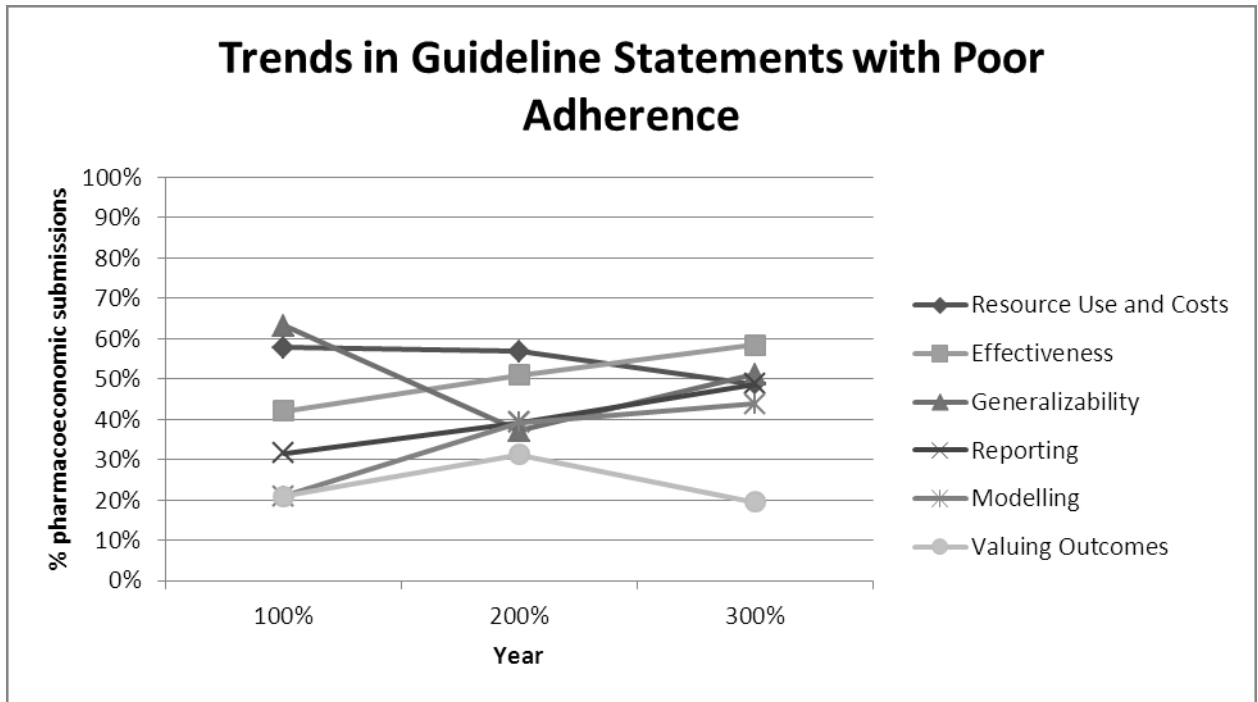
In terms of the five guidelines statements that received fair adherence, a rise in adherence to Safety can be found; whereas Comparators, and Variability and Uncertainty appear to have no evident trend. The range in % of guideline statements scoring fair adherence remains narrow over time (Figure 3).

**Figure 3 Trends in guideline statements with fair adherence**



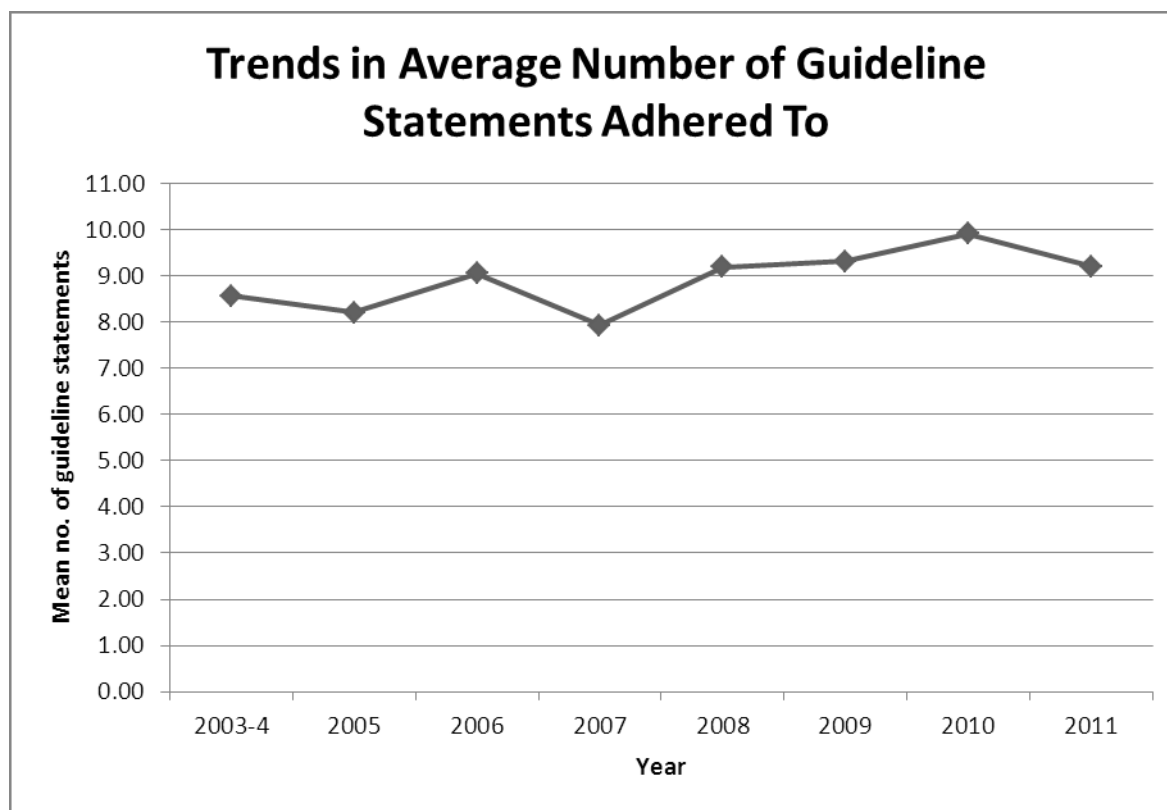
With regards to the six guideline statements scoring poor adherence, there is an upward trend in adherence to Effectiveness, Reporting, and Modelling, a fall in adherence to Resource Use and Cost, and no apparent trend in adherence to Generalizability and Valuing Outcomes. The range in % of guideline statements scoring poor adherence remain broad over time (Figure 4).

Figure 4 Trends in guideline statements with poor adherence



Finally, when examining the trends in average number of guideline statements adhered to per year, there is no distinct trend. The mean number of guideline statements adhered to remained closed to 9, ranging from 7.93 – 9.91 throughout the years (Figure 5).

**Figure 5 Trends in average number of guideline statements adhered to**



#### **4.4 Methodology Analysis**

In the matter of basic methodology, 16 out of 111 pharmacoeconomic submissions were cost-effectiveness analysis only and 52 out of 111 pharmacoeconomic submissions were cost-utility analysis only. Thus, more than a third of pharmacoeconomic submissions were both cost-effectiveness analysis and cost-utility analysis (43 out of 111). The proportion of studies including a cost-utility analysis increased from 58% in 2003-2005 to 92% in 2009-2011 (Table 12).

Nearly all included a government perspective; the perspective preferred within the Guidelines (108 out of 111) (Table 12).

Of the 111 pharmacoeconomic submissions, 28 included a time horizon of one year or less and 41 included a time horizon greater than one year but less than a lifetime. Lifetime was the most prevalent time horizon used (44% - 49 out of 111) (Table 12).

The majority of submissions included usual care or existing practice as a comparator. Best supportive care or no treatment was included as a comparator in 41 out of 111

submissions though the proportion fell from 42% in 2003-05 to 24% in 2009-11. Similarly, the proportion of submissions including a drug in the similar class that is not currently funded or standard of care has declined (Table 12).

More than half of pharmacoeconomic submissions used a Markov model, whereas, less than a fifth used only a decision tree (61, 21 out of 111 respectively). In some cases, hybrids and other types of models such as discrete events simulations were used. The use of models remained relatively consistent over time (Table 12).

**Table 12 Basic methodology by grouped year**

	<b>2003-2005</b> n= 19	<b>2006-2008</b> n= 51	<b>2009-2011</b> n=41
<b>Form of Analysis<sup>a</sup></b>			
Cost-Effectiveness Analysis Only	6 (32%)	7 (14%)	3 (7%)
Cost-Utility Analysis Only	5 (26%)	28 (55%)	19 (46%)
Both Cost-Effectiveness Analysis & Cost-Utility Analysis	8 (42%)	16 (31%)	19 (46%)
<b>Primary Perspective<sup>a</sup></b>			
Drug Plan	1 (5%)	0 (0%)	0 (0%)
Societal	1 (5%)	1 (2%)	0 (0%)
Government	17 (89%)	50 (98%)	41 (100%)
<b>Time Horizon<sup>b</sup></b>			
1 Year or Less	7 (37%)	15 (29%)	6 (15%)
Greater than 1 Year, Less than Lifetime	6 (32%)	16 (31%)	19 (46%)
Lifetime	7 (37%)	26 (51%)	16 (39%)
<b>Comparator Represents<sup>b</sup></b>			
Usual Care or Existing Practise	15 (79%)	36 (71%)	32 (78%)
Drug in Similar Class, But Not Currently Funded	5 (26%)	1 (2%)	1 (2%)
Previous Standard of Care	0 (0%)	2 (4%)	0 (0%)
Best Supportive Care or No Treatment	8 (42%)	23 (45%)	10 (24%)
<b>Model Type<sup>a</sup></b>			

Markov Model	12 (63%)	28 (55%)	23 (56%)
Decision Tree	5 (26%)	9 (18%)	7 (17%)
Hybrid	0 (0%)	4 (8%)	4 (10%)
Other <sup>c</sup>	2 (11%)	10 (20%)	7 (17%)

<sup>a</sup> Total may not equate to 100% due to rounding

<sup>b</sup> Total may exceed 100%; some pharmacoeconomic submissions included more than one options

<sup>c</sup> Discrete events simulations, survival and mapping models

In terms of efficacy data used in the economic evaluation, about a quarter of pharmacoeconomic submissions used head to head randomized controlled trials (27 out of 111) with the proportion of submissions including this evidence increasing from 11% in 2003-03 to 32% in 2009-11. The most prevalent source of efficacy data was randomized placebo controlled trials (49 of 111), although the use of this declined from 58% of submissions in 2003-05 to 41% of submissions in 2009-11. Indirect treatment comparisons and open label or cohort studies were increasingly used (Table 13).

The majority of pharmacoeconomic submission used placebo controlled trials/indirect treatment comparison as highest quality of efficacy data; this remained consistent over time (Table 13).

CDR pharmacoeconomic reviewers had concerns over the data used to estimate clinical effectiveness for 49 of the 111 pharmacoeconomic submissions. Regarding this, there are no evident trends (Table 13).

**Table 13 Efficacy data by grouped year**

	<b>2003- 2005 n= 19</b>	<b>2006- 2008 n= 51</b>	<b>2009- 2011 n= 41</b>
<b>Efficacy Data Used In Pharmacoeconomic Evaluation<sup>a</sup></b>			
RCT <sup>b</sup> Head to Head	2 (11%)	12 (24%)	13 (32%)

RCT <sup>b</sup> Placebo Controlled	11 (58%)	21 (41%)	17 (41%)
Open Label/ Cohort Studies/ RCT <sup>b</sup> Open Label	2 (11%)	9 (18%)	8 (20%)
Expert Opinion	1 (5%)	2 (4%)	0 (0%)
Indirect Treatment Comparison	4 (21%)	19 (37%)	15 (37%)
Other <sup>c</sup>	3 (16%)	6 (12%)	5 (12%)
<b>Highest Quality of Efficacy Data Used In Pharmacoeconomic Evaluation</b>			
RCT <sup>b</sup> Head to Head	2 (11%)	12 (24%)	13 (32%)
RCT <sup>b</sup> Placebo Controlled/Indirect Treatment Comparison	12 (63%)	33 (65%)	25 (61%)
Other <sup>d</sup>	5 (26%)	6 (12%)	3 (7%)
<b>Did CDR<sup>e</sup> pharmacoeconomic reviewer report concerns over data used to estimate clinical effectiveness?</b>			
Yes	10 (53%)	21 (41%)	18 (44%)

<sup>a</sup> Total % exceed 100%; some pharmacoeconomic submission use multiple sources

<sup>b</sup> Randomized controlled trials

<sup>c</sup> Observational studies, administrative and published economic evaluation data

<sup>d</sup> Open Label/ Cohort Studies/ RCT Open Label, Expert Opinion, Other<sup>b</sup>

<sup>e</sup> Common Drug Review pharmacoeconomic reviewer

Most pharmacoeconomic submissions included quality of life, although in more than half the submissions estimates were not based on good quality information (Table 14).

Although there is a decrease in pharmacoeconomic submissions not including quality of life estimates when relevant, there is a simultaneous increase in including quality of life estimates not based on good quality information. Thus, there is no discernible improvement in the use of good quality of life data (Table 14).

**Table 14 Inclusion of quality of life by grouped year**

	<b>2003- 2005</b>	<b>2006- 2008</b>	<b>2009- 2011</b>
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	<b>n= 19</b>	<b>n= 51</b>	<b>n= 41</b>
<b>Inclusion of Quality of Life in Pharmacoeconomic Evaluation</b>			
Not Included, But Relevant For Disease/Disorder	6 (32%)	7 (14%)	3 (7%)
Included, But Not Based On Good Quality Information	7 (37%)	24 (47%)	26 (63%)
Included Based On Good Quality Information	6 (32%)	20 (39%)	12 (29%)

In terms of method of validation, more than half the economic models in the pharmacoeconomic submissions were not validated – although this declined from 79% in 2003-05 to 46% in 2009-2011. There is an increase in the uptake of validation exercises relating to face validity and predictive/external validity. Few submissions considered both of these forms of validity checks (Table 15).

**Table 15 Model validation by grouped year**

	<b>2003- 2005 n= 19</b>	<b>2006- 2008 n= 51</b>	<b>2009- 2011 n= 41</b>
<b>Method of Validation</b>			
Face Validity	2 (11%)	14 (27%)	13 (32%)
Predictive/External Validity	2 (11%)	2 (4%)	8 (20%)
Face Validity & Predictive/External Validity	0 (0%)	6 (12%)	1 (2%)
None	15 (79%)	29 (57%)	19 (46%)

More than half the pharmacoeconomic submissions required CDR pharmacoeconomic reviewer to reanalyze the submission based on alternative assumptions or data inputs (60 of 111). Fifty out of 111 had significantly different results from the manufacturer. The most prevalent reanalysis involved simply changing a single parameter estimate (one-way) with other reanalyses involving multi-way sensitivity analysis or analysis of extremes. In terms of trends, there is an increase in reanalysis based on alternative assumptions or data inputs, as well as an increase in significantly different results (Table 16).

Of 50 pharmacoeconomic submissions with significantly different results, most major drivers of the reanalysis included efficacy, quality of life, cost, and time horizon (Refer to Appendix I - Additional CDR Reanalysis Analysis).

**Table 16 CDR reanalysis by grouped year**

	<b>2003- 2005 n= 19</b>	<b>2006- 2008 n= 51</b>	<b>2009- 2011 n= 41</b>
<b>Did CDR reviewer <sup>a</sup> conduct a reanalysis based on alternative assumptions or data inputs?</b>			
Yes	3 (15%)	23 (45%)	34 (83%)
<b>Were the results significantly different <sup>b</sup> from the manufacturer?</b>			
Yes	1 (5%)	20 (39%)	29 (71%)
<b>Type of Reanalysis</b>			
One-Way Sensitivity Analysis	3 (16%)	17 (33%)	27 (66%)
Multi-Way Sensitivity Analysis	0 (0%)	8 (16%)	13 (32%)
Analysis of Extremes	0 (0%)	2 (4%)	4 (10%)
Threshold Analysis	0 (0%)	0 (0%)	0 (0%)
Monte Carlo Simulation	0 (0%)	0 (0%)	0 (0%)
Other Type of Sensitivity Analysis <sup>c</sup>	0 (0%)	3 (6%)	2 (5%)

<sup>a</sup> Common Drug Review pharmacoeconomic reviewers

<sup>b</sup> Defined as change to dominated, change to dominant, change from under 80 000 to over 100 000, change from over 100 000 to under 80 000, change from over 60 000 to under 40 000, or change from under 40 000 to over 60 000

<sup>c</sup> reanalysis as using cost-minimization analysis, reanalysis using treatment sequence or different comparator, and reanalysis with no product agreement

In the matter of assumptions, the majority of studies included assumptions made relating to efficacy/effectiveness (82 of 111). More than half the pharmacoeconomic submissions made assumptions relating to safety, cost, quality of life and natural history of

disease. In terms of trends in model assumptions, there is a decline in studies including assumptions relating to resource use and a slight decrease in studies including assumptions regarding efficacy/effectiveness. In terms of the number of data elements with assumptions within studies, most pharmacoeconomic submissions made assumptions relating to 2-5 data elements; with the most number of assumption being 7 (2 of 111) with an overall mean of 3.62. The mean number of data elements requiring assumptions fell marginally from 4.05 in 2003-2005 to 3.71 in 2009-2011 (Table 17).

**Table 17 Model assumptions by grouped year**

	<b>2003-2005</b> n= 19	<b>2006-2008</b> n= 51	<b>2009-2011</b> n= 41
<b>Were assumptions made relating to:</b>			
Efficacy/Effectiveness	16 (84%)	37 (73%)	29 (71%)
Safety	11 (58%)	32 (63%)	15 (37%)
Cost	13 (68%)	27 (53%)	22 (54%)
Resource Use	10 (53%)	20 (39%)	10 (24%)
Quality of Life	8 (42%)	27 (53%)	29 (71%)
Natural History of Disease	11 (58%)	22 (43%)	25 (61%)
Other <sup>a</sup>	8 (42%)	8 (16%)	22 (54%)
<b>Number of data elements with assumptions <sup>b</sup></b>			
<b>1</b>	0 (0%)	3 (6%)	1 (2%)
<b>2</b>	4 (21%)	13 (25%)	4 (10%)
<b>3</b>	5 (26%)	12 (24%)	14 (34%)
<b>4</b>	2 (11%)	12 (24%)	13 (32%)
<b>5</b>	3 (16%)	6 (12%)	6 (15%)
<b>6</b>	4 (21%)	5 (10%)	2 (5%)
<b>7</b>	1 (5%)	0 (0%)	1 (2%)
<b>Mean (Standard Deviation)</b>	4.05 (1.65)	3.39 (1.40)	3.71 (1.21)

<sup>a</sup> Compliance, duration of administration, treatment sequence, and treatment switching

<sup>b</sup> Total may not equate to 100% due to rounding

Almost half (49%) of the pharmacoeconomic submissions made inappropriate assumptions relating to efficacy/effectiveness. A substantial proportion of submissions also included inappropriate assumptions relating to safety (30%), cost (37%), and quality of life (32%) (Table 18).

