PROPOSALS FOR UPDATING THE CANADIAN PATENTED MEDICINE PRICES REVIEW BOARD PHARMACEUTICAL BUDGET IMPACT ANALYSIS GUIDELINES FOR NEW DRUG SUBMISSIONS TO PUBLIC AND PRIVATE PAYERS

PROPOSALS FOR UPDATING THE CANADIAN PATENTED MEDICINE PRICES REVIEW BOARD PHARMACEUTICAL BUDGET IMPACT ANALYSIS GUIDELINES FOR NEW DRUG SUBMISSIONS TO PUBLIC AND PRIVATE PAYERS

By

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ABSTRACT

Background: The main objective of this thesis was to provide a proposal for updating the Patented Medicine Prices Review Board (PMPRB) 2007 pharmaceutical budget impact analysis (BIA) guidelines in accordance with the best national and transnational practices in BIA methodology and Canadian stakeholder feedback.

Methods: National, transnational and Canadian federal, provincial and private BIA guidelines were reviewed and recommendations were abstracted. A mixed methods study, consisting of semi-structured interviews and a written survey, was designed for obtaining feedback from Canadian stakeholders on the list of BIA recommendations which were either not included or discussed differently in the PMPRB 2007 BIA guidelines.

Results: Sixteen BIA guidelines were reviewed and discordant recommendations between the PMPRB 2007 BIA guidelines and rest of the reviewed guidelines were identified. The stakeholder analysis included thirty-five participants and showed support for the inclusion of 56% of the proposed recommendations into the guidelines. These recommendations pertained to the use of expert opinions, data extrapolated from the payers' database, scenario analysis, and dynamic population. Thirty percent of the recommendations, such as off-label indications in the base-case scenario, indirect costs, and cost transfers from other

jurisdictions, were not supported by stakeholders. There was no consensus with respect to the inclusion of recommendations for cost offsets or patient adherence. The final proposal is 49% identical with the PMPRB 2007 BIA guidelines. Thirty-six percent of the proposed recommendations (n=26) are new and the remainder (15%; n=11) are modified.

Conclusions: This series of studies has provided sufficient insights to enable the creation of a penultimate version of revised PMPRB BIA guidelines. This penultimate version would be subject to a broader consultation process among stakeholders prior to the adoption of a final revision. Further Canadian stakeholder feedback is required for recommendations where consensus is lacking.

PREFACE

This thesis is a "sandwich thesis" consisting of three individual projects each prepared for publication in a peer-reviewed journal. Two of the papers have been published, and the third paper is ready to be submitted to a peer-reviewed journal. The contributions of Naghmeh Foroutan to all of the papers in this thesis include: developing the research ideas and objectives, data collection, literature review, analysis of results, and writing and submitting the manuscripts for peer-reviewed journals. The work in this thesis was conducted between fall 2016 and spring 2019.

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LIST OF ABBREVIATIONS

AMCP	Academy of Managed Care Pharmacy
BIA	Budget Impact Analysis
CADTH	Canadian Agency for Drugs and Technologies in Health
CEA	Cost-Effectiveness Analysis
CEPS	French health care products pricing committee (Comité Economique des Produits de Santé)
CPI	Consumer Price Index
CUA	Cost-Utility Analysis
DPMA	Dispensed Price for Maximum Amount
EUnetHTA	European Network for Health Technology Assessment
FTA	Fast Track technology Appraisal
HAS	French national authority for health (La Haute Autorité de Santé)
HTA	Health Technology Assessment
HTAi	Health Technology Assessment International
HSE	Health Service Executive (Irish)
ICER	Incremental Cost-Effectiveness Ratio
iHEA	International Health Economics Association
INAHTA	International Network of Agencies for Health Technology Assessment
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KCE	Health Care Knowledge Centre
KT	Knowledge Translation
LCA	Least Cost Alternative price
NFZ	Polish National Health Fund (Narodowy Fundusz Zdrowia)
NHS	National Health System
NICE	National Institute for Health and Care Excellence
NIHBP	Non-Insured Health Benefits Program
NPDUIS	National Prescription Drug Utilisation Information System
OECD	Organization for Economic Co-operation and Development
PBAC	Pharmaceutical Benefits Advisory Committee
pCODR	pan-Canadian Oncology Drug Review
pCPA	pan-Canadian Pharmaceutical Alliance
PMPRB	Patented Medicine Prices Review Board
PSA	Probabilistic Sensitivity Analysis
QALY	Quality Adjusted Life Years
RIA	Resource Impact Assessment

CHAPTER 1

Introduction

The rapid growth of healthcare expenditures coupled with a slowdown in the growth of the general economy is a primary concern for healthcare policy makers [1, 2]. This, in turn, has made them more likely to consider strict cost containment measures for new highly specialized and expensive medicines which have led to an increased interest in health-economic and budget impact analysis of healthcare programs [3]. Health economic evaluations, which demonstrate the cost-effectiveness or cost-utility (value for money) of new intervention mainly assist with the prioritization of interventions, while BIA as a financial analysis addresses the issue of "affordability." The cost-effectiveness and affordability assessment have been labeled as the "fourth and fifth hurdle" to market, in addition to the traditional three hurdles of safety, efficacy, and quality that are required for the licensing of a new medical technology [2]. In the process of drug market authorization and reimbursement, decision-makers would like to know if the new drug is safe, effective, cost-effective and affordable.