All pharmacoeconomic submissions except for 9 had at least one inappropriate assumption. Only 10% of submissions had inappropriate assumptions relating to four or more types of data elements. There is no evidence of changes in inappropriate assumptions over time (Table 18).

**Table 18 Model inappropriate assumptions by grouped year**

	<b>2003-2005</b> <b>n= 19</b>	<b>2006-2008</b> <b>n= 51</b>	<b>2009-2011</b> <b>n= 41</b>
<b>Were inappropriate assumptions made relating to:</b>			
Efficacy/Effectiveness	10 (53%)	25 (49%)	19 (39%)
Safety	8 (42%)	17 (33%)	8 (20%)
Cost	5 (26%)	17 (33%)	19 (46%)
Resource Use	6 (32%)	10 (20%)	5 (12%)
Quality of Life	2 (11%)	17 (33%)	17 (41%)
Natural History of Disease	5 (26%)	5 (10%)	9 (22%)
Other <sup>a</sup>	5 (26%)	4 (8%)	11 (27%)
<b>Number of data elements with inappropriate assumptions <sup>b</sup></b>			
<b>0</b>	1 (5%)	5 (10%)	3 (7%)
<b>1</b>	2 (11%)	17 (33%)	8 (20%)
<b>2</b>	11 (58%)	16 (31%)	18 (44%)
<b>3</b>	3 (16%)	8 (16%)	8 (20%)
<b>4</b>	2 (11%)	3 (6%)	3 (7%)
<b>5</b>	0 (0%)	2 (4%)	1 (2%)
<b>6</b>	0 (0%)	0 (0%)	0 (0%)

7	0 (0%)	0 (0%)	0 (0%)
<b>Mean (Standard Deviation)</b>	2.16 (0.96)	1.86 (1.22)	2.07 (1.10)

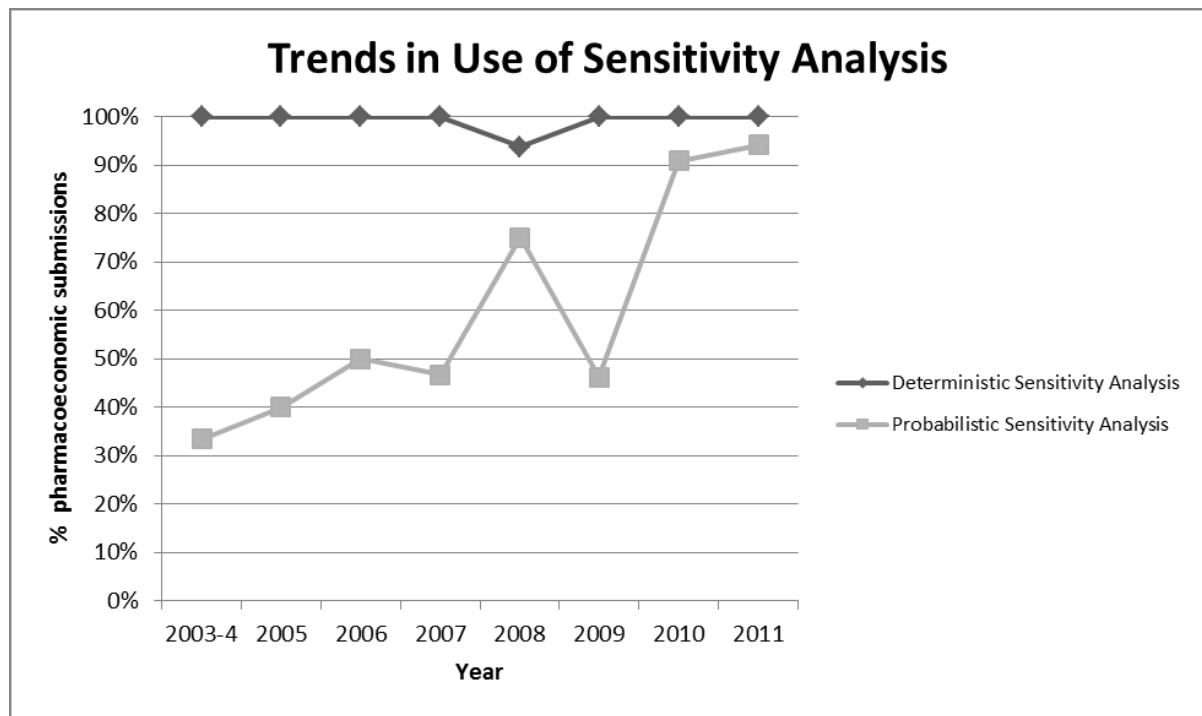
<sup>a</sup> Compliance, duration of administration, treatment sequence, and treatment switching

<sup>b</sup> Total may not equate to 100% due to rounding

#### 4.5 Sensitivity Analysis Analysis

With regards to the trends in adoption and practice of sensitivity analysis, all pharmacoeconomic submissions included either deterministic sensitivity analysis (99% - 110 out of 111) and/or PSA (61% - 68 out of 111). The only study not including deterministic sensitivity analysis did include a PSA. The use of PSA increased from 33% in 2004 to 94% by 2011 (Figure 6).

**Figure 6 Trends in use of sensitivity analysis from 2003-2011**



All 110 pharmacoeconomic submissions including deterministic sensitivity analysis included simple one-way sensitivity analyses. As well, 23 out of the 110 pharmacoeconomic submissions adopted additional forms of deterministic sensitivity analysis. There is no apparent trend in adoption of additional forms of deterministic sensitivity analysis (Table 19).

**Table 19 Forms of deterministic sensitivity analysis from 2003-2011**

	2003-4	2005	2006	2007	2008	2009	2010	2011
<b>Include DSA<sup>a</sup></b>	9	10	20	15	15	13	11	17
<b>Forms of DSA<sup>a</sup> Used</b>								
One-way	9 (100%)	10 (100%)	20 (100%)	15 (100%)	15 (100%)	13 (100%)	11 (100%)	17 (100%)
Multi-way	0 (0%)	3 (30%)	3 (15%)	3 (20%)	1 (7%)	2 (15%)	0 (0%)	0 (0%)
Analysis of Extremes	2 (22%)	0 (0%)	2 (10%)	0 (0%)	1 (7%)	0 (0%)	0 (0%)	0 (0%)
Threshold Analysis	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (18%)
Alternate Perspective	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (18%)	0 (0%)
<b>Include PSA</b>	3	4	10	7	12	6	10	16

<sup>a</sup>Deterministic sensitivity analysis

In terms of the practice of PSA, only 15 of the 68 pharmacoeconomic submissions considered all relevant parameters in their analysis. There is no evident trend in improvements in the consideration of all relevant parameters over time; the percent of pharmacoeconomic evaluations that considered all relevant parameters in their PSA remained low.

Of the 68 pharmacoeconomic submissions including PSA, 22 (32%) adopted the appropriate functional form for transition probabilities, whereas 34 (50%) adopted the appropriate functional forms for costs and utilities, and 21 (31%) adopted the appropriate functional form for treatment effects. There are no apparent trends in adoption of appropriate functional forms.

With regards to reporting methods, PSA results were rarely presented as confidence interval (2 out of 68). 44 pharmacoeconomic submissions reported PSA results in the form of a scatter plot, and 51 reported PSA results as a cost-effectiveness acceptability curve (Table 20).

**Table 20 Treatment of parameter uncertainty and reporting methods for PSA from 2004-2011**

	2004	2005	2006	2007	2008	2009	2010	2011
<b>Include PSA <sup>a</sup></b>	3	4	10	7	12	6	10	16
<b>Treatment of Parameter Uncertainty</b>								
All Relevant Parameters Considered in PSA <sup>a</sup>	1 (33%)	0 (0%)	1 (10%)	0 (0%)	4 (33%)	1 (17%)	2 (20%)	6 (38%)
Adopted Appropriate Functional Form for:								
Transition Probabilities	0 (0%)	0 (0%)	4 (40%)	2 (29%)	6 (50%)	0 (0%)	3 (30%)	7 (44%)
Costs	1 (33%)	0 (0%)	4 (40%)	3 (43%)	6 (50%)	2 (33%)	9 (90%)	9 (56%)
Utilities	1 (33%)	0 (0%)	3 (30%)	3 (43%)	9 (75%)	4 (67%)	5 (50%)	9 (56%)
Treatment Effects	1 (33%)	0 (0%)	2 (20%)	1 (14%)	6 (50%)	2 (33%)	4 (40%)	5 (31%)
<b>Reporting Methods for PSA <sup>a</sup></b>								
Confidence Interval	0 (0%)	0 (0%)	2 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Scatter Plot	1 (33%)	3 (75%)	6 (60%)	4 (57%)	5 (42%)	6 (100%)	7 (70%)	12 (75%)
Cost-Effectiveness Acceptability Curve	2 (67%)	3 (75%)	6 (60%)	5 (71%)	9 (75%)	5 (83%)	7 (70%)	14 (88%)

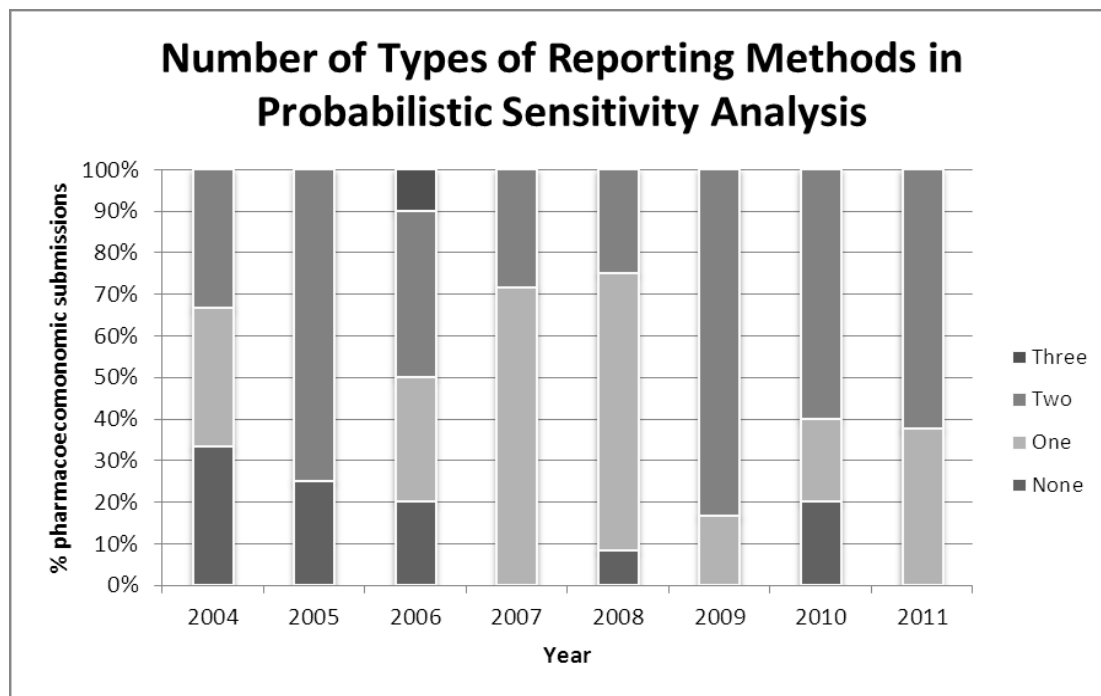
<sup>a</sup> PSA

In reference to the number of types of reporting methods for PSA, the majority of pharmacoeconomic submissions presented at least one type of reporting method; almost all of which were in the form of scatter plot and/or cost-effectiveness acceptability curve. In 2004, a third of pharmacoeconomic submissions did not present any reporting method (i.e.: results were only presented as expected values), another third presented one type, and the

remaining third presented two types of reporting methods. By 2011, approximately two thirds of pharmacoeconomic submissions reported PSA results as both scatter plot and cost-effectiveness acceptability curve and the remaining third presented results as a scatter plot or cost-effectiveness acceptability curve (Figure 7).

There are no evident trends in specific types of distributions used for transition probabilities, costs, utilities and treatment effects. The most prevalent type of distributions were beta (for transition probability and utilities), gamma (for costs), and log normal (for treatment effects) (Appendix J - Additional Analysis on Probabilistic Sensitivity Analysis).

**Figure 7 Number of types of reporting methods in PSA from 2004-2011**



#### 4.6 Indirect Treatment Comparison

With regards to the use of indirect treatment comparison, more than a third of pharmacoeconomic submissions (38) included an indirect treatment comparison with the proportion of submissions including an indirect treatment comparison increasing from 21% in 2003-05 to 37% in both 2006-08 and 2009-11. Of the 38 pharmacoeconomic submissions, 12 conducted a naïve comparison, 8 conducted an informal comparison, and 9 conducted an adjusted comparison. 11 out of 38 pharmacoeconomic submissions conducted a network

meta-analysis. In terms of trends, an increase in network meta-analyses can be found from 0 in 2003-05 to 20% of submissions by 2009-11 (Table 21).

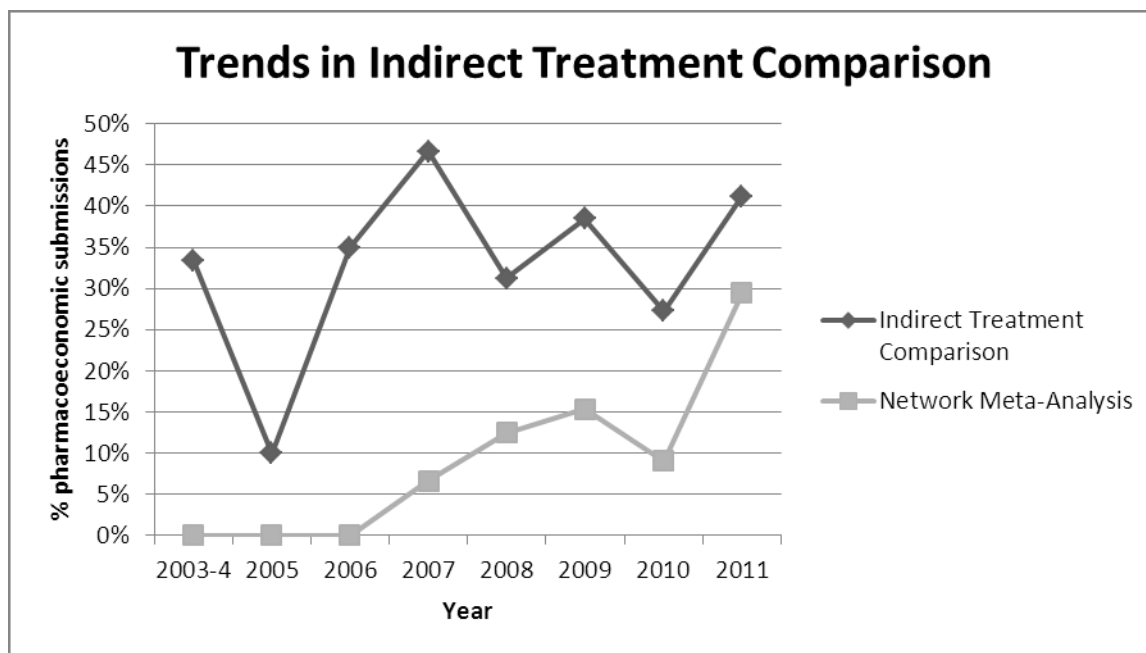
**Table 21 Use of indirect treatment comparison by grouped year**

	<b>2003-2005</b> <b>n=19</b>	<b>2006-2008</b> <b>n=51</b>	<b>2009-2011</b> <b>n=41</b>
<b>Conducted Indirect Treatment Comparison</b>	4 (21%)	19 (37%)	15 (37%)
<b>Indirect treatment Comparison <sup>a</sup></b>			
Naïve	2 (11%)	6 (12%)	4 (10%)
Informal	0 (0%)	7 (14%)	1 (2%)
Adjusted	2 (11%)	4 (8%)	3 (7%)
Network Meta-Analysis	0 (0%)	3 (6%)	8 (20%)

<sup>a</sup> Some pharmacoeconomic submissions included more than one type of indirect treatment comparison

When examining the trends in use of indirect treatment comparison per year, there is a slight increase; more obvious, however, is the greater relative increase in network meta-analysis. Network meta-analysis emerged in 2007 and by 2011 and was a constituent component of the majority of indirect treatment comparisons (Figure 8).

**Figure 8 Trends in indirect treatment comparison and network meta-analysis from 2003-2011**



With regards to reporting items in indirect treatment comparisons, less than a quarter of pharmacoeconomic submissions with an indirect treatment comparison had clear methods for study identification (9 out of 38), clear methods for analysis (9 out of 38), and sufficient information to replicate the analysis (9 out of 38). More submissions included all relevant studies in the indirect treatment comparison analysis (17 out of 38), although this was still less than half of the submissions (45%). None included a meta-regression and few considered the sensitivity of results by including/excluding studies (Table 22).

Overall, there is no evident trend that the quality of indirect treatment comparison analysis has improved over time; with the only potential inference being that there is a decline in all relevant studies being included (Table 22).

**Table 22 Reporting items in indirect treatment comparisons by grouped year**

	2003-2005 n=4	2006-2008 n=19	2009-2011 n=15
<b>Reporting Items</b>			
Clear Methods For Study Identification	0 (0%)	5 (26%)	4 (27%)

All Relevant Studies Included	3 (75%)	9 (47%)	5 (33%)
Clear Methods for Analysis	1 (25%)	4 (21%)	4 (27%)
Sufficient Information to Replicate	1 (25%)	3 (16%)	5 (33%)
Analysis Included Meta-Regression	0 (0%)	0 (0%)	0 (0%)
Analysis Considered Sensitivity of Results	0 (0%)	0 (0%)	3 (20%)

Overall, the indirect treatment comparisons within pharmacoeconomic submissions were of poor quality with the majority of pharmacoeconomic submissions adhering to no more than two of the reporting items listed above. 42% of the indirect treatment comparisons within the submissions did not adhere to any of the reporting items listed (42%). Two of the indirect treatment comparison within the pharmacoeconomic submissions (5%) can be judged of good quality in that they adhered to five of the six reporting items, both of which excluded meta-regressions (Table 23).

**Table 23 Quality of individual studies with respect to reporting of indirect treatment comparison**

	N	%
<b>Include Indirect Treatment Comparison</b>	<b>38</b>	
<b>Number of Reporting Items Adhered to <sup>a</sup></b>		
<b>0</b>	16	42%
<b>1</b>	10	26%
<b>2</b>	5	13%
<b>3</b>	3	8%
<b>4</b>	2	5%
<b>5</b>	2	5%
<b>6</b>	0	0%

<sup>a</sup> Total does not equate to 100% due to rounding

A further analysis was conducted incorporating evidence on the use of indirect treatment comparisons within CMA. Of the 76 CMA, 15 included an indirect treatment

comparison –with the proportion increasing from 7% in 2003-05 to 34% in 2009-2011. Six conducted a naïve comparison, four conducted an informal comparison, two conducted an adjusted comparison, and three conducted a network meta-analysis (Table 24).

**Table 24 Use of indirect treatment comparison in cost-minimization analysis by grouped year**

	<b>2003-2005</b> <b>n=14</b>	<b>2006-2008</b> <b>n=30</b>	<b>2009-2011</b> <b>n=32</b>
<b>Conducted Indirect Treatment Comparison</b>	1 (7%)	3= (10%)	11 (34%)
<b>Indirect treatment Comparison</b>			
Naïve	1 (7%)	3 (10%)	2 (6%)
Informal	0 (0%)	0 (0%)	4 (13%)
Adjusted	0 (0%)	0 (0%)	2 (6%)
Network Meta-Analysis	0 (0%)	0 (0%)	3 (9%)

There is a greater proportion of indirect treatment comparisons in CEA/CUA than CMA (34% - 38 out of 111 versus 21% - 15 out of 76), with overall, more than a quarter of drug submissions (53 of 187) including indirect treatment comparisons. There is also a greater percent of CEA/CUA including all relevant studies (45% versus 20%) and a slight greater proportion of CEA/CUA considering the sensitivity of results compared to CMA (8% versus 0% respectively). As well, there is a greater proportion of CMA with indirect treatment comparisons having clear methods for study identification, clear methods for analysis, sufficient information to replicate and included a meta-regression compared to CEA/CUA (Table 25).

The quality of indirect treatment comparisons within CMA was no better than for the studies within CEA/CUA. Overall, drug submissions which included indirect treatment comparison scored poor adherence to reporting items, ranging from 14-38% adherence (Table 25).

**Table 25 Comparison of reporting items in cost-effectiveness analysis/cost-utility analysis and cost-minimization analysis**

	CEA/CUA		CMA		Both	
	n	%	N	%	n	%
<b>Include Indirect Treatment Comparison</b>	<b>38</b>	100%	<b>15</b>	100%	<b>53</b>	100%
<b>Reporting Items</b>						
Clear Methods For Study Identification	9	24%	5	33%	14	26%
All Relevant Studies Included	17	45%	3	20%	14	26%
Clear Methods for Analysis	9	24%	6	40%	20	38%
Sufficient Information to Replicate	9	24%	5	33%	15	28%
Analysis Included Meta-Regression	0	0%	2	13%	14	26%
Analysis Considered Sensitivity of Results	3	8%	0	0%	2	4%

There were no differences in the proportion of indirect treatment comparisons adhering to number of reporting items. Most adhered to none of the reporting items and none adhered adhere to all reporting items (Table 26).

**Table 26 Comparison of adherence to reporting items in cost-effectiveness analysis/cost-utility analysis and cost-minimization analysis**

	CEA/CUA		CMA		Both	
	n	%	n	%	N	%
<b>Include Indirect Treatment Comparison</b>	<b>38</b>	100%	<b>15</b>	100%	<b>53</b>	100%
<b>Number of Reporting Items Adhered to <sup>a</sup></b>						
<b>0</b>	16	42%	7	47%	23	43%
<b>1</b>	10	26%	2	13%	12	23%
<b>2</b>	5	13%	1	7%	6	11%
<b>3</b>	3	8%	3	20%	6	11%
<b>4</b>	2	5%	2	13%	4	8%
<b>5</b>	2	5%	0	0%	2	4%

6	0	0	0	0%	0	0%
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<sup>a</sup>Total may not equate to 100% due to rounding

#### 4.7 Determinants of Formulary Listing Recommendation

Candidate variables used for the multivariable regression model which would identify key methodological factors (determinants of formulary listing recommendation) included: clinical concerns, population, quality of life, transparency, probabilistic sensitivity analysis, indirect treatment comparison, adherence to target population, adherence to effectiveness, adherence to valuing outcome, adherence to resource use and costs, adherence to reporting, and year of drug submission. These variables had a Fisher’s Exact Test p value of  $\leq 0.20$  (Table 27).

There is a statistically significant association between clinical concerns and formulary listing recommendation, transparency and formulary listing recommendation, probabilistic sensitivity analysis and formulary listing recommendation, and adherence to reporting and formulary listing recommendation (Table 27).

All other selected variables that were not considered candidate variables can be found in Appendix H - Additional Results from Fishers Exact Test; those variables had a Fisher’s Exact Test p value of  $> 0.20$ .

**Table 27 Candidate variables for regression analysis**

Candidate Variables for Regression Analysis	Description	Fisher’s Exact Test (P value)
Clinical Concerns	CDR pharmacoeconomic reviewers had a concern regarding the clinical data used in the model versus not	0.002
Population	Had same population model as reimbursement population sought by manufacturer versus not	0.105
Quality of Life	Had quality life measure based on	0.070

	good information versus not	
Transparency	Had clear and transparent methods and analysis versus not	0.007
Probabilistic Sensitivity Analysis	Conducted a PSA versus not	0.050
Indirect Treatment Comparison	Conducted indirect treatment comparison versus not	0.159
Adherence to Target population	Adhered to target population guideline statement versus not	0.105
Adherence to Effectiveness	Adhered to effectiveness guideline statement versus not	0.182
Adherence to Valuing Outcome	Adhered to valuing outcome guideline statement versus not	0.187
Adherence to Resource use and costs	Adhered to resource use and costs guideline statement versus not	0.132
Adherence to Reporting	Adhered to the reporting guideline statements versus not	0.007
Year of Drug Submission	Grouped year the drug submission was submitted to the Common Drug Review - 2003-2005, 2006-2008 or 2009-2011	0.188

Without considering multiple variables – only considering the association between the outcome and one variable, the odds of having a positive listing recommendation were 3.45 times lower if there were clinical concerns regarding the clinical effectiveness data used in the economic model compared to a pharmacoeconomic evaluations without clinical concerns. Having clear and transparent methods and analysis increased the odds of a positive listing recommendation by 3.04. Conducting a probabilistic sensitivity analysis increased the odds of a positive listing recommendation by 2.33. Adhering to reporting guideline statement increased the odds of a positive listing recommendation by 3.04 (Table 28).

Having the identical population modelled as the population request for reimbursement, including quality of life measure based on good information, conducting an indirect treatment comparison, adhering to target population guideline statement, adhering to effectiveness guideline statement, adhering to valuing outcome guideline statement, and having a drug submission post 2005 all increased the odds of a positive listing recommendation, but were not statistically significant. The odds of having a positive listing recommendation were 1.82 times lower if resource use and costs were adhered to; however, it was not statistically significant.

**Table 28 Odds ratio of candidate variables for multivariable regression analysis**

<b>Candidate for Multivariable Regression Analysis</b>	<b>Odds Ratio (Univariate Analysis)</b>
Clinical Concerns	0.29 (0.13, 0.64)
Population	2.37 (0.89, 6.29)
Quality of life	2.21 (0.99, 4.91)
Transparency	3.04 (1.39, 6.66)
Probabilistic Sensitivity Analysis	2.33 (1.05, 5.17)
Indirect Treatment Comparison	1.87 (0.85, 4.14)
Adherence to Target Population	2.37 (0.89, 6.29)
Adherence to Effectiveness	1.77 (0.83, 3.77)
Adherence to Valuing Outcome	1.92 (0.81, 4.57)
Adherence to Resource Use and Costs	0.55 (0.26, 1.18)
Adherence to Reporting	3.04 (1.39, 6.66)
Year of Drug Submission	
2003-2005 versus 2006-2008	2.49 (0.78, 7.93)
2003-2005 versus 2009-2011	2.94 (0.89, 9.67)

Correlations between variables were examined and a perfect correlation (1.0) between adherence to target population and population as well as adherence to reporting and transparency were found. A decision to remove one of the two correlated variables was then required and therefore, the odds ratios of the correlated variable was consulted to determine

which variable to remove. However, with respect to each correlated variable, the magnitude of association between the variable and outcome were identical (Table 28). Adherence to target population and adherence to reporting were then arbitrarily removed from the listed of variables used in the multivariable regression analysis. Collinearity diagnostics revealed that no variables had high collinearity.

When considering multiple variables – the association between the outcome and multiple variables, the odds of having a positive listing recommendation were 3.70 times lower if there were clinical concerns regarding the clinical effectiveness data used in the economic model compared to a pharmacoeconomic evaluations without clinical concerns. Having clear and transparent methods and analysis increased the odds of a positive listing recommendation by 2.79 times (Table 29).

Having an indirect treatment comparison, having the identical population modelled as the population request for reimbursement, and including quality of life measure based on good information all increased the odds of a positive listing recommendation, but were not statistically significant (Table 29).

**Table 29 Key methodological factors**

	<b>Odds Ratio</b>	<b>95% CI <sup>a</sup></b>	<b>P value</b>
<b>Methodological Factor</b>			
Indirect Treatment Comparison	2.09	(0.83, 5.26)	0.119
Population	2.40	(0.83, 6.95)	0.107
Clinical Concerns	0.27	(0.11, 0.66)	0.004
Quality of Life	1.83	(0.75, 4.47)	0.185
Transparency	2.79	(1.19, 6.58)	0.019

<sup>a</sup> confidence interval

#### **4.8 Summary**

This chapter presented the results from the descriptive and statistical analyses; the following section will provide an interpretation of the results presented in this chapter.

## **Chapter 5 Discussion and Conclusion**

### **5.1 Discussion**

This thesis is a retrospective examination of pharmacoeconomic evaluations submitted for review to the CDR process. Its purpose was to determine the pattern of adherence to guidelines, trends in methodological quality, and transparency, changes in the adoption and practice of sensitivity analysis and probabilistic methods, use of indirect treatment comparison, and identify methodological factors which are determinants of recommendations. Using an instrument that was developed and tested, information from 201 pharmacoeconomic submissions was collected and analysed.

It is difficult to compare the findings of this thesis with other literature since no Canadian study has examined pharmacoeconomic submissions to this extent; therefore, the following section involves an interpretation of the results rather than a comparison with existing literature.

#### Adherence to Guidelines for the Economic Evaluation of Health Technologies: Canada

Adherence to guidelines is important as it is a measurement of the extent to which pharmacoeconomic submissions are reflective of best practices. Within this thesis, pharmacoeconomic submissions were shown to only partially adhere to the Guidelines for the Economic Evaluation of Health Technologies. Adherence to guidelines was defined as the ability to satisfy 14 guideline statements. Only 1 pharmacoeconomic submission adhered to all 14 guideline statements, with the majority of submissions adhering to 8-11 guideline statements. Moreover, pharmacoeconomic submissions tended to adhere more to less technically difficult guideline statements rather than technically difficult ones. Perspective, Types of Evaluations, Discounting, Time Horizon, Target Population for which there is good-very good adherence are non-technically challenging guideline statement, whereas, Variability and Uncertainty, Modelling, and Valuing Outcomes for which there is fair-poor adherence are technically difficult guideline statements. The latter are likely to have a much greater impact on applicability and relevance and are likely to substantially impact study results.

As adherence to guidelines measures the extent to which pharmacoeconomic submissions are reflective of best practices, the results of this thesis suggest that pharmacoeconomic submission partially reflect best practices. With partial reflection of best practices, evidence based decision making may be limited because evidence based decision making is grounded on the best available research evidence and if pharmacoeconomic submission only partially reflect best practices, this may affect the applicability of the pharmacoeconomic submissions in the reimbursement context.

Although there were improvements in adherence to certain guidelines such improvements appeared minimal. Any improvements tended to be related to the less technical guideline statements such as Discounting, Time Horizon and Target Population. There were improvements in adherence with Effectiveness, Reporting, and Modelling – although the proportion of submissions adhering to these guidelines in 2009-2011 was still less than 60%. Improvements of adherence to guidelines are therefore insubstantial.

Reliance on adherence to guidelines alone is not indicative of the quality of pharmacoeconomic submissions, as adherence was limited to 14 guideline statements. Therefore, the quality of the methods used in the pharmacoeconomic submissions was examined.

### Methodological Quality

Within this thesis, there is evidence of some modest improvements in quality relating to certain methodological areas. Methodology quality in terms of choice of data (efficacy data and inclusion of quality of life estimate) and modelling techniques (model validation and assumptions) were assessed.

Analysis found modest improvements in the quality of efficacy data used. For instance, there was an increase in the use of data from head to head randomized controlled trials and a decline in lesser quality of evidence such as open label trials, expert opinion and observational data. However, almost two-thirds of submissions still use placebo controlled trials or indirect treatment comparison as the highest level of evidence. This suggests that economic evaluations are still limited by the lack of comparative clinical trials and are still reliant on comparing alternate treatment options through indirect evidence. Thus, the lack of

highest level evidence restricts the ability of studies to give an accurate representation of the relative cost-effectiveness of treatments.

The thesis found conflicting evidence on the quality of quality of life data. There is evidence of increasing inclusion of quality of life estimates in submissions, although there appears to be no increase in the use of quality of life estimates based on good quality data. Quality of life estimates are a key variable in cost-utility analysis as these estimates along with the treatment effect are used to estimate the health outcome – the quality-adjusted life years. The results of this thesis suggest that cost-utility analysis submitted by manufactures include inappropriate data in obtaining quality of life estimates. This may lead a potential bias in the relative cost-effectiveness of the drug. Thus, the lack of quality of life estimates based on good quality data restricts the ability of cost-utility analysis to give an accurate representation of the relative cost-effectiveness of the drug.

This thesis found evidence that there have been improvements in terms of validating the economic model. Although there have been improvements over time, almost half the models had no formal validation in 2009-11. Model validation is important because it involves testing the model to confirm that the model does what it is expected to do. Without validating a model to ensure that the model does what it is expected to do, the reliability and the validity of the relative cost-effectiveness of the drug are questionable.

Finally, in terms of model assumptions, there was conflicting evidence regarding the adoption of inappropriate parameter assumptions. For instance, there was gradual improvement over time in inappropriate assumptions relating to efficacy, however almost 40% of submissions accounted for inappropriate assumptions relating to efficacy by 2009-11.

Although almost all pharmacoeconomic submissions had at least one inappropriate assumption, not all inappropriate assumptions are considered crucial. Of the 111 CEA/CUA, CDR pharmacoeconomic reviewers conducted a reanalysis based on alternative assumptions or data inputs on 60 submissions. Of the 60 pharmacoeconomic submissions which were reanalysed, 50 had significantly different results. This suggests that although almost all submissions had at least one inappropriate assumption, and that many of these assumptions

can be considered crucial given that almost reanalysis of almost half the submissions resulted in significantly different results compared to the manufacturer's submitted estimates.

Overall, there were modest developments in methodology in terms of efficacy data, inclusion of quality of life data, model validation, and model assumptions. However, such improvements can be considered minimal.

### Transparency of Reporting

Transparency in the reporting is important since lack of transparency may lead to improper interpretation of the results, and lead to doubts regarding the credibility of the pharmacoeconomic evaluation (McDaid et al., 2002). With respect to trends in transparency of pharmacoeconomic submissions, there are limited improvements over time. Transparency of reporting, on the basis of adherence to Reporting guideline statements, is defined as having clear and transparent methods and analysis as well as reported results in incremental cost-effectiveness ratios. Overall, 41% of pharmacoeconomic submissions were transparent, indicating in general poor adherence with respect to reporting.

For the pharmacoeconomic reviewer and CDEC, having transparent reporting may facilitate the review process and lead to proper interpretation of the results as well as maintains the credibility of the pharmacoeconomic evaluation used for decision making. Therefore, poor adherence with respect to reporting may hinder the review process and may lead to improper interpretation of the results and doubts regarding the credibility of the pharmacoeconomic evaluation.

### Adoption of Sensitivity Analysis

With regards to the adoption of sensitivity analysis, there are improvements in inclusion of both deterministic sensitivity analysis and PSA over time, but no improvements in methods of handling parameter uncertainty in PSA over time.

First, all pharmacoeconomic submissions included at least one form of sensitivity analysis and there was an identifiable increase in the adoption of PSA. In 2003, a third of pharmacoeconomic submissions included both deterministic sensitivity analysis and PSA

and by 2011, 94% included both forms of sensitivity analysis, therefore suggesting a trend in adoption of both types of sensitivity analysis.

Secondly, although submissions include PSA, the methods of handling parameter uncertainty in PSA have not improved over time. In fact, there is no change over time and the appropriate functional forms for transition probabilities, costs, utilities, and treatment effects remain low. Less than half of pharmacoeconomic submissions with PSA used the appropriate functional forms to handle uncertainty. Therefore, suggesting that the inclusion of PSA is not indicative of a good quality sensitivity analysis.

The right choice of distribution can in fact affect the incremental cost-effectiveness ratio (Thompson & Nixon, 2005). Therefore, for more than half the pharmacoeconomic submissions with PSA which did not use the appropriate functional form, the PSA results may be inaccurate. Subsequently, the decision uncertainty around the incremental cost-effectiveness ratio may be inaccurate and can therefore lead to inaccurate interpretation of the results.