In the Health Technology Assessment process, cost-effectiveness analysis (CEA) gets more attention, however over last decade, BIA has undoubtedly become more critical to the subsequent steps, including the adoption decision [4]. With the necessity of doing comprehensive economic evaluations (CEA along with BIA)

increasing dramatically over last decade [5-9], more time and effort needs to be spent in addressing BIA in an environment with increasing highly specialized and expensive new healthcare technologies. Pharmaceutical budget impact analysis (BIA) estimates the financial consequences of adoption and diffusion of a new health intervention or implementing evidence-based guidelines within a specific health care setting or system context in the short to medium term [3, 9-11].

In any healthcare system, budget holders or purchasers of pharmaceuticals and health services are the primary target audience for BIA reports. BIA is typically used by the healthcare budget policymakers to assess whether the funding required to implement the new medicine falls within the available budget for the period of interest [12-14]. A CEA may take a societal perspective and a long time horizon to include all the effects of new technology, even requiring more complicated modeling techniques for lifetime estimates. This approach does not fulfill budget holder's expectations since they can only manage their budget, and often do not show interest in intangible social consequences such as productivity losses [14, 15]. The complexity of CEA and lack of certain thresholds for the incremental cost-effectiveness ratio (ICER) in many jurisdictions have put additional stress on performing BIA which is directly informing budget allocation decisions [12-14].

Budget impact analyses inform real short-term decisions about how to allocate resources to maximize the quality of health care within a given budget [16]. In the recent years, there has been a rapid increase in drug expenditures at a rate greater than inflation. This has occurred particularly in countries where cost-effectiveness (CEA) is used as the only criterion for making reimbursement decisions within their technology assessment agencies, ignoring budget impact. This observation raise questions regarding the validity of willingness-to-pay (WTP) threshold[1] in informing affordability [17].

Using empirical evidence, Birch et al. showed that the substantial growth in treatment cost is the consequence of only relying on ICER thresholds for reimbursement decisions [18]. The introduction of Hepatitis C medications (e.g., Sovaldi) in 2013 (a cost-effective medications with a considerable market size) was a typical example of the contrast between the concepts of "cost-effectiveness" and "affordability" and explicitly shows that relying only on the ICER threshold is misleading about the affordability of new drugs [16, 18-21]. The "affordability problem" comes from the fact that none of the determinants of an ICER threshold (e.g., societal willingness to pay) inform affordability or provide any information about the availability of financial resources for the payer [16, 18].

On the other hand, solely focusing on the short-term affordability (budget impact)

[1] Incremental cost-effectiveness ratio (ICER) threshold

blinds policymakers to the long-term pay off of investing in new, and potentially expensive medications that will help patients in the long-term [16]. Hence, in the value-based pricing, the cost-effectiveness and budget impact of a new drug should be reviewed at the same time for informing price adjustments and reimbursement decisions [21]. Over the last couple of years, countries such as the United Kingdom have integrated affordability mechanisms into their health technology assessment process [20].

The PMPRB 2007 BIA Guidelines are the most comprehensive national reference for conducting BIA for new drug submissions in Canada, nevertheless, the guidelines are currently outdated and might not have kept pace with the evolution of BIA guidelines over the past decade. There is a real need for an updated comprehensive standard national document which cover all provincial differences (apart from providing the most up-to-date standard BIA methodology) in BIA requirements and is endorsed and adopted by both public and private payers.

The present study was designed to update the PMPRB 2007 BIA guidelines in accordance with the most up-to-date BIA methodology worldwide as well as the Canadian stakeholder requirement and expertise.

Historical background

Since the 1990s, several regions in the world including Australia, North America

(Canada, United States), and Europe (England and Wales, Belgium, France, Ireland, Hungary, Italy, and Poland) have included a request for BIA alongside the CEA, when submitting evidence to support formulary approval or reimbursement. At present, many jurisdictions around the world have published national BIA guidelines based on their specific new drug submission requirements [3, 10, 11, 22-32].

The first BIA model structure framework was published by Mauskopf et al. in 1998 [8]. In 2001, Trueman et al. [9] provided essential suggestions of best practice for undertaking BIA in addition to some foundations upon which future research could build. They were the first to introduce BIA in the healthcare literature [14].

The Polish guidelines in 2004 [2] used a framework for standardization of BIA that was similar to the one proposed by Trueman et al. [9] and they also followed the Australian guidelines (2002) and the National Institute for Health and Clinical Excellence (NICE) guidelines (2004) , provided detailed recommendations on the "general and detailed remarks" of a BIA analytical framework [12].

In Canada, the Patented Medicine Prices Review Board (PMPRB) initiated the development of the Canadian BIA Guidelines in 2005 on behalf of the National Prescription Drug Utilization Information System (NPDUIS). They were eventually published in 2007. The PMPRB BIA guidelines are supplemented by an Excel-based® interactive model template including provincial and Non-Insured Health Benefits Program (NIHBP) BIA requirements. Subsequently, these guidelines were approved and adopted by most of the Canadian provincial governments [33].

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) first task force report on good practice in BIA was published in 2007 [10] which was not meant to instruct individuals on how to do BIA but to illustrate that there are several general concepts that all BIA reports should address and provided a standard backbone for a comprehensive BIA [13]. Germany [23] and France [34] published their first BIA guidelines in 2008.