#### Use of Indirect Treatment Comparison

Although the Guidelines mention indirect treatment comparisons, the types of indirect treatment comparisons such as network meta-analysis are not covered in the Guidelines. More than a quarter of CEA/CUA and CMA included indirect treatment comparisons; these included naive, informal and adjusted comparisons and network meta-analysis. For CEA/CUA, there is an increasing use of network meta-analysis; by 2011, network meta-analyses represented the majority of indirect treatment comparisons; although a trend in use of network meta-analysis in CMA is less apparent.

Despite the inclusion of indirect treatment comparison and increase uptake of network meta-analysis, reporting methodology was limited. For instance, adherence to reporting items such as clear methods of study identification, clear methods for analysis is poor, scoring below 50% adherence and meta-regression and consideration of the sensitivity of results are included by few if at all.

Just as transparency of reporting of pharmacoeconomic evaluations are important for the proper interpretation of the results and the credibility, the reporting methodology is important for the proper interpretation of the results and the credibility of indirect treatment comparisons. With limited reporting methodology, the quality of evidence with respect to the indirect treatment comparison may lead to distrust in the clinical effectiveness estimates. Including clear methods for study identification, clear methods for analysis and sufficient information to replicate are important for the reproducibility as well as the credibility of the indirect treatment comparison, yet less than half of pharmacoeconomic evaluations with indirect treatment comparisons adhered to the latter. Consequently, limited reporting methodology may result in poor quality evidence that is not useful for decision makers.

It must be noted, however, that an obvious limitation of the study was that I examined only certain aspects of quality within indirect treatment comparisons. This was because the main focus of the thesis was on the quality of pharmacoeconomic evaluations and further focus on indirect treatment comparison would lead to moving the focus away from the primary objective. A more detailed review of the quality focusing on additional issues such as goodness-of-fit, choice of priors, convergence, and consistency is warranted and could be the focus of further research.

#### Determinants of Formulary Listing Recommendation

A multivariable regression analysis was conducted to identify key methodological factors which are determinants of formulary listing recommendation. Candidate variables were selected from the previous analyses – adherence to guidelines, methodological quality, transparency, sensitivity analysis and indirect treatment comparison, to create a multivariable regression model. The multivariable regression analysis resulted in five key methodological factors associated with formulary listing recommendations: indirect treatment comparison (conducting an indirect treatment comparison); clinical concerns (having concerns over clinical data used to estimate the clinical effectiveness of the drug in the economic model); population (having the same population in the economic model as the population for whom the drug manufacturer sought reimbursement for); transparency (having clear and transparent methods and analysis); and quality of life (including quality of life estimates based on good information).

The key methodological factors identified as determinants of the formulary listing recommendation seem consistent. First, conducting an indirect treatment comparison had a positive influence the recommendation. This seems reasonable because when little or no direct evidence is available, indirect comparison can provide a way to compare two drugs. Failure to include an indirect treatment comparison when head to head data is not available will hinder CDEC's ability to make comparison of the new therapy's relative cost effectiveness when compared to existing funded products.

Second, having concerns over clinical data used to estimate the clinical effectiveness of the drug in the economic model lowers the chances of a positive listing recommendation in comparison to not having concerns regarding clinical data. It is intuitive since concerns regarding clinical effectiveness estimate negatively impacts ones' confidence in the economic model and therefore the results of the economic analysis.

Furthermore, having the same population in the economic model as the population for whom the drug manufacturer sought reimbursement for had an impact on the recommendation. It is only natural, as a recommendation to reimburse a drug for a given population is not likely to be given, if the population used in the economic model is not representative of the population for whom reimbursement is being sought.

Moreover, having clear and transparent methods and analysis had a positive influence on the formulary listing recommendation. This is sensible seeing as the Guidelines emphasize transparency of reporting.

Finally, including quality of life estimates based on good quality information had an impact on positive recommendation. This is reasonable since the Guidelines emphasize use of appropriate measures to estimate quality of life.

### Interpretations and Recommendations

There are multiple ways of interpreting the findings of this thesis with respect to adherence, methodological quality, transparency, practise of PSA and indirect treatment comparison. In this section, I highlight four possible explanations for the minimal improvements found in this thesis and recommendations to accompany each explanation.

The first is that there is information missing from the Guidelines that reflects best practices and therefore, the Guidelines need to be updated. Another possibility is that the Guidelines lack clarity and thus, the Guidelines could be revised to improve clarity. The third interpretation is that the Guidelines are clear; however, manufacturers lack expertise and thus, require more training. Another alternative is that the Guidelines are clear and manufacturers are not willing to adhere; therefore, additional emphasis by CADTH is required.

To begin, there is information missing from the Guidelines that reflects best practices. This could be a possible explanation for the lack of appropriate functional forms used in PSA. The Guidelines do not mention the implications of improper distributional assumptions used in PSA as well as description of the appropriate functional forms. As mentioned previously, improper distributional assumptions used in PSA may lead to inaccurate PSA results and subsequently, the decision uncertainty around the incremental cost-effectiveness ratio may be inaccurate. Therefore, I recommend that a brief explanation of the importance of selecting the appropriate functional form in PSA should be incorporated in the Guidelines; and perhaps a table with the appropriate functional distribution for each parameter similar to the table featured in the methods section of this thesis (Refer to Table 3 Appropriate functional forms for parameters in PSA) should be included as well. In addition, a further stand-alone document providing more details of appropriate PSA methodology may be required.

Another possibility is that the Guidelines lack clarity. The Guidelines state that “*the analyst may use indirect comparisons based on appropriate techniques*” (Canadian Agency for Drugs and Technologies in Health, 2006), however it is unclear what the appropriate techniques in indirect treatment comparison are since the types of indirect treatment comparisons are not mentioned in the Guidelines. For instance, the Guidelines do not mention network meta-analyses and as discussed earlier in the introduction, network meta-analysis is a complex method developed to allow consideration of both direct and indirect evidence rather than the restricted focus of conventional meta-analysis (Lumley, 2002). This lack of clarity with respect to indirect treatment comparisons based on appropriate techniques could have accounted for the pharmacoeconomic submissions with indirect

comparisons based on inappropriate techniques such as naïve and informal comparisons. In addition, as conducting an indirect treatment comparison is a determinant of a positive listing recommendation, it would seem fit that CADTH revise the Guidelines to include a clear explanation of the appropriate techniques regarding indirect treatment comparisons.

Moreover, the Guidelines state “*methods used to synthesize indirect comparisons should be explained;*” however, the Guidelines are not clear on the expectations of reporting indirect treatment comparisons (Canadian Agency for Drugs and Technologies in Health, 2006). Perhaps the reason for limited reporting is because of the lack of clarity. Consequently, drug manufacturers require more guidance in terms of reporting indirect treatment comparisons. Therefore, I recommend that the guidelines incorporate a brief description on how to report indirect treatment comparisons; perhaps even a checklist of reporting items similar to the reporting methodology items used in the methods section of this thesis (Refer to Methods Indirect Treatment Comparison for reporting items) could be included. In addition, a further stand-alone document providing more details of appropriate indirect treatment comparisons methodology may be required.

An alternate explanation is that Guidelines are clear; however, manufacturers lack expertise. The Guidelines state “*use appropriate preference-based measures to value meaningful differences between the intervention and alternatives in terms of HRQL [health related quality of life]*” (Canadian Agency for Drugs and Technologies in Health, 2006). The Guidelines also include details regarding types of preference-based measures and inappropriate methods; however, more than half the submissions included quality of life estimates not based on good information. Therefore, it is possible that although the Guidelines are clear, manufacturers lack the expertise with respect to the appropriate preference-based measures. Perhaps manufacturers require more guidance on appropriate preference-based measures to measure health related quality of life.

Seeing as the inclusion of quality of life estimates based on good information is a determinant of a positive listing recommendation, it would seem fit that CADTH offer training on how to conduct better quality of life studies to measure health related quality of life. Perhaps offering information on how to conduct better quality of life studies specific to diseases/disorders would be beneficial to manufacturers.

Another possibility is that the Guidelines are clear, yet the manufacturers are not willing to adhere to the Guidelines. The Guidelines are clear about the inclusion of model validation, stating “*formally validate the model, and state how this was done*” (Canadian Agency for Drugs and Technologies in Health, 2006). The Guidelines provide an explanation for model validation as well as a description of how to formally validate a model. Despite the clear expectation for model validation, almost half pharmacoeconomic submissions did not have formally validated models in 2009-2011. Therefore, the findings of this thesis suggest that manufacturers are not willing to provide validated models, given the clear expectation to formally validated models. I then recommend that CADTH emphasize the need for formal validation of models and perhaps provide additional guidance on how to formally validate a model.

Moreover, the Guidelines state: “*report the evaluation in a transparent and detailed manner*” and a section in the Appendix of the Guidelines provide extensive details on how to properly report a pharmacoeconomic evaluation to ensure that “*studies are thoroughly presented, and organized consistently to facilitate review and comparison by decision makers*” (Canadian Agency for Drugs and Technologies in Health, 2006). Despite the clear expectation for transparency of reporting, less than 50% of pharmacoeconomic submissions had transparent reporting in 2009-2011. Therefore, the findings of this thesis suggest that manufacturers are not willing to provide transparent pharmacoeconomic submissions given the clear expectation for transparency of reporting in the Guidelines.

Considering as transparency is important for proper interpretation of the results and credibility of pharmacoeconomic evaluation (McDaid et al., 2002) and is a determinant for a positive listing recommendation, I recommend that CADTH emphasize the need for transparency of reporting, so that manufactures improve efforts in the transparency of reporting of pharmacoeconomic evaluations and in doing so, this could increase their chances of a positive listing recommendation.

### Strengths and Limitations

Several measures throughout the instrumentation, data collection, and analysis process were made to maintain internal validity of this study. For content validity, content

experts were consulted and a literature review was conducted to ensure that the instrument contained appropriate methodology content. For face validity, the instrument was piloted on nine pharmacoeconomic submissions. Although the nine pharmacoeconomic submissions were hand selected, and therefore subject to selection bias, they were chosen to reflect the range in complexity of submissions. Inter-rater reliability tests were conducted to demonstrate the reproducibility of the instrument. For this, pharmacoeconomic submissions were randomly selected.

In terms of the analysis process, although the variables considered in the non-parametric testing are subject to selection bias, a selection method was used to reduce selection bias during the development of the multivariable model.

There are potential limitations to this thesis. Although data abstraction took approximately 2 hours per study and therefore, highlighted the rationale for only one data abstractor, there are potential limitations to consider: data collection is subject to potential investigators bias and data may have been incorrectly coded due human error or lack of expertise. Furthermore, the findings are limited to the information collected using the instrument, collection of qualitative information was limited given the nature of questionnaire. Qualitative information could provide insights on justifications for certain methods or lack thereof. In addition, the findings of this thesis with regards to adherence is subjective, therefore should be interpreted with caution. Finally, the pharmacoeconomic submissions are unique to the Common Drug Review and therefore, the results of this study are not transferrable to pharmacoeconomic evaluations in other formulary listing processes such as pan-Canadian Oncology Drug Review.

### Future Implications

The findings and recommendations of this thesis have the ability to impact future pharmacoeconomic submissions and the formulary listing recommendation decision making process. This thesis brings to light areas in pharmacoeconomic submissions that need to be improved. This could be interpreted a call for action for both manufacturers and CADTH. As suggested above, additions to the Guidelines can be made to assist manufacturers in producing probabilistic sensitivity analysis with appropriate functional forms. As well, the

provision of clearer guidelines with respect to indirect treatment comparisons may assist manufacturers in producing appropriate clinical effectiveness estimates used in economic evaluations. Moreover, the provision of training on how to conduct better quality of life studies to measure health related quality of life can help manufactures in including quality of life estimates based on good information.

CADTH is currently in the process of updating the Guidelines to the 4<sup>th</sup> edition. It is expected that the findings of this thesis are being considered and it is hoped that the recommendations discussed above will also be considered in the revision of the Guidelines as well as provision of guidance in the form of training for manufacturers.

## **5.2 Conclusion**

Pharmacoeconomic submissions may have improved over time in terms of adherence, methodological quality, transparency, use of PSA and indirect treatment comparison. However, such improvements have been minimal and the overall level of adherence to guidelines is poor. Further efforts are needed to better improve pharmacoeconomic submissions in the future. Given scarce resources, an increased effort to help provide reliable and relevant information for decision maker should be made. Therefore, the onus is on both manufacturers to improve the quality of economic evaluations and on health technology assessment organizations to provide clearer guidance and training where warranted. These efforts can better assist in the allocation of health care resource and in turn, reduce the burden on health care for Canadians.

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## Appendices

### Appendix A - Example of Scenarios for Each Formulary Listing Recommendation

<b>CDEC Recommendation Options</b>	<b>Example of Scenarios <sup>a</sup></b>
Do not list	<i>“A drug does not demonstrate comparable clinical benefit relative to one or more appropriate comparators.”</i>
List with clinical criteria and/or conditions	<p><i>“A drug demonstrates comparable or added clinical benefit and acceptable cost/cost-effectiveness relative to one or more appropriate comparators in a subgroup of patients within the approved indication. In such cases, the subgroup is specified through ‘clinical criteria.’”</i></p> <p><i>“A drug demonstrates added clinical benefit, but the cost/cost-effectiveness relative to one or more appropriate comparators is unacceptable. In such a condition may include a reduced price.”</i></p>
List	<i>“A drug demonstrates comparable or added clinical benefit and acceptable cost/cost-effectiveness relative to one or more appropriate comparators.”</i>
Do not list at the submitted price	<i>“A drug demonstrates added clinical benefit, but the cost/incremental cost-effectiveness ratio far exceeds that of existing treatment options and precludes a recommendation to list with clinical criteria and/or conditions.”</i>

<sup>a</sup> Examples taken directly from the CADTH website

## Appendix B - Guideline Statements

Types of Evaluations
<ul style="list-style-type: none"> <li>• <i>State and justify the type(s) of economic evaluation chosen. Select the appropriate type of evaluation based on the nature of the research question, the condition of interest, and the availability of data on outcomes.</i></li> </ul>
<ul style="list-style-type: none"> <li>• <i>In the denominator of the incremental cost-effectiveness ratio (ICER), use a valid outcome measure that is most important to the health of the patient (i.e., important patient outcome).</i></li> </ul>
<ul style="list-style-type: none"> <li>• <i>Use a cost-utility analysis (CUA) as the Reference Case where meaningful differences in health-related quality of life (HRQL) between the intervention and comparators have been demonstrated.</i></li> </ul>
<ul style="list-style-type: none"> <li>• <i>Use a cost-effectiveness analysis (CEA) as the Reference Case when a CUA is an inappropriate choice. Use a final outcome (e.g., life-years gained), or if that is impossible, an important patient outcome. Only use a surrogate outcome if it has a well-established link (i.e., validated) with one of those outcomes. Consider a CEA as a secondary analysis when the use of one important patient outcome measure [other than a quality-adjusted life-year (QALY) gained] in the denominator of the ICER can be justified, provided that there is a meaningful difference in such an outcome.</i></li> </ul>
<ul style="list-style-type: none"> <li>• <i>A cost-minimization analysis (CMA) is appropriate as the Reference Case when the evidence shows that the important patient outcomes of the intervention and comparators are essentially equivalent. Provide justification for conducting a</i></li> <li>• <i>CMA.</i></li> </ul>
<ul style="list-style-type: none"> <li>• <i>A cost-benefit analysis (CBA) may be useful in some situations, but generally, it should be considered as a secondary analysis. Explain all the steps taken to convert outcomes into monetary values, and analyze key assumptions using a sensitivity analysis.</i></li> </ul>
<ul style="list-style-type: none"> <li>• <i>A cost-consequence analysis (CCA) is generally not expected to be used as the Reference Case, unless a CEA or a CUA are inappropriate to use. To enhance reporting transparency, use a CCA as an intermediate step in reporting the other</i></li> </ul>

<i>types of economic evaluations</i>
<b>Target Population</b>
<ul style="list-style-type: none"> <li>• <i>Specify the target population(s) for the intervention and its expected use.</i></li> </ul>
<ul style="list-style-type: none"> <li>• <i>Perform the analysis for the entire target population that is specified in the study question. This may include the population representing the majority or all of its expected use. The efficacy-effectiveness data used in the analysis should be relevant to the target population in the analysis.</i></li> </ul>
<ul style="list-style-type: none"> <li>• <i>Conduct stratified analysis of smaller, more homogeneous subgroups, where appropriate, if there is variability (heterogeneity) in the target population.</i></li> </ul>
<ul style="list-style-type: none"> <li>• <i>Analysts are encouraged to analyze situations where it is anticipated that there will be inappropriate, suboptimal, or unintended use of the intervention.</i></li> </ul>
<b>Comparators</b>
<ul style="list-style-type: none"> <li>• <i>Relate the choice of comparators to the study population, and the local context or practice in which the decision is being made. In principle, consider all technically feasible, acceptable, and relevant alternatives as potential comparators. Then, select the appropriate comparators. Describe and justify the comparators that are chosen for evaluation, and justify those that are not chosen.</i></li> </ul>
<ul style="list-style-type: none"> <li>• <i>In the Reference Case, use “usual care” (i.e., the most common or frequently used care) which the intervention is intended to replace. In some cases, “usual care” may include more than one relevant, widely used alternative for the same indication.</i></li> </ul>
<ul style="list-style-type: none"> <li>• <i>Consideration should be given to the following when choosing comparators.</i> <ol style="list-style-type: none"> <li><i>Add “recommended care” as a comparator when usual care does not reflect appropriate (high quality) care. It can be regarded as the first choice in practice or care, as recommended in clinical practice guidelines.</i></li> <li><i>Where the alternatives are different treatment strategies, distinguish between situations where the intervention is an additional element in the strategy, a different treatment sequence, or a distinct alternative that could replace another element in the treatment strategy. Comparators may be alternative packages of care that consist of many elements. Analyze each strategy separately and explain the alternatives.</i></li> </ol> </li> </ul>

c) *At times, it may be prudent to analyze the entry of future comparators, including the anticipated entry of lower cost technologies (e.g., generic drugs).*

d) *For drugs, the alternative agents listed in a formulary may be the most relevant, although those that are not listed should not be excluded. The comparators should include the lowest cost available alternative that is often used for the same indication. Include the cost of the drug and any drug administration costs. Dosing regimens used in the analysis should reflect the dose and duration supporting the effectiveness data for the agent.*

### **Perspective**

- *State the perspective(s) of the study in terms of the costs included in the evaluation.*
- *In the Reference Case, use the perspective of the publicly funded health care system.*
- *Consider reporting separately the costs associated with adopting a wider perspective, where it is likely that they have a substantial impact on the results of the analysis. Quantify such costs separately, where possible, or at least discuss their likely magnitude and impact on the results of the analysis.*

### **Effectiveness**

- *Use a systematic review of the available literature to form the basis for evidence about the efficacy-effectiveness of the intervention. Justify failure to conduct a systematic review. Report the included studies and methods used to conduct the review and analyze or combine data.*
- *Where feasible and scientifically credible, translate efficacy data into the best quantitative estimate of effectiveness in the Reference Case, using the best available evidence and appropriate modelling techniques. This may involve linking surrogate outcomes to important patient outcomes or extrapolating data beyond the duration of the trial.*
- *Where feasible in the Reference Case, incorporate “real world” factors that modify the effect of the intervention, where there are established links to important patient outcomes based on the best available evidence. These factors include patients’ adherence to treatment, screening and diagnostic accuracy, and health care providers’ compliance and skill. State the nature of the factor, measures used to quantify the effect, and the methods and assumptions used for modelling.*

- *The evaluation of medical devices should focus more broadly on the entire episode of care rather than on only the technical performance of the device. The outcomes of medical and surgical procedures and diagnostic technologies may depend on the operator's skill and experience. The extensive use of sensitivity analysis may be required to properly evaluate situations where the evidence of efficacy effectiveness is weak.*

- *Where feasible, include the impact of adverse events associated with the intervention if they are clinically or economically important, and analyze them appropriately. Depending on the nature, frequency, duration, and severity, adverse events may have an impact on patients' adherence, mortality, morbidity, health related quality of life (HRQL) (utilities), or resource use. Value these in a manner that is consistent with the principles outlined in the Economic Guidelines.*

- *In the Reference Case, extrapolate data based on the best quantitative estimate of the relevant parameters, using the best available evidence and appropriate modelling techniques. Describe the strength of the evidence for extrapolating data and assess uncertainty through a sensitivity analysis. Unless such an analysis is based on high quality evidence, identify it as speculative, and give appropriate caveats in the report.*

#### **Time Horizon**

- *Base the time horizon on the natural course of the condition and the likely impact that the intervention will have on it. State and justify the time horizon(s) of the evaluation.*

- *In the Reference Case, ensure that the time horizon is long enough to capture all relevant differences in future costs and outcomes of the alternatives being analyzed. Apply the same time horizon to costs and outcomes. Consider using a lifetime time horizon, and justify where a shorter time horizon is used.*

- *If the long-term costs and outcomes are modelled, it may be appropriate to present the shorter-term analysis based on primary data, and the longer-term analysis using the extrapolated or modelled data. Multiple time horizons might be appropriate for exploring alternative scenarios in some cases. Explain the causal relationships and techniques that are used to extrapolate or model the data.*

## Modelling

- *Modelling considerations*

a) *Follow good modelling practices when constructing the model used to conduct the evaluation. Analysts are encouraged to consult good modelling practice guidelines as required.*

b) *Describe the model, including its scope, structure, and assumptions. Provide justification for assumptions and choices.*

c) *Use a model structure that is appropriate for addressing the study question. Build the model in such a way to permit updating of results as more data become available.*

d) *Explain and justify any causal relationships and extrapolation techniques used in the model. Base the extrapolation of data on valid techniques that reflect reasonable scientific evidence, and test through sensitivity analysis.*

e) *Formally validate the model, and state how this was done.*

- *Data considerations*

a) *Systematically identify, collect, and assess the data used in the model.*

b) *Report and identify all data sources. Explain and justify all parameter choices and assumptions.*

c) *Describe the quality (e.g., strength of evidence) of the data used in the model. Be explicit about data limitations and how they were dealt with. Try to quantify the impact of the limitations on the uncertainty of the evaluation results.*

d) *Gather the best available evidence on key model parameters for which the model results are most sensitive. Justify any failure to gather the best available evidence of such parameters. Use caution when expert opinion is used to establish parameter values. Justify its use; and describe the source of the opinion, the method of elicitation, and the results of the exercise. Assess such estimates through a sensitivity analysis.*

f) *Use appropriate methods to analyze or combine data from different sources. Explain and justify the methods used, and report the results of the analysis. Report limitations in the methods or data used, and where feasible, test through a sensitivity analysis.*

g) *Incorporate data into the model using appropriate techniques, and explain the methods used. If data are incorporated as point estimates, use mean estimates of parameters in the*

*base case. If estimates are incorporated as probability distributions, state and justify the form of the distributions.*

### **Valuing Outcomes**

- *Use appropriate preference-based measures to value meaningful differences between the intervention and alternatives in terms of HRQL.*

- *Measure the outcome for a CUA in terms of the QALYs gained. Report changes in the length of life and quality-weight separately, and report the procedure for combining them. State the assumptions and methods used to estimate QALYs. Justify using alternative outcome measures in a CUA.*

- *Preferences (utilities) can be measured directly or indirectly. Study the alternative methods a priori and select in advance the one that is most appropriate or the condition and study question. Justify the selection and method, report on the validity and reliability of the method selected, and explain the steps undertaken to measure preferences.*

- *Where preferences are measured directly, use the standard gamble or time trade-off approaches. To avoid double-counting, subjects in exercises measuring preferences should be asked to value lost leisure time in terms of changes in preferences, and to assume that health care costs and income losses are fully reimbursed.*

- *A representative sample of the general public, suitably informed, is the preferred source for preferences. Patients who have direct experience of the relevant health states may be an acceptable source. Describe the population from which the preferences were derived, and their relevance to the Canadian population.*

- *Willingness-to-pay methods for valuing outcomes in a CBA are regarded as a secondary type of analysis. Explain the steps to convert outcomes into monetary terms. Validate key assumptions, and test through a sensitivity analysis.*

### **Resource Use and Costs**

- *General*

*a) Systematically identify, measure, and value resources that are relevant to the study perspective(s). Classify resources in categories that are appropriate to the relevant decision maker (e.g., primary care, drug plan, hospitals).*

- *Resource identification*

a) *Exclude protocol-driven costs taken from clinical trials. Transfer payments should be excluded from the public payer and societal perspectives.*

b) *Unrelated costs that are incurred during normal life-years should be excluded from the evaluation. Unrelated costs that are incurred during life-years gained from the intervention may be included at the analyst's discretion in a sensitivity analysis.*

- *Resource measurement*

a) *Report quantities of resources in physical units.*

b) *Report the costing method used and justify the approach taken. Measure and value with greater precision those resources that contribute most to total and incremental costs. Where lower quality cost estimates are used, use a sensitivity analysis to determine the impact of cost assumptions.*

c) *Where feasible, base resource use estimates on data for Canadian routine practice. Where resource use data are from international sources, clinical trials, or non-observational sources (clinical practice guidelines), validate or adjust them for Canadian routine practice, using appropriate methods.*

- *Resource valuation*

a) *Conceptually, use economic (opportunity) costs as the basis for valuing resources. In principle, use total average cost (including capital and allocated overhead costs) as the unit cost measure.*

b) *Report the valuation methods used, and justify the approach where appropriate. Use market prices where available. Standard costs can be used where available and appropriate. Where costs are directly calculated or imputed, they should reflect the full economic cost of all relevant resources at normal operating levels.*

c) *When evaluating the public payer perspective, use the full cost (i.e., contributions paid by the public payer, private insurers, and patients) of the intervention and comparators in the Reference Case. For interventions involving cost-sharing arrangements with patients that are likely to have a noticeable impact on the results, use a sensitivity analysis to assess the implications of variations in the proportion of the cost of the intervention and comparator paid by the public payer. Use the same proportions for the intervention and comparators, unless there is a reason to do otherwise.*

d) Adjust any cost obtained from earlier times to the current period. Use appropriate methods, and provide justification when converting costs (i.e., resource quantities and unit costs) from another country to Canadian currency.

e) Consider a separate analysis of the impact of the intervention on lost time by patients and informal caregivers, where it is likely to have a substantial impact on the results.

f) Use the friction cost approach to value lost time from paid work. Report the friction period and unit cost used to value lost productivity. Gross wage rates plus the costs associated with recruiting and training replacement workers can be used to value long-term absences from work. Exclude the lost time from paid work due to premature death that occurs beyond the friction period.

g) There are several acceptable methods for valuing lost time by patients and informal caregivers, but there is no preferred alternative.

h) Describe the methods, data, and assumptions used to measure and value lost time by patients and informal caregivers. Present quantities and unit costs of lost time separately before combining them. Conduct a sensitivity analysis using alternative methods and assumptions.

#### **Discounting**

- In the Reference Case, discount the costs and health outcomes that occur beyond one year to present values at the (real) rate of 5% per year.
- Conduct sensitivity analyses using (real) discount rates of 0% and 3%.
- When different discount rates are used from those recommended, present results in a sensitivity analysis, and justify the relevance.

#### **Variability and Uncertainty**

- Handling variability

a) Variability can be attributed to diverse clinical practice patterns in different geographical areas or settings, or to inherent variability in the patient population (i.e., patient heterogeneity). Handle variability in practice patterns through further analysis.

b) Deal with variability in the population by stratifying the target population into smaller, more homogeneous groups. Identify the basis for the stratification. Define subgroups preferably at the planning stage, because post-hoc analysis may be unacceptable, unless a

*strong justification is given.*

- *Handling uncertainty*

*a) Uncertainty can be attributed to two types of model inputs: parameter and model (structure, methods, and assumptions). Deal with both types of uncertainty systematically and thoroughly, and fully assess the impact on the results and conclusions.*

*b) In the Reference Case, at a minimum, conduct a deterministic sensitivity analysis (DSA). Perform the analysis for all model inputs to determine the impact on the results. Justify the omission of any model input from the sensitivity analysis. Identify and fully assess the key model inputs contributing most to uncertainty.*

*The choice of analysis should involve more than a one-way sensitivity analysis. Perform multi-way sensitivity analysis, threshold analysis, and analysis of extremes (e.g., best and worst case scenarios) for key model inputs. Assess the full range of plausible values for each parameter, and plausible alternatives for each assumption. State and justify the ranges of values selected, and the alternative assumptions used.*

*Alternative assumptions should take into account the variability between the jurisdictions or settings of the target audience.*

*c) A probabilistic sensitivity analysis (PSA) of parameter values that can be defined probabilistically is encouraged to more appropriately assess parameter uncertainty. The analysis should take the form of a Monte Carlo simulation. State and justify any assumptions regarding the range of values for key parameters, the form of probability distributions, and the number of Monte Carlo iterations.*

*Model uncertainty should be assessed through a DSA and model validation methods, with separate (probabilistic) results shown for each alternative analysis. Parameter uncertainty can be assessed using a DSA and a PSA.*

*d) Where a PSA has been used, quantify the contribution of each parameter to decision uncertainty. Value-of-information methods can be used to indicate where the collection of additional information may be helpful for making decisions.*

- *Address generalizability in the design of the evaluation and in the interpretation of its findings. There are three aspects of generalizability to be addressed: distinction between efficacy and effectiveness of the intervention handling of data on costs and preferences (utilities) that are derived from another setting handling of data from*

<p><i>trials involving several countries, including that of the decision maker.</i></p>
<ul style="list-style-type: none"> <li>• <i>Justify any data derived from outside Canada and verify for the Canadian setting. If data are adjusted for the Canadian setting, describe and justify the methods used. Report, analyze, and justify the use of cost data from multinational trials.</i></li> </ul>
<ul style="list-style-type: none"> <li>• <i>Where there is local variation in clinical practice or other model parameters, the Reference Case can be performed at a national (or aggregate) level using the most widespread or best available practice or data. A sensitivity analysis can be performed using regional or local practice and data. If a DSA is used, test the key model parameters throughout the range of values that apply in the jurisdictions representing the target audience.</i></li> </ul>
<ul style="list-style-type: none"> <li>• <i>Present the results in a disaggregated manner to facilitate the interpretation of results for different settings. Report the quantities of resources consumed and unit costs separately.</i></li> </ul>
<ul style="list-style-type: none"> <li>• <i>State the extent to which the findings of the evaluation can be generalized to the jurisdiction(s) or setting(s) of the target audience, including any study limitations that affect the generalizability of the evaluation findings.</i></li> </ul>
<p style="text-align: center;"><b>Reporting</b></p>
<ul style="list-style-type: none"> <li>• <i>Report the evaluation in a transparent and detailed manner. Provide enough information to enable the audience to critically evaluate the validity of the analysis. Use a well-structured report format (Appendix 3).</i></li> </ul>
<ul style="list-style-type: none"> <li>• <i>Include a summary and a conclusion of the evaluation that are written in nontechnical language and that are accessible to the target audience.</i></li> </ul>
<ul style="list-style-type: none"> <li>• <i>Present the analysis in disaggregated detail first, showing total, undiscounted costs and outcomes separately for the intervention and each comparator.</i></li> <li>• <i>Introduce aggregations, incremental results, and value judgments as late as possible.</i></li> </ul>
<ul style="list-style-type: none"> <li>• <i>Report final results as incremental cost-effectiveness ratios (ICERs), based on incremental differences of expected costs and expected outcomes of the alternatives. Follow standard decision rules for estimating ICERs, including the exclusion of dominated alternatives. To aid understanding, analysts are encouraged to present the results of the analysis in graphical or visual form, in addition to tabular presentation.</i></li> </ul>

<ul style="list-style-type: none"> <li>• Describe funding and reporting relationships of the evaluation, and disclose any conflicts of interest</li> </ul>
<ul style="list-style-type: none"> <li>• Make documents demonstrating quality assurance in the conduct of the evaluation available to decision makers. If requested, make a copy of the model available to decision makers for review.</li> </ul>
<b>Study Question</b>
<ul style="list-style-type: none"> <li>• State the study question to be addressed by the evaluation. The question should be well defined, stated in an answerable form, and relevant to the decision facing the target audience. Relevant and related secondary questions should be included (e.g., the impact of the intervention on subgroups).</li> </ul>
<ul style="list-style-type: none"> <li>• Define the patients or population, intervention, and comparators relevant to the study question. The primary perspective of the study may also be stated in the question.</li> </ul>
<ul style="list-style-type: none"> <li>• Identify the target audience for the study. Secondary audiences may also be listed.</li> </ul>
<b>Equity</b>
<ul style="list-style-type: none"> <li>• State the implicit and explicit equity assumptions made in the evaluation. If possible, state the implications of the assumptions on the results of the analysis.</li> </ul>
<ul style="list-style-type: none"> <li>• Identify the equity-relevant characteristics of the subgroups that may benefit from, or be adversely affected by, the intervention. Population characteristics such as age, sex, ethnicity, geographical area, socioeconomic group, or health status, may be relevant for equity purposes.</li> </ul>
<ul style="list-style-type: none"> <li>• Analysts are encouraged to provide information on the distributional impact (e.g., benefits, harms, and costs) and cost-effectiveness of the intervention for those subgroups predetermined to be relevant for equity purposes.</li> </ul>
<ul style="list-style-type: none"> <li>• Use equal equity weights for all outcomes in the Reference Case. Present the analysis in a disaggregated and transparent manner to allow decision makers to assess the distributional impacts and the trade-off between equity and the efficient allocation of resources.</li> </ul>

\* Taken directly from Guidelines for the Economic Evaluation of Health Technologies: Canada

## **Appendix C - Literature Review Search Terms, Strategy and Flow Chart**

### Database Search terms

In Medline, MeSH terms included: “economics, pharmaceuticals,” OR text words included: “pharmacoeconomics”, “pharmacoeconomic submission” OR keyword: “dossier” AND exploded MeSH terms included: “Pharmacopoeias as Topics”, “Formularies as Topic”, “Formularies as Topic/Economics”, “Insurance, Health, Reimbursement/Economics” OR keyword: “formulary listing” OR text word: “formulary listing” AND keyword: “quality” were used.

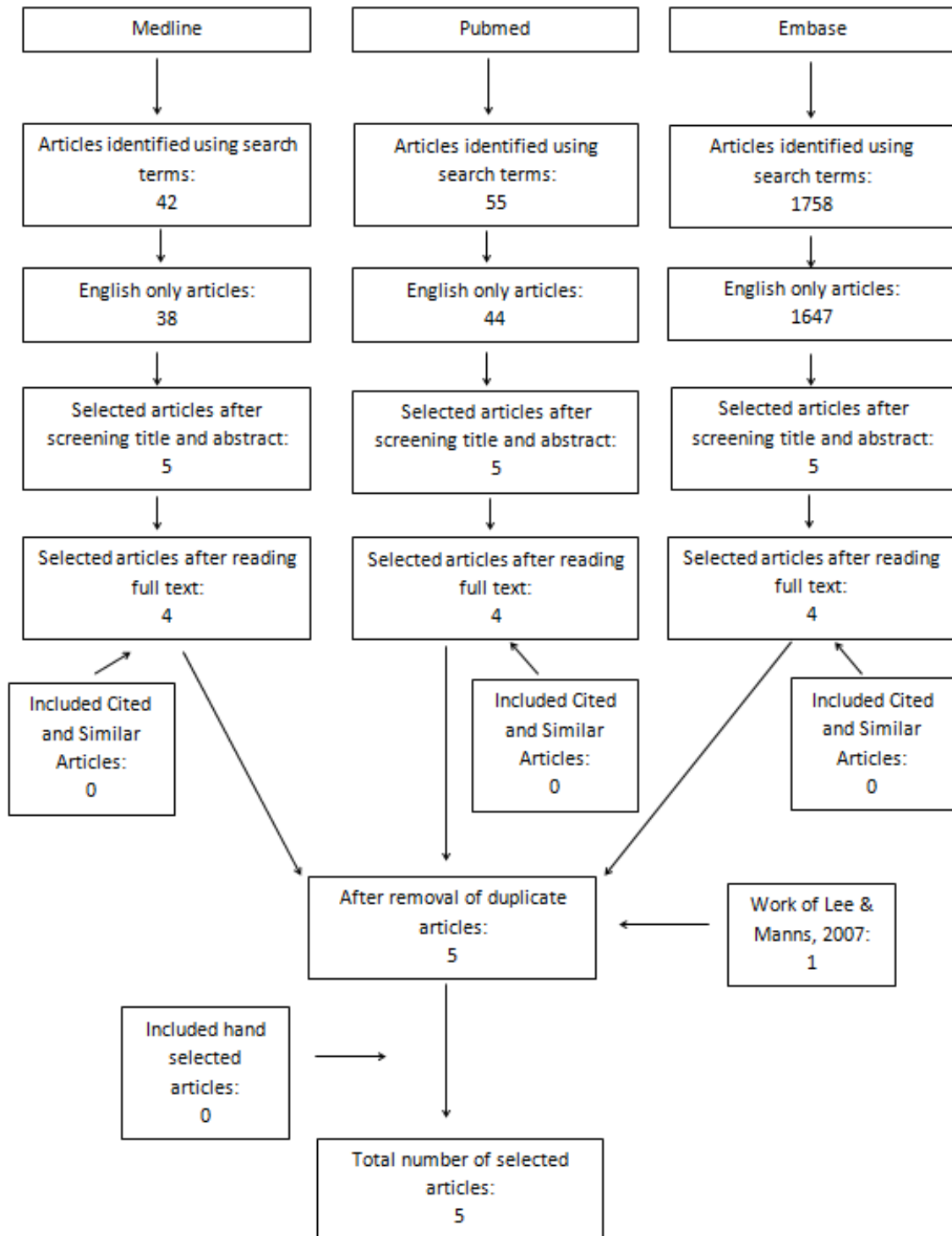
In Pubmed, search term items were the following - MeSH terms included: “economics, pharmaceutical,” ““pharmacoeconomics’ + ‘submission (in all fields)’” OR text word: “dossier” AND MeSH terms included: “Pharmacopoeias as Topics”, “Formularies as Topic”, “Insurance, Health, Reimbursement/Economics” OR text word: “formulary listing,” AND text word: “quality”.