The UK (2017) [27], France (2017) [3], Australia (2016) [25], Poland (2016) [26], Ireland (2015) [24], Belgium (2014) [32] and some of Canadian provinces[2] have updated their BIA guidelines over last decade. ISPOR published their second task

[2] Ontario (2016), Alberta (2014), Manitoba (2016) and Quebec (2017)

force report on good practices for conducting BIA in 2014 [11]. In the developing countries including Brazil (2012) [29], Iran (2014) [35] and Thailand (2014) [31] there have been initiatives regarding drug reimbursement decision-making based on clinical, safety and economic and financial evidence [6, 31, 36-41]. Iran (2014) [35], Thailand (2014) [31] and the United States [42] adopted ISPOR BIA guidelines, and Wales [43] and Scotland [44] are mostly referring to the NICE (UK) recommendations [28].

Research questions

1) What are the national and transnational pharmaceutical BIA guidelines published over the last 20 years? (since 1998)
2) What Canadian federal, provincial and territorial (F/P/T) BIA guidelines were published/updated since 2007?
3) What are the differences between the recommendations that were listed in the 2007 PMPRB BIA guidelines compared with the BIA guidelines used by either Canadian F/P/T, or outside of Canada? What is not discussed or recommended differently in the 2007 PMPRB BIA guidelines?
4) What should be included in a proposal for updating the 2007 PMPRB BIA guidelines based upon Canadian stakeholders' feedback on an expanded list of recommendations?

Thesis objectives

The thesis projects aimed to:

a) Systematically review national and transnational BIA guidelines published between 2007 and 2017 and to abstract and to pool all guidelines recommendations.

b) Perform a comparative review of transnational, national and Canadian provincial BIA guidelines and to provide a list of recommendations relating to the BIA key elements which were not included in the Canadian PMPRB BIA guidelines.

c) Obtain Canadian stakeholders' feedback and opinion on the current gaps and challenges in using and producing BIA reports in the Canadian pharmaceutical context and on the proposed recommendations collected from the comparative literature review.

d) Provide a final proposal for updating 2007 PMPRB BIA guidelines based on the results of the literature review and Canadian stakeholders' feedback and opinion.

Thesis outline

The present dissertation is divided into five chapters.

Chapter #1: Introduction (current chapter)

The first chapter includes historical background, research questions, and the objectives of the project. We also provide a brief outline of the dissertation chapters.

Chapter #2: A methodological review of national and transnational pharmaceutical budget impact analysis guidelines for new drug submissions.

A systematic review of national and transnational BIA guidelines which were published or updated since 1998 [45].

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This review, which assessed a broad range of bibliographic resources with no limitations of language, resulted in a transnational framework for developing or updating BIA guidelines worldwide. The outputs from this review assisted in making a comparison between the PMPRB 2007 BIA guidelines recommendations with the recommendations used by the rest of the world (outside Canada).

Chapter #3: A comparison of pharmaceutical budget impact analysis (BIA) recommendations amongst the Canadian Patented Medicine Prices Review Board (PMPRB), public and private payers

A comparative literature review of Canadian F/P/T and 2007 PMPRB BIA guidelines to identify recommendations adopted in various jurisdictions across Canada since the publication of the 2007 PMPRB BIA guidelines. (*Publication:* Foroutan, N., et al., A Comparison of Pharmaceutical Budget Impact Analysis (BIA) Recommendations Amongst the Canadian Patented Medicine Prices Review Board (PMPRB), Public and Private Payers. PharmacoEconomics - Open, 2019).

This chapter provided a Canadian perspective of BIA guidelines, acknowledging differences across provinces as well as the private payers. This information provides the foundation for updating the Canadian PMPRB BIA guidelines. It is also of value to potential sponsors of drugs that would require a BIA submission in a request for formulary listing and reimbursement in Canada.

Chapter #4: Stakeholders' feedback and opinion on the proposed recommendations for updating the Canadian budget impact analysis guidelines for new drug submissions to public and private payers

The Canadian stakeholder feedback on the BIA recommendations, obtained through the use of qualitative and quantitative methods, provides additional insight to help define an appropriate set of BIA guidelines from a Canadian perspective. This information can also be of preliminary value for updating or creating a BIA guideline worldwide.

Chapter #5: Conclusions

The last chapter introduces a proposal for a revised version of the recommendations to be included in an updated version of the PMPRB BIA guidelines. Moreover, we acknowledged the research limitations and

recommended future research for removing those limitations.

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CHAPTER 2

A Methodological Review of National and Transnational Pharmaceutical Budget Impact Analysis (BIA) Guidelines for New Drug submissions

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Abstract

Introduction: Budget impact analysis (BIA) in health care, sometimes referred to as resource impact, is the financial change in the use of health resources associated with adding a new drug to a formulary or the adoption of a new health technology. Several national and transnational organizations worldwide have updated their BIA guidelines in the past four years. The aim of the present review was to provide a comprehensive list of the key recommendations of BIA guidelines from different countries that may be of interest for those who wish to build or to update BIA guidelines.

Methods: National and transnational BIA guidelines were searched in databases including MEDLINE, EMBASE, Cochrane, EconLit, CINAHL, Business Source Premier, HealthSTAR and the gray literature including regulatory agency websites. Data were reviewed and abstracted based on key elements in a standard BIA model (analytical model structure, input and data sources, and reporting format).