In Embase, exploded MeSH term included: “pharmacoeconomics,” OR keyword: “dossier,” OR text word: “pharmacoeconomic submission” AND MeSH term included: “drug formulary,” OR exploded MeSH terms included: “medical literature,” “publication,” reimbursement OR keyword: “formulary listing” AND keyword: “quality” were applied.

### Search Strategy

Listed databases were consulted and search terms listed above were included. Studies were limited to English only and were not limited to Canadian studies. Articles were identified and selected by the researcher through reading of the title and abstract of each article. Articles similar to selected articles as well as articles which cited selected articles were screened using their title and abstract to determine its inclusion. Journals from which selected articles originated from were consulted for Canadian and international English articles (published from conception to present) which examined the quality of pharmacoeconomic evaluations for formulary listing; articles worthy of inclusion were hand selected by me by reading of title and abstract of each identified article. A pdf copy of each selected articles was obtained and I read the full text of each selected article to determine its inclusion. Duplicates of selected article were removed.

## Search Strategy Flow Chart



## Appendix D - Existing Instrument (Lee and Manns 2007)

### General information

1. Type of drug:
  - First treatment for disease/disorder
  - Not 1<sup>st</sup> in class but first drug in class that could be listed for disease/disorder
  - Other drugs in class currently listed, only placebo controlled trials available
  - Other drugs in class currently listed, head to head trials showing superior safety and/or efficacy
  - Other drugs in class currently listed, head to head trials showing similar safety and efficacy
2. Drug intended to increase:
  - Quality of life
  - Length of life (survival)
  - Both
  - Other
3. Clinical trials (pivotal) were considered:
  - Positive (clear clinical benefits, safety benefits)
  - Neutral (similar in safety and efficacy)
  - Negative (worse clinical benefits and/or safety)

### I Quality of PE submissions

1. Comparator(s) used represents:
  - Usual care or existing practice
  - Drug in similar class, but not currently funded
  - Previous standard of care
  - Best supportive care (probably the better term), or no treatment (first in class)
  - Comparator not appropriate
2. Assumptions in the model:

- Are used for key variables (e.g., efficacy, utility values, unit costs) for which data is available (i.e. inappropriate since it would have been more appropriate to use this data)
- Are used for some key variables for which no data is available (i.e. potentially appropriate)
- Are used for some variables but have provided based on some information (ie. reasonable)
- Have not been used

2(a). Questionable assumptions were used in the economic evaluation for:

- Efficacy
- Costs
- Resource use
- Quality of life
- Other

3. Time horizon used is:

- Appropriate (sufficiently long to capture all costs/benefits)
- Too short – to capture all relevant downstream costs and benefits
- Too long – given available clinical information

4. Study population modelled is:

- Same as Health Canada indication
- Specific group for which manufacturer is seeking reimbursement
- Different from indication
- Not the specific group for which the manufacturer is seeking reimbursement

5. Clinical data was taken from:

- RCTs (head to head)
- RCTs (placebo controlled)
- Open label/cohort studies
- Expert opinion
- Other

6. Clinical data used in the model was:

- Supported by the CDR clinical review

- Partially supported by the CDR clinical review
  - Used clinical information not included in the CDR clinical review
  - Not supported by the CDR clinical review
7. Clinical data used in the model was based on:
- Study(ies) that enrolled the same group for which the manufacturer is seeking reimbursement
  - Study(ies) that enrolled patients not in the same group for which the manufacturer is seeking reimbursement
  - Not based on clinical studies
8. Clinical inputs to the economic model are:
- Final outcomes - based on trial
  - Final outcomes – extrapolated from validated surrogate outcomes
  - Final outcomes – extrapolated from unvalidated surrogate outcomes
  - Intermediate outcomes
  - Other
9. Was the impact of the treatment on QOL considered in the analysis (i.e. through use of a QALY or similar rubric):
- Not included but relevant for disease/disorder
  - Included, but not based on good quality information
  - Included and relevant for disease/disorder
  - Not relevant for inclusion
10. Applicability of analysis to Canadian setting:
- Based on Canadian trial and costs
  - Based on international trials and Canadian costs & resource use
  - Based on international trials & resource use and Canadian costs
  - Based on no Canadian data (includes cases where only Canadian drug costs used)
11. Results are presented:
- In both an aggregate and disaggregate manner
  - In only as an aggregate
  - Only disaggregately

- Not reported
12. Computational errors:
- Economic evaluation contains computational errors, CDR unable to correct
  - Economic evaluation contains computational errors, CDR able to correct
  - Economic evaluation contains no computation errors
13. Methods are transparent:
- Methods for the performance of the economic evaluation were generally clear and transparent
  - When the model was provided, it was generally clear and transparent (i.e. replication would be possible) (without requiring access to model)
  - When the model was provided, the model was only comprehensible after examination of model
  - When the model was provided, it was still not comprehensible after examination of model
  - Model not provided but model was comprehensible
  - Model not provided, unable to clearly understand model
14. Sensitivity analysis conducted was:
- None conducted
  - Insufficient - Some variables, only one-way analyses
  - Partial sufficient – key variables, one way analysis
  - Sufficient – all variables for which there is uncertainty, one-way and multi-way analyses, Monte Carlo simulation, where relevant
15. If a model was used, validation was conducted:
- Face validity
  - Predictive validity
  - External validity
  - All three (above)
  - None
  - Not applicable – did not model
16. Was discounting conducted in the analysis:
- Costs and benefits were discounted at 5% (as per CADTH guidelines)

- Costs and benefits were discounted at the same rate, other than 5%
- Costs and benefits were discounted at different rates
- No discounting was conducted, but relevant
- Not applicable, time horizon less than 1 year

## **II Use of PE information by CDEC**

### 1. Used in recommendations

- Not considered in RfR
- Considered but not included in RfR
- Considered and included limitations in RfR
- Considered and included results of analyses in RfR
- Used as a basis for RfR

### 2. CDEC minutes

- CDEC did not consider the results from the manufacturer's submission valid and therefore did not consider the results in the decision making process
- CDEC considered results from manuf's submission to be partially valid, but did not factor into rec
- CDEC considered results from manuf's submission to be partially valid, and the results were one of the factors that went into the recommendation
- CDEC based rec on manufacturer's analysis

### 3. Presenters' reports

- Presenters did not consider the results from manufacturer's submission valid
- Presenter's considered results from manuf's submission to be partially valid, but did not factor into rec
- Presenter's considered results from manuf's submission to be partially valid, and the results were one of the factors that went into the recommendation
- Presenter's based rec on manufacturer's analysis

\* Taken from Lee K, Manns B. Better modeling techniques, better models? Medical Decision Making 2007; 27 : e35.

## Appendix E - Initial Revised Instrument

### Submission Information [Fill in the following information]

1. Drug Name: \_\_\_\_\_
2. Date of Submission: \_\_\_\_\_
3. Date of Final Submission: \_\_\_\_\_
4. Type of submission:
  - Original by manufacturer
  - Drug Plan submission
  - Resubmission
  - Reduced pricing during embargo
5. If resubmission, date of the original submission: \_\_\_\_\_
6. Listing criteria sought: \_\_\_\_\_
7. Manufacturer: \_\_\_\_\_
8. Who conducted the economic submission: \_\_\_\_\_

### II Economic Evaluation Details [Fill in the following information]

1. Perception: \_\_\_\_\_
2. Time horizon: \_\_\_\_\_
3. Stated economic evaluation: \_\_\_\_\_
4. Actual economic evaluation: \_\_\_\_\_
5. Comparators: \_\_\_\_\_
6. Outcomes: \_\_\_\_\_

### III General Information

1. Type of drug:
  - First treatment for disease/disorder
  - Not 1<sup>st</sup> in class but first drug in class that could be listed for disease/disorder
  - Other drugs in class currently listed, only placebo controlled trials available
  - Other drugs in class currently listed, head to head trials showing superior safety and/or efficacy

Other drugs in class currently listed, head to head trials showing similar safety and efficacy

2. Drug intended to increase:

- Quality of life
- Length of life (survival)
- Convenience
- Other

3. Clinical trials (pivotal) were considered:

- Positive (clear clinical benefits, safety benefits)
- Neutral (similar in safety and efficacy)
- Negative (worse clinical benefits and/or safety)

4. Analytical technique used:

- Cost-minimization analysis
- Cost-effectiveness analysis
- Cost-utility analysis
- Cost-benefit analysis
- Cost-consequence analysis

5. Type of model was used:

- Decision tree
- Markov Model
- Hybrid
- Other

#### **IV Quality of PE submissions**

1. Comparator(s) used represents:

- Usual care or existing practice
- Drug in similar class, but not currently funded

- Previous standard of care
- Best supportive care (probably the better term), or no treatment (first in class)

2. Within the CDR PE Review was the comparator considered appropriate?

- Yes
- No

3. Within the CDR PE review for which of the following variables were assumptions identified?

- Efficacy
- Costs
- Resource use
- Quality of life
- Natural History of Disease
- Other

4. Within the CDR PE review for which of the following variables were assumptions which were considered inappropriate?

- Efficacy
- Costs
- Resource use
- Quality of life
- Natural History of Disease
- Other

5. Within the CDR PE review, the time horizon used was considered:

- Appropriate (sufficiently long to capture all costs/benefits)
- Too short – to capture all relevant downstream costs and benefits
- Too long – given available clinical information

6. Study population modelled is:

- Exactly the same as Health Canada indication
- A specified sub group of the population for the HC indication
- Different from indication

7. Within the CDR PE Review was the population modeled considered the same as the population for whom the manufacturer was seeking reimbursement:

- Yes
- No

8. Clinical data was taken from:

- RCTs (head to head)
- RCTs (placebo controlled)
- Open label/cohort studies
- Expert opinion
- Other

9. Within the CDR PE review were there concerns that the clinical data used in the model was not supported by the CDR clinical review:

- Yes
- No

10. Clinical inputs to the economic model are:

- Final outcomes - based on trial
- Final outcomes – extrapolated from validated surrogate outcomes
- Final outcomes – extrapolated from unvalidated surrogate outcomes
- Intermediate outcomes
- Other

11. Was the impact of the treatment on QOL considered in the analysis (i.e. through use of a QALY or similar rubric):

- Not included but relevant for disease/disorder

- Included, but not based on good quality information
- Included and relevant for disease/disorder
- Not relevant for inclusion

12. Applicability of analysis to Canadian setting:

- Based on Canadian trial and costs
- Based on international trials and Canadian costs & resource use
- Based on international trials & resource use and Canadian costs
- Based on no Canadian data (includes cases where only Canadian drug costs used)

13. Costs, outcomes and cost effectiveness ratios are presented:

- In both an aggregate and disaggregate manner
- In only an aggregate form (e.g. cost effectiveness ratio)
- Only in a disaggregate form (costs and utilities but no ratios)
- Not reported

14. Computational errors:

- Economic evaluation contains computational errors, CDR unable to correct
- Economic evaluation contains computational errors, CDR able to correct
- Economic evaluation contains no computation errors

15. Within the CDR PE Review are the methods and analysis described as clear and transparent?

- Yes
- No
- Somewhat

16. If not yes, were the concerns about clarity and transparency from the:

- Written report
- Economic model

Both

17. What form of model validation was reported?

- Face validity
- Predictive validity
- External validity
- All three (above)
- None
- Not applicable – did not model

18. Was discounting conducted in the analysis:

- Costs and benefits were discounted at 5% (as per CADTH guidelines)
- Costs and benefits were discounted at the same rate, other than 5%
- Costs and benefits were discounted at different rates
- No discounting was conducted, but relevant
- Not applicable, time horizon less than 1 year

## **V Sensitivity Analysis**

1. Sensitivity analysis conducted was:

- None conducted
- Insufficient - Some variables, only one-way analyses
- Partial sufficient – key variables, one way analysis
- Sufficient – all variables for which there is uncertainty, one-way and multi-way analyses, Monte Carlo simulation, where relevant

2. If conducted, what type(s) of sensitivity analysis/es was/were conducted:

- Deterministic sensitivity analysis
- Probabilistic sensitivity analysis
- Both

3. Which deterministic sensitivity analysis/es was/were conducted to deal with uncertainty (select all that apply):

- One-way
- Multi-way
- Threshold
- Extreme values
- Other

4. Did the CDR PE review include a reanalysis based on alternative assumptions or data inputs?

- Yes
- No

5. If additional reanalysis were conducted by CDR, were the results significantly different from the manufacturers?

- Yes
- No

6. If additional reanalysis were conducted, did it include additional sensitivity analyses not included by the manufacturer in the original submission?

- Yes
- No

7. If results were significantly different from the manufacturer, what were the major drivers of the different results?

- Efficacy
- Costs
- Resource use
- Quality of life
- Natural History of Disease
- Other

8. If PSA was conducted, were all relevant parameters considered uncertain?

- Yes
- No

9. If transition probabilities are assumed uncertain, how was this handled? (Select all that apply)

- Beta distribution
- Normal distribution
- Dirichlet distribution
- Triangular distribution
- Uniform distribution
- Other

10. If utility values were assumed uncertain, how was this handled? (Select all that apply)

- Beta distribution
- Gamma distribution
- Normal distribution
- Log normal distribution
- Triangular distribution
- Uniform distribution

11. If resource use and cost were assumed uncertain, how was this handled? (Select all that apply)

- Gamma distribution
- Normal distribution
- Log normal distribution
- Triangular distribution
- Uniform distribution

12. If relative treatment effects were assumed uncertain, how was this handled?

- Normal distribution
- Log normal distribution
- Triangular distribution
- Uniform distribution
- Other

13. If absolute treatment effect were assumed uncertain, how was this handled?

- Normal distribution
- Log normal distribution
- Triangular distribution
- Uniform distribution
- Other

14. Within the CDR PE Review process, were expected values for cost-outcomes and cost-effectiveness calculated properly?

- Yes
- No

15. How were the results of the probabilistic sensitivity analysis presented?

- Confidence intervals or credible intervals
- Scatter plots
- Cost-effective acceptability curves
- None of the above

## **VI Indirect Treatment Comparison**

1. Did the analysis include indirect treatment comparison?

- Yes
- No

2. What type of indirect comparison was conducted?

- Naïve indirect comparison
- Informal indirect comparison
- Adjusted indirect comparison
- Network meta-analysis

3. Were the methods for study identification clearly presented?

- Yes
- No

4. Were all relevant studies included?

- Yes
- No

5. Were the methods of analysis clearly presented?

- Yes
- No

6. Was information used in the analysis sufficient to replicate?

- Yes
- No

7. Did the analysis include meta-regression?

- Yes
- No

8. Did the analysis consider the sensitivity of results to the exclusion and inclusion of specific studies?

- Yes
- No

## **VII Use of PE information by CDEC**

1. Was PE information considered in the CDEC Reason for Recommendation (RfR)?

Yes

No

2. If yes, what type of PE information was included in RfR? [Select all that applies]

Price

Cost-effectiveness

3. Type of listing

Do not list

List

List with signal

## Appendix F - Research Instrument

### I Submission Information

1. Record Identification#: \_\_\_\_\_
2. Brand Name: \_\_\_\_\_
3. Generic Name: \_\_\_\_\_
4. Date of Submission: \_\_\_\_\_
5. Date Recommendation Issued: \_\_\_\_\_
6. Type of submission:
  - Original by manufacturer (Skip I, #7)
  - Drug Plan submission (Skip I, #7)
  - Resubmission
  - Reduced pricing during embargo (Skip I, #7)
7. If resubmission, date of the original submission: \_\_\_\_\_
8. Listing criteria sought: \_\_\_\_\_
9. Manufacturer: \_\_\_\_\_
10. Who conducted the economic submission: \_\_\_\_\_

### II Economic Evaluation Details

1. Perspective:  Government  Drug Plan  Societal
2. Time horizon: \_\_\_\_\_
3. Stated economic evaluation: \_\_\_\_\_
4. Actual economic evaluation: \_\_\_\_\_
5. Comparators: \_\_\_\_\_  
\_\_\_\_\_
6. Outcome Measures: \_\_\_\_\_

### III General Information

1. Type of drug:
  - First treatment for disease/disorder
  - Not first type but first drug in class that could be listed for disease/disorder
  - Other drugs in class currently listed, only placebo controlled trials available

- Other drugs in class currently listed, head to head trials showing superior, inferior or mixed safety and/or efficacy
- Other drugs in class currently listed, head to head trials showing similar safety and efficacy

2. Drug is intended to increase: (Select all that apply)

- Quality of life
- Length of life (survival)
- Convenience
- Other

3. Clinical trials (pivotal) were considered:

- Positive (clear clinical benefits and /or safety benefits)
- Neutral (similar in safety and efficacy)
- Negative (worse clinical benefits and/or safety)
- Mixed (clinical benefits but worse safety)
- Insufficient information to assess drug

4. Analytical technique used: (Select all that apply)

- Cost-minimization analysis (Proceed to Questions 5 and Section VI & VII)
- Cost-effectiveness analysis (Skip II#5)
- Cost-utility analysis (Skip II#5)
- Cost-benefit analysis (Skip II#5)
- Informal economic analysis (i.e.: Cost-consequence analysis) (Proceed to Section VII)
- Manufacturer Submitted a Cost-effectiveness or cost-utility analysis, however CDR analysed the submission using a Cost-minimization analysis (Proceed to Section VI & VII)

5. According to the CDR PE Review, was a cost-minimization analysis the appropriate form of analysis:

- Yes
- No
- Unclear

6. Type of economic model was used: (Select all that apply)

- Decision tree
- Markov model
- Hybrid
- Other

#### **IV Quality of PE submissions**

1. Comparator(s) used represents: (Select all that apply)

- Usual care or existing practice
- Drug in similar class, but not currently funded
- Previous standard of care
- Best supportive care or no treatment (placebo or first in class)

2. Within the CDR PE Review, was the comparator considered appropriate?

- Yes
- No

3. Within the CDR PE Review was the choice of economic analysis considered appropriate?

- Yes
- No

4. Within the CDR PE Review, for which of the following variables were assumptions identified? (Select all that apply)

- Efficacy/ Effectiveness
- Safety
- Costs
- Resource use
- Quality of life

- Natural History of Disease
- Other

5. Within the CDR PE Review, which of the following variables were considered limitations with methodology and/or assumptions were considered inappropriate?