Results: Eight national (Australia, United Kingdom, Belgium, Ireland, France, Poland, Brazil, and Canada) and one transnational (ISPOR) BIA guidelines were included in this review and a comprehensive list of BIA recommendations was

identified. The review showed that certain recommendations such as patient population assessment, drug-related direct costs, discounting and disaggregating results were common across the various jurisdictions. BIA guidelines differed from each other in terms of the number and scope of recommendations, the terminology used (e.g., the definition of comparators or cost offsets) and the direction of the recommendations (i.e., to include or not to include) with respect to such items as off-label indications, indirect costs, clinical outcomes and resource utilization.

Conclusions: While there was a common purpose for all of the BIA guidelines that were identified, substantial differences did occur in the specific recommendations. The pharmaceutical financing system structure might explain why guidelines from the UK, Australia, and Canada have more country-specific recommendations. The desire to be consistent with adopted economic evaluation assumptions might be another reason for some observed differences between countries. Further research is required to assess the source of the heterogeneity between BIA recommendations are identified in different guidelines.

Keywords: Budget impact analysis, financial impact, resource impact assessment, pharmaceutical reimbursement, new drug submissions, guidelines

1. Introduction

The first BIA analytic framework was published by Mauskopf et al in 1998 [1]. In 2001, Trueman et al [2] provided essential suggestions for conducting a BIA, and the Polish BIA guidelines in 2004 [3] followed the initial framework of BIA proposed by Trueman et al. [2] In 2005 in Canada, the Patented Medicine Prices Review Board (PMPRB) initiated the development of the Canadian BIA guidelines which were subsequently published in 2007 [4] The International Society For Pharmacoeconomics and Outcomes Research (ISPOR) task force published the first transnational guidelines for the execution of a BIA in 2007 [5], followed by Germany [6] and France [7] in 2008.

During the past decade, many jurisdictions around the world have updated their BIA guidelines, including the United Kingdom (2017), France (2017), Australia (2016), Poland (2016), Ireland (2015), and Belgium (2014) [8-14]. ISPOR published their second task force report on good practices for conducting BIA in 2014 [15]. In Asia (i.e., Iran, Thailand) [16-19] and Latin America (i.e., Brazil, Chile, Colombia, Cuba and Mexico) [20, 21], there have been initiatives regarding drug reimbursement decision-making based on standard economic evaluation and budget impact analysis guidelines. Brazil has published their BIA guidelines in 2012 and Chile, Colombia and Mexico require BIA as part of their Health Technology Assessment (HTA) process [20, 21].

A number of systematic reviews of BIA empirical studies have recently been published [22-26] and literature reviews of national and transnational BIA guidelines have been conducted as part of national BIA guidelines development (e.g., France [2017], Belgium [2015] and Canada [2008]) [12-14]. However, the Belgian and Canadian guidelines did not systematically review the BIA literature. In contrast, the French BIA guidelines provide a comprehensive review of the BIA literature, including 9 national BIA guidelines, 5 recommendations of good practices developed by national and international societies for health economics and 14 methodological publications on existing BIAs, published between 2000 and 2016. Nevertheless, the French literature review in detail was not published as a systematic review in English. In the English version of the French BIA guidelines, the literature review results were briefly listed in a table in an aggregated form rather than providing a complete detailed list of the BIA recommendations. The present study has been designed to identify and abstract all guidelines recommendations relating to three key aspects in designing a standard pharmaceutical BIA (analytical model structure, input data, and sources and reporting format). This paper presents a comparative review of the BIA key element recommendations that are discussed in national and transnational BIA guidelines and, as well, provides a list of the relevant components that are needed in order to conduct a comprehensive pharmaceutical BIA.

2. Methods

2.1.Data sources

A systematic search of the literature was undertaken to identify BIA guidelines published from 1998 to June 30, 2018. The following bibliographic databases were searched through the Ovid interface: MEDLINE, EMBASE, Cochrane, EconLit, CINAHL, Business Source Premier, and HealthSTAR. We also searched the grey literature (Appendix 1) including INAHTA and non-INAHTA members (e.g., NICE, PHARMAC) as well as EUnetHTA; HTAi; iHEA; and ISPOR. The search strategy included a combination of text words and Medical Subject Headings terms and synonyms of budget/financial analysis, guidelines, and methodology/modeling. The keywords used for the searches are shown in Appendix 1.

2.2.Inclusion and exclusion criteria

The inclusion criteria were limited to BIA guidelines published since 1998 by different countries or international organizations (e.g., ISPOR) that presented recommendations on all three key elements of designing a BIA (i.e., analytical model structure, input and data sources, and reporting format). The titles and abstracts identified in these searches were screened to find eligible published

national and transnational BIA guidelines (peer-reviewed or online multimedia). When a country or transnational BIA guidelines were updated, we only included the latest updated version of the BIA guidelines for each organization in order to avoid duplication in data abstraction.

Citations that reported BIA for any specific drug or medical device (empirical studies), or review articles of empirical BIAs, abstracts and conference proceedings and methodological publications other than guidelines for conducting a pharmaceutical BIA were excluded. National guidelines were excluded if they did not explicitly discuss the key elements of a BIA model or if they did not add any additional information beyond the guideline that had been adopted from, and where the latter was already included in the review.

2.3.Study selection, data abstraction, and synthesis

Titles and abstracts of all articles were screened (level 1 screening) for inclusion by one reviewer. Following level 1 screening, the full text of the selected articles was retrieved (level 2 screening) and assessed by two independent reviewers for eligibility for final inclusion. The disagreement was resolved through consensus and, if persistent, arbitrated through discussion with a third person.

Using a data abstraction template, all included guidelines were reviewed by two independent reviewers to abstract key elements which were discussed in each BIA guideline. An Excel-based data abstraction form was developed based on the pre-determined BIA key elements in accordance with ISPOR BIA guidelines [15]. All the listed recommendations were for a base-case BIA model. The Excel-based data abstraction form was initially tested using two (Irish and Belgian) BIA guidelines before being used to abstract the data/recommendations from all the included BIA guidelines.

For the purpose of this paper, the BIA key elements were categorized into three groups: analytic model structure, input and data sources, and the reporting format. In each category, we defined primary and secondary elements. The primary elements were the main components within each category (e.g., perspective, time horizon, target population, scenarios to compare, costing, modeling and uncertainty) and secondary elements were more specific and detailed considerations related to the primary elements (e.g., off-label use, the degree of implementation and scenario analysis). The analytic model structure contains a discussion of twelve primary BIA elements (e.g., model design, model validation, perspective, time horizon, target population, costing, comparators, discounting and inflation, and handling the uncertainty). The data input category

mainly addresses data sources for market-share estimation and epidemiologic analyses. The reporting format section describes details for reporting BIA results based on the payer's requirements and the standard practices in conducting and reporting BIAs (e.g., aggregated and disaggregated results in each year of the time horizon and outcomes are presented in natural and monetary units). All terminologies, categories and BIA key elements were defined in accordance with ISPOR BIA guidelines.[15]

3. Results

3.1.Literature search results

A total of 3804 potential citations were identified through the systematic and the manual searches (having removed duplicates). 52 citations were included after the title and abstract review of which 43 were excluded for not meeting the eligibility criteria, resulting in a total of 9 national and transnational BIA guidelines published between 1998 and 2018 [8-15]. Figure 1 shows the detailed study selection process, and a summary of the included guidelines in the review is shown in Table 1.

Country-specific (national) guidelines from 8 countries (Australia, UK, Belgium, Ireland, France, Poland, Brazil, and Canada) were included. The guidelines from

five countries were excluded. Germany (2008) [6], Thailand (2014) [19] and the United States [27] each adopted the ISPOR BIA guidelines, while the Wales [28] and Scotland [29] guidelines were derived from the UK National Institute for Health and Care Excellence (NICE) recommendations [12] None of these five countries provided any additional methodological information beyond the source guidelines that they had adopted (which were already included in this review as a primary guideline). A summary of the countries that have developed national BIA guidelines and their associated drug plans is provided in Appendix 2.

3.2.Guidelines recommendations pertaining to the BIA key elements

A comprehensive list of all the BIA guideline recommendations was derived from the nine reviewed guidelines and is presented in Table 2. Figure 2 shows the number of guidelines that have made specific recommendations. The following sections provide a synthesis of the key similarities and differences among the nine guidelines.

3.2.1. Analytical model structure

Perspective

In most BIAs, using the perspective of the primary health care budget holder is recommended. However, in the Polish[10], French[12] and Canadian[13] BIA guidelines there is a recommendation to use the patient's perspective as a

complementary analysis to the base-case analysis. In contrast, Australia[9] explicitly requires the exclusion of any co-payment from any other source beyond the identified budget.

Time horizon

It is recommended in the Polish [10] and Belgian [14] guidelines to present the budget impact up to the steady state, with a minimum time horizon of 2-3 years. The minimum time horizon in the Canadian BIA guidelines [13] is 3 years, whereas in the updated Australian and NICE guidelines a longer time duration is recommended (6 and 5 years respectively). France [12] and ISPOR [15] recommend a BIA time horizon varying from 3 to 5 and 1 to 5 years in the base-case analysis, respectively. The Brazilian guidelines have also taken a time horizon from 1 to 5 years [20] The base-case analysis should estimate the annual financial impact over a minimum timeframe of 5 years in the recently updated Irish guidelines [8] A comparison of the time horizon recommended in different guidelines is shown in Figure 3.

Target population

Four guidelines have defined the target population as the "entire population of patients affected by the assessed indications, targeted by the proposed medicine,

over a specified time horizon [8, 10, 14, 15].” French guidelines have introduced two population groups to be included in the analysis, “the target population and the expected treated (forecasted population to be actually treated by the intervention in the real-life practice) population for all indications[12].” Based on the Canadian BIA guidelines, the target population is defined as “all drug plan beneficiaries who are expected to be diagnosed and treated for the conditions of interest and are eligible to use the new drug [13]. ”

Subpopulation analyses can be performed for BIA if there are appropriate justifications: by beneficiary, differences in safety, treatment effect, baseline risks, costs or market share [8, 9, 12, 14, 15, 20]. For the target population estimation, there are two approaches: Top-down or epidemiological and bottom-up or market-share (claims-based analyses). An epidemiological approach is usually preferred if the submission indicates a superior therapeutic conclusion in clinical studies, whereas a market-share approach might be preferred if the submission indicates a non-inferior therapeutic conclusion [9]. In the epidemiological approach, disease severity shifts, incidence, and prevalence are required, and it is usually inevitable to use data from different sources [13]. Apart from the UK[11], Poland [10] and ISPOR [15] (which only ask for the epidemiologic approach), other guidelines recommend BIA results obtained from both epidemiologic and market-share approaches for all new drug submissions.