(Select all that apply)

- Efficacy/ Effectiveness
- Safety
- Costs
- Resource use
- Quality of life
- Natural History of Disease
- Other
- None – no mention of inappropriate parameter assumptions

6. Within the CDR PE Review, the time horizon used was considered:

- Appropriate (sufficiently long to capture all costs/benefits)
- Too short – to capture all relevant downstream costs and benefits
- Too long – given available clinical information

7. Study population modelled is:

- Exactly the same as Health Canada indication
- A specified sub group of the population for the HC indication
- Different from indication

8. Within the CDR PE Review, was the population modeled considered the same as the population for whom the manufacturer was seeking reimbursement:

- Yes
- No

9. Efficacy data used in the economic evaluation was taken from: (Select all that apply)

- RCTs (head to head)
- RCTs (placebo controlled)
- Open label/cohort studies/ RCT open label
- Expert opinion
- Indirect comparison
- Other

10. Safety data used in the economic evaluation was taken from: (Select all that apply)

- RCTs (head to head)
- RCTs (placebo controlled)
- Open label/cohort studies/ RCT open label
- Expert opinion
- Indirect comparison
- Other
- Not included

11. Within the CDR PE Review, were there concerns that the clinical data used in the model was not supported by the CDR clinical review:

- Yes
- No

12. Clinical effectiveness input within the economic model are based on:

- Final outcomes
- Intermediate outcomes
- Surrogate outcomes
- Other

13. Was the impact of the treatment on quality of life considered in the analysis (i.e. through use of a QALY or similar rubric):

- Not included but relevant for disease/disorder
- Included, but not based on good quality information
- Included and relevant for disease/disorder
- Not relevant for inclusion

14. Applicability of analysis to Canadian setting:

- PE information was based on Canadian trial and costs
- PE information was based on international trials and Canadian costs & resource use
- PE information was based on Canadian and international trials and Canadian costs & resource use
- PE information was based on only Canadian costs

15. Costs are presented:

- In both an aggregate and disaggregate manner
- In only an aggregate form
- Not reported

16. Computational errors:

- Economic evaluation contains computational errors, CDR unable to correct
- Economic evaluation contains computational errors, CDR able to correct
- Economic evaluation contains no computation errors

17. Within the CDR PE Review, are the methods and analysis described as clear and transparent?

- Yes (Skip IV#18)
- No

18. If not yes, were the concerns about clarity and transparency from the:

- Written report
- Economic model

Both

19. What form of model validation was reported?

- Face validity
- Predictive & External validity
- All of the above
- None

20. Was discounting conducted in the analysis:

- Costs and benefits were discounted at 5% (as per CADTH guidelines)
- Costs and benefits were discounted at the same rate, other than 5%
- Costs and benefits were discounted at different rates
- No discounting was conducted, but relevant
- Not applicable, time horizon  $\leq$  1 year

21. Within the CDR PE Review, were expected values for cost-outcomes and cost-effectiveness calculated properly?

- Yes
- No

22. Within the CDR PE Review, sensitivity analysis was conducted on:

- Some variables
- Key variables
- All variables
- None conducted (Skip V)

## **V Sensitivity Analysis**

1. If conducted, what type of sensitivity analysis was conducted:

- Deterministic sensitivity analysis (DSA) [if no PSA, skip V, #3-9]
- Probabilistic sensitivity analysis (PSA) [if no DSA skip V, #2]
- Both

2. Which deterministic sensitivity analysis/es was/were conducted to deal with uncertainty (Select all that apply):
- One-way
  - Multi-way
  - Threshold
  - Extreme values
  - Other
3. If PSA was conducted, were all relevant parameters considered uncertain?
- Yes
  - No
4. If transition probabilities are assumed uncertain, how was this handled? (Select all that apply)
- Beta distribution
  - Normal distribution
  - Dirichlet distribution
  - Triangular distribution
  - Uniform distribution
  - Other
  - None
  - Did not provide sufficient information
5. If utility values were assumed uncertain, how was this handled? (Select all that apply)
- Beta distribution
  - Gamma distribution
  - Normal distribution
  - Log normal distribution
  - Triangular distribution

- Uniform distribution
- None
- Did not provide sufficient information

6. If resource use and cost were assumed uncertain, how was this handled? (Select all that apply)

- Gamma distribution
- Normal distribution
- Log normal distribution
- Triangular distribution
- Uniform distribution
- None
- Other
- Discrete value
- Did not provide sufficient information

7. If relative/absolute treatment effects were assumed uncertain, how was this handled? (Select all that apply)

- Normal distribution
- Log normal distribution
- Triangular distribution
- Uniform distribution
- Beta Distribution
- Other
- None
- Did not provide sufficient information

8. How were the results of the probabilistic sensitivity analysis presented? (Select all that apply)

- Confidence intervals or credible intervals
- Scatter plots

- Cost-effective acceptability curves
- None of the above

9. Did the CDR PE Review include a reanalysis based on alternative assumptions or data inputs?

- Yes
- No (Skip V#10-13)

10. If additional reanalysis were conducted by CDR, were the results significantly different (change to dominated, change to dominant, change from under 80 000 to over 100 000, change from over 100 000 to under 80 000, change from over 60 000 to under 40 000, change from under 40 000 to over 60 000) from the manufacturers?

- Yes
- No (Skip V#12&13)

11. If additional reanalysis were conducted, what type(s) of additional sensitivity analysis/es was/were conducted by CDR? (Select all that apply)

- One-way
- Multi-way
- Threshold
- Extreme values
- Monte Carlo Simulation
- Other

12. If results were significantly different from the manufacturer, what was/were the major driver(s) of the different results? (Select all that apply)

- Efficacy (Skip V#14)
- Safety (Skip V#14)
- Costs (Skip V#14)
- Resource use (Skip V#14)

- Quality of life (Skip V#14)
- Natural History of Disease (Skip V#14)
- Time horizon (Proceed to V#14)
- Choice of comparator (Skip V#14)
- Other (Skip V#14)

13. If time horizon was considered a major driver, were the concerns due to :

- Duration of treatment effect
- Natural history of disease
- Unclear

## **VI Indirect Treatment Comparison**

1. Did the analysis include indirect treatment comparison?

- Yes
- No (Skip VI#2-8)

2. What type of indirect comparison was conducted?

- Naïve indirect comparison (Proceed only to VI#4)
- Informal indirect comparison
- Adjusted indirect comparison
- Network meta-analysis

3. Were the methods for study identification clearly presented?

- Yes
- No

4. Were all relevant studies included?

- Yes
- No – as mentioned in CDR report or RCT used in CDR report not included
- Unclear

5. Were the methods of analysis clearly presented?

Yes

No

6. Was information used in the analysis sufficient to replicate?

Yes

No

7. Did the analysis include meta-regression?

Yes

No

8. Did the analysis consider the sensitivity of results to the exclusion and inclusion of specific studies?

Yes

No

**VII Use of Pharmacoeconomic (PE) Information by Canadian Drug Expert Committee (CDEC)/ Canadian Expert Drug Advisory Committee (CEDAC)**

1. Was PE information considered in the CEDAC/CDEC Reasons for Recommendation (RfR)?

Yes

No (Skip VII#2)

2. If yes, what type of PE information was included in RfR? [Select all that applies]

Price/ Cost

Cost-effectiveness

3. Type of listing:

Do not list

List

List with signal

4. Recommendation by:

CEDAC

CDEC

## Appendix G - Guideline Statements Linked with Research Instrument

<b>2.2 Types of Evaluations</b>	
<p>❖ <b>In order for a pharmacoeconomic submission to be considered adherent to guidelines in terms of type of evaluations, the pharmacoeconomic submission must respond “Yes” to guideline statement to 2.2.1</b></p>	
<p><i>2.2.1 State and justify the type(s) of economic evaluation chosen. Select the appropriate type of evaluation based on the nature of the research question, the condition of interest, and the availability of data on outcomes.</i></p>	<p>If 4.3 answer is “Yes”, then, pharmacoeconomic submission adheres to guidelines</p> <p>4.3) Within the CDR PE Review was the choice of economic analysis considered appropriate?</p> <p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p>
<b>2.3 Target Population</b>	
<p>❖ <b>In order for a pharmacoeconomic submission to be considered adherent to guidelines in terms of target population, the pharmacoeconomic submission must respond “Exactly the same as Health Canada indication” OR “A specified sub group of the population for the HC indication” AND “Yes” in guideline statements 2.3.1 and 2.3.2</b></p>	
<p><i>2.3.1 Specify the target population(s) for the intervention and its expected use.</i></p>	<p>If 4.7 answer is “Exactly the same as Health Canada indication” OR “A specified sub group of the population for the HC indication” then pharmacoeconomic submission adheres to guidelines</p> <p>4.7) Study population modelled is:</p> <p><input type="checkbox"/> Exactly the same as Health Canada indication</p> <p><input type="checkbox"/> A specified sub group of the population</p>

	<p>for the HC indication</p> <p><input type="checkbox"/> Different from indication</p>
<p>2.3.2 <i>Perform the analysis for the entire target population that is specified in the study question. This may include the population representing the majority or all of its expected use. The efficacy-effectiveness data used in the analysis should be relevant to the target population in the analysis.</i></p>	<p>If 4.8 answer is “Yes,” then, pharmacoeconomic submission adheres to guidelines</p> <p>4.8) Within the CDR PE Review, was the population modeled considered the same as the population for whom the manufacturer was seeking reimbursement:</p> <p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p>
<p><b>2.4 Comparators</b></p>	
<p><b>❖ In order for a pharmacoeconomic submission to be considered adherent to guidelines in terms of comparators, the pharmacoeconomic submission must respond “Yes” in guideline statement 2.4.2</b></p>	
<p>2.4.2 <i>In the Reference Case, use “usual care” (i.e., the most common or frequently used care) which the intervention is intended to replace. In some cases, “usual care” may include more than one relevant, widely used alternative for the same indication.</i></p>	<p>If 4.2 answer is “Yes,” then, pharmacoeconomic submission adheres to guidelines</p> <p>4.2) Within the CDR PE Review, was the comparator considered appropriate?</p> <p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p>
<p><b>2.5 Perspective</b></p>	
<p><b>❖ In order for pharmacoeconomic submission to be considered adherent to guidelines in terms of perspective, the pharmacoeconomic submission must respond “Government” in guideline statement 2.5.2</b></p>	
<p>2.5.2 <i>In the Reference Case, use the perspective of the publicly funded health care system.</i></p>	<p>If 2.1 answer is “government”, then, pharmacoeconomic submission adheres to guidelines.</p>

		2.1) Perspective: <input type="checkbox"/> Government <input type="checkbox"/> Drug Plan <input type="checkbox"/> Societal
<b>2.6 Effectiveness</b>		
<p>❖ In order for a pharmacoeconomic submission to be considered adherent to guidelines in terms of effectiveness, the pharmacoeconomic submission must not solely respond “Open Label/Cohort Study/ RCT Open label” OR “expert opinion” AND/OR must not have inappropriate “Efficacy/Effectiveness”</p> <p>❖ In order for a pharmacoeconomic submission to be considered adherent to guidelines in terms of safety the pharmacoeconomic submission must not solely respond “expert opinion” AND/OR inappropriate “Safety” assumptions in guideline statements 2.6.1 and 2.6.5</p>		
<b>Guideline Statement 2.6 Effectiveness</b>	<b>Guideline Statement Effectiveness</b>	<b>Guideline Statement Safety</b>
<p><i>2.6.1 Use a systematic review of the available literature to form the basis for evidence about the efficacy-effectiveness of the intervention. Justify failure to conduct a systematic review. Report the included studies and methods used to conduct the review and analyze or combine data.</i></p>	<p>If 4.9 answer is solely “Open label/cohort studies/ RCT open label” AND/OR “Expert opinion,” then pharmacoeconomic submission DID NOT adhere to guidelines</p> <p>4.9) Efficacy data used in the economic evaluation was taken from: (Select all that apply)</p> <p>✓ RCTs (head to head)</p> <p>✓ RCTs (placebo controlled)</p> <p><input checked="" type="checkbox"/> Open label/cohort studies/ RCT open label</p>	<p>If 4.9 answer is solely “Open label/cohort studies/ RCT open label” AND/OR “Expert opinion,” then pharmacoeconomic submission DID NOT adhere to guidelines</p> <p>4.10) Safety data used in the economic evaluation was taken from: (Select all that apply)</p> <p>✓ RCTs (head to head)</p> <p>✓ RCTs (placebo controlled)</p> <p>✓ Open label/cohort studies/ RCT open label</p> <p><input checked="" type="checkbox"/> Expert opinion</p>

	<input checked="" type="checkbox"/> Expert opinion ✓ Indirect comparison ✓ Other	✓ Indirect comparison ✓ Other ✓ Not Included
2.6.5 <i>Where feasible, include the impact of adverse events associated with the intervention if they are clinically or economically important, and analyze them appropriately. Depending on the nature, frequency, duration, and severity, adverse events may have an impact on patients' adherence, mortality, morbidity, health related quality of life (HRQL) (utilities), or resource use. Value these in a manner that is consistent with the principles outlined in the Economic Guidelines.</i>	If 4.5 answer is "Efficacy/ Effectiveness" then pharmacoeconomic submission DID NOT adhere to guidelines.  4.5) Within the CDR PE Review, which of the following variables were considered limitations with methodology and/or assumptions were considered inappropriate? (Select all that apply) <input checked="" type="checkbox"/> Efficacy/ Effectiveness ✓ Safety ✓ Costs ✓ Resource use ✓ Quality of life ✓ Natural History of Disease ✓ Other ✓ None – no mention of inappropriate parameter assumptions	If 4.5 answer is "Safety," then pharmacoeconomic submission DID NOT adhere to guidelines.  4.5) Within the CDR PE Review, which of the following variables were considered limitations with methodology and/or assumptions were considered inappropriate? (Select all that apply)  ✓ Efficacy/ Effectiveness <input checked="" type="checkbox"/> Safety ✓ Costs ✓ Resource use ✓ Quality of life ✓ Natural History of Disease ✓ Other ✓ None – no mention of inappropriate parameter assumptions
<b>2.7 Time Horizon</b>		

❖ **In order for a pharmacoeconomic submission to be considered adherent to guidelines in terms of time horizon; the pharmacoeconomic submission must respond “Appropriate” in guideline statement 2.7.2.**

<p><i>2.7.2 In the Reference Case, ensure that the time horizon is long enough to capture all relevant differences in future costs and outcomes of the alternatives being analyzed. Apply the same time horizon to costs and outcomes. Consider using a lifetime time horizon, and justify where a shorter time horizon is used.</i></p>	<p>If answer 4.6 is “Appropriate”, then pharmacoeconomic submission adheres to guidelines.</p> <p>4.6) Within the CDR PE Review, the time horizon used was considered:</p> <p><input type="checkbox"/> Appropriate (sufficiently long to capture all costs/benefits)</p> <p><input type="checkbox"/> Too short – to capture all relevant downstream costs and benefits</p> <p><input type="checkbox"/> Too long – given available clinical information</p>
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**2.8 Modelling**

❖ **In order for a pharmacoeconomic submission to be considered adherent to guidelines in terms of modelling, the pharmacoeconomic submission must respond “Face validity” OR “Predictive & External validity” OR “All of the above” AND “Yes” OR “Written Report” in guideline statements 2.8.1 and 2.8.2**

<p><i>2.8.1 Modelling considerations</i></p> <p><i>a) Follow good modelling practices when constructing the model used to conduct the evaluation. Analysts are encouraged to consult good modelling practice guidelines as required.</i></p> <p><i>b) Describe the model, including its scope, structure, and assumptions. Provide justification for assumptions and choices.</i></p> <p><i>c) Use a model structure that is appropriate for addressing the study</i></p>	<p>If 4.19 answer is “None,” then pharmacoeconomic submission DID NOT adhere to guidelines.</p> <p>4.19) What form of model validation was reported?</p> <p><input type="checkbox"/> Face validity</p> <p><input type="checkbox"/> Predictive &amp; External validity</p> <p><input type="checkbox"/> All of the above</p> <p><input type="checkbox"/> None</p>
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<p><i>question. Build the model in such a way to permit updating of results as more data become available.</i></p> <p><i>d) Explain and justify any causal relationships and extrapolation techniques used in the model. Base the extrapolation of data on valid techniques that reflect reasonable scientific evidence, and test through sensitivity analysis.</i></p> <p><i>e) Formally validate the model, and state how this was done.</i></p>	
<p><b>2.8.2 Data considerations</b></p> <p><i>a) Systematically identify, collect, and assess the data used in the model.</i></p> <p><i>b) Report and identify all data sources. Explain and justify all parameter choices and assumptions.</i></p> <p><i>c) Describe the quality (e.g., strength of evidence) of the data used in the model. Be explicit about data limitations and how they were dealt with. Try to quantify the impact of the limitations on the uncertainty of the evaluation results.</i></p> <p><i>d) Gather the best available evidence on key model parameters for which the model results are most sensitive. Justify any failure to gather the best available evidence of such parameters. Use caution when expert opinion is used to establish parameter values. Justify its use; and describe the source of the opinion, the</i></p>	<p>If 4.17 answer is “Yes” or 4.18 answer is “Written Report” then pharmacoeconomic submission adheres to guidelines.</p> <p>4.17) Within the CDR PE Review, are the methods and analysis described as clear and transparent?</p> <p><input type="checkbox"/> Yes (Skip IV#18)</p> <p><input type="checkbox"/> No</p> <p>4.18) If not yes, were the concerns about clarity and transparency from the:</p> <p><input type="checkbox"/> Written report</p> <p><input type="checkbox"/> Economic model</p> <p><input type="checkbox"/> Both</p>