The degree of implementation (full replacement or partial substitution of existing technologies or shifts in the target population, market growth or expansion) is essential in both approaches and recommended by most guidelines. In the Canadian guidelines, it is advised that the treatment displacement assumptions regarding the changes to the market share of each competitor after the introduction of the new drug be tested in the sensitivity analysis [13]. The population is dynamic in the ISPOR, Polish, Irish, Brazilian and Belgian guidelines meaning that patients could be added to or removed from the analysis based on whether they meet the inclusion criteria or not over time [8, 10, 14, 15, 20] In some cases, when the technology applies to a well-defined group of patients, the BIA may require a defined closed population [10].

In addition, the Brazilian, French, Belgian and ISPOR (for the current treatment mix) BIA guidelines [12, 14, 15, 20] recommend consideration of off-label usage in all indications for the assessed medicine as complementary to the base-case analysis; this is especially relevant if there is available evidence for cost-effectiveness and, more importantly, it is noted by the payer [12]. In the Canadian BIA guidelines, the off-label use is only considered in the sensitivity analysis [13]. The catch-up effect which applies to the chronic conditions for patients who

switch to the new drug is recommended in the Irish and ISPOR guidelines [8, 15]. Any planned local regulations and legislation which would limit new drug access in a subpopulation should be considered [10, 13, 15, 20].

Scenarios to compare (comparators)

In most of the reviewed guidelines, the current scenario/practice (including "no intervention") should be 'routine care' or the best clinical practice, including the most cost-effective alternatives. The new scenario is the "current scenario" with the new intervention added to or replacing the current interventions entirely or partially [14, 15]. NICE considers a broader picture of the budget impact and defines the current and new scenarios as current and future clinical practice activities (at activity levels) resulting from adopting the NICE guidelines in the NHS [12]. In Canada, the comparator definition is more market-oriented. According to the Canadian BIA guidelines, reference scenario is the current market share distribution of all comparators without the new drug, whereas new drug scenario is forecasted market share of same comparators with the inclusion of the new drug [13]. Multi-drug treatment (i.e., treatment mix or set [15], treatment set [12], treatment mix [9] and strategy-based treatment [13]) rather than individual interventions is recommended in most of the guidelines [8-10, 12, 13, 15, 20].

Cost analysis

The inclusion of cost items is directly related to the chosen perspective. Canada, Australia, France, Brazil, Ireland, Poland, and ISPOR consider costing based on multi-drug treatment strategy (including adjunct therapies) [8-10, 12, 13, 15, 20]. The BIA should, therefore, identify all medicines likely to be affected by the new drug.

Most of the guidelines agree on the fact that direct healthcare-related costs for the most relevant perspective should be included in the base-case, similar to the guidelines for economic evaluations [8, 10-12, 14, 15, 20]. However, the Australian [9] and Canadian [13] BIA guidelines exclude the costs associated with changes in outcomes, costs associated with clinical consequences/complications (e.g., adverse drug reactions) and resource utilization (e.g., hospitalization, emergency room admission), while other guidelines suggest to review such non-drug related costs. In the latest version of the Irish guidelines, for pharmaceuticals, direct costs include the cost of the drug and any other drug-related costs (concomitant therapies, adverse events and infusion-related costs such as consumables and staffing) [8] The impact on indirect, non-healthcare related costs (e.g., productivity, transport, capacity, and workforce) are not usually included in a BIA base-case analysis, except for the NICE guidelines

(Table 2) [8, 12, 14, 15].

Other differences between BIA guidelines were related to the scope of costs [30] (e.g., costs related to personnel training, budget transfers between different governments and patients) [8, 12, 14, 15]. According to the Irish, Polish and ISPOR guidelines, it is important to consider additional resources that must be taken from the existing services when implementing a new technology which are called "opportunity costs". Opportunity costs are the costs that arise when implementing the technology or clinical guidelines that might not be reflected in the "actual costs" at the time of doing BIA analysis [8, 10, 15]. In the case of including condition-related costs (i.e., health outcomes and resource use), the actual opportunity costs are relevant in the ISPOR guidelines. In such cases, analysts may use cost accounting approaches if actual opportunity costs are not available for a particular jurisdiction [15]. According to the Irish guidelines "Actual costs" are cash payments which occur from implementing the technology or clinical practice guidelines [8] The BIA should clearly state which unit of analysis is adopted in measuring the outcomes. There are two possible units of analysis: per patient or episode of care. Specified interventions may range from once-only, repeated, periodic or continuous interventions; it needs to be clear the number of times or the length of time people might experience the intervention or how many treatment events might arise" [8, 9, 20].

Cost of the treatment should be adjusted to consider mark-ups, discounts, inventory allowance [8, 13, 15], business-related costs to the pharmacy covered by the drug plans, and dispensing fees and patient co-payments, as requested by drug plans in Canada [13]. In the Canadian BIA guidelines, drug prices can be obtained from provincial formulary websites, public drug plan databases and manufacturers' market access department for preparing BIA reports [13]. There are also recommendations on how to deal with New Chemical Entities and generic drug prices for BIAs in the Canadian BIA guidelines [13]. In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) also recommends "dispensed price for maximum amount (DPMA)" for BIA [9]. It is recommended that uncertainties regarding the drug reimbursement price should be targeted through a sensitivity analysis [13].

In the Irish guidelines, the value-added tax could be considered if applicable,[8] and in the Canadian and Belgian BIA guidelines, protocol-driven costs should be excluded (e.g., costs related to the patient enrollment process and additional laboratory tests specific to the clinical trial design).[13, 14] None of the guidelines recommends inflation and discount rates, however, in the Canadian, Brazilian, Irish and ISPOR BIA guidelines, they are permitted in certain circumstances and

if there is justification for being included (e.g., confirmed information on pricing policy, implementation of an approved new policy rule in the near future or price changes after patent expiration).

Modeling

Transparency, validity, simple and user-friendly design along with explicit definitions and assumptions are the most favorable features of a BIA model. It is recommended that the model be designed based on the projected disease condition and be flexible enough to capture long-term outcomes/costs in chronic diseases [12]. Similar to cost-effectiveness analyses, in the Belgian and Brazilian BIA guidelines, decision trees or Markov models can be helpful to be consistent with the economic evaluations [14, 20]. Most guidelines recommend using an Excel-based model (rather than more complicated software) to calculate the budget impact [9, 11-13, 15, 20]. This allows for extending the analysis to the appropriate time horizon and using different data sources. Face, internal and external validity have to be checked and documented. The model validity and transparency could be assessed using recommendations provided by ISPOR and the Society for Medical Decision Making task force report.

Handling the uncertainty

Decreasing uncertainty is an essential consideration in BIA. Although probabilistic sensitivity analysis is not recommended in the Canadian BIA

guidelines, one-way, univariate deterministic sensitivity analysis or multivariate scenario analysis are acceptable for the most important variables such as prices, population and market shares [13]. Sensitivity analysis of data obtained from clinical trials [9], drug dosage [13] and price [13] and market data from other jurisdictions [13] are also recommended [8-10, 12, 13, 15].

Scenario analysis is recommended by Australia, Belgium, France, ISPOR and Ireland [9, 12, 14, 15]. PBAC [9] has provided a very detailed list of recommended scenarios to be considered in reporting the budget impact results, e.g., the effects of promotional efforts on prescriber and consumer behavior. Risk sharing agreements with the manufacturers and a more extended introduction phase for the proposed drug have also been recommended by Australia and the UK for managing uncertainty in early BIA results [9, 11].

3.2.2. Input and data sources

National statistics and registries are recommended sources for epidemiologic data (e.g., disease prevalence and incidence) [8, 10, 12, 13, 15, 20]. The best sources for the claims-based and market research information are the payer database [15] and the manufacturer's marketing department [13, 15]. In the Polish, Canadian, Brazilian and ISPOR guidelines, data from foreign markets are acceptable if local

information are not available (Table 2) [10, 13, 15, 20]. The BIA reports from manufacturers with clear supporting data could also be helpful [13, 15]. Consensus expert opinion is an option when market intelligence for forecasting the new drug market share is not available [8, 10, 12, 13, 20].

3.2.3. Reporting format

There are specific requirements for reporting the results in the reviewed guidelines. Newly updated guidelines have put more attention to the details and the manner BIA results are reported, mainly based on the policymakers' interest and requirements.

Total and incremental impact on the primary payer's budget should be presented in the Polish, Irish, French and Australian guidelines. The Canadian guidelines only require an incremental impact on the annual budget [13]. Results should be both aggregated and disaggregated in each year of the time horizon in the Irish, French and Australian guidelines.[8, 9, 12]

The budget impact can be presented in natural (e.g., number of unpaid working days) and monetary units separately for the different healthcare payers [14]. A

table of assumptions, inputs, and outputs, a schematic representation of any uncertainty analyses (e.g., Tornado diagram), appendices and references should be included [10, 15, 20]. Estimated financial implications for the health budget (other health sectors), the impact of uncertainty (quantify how precise are the results), activities to support the quality use of medicines and post-marketing surveillance amendments are recommended by PBAC.[9] In their new resource impact assessment manual, NICE classifies results as "substantial" if the implementation of a single recommendation in the UK costs higher than a specific threshold [11].

NICE recommends publishing the resource planner, a word file of resource impact reports, resource impact statements, quality assurance, and publication, as well as making post-publication amendments. Resource Impact Assessment results should be published at the same time as NICE evidence-based guidelines and performed in parallel with economic evaluations [11].

4. Discussion

In the present review, we identified BIA guidelines from Canada, Australia, UK, Poland, Ireland, Belgium, France, Brazil and ISPOR and reviewed all their recommendations related to the analytical model structure, input and data sources, and reporting format of BIAs [8-15]. It is the first peer-reviewed evidence in the

health literature at which a systematic review of national and transnational BIA guidelines was published as a robust and comprehensive basis for future research.

There are some similarities in guidelines recommendations (e.g., using drug-related direct costs from the primary payer's perspective, top-down or bottom-up approaches for population assessment, simple (not complicated) modeling techniques and deterministic sensitivity analysis as the minimum requirements for a BIA base-case analysis). Differences between guidelines were related to the number, scope, and direction (yes/no) of recommendations [e.g., inclusion of off label indications, indirect costs, clinical outcomes and health care resource utilization; duration of time horizon; dealing with uncertainty (e.g., deterministic analysis vs PSA) and reporting format]. Moreover, there are differences in the terminologies which are used in different guidelines/countries for defining specific concepts in designing a BIA (e.g., multi-drug treatment in assessing the comparators, target population definition such as "open population" or cost off-sets).