<p><i>method of elicitation, and the results of the exercise. Assess such estimates through a sensitivity analysis.</i></p> <p><i>f) Use appropriate methods to analyze or combine data from different sources. Explain and justify the methods used, and report the results of the analysis. Report limitations in the methods or data used, and where feasible, test through a sensitivity analysis.</i></p> <p><i>g) Incorporate data into the model using appropriate techniques, and explain the methods used. If data are incorporated as point estimates, use mean estimates of parameters in the base case. If estimates are incorporated as probability distributions, state and justify the form of the distributions.</i></p>	
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**2.9 VALUING OUTCOMES**

**❖ In order for a pharmacoeconomic submission to be considered adherent to guidelines in terms of value outcomes, the pharmacoeconomic submission must respond “Included and relevant for disease/disorder” OR “Not relevant for inclusion” AND did not respond “Quality of life” in guideline statements 2.9.1 and 2.9.2**

<p><i>2.9.1 Use appropriate preference-based measures to value meaningful differences between the intervention and alternatives in terms of HRQL.</i></p>	<p>If 4.13 answer is “Not included but relevant for disease/disorder” or “Included, but not based on good quality information” then pharmacoeconomic submission DID NOT adhere to guidelines</p> <p>4.13) Was the impact of the treatment on</p>
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	<p>quality of life considered in the analysis (i.e. through use of a QALY or similar rubric):</p> <p><input type="checkbox"/> Not included but relevant for disease/disorder</p> <p><input type="checkbox"/> Included, but not based on good quality information</p> <p><input type="checkbox"/> Included and relevant for disease/disorder</p> <p><input type="checkbox"/> Not relevant for inclusion</p>
<p>2.9.2 Measure the outcome for a CUA in terms of the QALYs gained. Report changes in the length of life and quality-weight separately, and report the procedure for combining them. State the assumptions and methods used to estimate QALYs. Justify using alternative outcome measures in a CUA.</p>	<p>If 4.5 answer is “Quality of life,” then pharmacoeconomic submission DID NOT adhere to guidelines.</p> <p>4.5) Within the CDR PE Review, which of the following variables were considered limitations with methodology and/or assumptions were considered inappropriate? (Select all that apply)</p> <p><input type="checkbox"/> Efficacy/ Effectiveness</p> <p><input type="checkbox"/> Safety</p> <p><input type="checkbox"/> Costs</p> <p><input type="checkbox"/> Resource use</p> <p><input type="checkbox"/> Quality of life</p> <p><input type="checkbox"/> Natural History of Disease</p> <p><input type="checkbox"/> Other</p> <p><input type="checkbox"/> None – no mention of inappropriate parameter assumptions</p>
<p style="text-align: center;"><b>2.10 Resource Use and Costs</b></p> <p><b>❖ In order for a pharmacoeconomic submission to be considered adherent to guidelines in terms of resource use and costs, the pharmacoeconomic submission must respond “PE information was based on Canadian trial and costs” OR “PE</b></p>	

<p><b>information was based on international trials and Canadian costs &amp; resource use” OR “PE information was based on Canadian and international trials and Canadian costs &amp; resource use” AND not respond “Costs” AND/OR “Resource use” in guideline statements 2.10.1 and 2.10.2.</b></p>	
<p><i>2.10.1 General</i></p> <p><i>a) Systematically identify, measure, and value resources that are relevant to the study perspective(s). Classify resources in categories that are appropriate to the relevant decision maker (e.g., primary care, drug plan, hospitals).</i></p>	<p>If 4.14 answer is “PE information was based on only Canadian costs,” then pharmacoeconomic submission DID NOT adhere to guidelines.</p> <p>4.14) Applicability of analysis to Canadian setting:</p> <p><input type="checkbox"/> PE information was based on Canadian trial and costs</p> <p><input type="checkbox"/> PE information was based on international trials and Canadian costs &amp; resource use</p> <p><input type="checkbox"/> PE information was based on Canadian and international trials and Canadian costs &amp; resource use</p> <p><input type="checkbox"/> PE information was based on only Canadian costs</p>
<p><i>2.10.2 Resource identification</i></p> <p><i>a) Exclude protocol-driven costs taken from clinical trials. Transfer payments should be excluded from the public payer and societal perspectives.</i></p> <p><i>b) Unrelated costs that are incurred during normal life-years should be excluded from the evaluation. Unrelated costs that are incurred during life-years gained from the intervention may be included at the analyst’s discretion in a sensitivity</i></p>	<p>If 4.5 answer is “Costs” AND/OR “Resource use,” then pharmacoeconomic submission DID NOT adhere to guidelines.</p> <p>4.5) Within the CDR PE Review, which of the following variables were considered limitations with methodology and/or assumptions were considered inappropriate? (Select all that apply)</p> <p><input type="checkbox"/> Efficacy/ Effectiveness</p> <p><input type="checkbox"/> Safety</p>

<i>analysis.</i>	<input type="checkbox"/> Costs <input type="checkbox"/> Resource use <input type="checkbox"/> Quality of life <input type="checkbox"/> Natural History of Disease <input type="checkbox"/> Other <input type="checkbox"/> None – no mention of inappropriate parameter assumptions
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**2.11 Discounting**

**❖ In order for a pharmacoeconomic submission to be considered adherent to guidelines in terms of discounting, the pharmacoeconomic submission must respond “Costs and benefits were discounted at 5%” OR “Not applicable, time horizon ≤ 1 year” in guideline statement 2.11.1**

*2.11.1 In the Reference Case, discount the costs and health outcomes that occur beyond one year to present values at the (real) rate of 5% per year.*

If 4.20 answer is “Costs and benefits were discounted at 5%” or “Not applicable, time horizon ≤ 1 year”, then, pharmacoeconomic submission adheres to guidelines.

4.20) Was discounting conducted in the analysis:

- Costs and benefits were discounted at 5% (as per CADTH guidelines)
- Costs and benefits were discounted at the same rate, other than 5%
- Costs and benefits were discounted at different rates
- No discounting was conducted, but relevant
- Not applicable, time horizon ≤ 1 year

**2.12 Variability and Uncertainty**

**❖ In order for a pharmacoeconomic submission to be considered adherent to guidelines in terms of variability and uncertainty, the pharmacoeconomic**

**submission must respond “Key variables” OR “All variables” in guideline statement 2.12.2**

*2.12.2 Handling uncertainty*

*a) Uncertainty can be attributed to two types of model inputs: parameter and model (structure, methods, and assumptions). Deal with both types of uncertainty systematically and thoroughly, and fully assess the impact on the results and conclusions.*

*b) In the Reference Case, at a minimum, conduct a deterministic sensitivity analysis (DSA). Perform the analysis for all model inputs to determine the impact on the results. Justify the omission of any model input from the sensitivity analysis. Identify and fully assess the key model inputs contributing most to uncertainty.*

*The choice of analysis should involve more than a one-way sensitivity analysis. Perform multi-way sensitivity analysis, threshold analysis, and analysis of extremes (e.g., best and worst case scenarios) for key model inputs. Assess the full range of plausible values for each parameter, and plausible alternatives for each assumption. State and justify the ranges of values selected, and the alternative assumptions used.*

*Alternative assumptions should take into account the variability between the*

If 4.22 answer is “Some variables” OR “None conducted,” then pharmacoeconomic submission DID NOT adhere to guidelines.

4.22) Within the CDR PE Review, sensitivity analysis was conducted on:

- Some variables
- Key variables
- All variables
- None conducted (Skip V)

*jurisdictions or settings of the target audience.*

*c) A probabilistic sensitivity analysis (PSA) of parameter values that can be defined probabilistically is encouraged to more appropriately assess parameter uncertainty. The analysis should take the form of a Monte Carlo simulation. State and justify any assumptions regarding the range of values for key parameters, the form of probability distributions, and the number of Monte Carlo iterations.*

*Model uncertainty should be assessed through a DSA and model validation methods, with separate (probabilistic) results shown for each alternative analysis.*

*Parameter uncertainty can be assessed using a DSA and a PSA.*

*d) Where a PSA has been used, quantify the contribution of each parameter to decision uncertainty. Value-of-information methods can be used to indicate where the collection of additional information may be helpful for making decisions.*

#### **2.14 Generalizability**

**❖ In order for a pharmacoeconomic submission to be considered adherent to guidelines in terms of generalizability, the pharmacoeconomic submission must respond “PE information was based on Canadian trial and costs” OR “PE information was based on international trials and Canadian costs & resource use” OR “PE information was based on Canadian and international trials and Canadian costs & resource use” AND “In both an aggregate and disaggregate manner” in**

<b>guideline statements 2.14.2 and 2.14.4.</b>	
<p><i>2.14.2 Justify any data derived from outside Canada and verify for the Canadian setting. If data are adjusted for the Canadian setting, describe and justify the methods used. Report, analyze, and justify the use of cost data from multinational trials.</i></p>	<p>If 4.14 answer is “PE information was based on only Canadian costs,” then pharmacoeconomic submission DID NOT adhere to guidelines.</p> <p>4.14) Applicability of analysis to Canadian setting:</p> <p><input type="checkbox"/> PE information was based on Canadian trial and costs</p> <p><input type="checkbox"/> PE information was based on international trials and Canadian costs &amp; resource use</p> <p><input type="checkbox"/> PE information was based on Canadian and international trials and Canadian costs &amp; resource use</p> <p><input type="checkbox"/> PE information was based on only Canadian costs</p>
<p><i>2.14.4 Present the results in a disaggregated manner to facilitate the interpretation of results for different settings. Report the quantities of resources consumed and unit costs separately.</i></p>	<p>If 4.15 answer is “In both an aggregate and disaggregate manner,” then pharmacoeconomic submission adheres to guidelines.</p> <p>4.15) Costs are presented:</p> <p><input type="checkbox"/> In both an aggregate and disaggregate manner</p> <p><input type="checkbox"/> In only an aggregate form</p> <p><input type="checkbox"/> Not reported</p>
<p><b>2.15 Reporting</b></p> <p><b>❖ In order for a pharmacoeconomic submission to be considered adherent to guidelines in terms of reporting, the pharmacoeconomic submission must respond</b></p>	

<b>“Yes” AND “YES” in guideline statements 2.15.1 and 2.15.4.</b>	
<p><i>2.15.1 Report the evaluation in a transparent and detailed manner. Provide enough information to enable the audience to critically evaluate the validity of the analysis. Use a well-structured report format (Appendix 3 of Guidelines).</i></p>	<p>If 4.17 answer is “Yes,” then pharmacoeconomic submission adheres to guidelines.</p> <p>4.17) Within the CDR PE Review, are the methods and analysis described as clear and transparent?</p> <p><input type="checkbox"/> Yes (Skip IV#18)</p> <p><input type="checkbox"/> No</p>
<p><i>2.15.4 Report final results as incremental cost-effectiveness ratios (ICERs), based on incremental differences of expected costs and expected outcomes of the alternatives. Follow standard decision rules for estimating ICERs, including the exclusion of dominated alternatives. To aid understanding, analysts are encouraged to present the results of the analysis in graphical or visual form, in addition to tabular presentation.</i></p>	<p>If 4.21 answer is “Yes,” then pharmacoeconomic submission adheres to guidelines.</p> <p>4.21) Within the CDR PE Review, were expected values for cost-outcomes and cost-effectiveness calculated properly?</p> <p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p>

## Appendix H - Additional Results from Fishers Exact Test

Other Selected Variables, Not Considered Candidate Variables	Fisher's Exact Test (P value)
Type of Drug	0.237
Highest Level of Clinical Outcome As Model Input	0.439
Time Horizon	0.348
Computational Errors	0.516
Significantly Different Reanalysis Results	0.305
Adherence to Types of Evaluation	0.729
Adherence to Comparators	0.835
Adherence to Perspective	0.251
Adherence to Safety	0.298
Adherence to Time Horizon	0.348
Adherence to Modelling	0.244
Adherence to Discounting	0.769
Adherence to Variability and Uncertainty	0.556
Adherence to Generalizability	1.000

All variables listed above had a p value greater than 0.20 and therefore were not considered as candidate variables.

## Appendix I - Additional CDR Reanalysis Analysis

### Major drivers of reanalysis with significantly different results from the manufacturer

	N	%
<b>Significantly different results from the manufacturer</b>	<b>50</b>	
<b>Major Drivers of Reanalysis</b>		
Efficacy	21	41%
Safety	1	0%
Cost	11	24%
Resource Use	1	0%
Quality of Life	12	27%
Natural History of Disease	6	8%
Time Horizon	10	20%
Duration of Treatment Effect	7	14%
Unclear	3	6%
Choice of Comparator	5	10%
Other <sup>a</sup>	9	19%

Other <sup>a</sup> Treatment sequence, perspective, different form of analysis

The major drivers in the Common Drug Review reanalysis were: efficacy (41%), quality of life (27%), cost (24%), and time horizon (20%).

## Appendix J - Additional Analysis on Probabilistic Sensitivity Analysis

**Table 30 Functional forms used for transition probabilities from 2004-2011**

	2004	2005	2006	2007	2008	2009	2010	2011
<b>Included PSA</b>	3	4	10	7	12	6	10	16
<b>Transition Probabilities Distributions</b>								
Beta	0 (0%)	0 (0%)	4 (40%)	2 (29%)	6 (50%)	0 (0%)	2 (20%)	4 (25%)
Normal	1 (33%)	0 (0%)	0 (0%)	1 (14%)	4 (33%)	0 (0%)	0 (0%)	2 (13%)
Dirichlet	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	3 (19%)
Triangular	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	2 (13%)
Uniform	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	1 (10%)	1 (6%)
Log Normal	1 (33%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (%)
Gamma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)

Of the 68 pharmacoeconomic submissions with a PSA, 22 used an appropriate form of probability distribution for transition probabilities. There was no evident trend in the use of specific types of transition probabilities distributions. Beta distributions were the most prevalent type of distribution used, with normal, gamma, log normal, triangular, uniform, and Dirichlet distributions also adopted.

**Table 31 Functional forms used for utilities from 2004-2011**

	2004	2005	2006	2007	2008	2009	2010	2011
<b>Included PSA</b>	3	4	10	7	12	6	10	16
<b>Utilities Distributions</b>								
Beta	1 (33%)	0 (0%)	2 (20%)	2 (29%)	6 (50%)	1 (17%)	4 (40%)	5 (31%)
Gamma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (6%)
Normal	0 (0%)	0 (0%)	1 (10%)	1 (14%)	3 (25%)	3 (50%)	1 (10%)	3 (19%)
Log Normal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (13%)
Triangular	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (13%)
Uniform	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (6%)

In terms of cost distributions, 34 out of 68 pharmacoeconomic submissions used an appropriate form of probability distribution. There was no distinct trend in the use of specific types of costs distributions. Gamma distributions were the most frequent type of distribution used, with normal, log normal, triangular, uniform, beta distributions, and discrete values also assumed.

**Table 32 Functional forms used for costs from 2004-2011**

	2004	2005	2006	2007	2008	2009	2010	2011
<b>Included PSA</b>	3	4	10	7	12	6	10	16
<b>Costs</b>								

<b>Distributions</b>								
Gamma	1 (33%)	0 (0%)	2 (20%)	2 (29%)	4 (33%)	1 (17%)	7 (70%)	8 (50%)
Normal	0 (0%)	0 (0%)	1 (10%)	0 (0%)	2 (17%)	1 (17%)	2 (20%)	1 (6%)
Log Normal	0 (0%)	0 (0%)	1 (10%)	1 (14%)	1 (8%)	0 (0%)	0 (0%)	1 (6%)
Triangular	1 (33%)	0 (0%)	0 (0%)	1 (14%)	2 (17%)	1 (17%)	0 (0%)	3 (19%)
Uniform	0 (0%)	1 (25%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Beta	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)
Discrete Values	0 (0%)	0 (0%)	1 (10%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)

Of the 68 pharmacoeconomic submissions, 34 (50%) used an appropriate form of probability distribution for utilities. There was no evident trend in the use of specific types of utility values distributions. Beta distributions were the most common type of distribution used, with gamma, normal, log normal, triangular and uniform distributions also adopted.

**Table 33 Functional forms used for treatment effects from 2004-2011**

	<b>2004</b>	<b>2005</b>	<b>2006</b>	<b>2007</b>	<b>2008</b>	<b>2009</b>	<b>2010</b>	<b>2011</b>
<b>Included PSA</b>	3	4	10	7	12	6	10	16
<b>Treatment Effects Distributions</b>								
Normal	0 (0%)	0 (0%)	0 (0%)	1 (14%)	2 (17%)	1 (17%)	1 (10%)	1 (6%)
Log Normal	1 (33%)	0 (0%)	1 (10%)	0 (0%)	3 (25%)	0 (0%)	3 (30%)	2 (13%)

Triangular	0 (0%)	1 (25%)	2 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (6%)
Uniform	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Beta	0 (0%)	0 (0%)	1 (10%)	1 (14%)	2 (17%)	1 (17%)	0 (0%)	2 (13%)
Dirichlet	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	1 (17%)	0 (0%)	0 (0%)
Gamma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)

Lastly, regarding treatment effects distributions, 21 of 68 pharmacoeconomic submissions used an appropriate form. There was no clear trend in the use of specific types of treatment effect distributions. Log normal distributions were the most prevalent type of distribution used, with normal, triangular, uniform, beta, Dirichlet and gamma distributions also assumed.