Some guidelines were closely aligned in their recommendations (e.g., French, Australian, Belgian and ISPOR BIA guidelines), while others had included more country-specific recommendations (e.g., Canada, Australia, and the UK). In some

guidelines/countries such as ISPOR, UK, Belgium, Ireland, and Australia, if an economic evaluation (EE) was performed, the BIA model should be consistent with the clinical and economic assumptions in EE. In the UK, BIA is called Resource Impact Assessment (RIA) and the estimation of costs and savings is based on the direct consequence of implementing NICE guidelines (not just drug comparators) [11].

The results of our review are similar to the French literature review [12] of BIA guidelines in terms of key aspects in designing BIA. However, our review used BIA more aligned with the ISPOR BIA guidelines [15]. The literature review that was conducted as part of the Belgian guidelines was not published with sufficient detail [14], and the literature review results in the French guidelines were summarized in an aggregated format. Thus there were insufficient details to provide a complete taxonomy of BIA guideline recommendations. A previous Canadian BIA literature review [13] included the older versions of the Polish (2004), Australian (2002) and ISPOR (2007) BIA guidelines. Our literature review was different in terms of (1) the review design (systematic), (2) the scope (focused on only BIA guidelines recommendations), (3) inclusion criteria (all BIA guidelines published since 1998, excluding any versions that were replaced by newer updates) and (4) reporting format (applicable details for future research).

The present review is the most recent systematic review of published national and transnational BIA guidelines that have been created or updated since 1998. A potential limitation of this study includes having only one reviewer for level 1 (title and abstract) screening which we believe that did not contribute to considerable bias. We did not include results from countries that simply adopt BIA guidelines from other jurisdictions (Germany, Thailand, United States, Scotland, and Wales) which might be considered a limitation in that it would underestimate the frequency of use for some recommendations. We also did not include published BIA methodologic papers as we were only interested in reviewing BIA guidelines recommendations.

5. Conclusion

To maintain sustainability in financing the health care systems, it is increasingly important to improve informed pricing and reimbursement decision-making at national and transnational levels. Our literature review showed that over the last 20 years, countries have become actively interested in comprehensive financial and economic evaluations and have tried to keep their BIA guidelines updated. Through a systematic review of national and transnational BIA guidelines published or updated since 1998 following Mauskopf et al.'s publication, we provided a full list (not a summary) of the details for conducting a standard

pharmaceutical BIA in accordance with the most up-to-date national and transnational BIA guidelines recommendations. The remaining challenge is how to embrace the heterogeneity of recommendations and terminologies that is evident across different guidelines. Further research is required to analyze each countries pharmaceutical financing system- in more detail- to assess any true relationship between country-specific healthcare parameters and BIA recommendations. The results of this review can be a starting point for countries who are initiating the development of national standard BIA guidelines based on their pharmaceutical reimbursement requirements. The present review can provide useful practical methodological information for BIA users and producers and provide a contribution to future research in the field of pharmaceutical BIA.

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7. Disclosure

The authors report no conflicts of interest in this work.

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30. Explain whether the listing of this medication will have a significant impact on health care services (e.g., laboratory testing, diagnostic testing, etc.)
31. National Committee for Health Technology Incorporation

Table 1: Summary of nine included guidelines in the review.

Country	Financing system	Year	Organization	Title
France[12]	French statutory social insurance scheme	2017	French National Authority for Health (HAS)	The French National Authority for Health (HAS) guidelines for conducting Budget Impact Analyses (BIA)
United Kingdom (UK)[11]	National health system (NHS)	2017	National Institute for Health and Care Excellence (NICE)	Proposals for changes to the arrangements for evaluating and funding drugs and other health technologies appraised through NICE's technology appraisal and highly specialized technologies programs (resource impact assessment)
Australia[9]	Pharmaceutical benefits scheme (PBS)	2016	Pharmaceutical Benefits Advisory Committee (PBAC)	Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee (Version 5.0)
Poland[10]	National health Funds (NHF)	2016	The Agency for Health Technology Assessment and Tariff System (AOTMiT)	HTA guidelines
Belgium[14]	Federal government, communities, patients	2015	Belgian Health Care Knowledge Centre (KCE)	Guidelines for Budget Impact Analyses
Ireland[8]	Publicly-funded Health and social care system (HSE)	2018	The Health Information and	Guidelines for the Budget Impact Analysis of Health

			Quality Authority (the authority)	Technologies in Ireland 2018
ISPOR[15]	NA	2014	International Society for Pharmacoeconomics and Outcomes Research	ISPOR taskforce report: Budget Impact Analysis—Principles of good practice: Report of the ISPOR 2012 Budget Impact Analysis good practice II task force
Brazil[20]	Unified Health System (SUS)	2012	Ministry of Health (CONITEC[31])	Diretriz para análises de impacto orçamentário de tecnologias em saúde no Brasil (Guidelines for budget impact analysis of health technologies in Brazil)
Canada[13]	Federal, provincial and territorial drug plans, private payers, patients	2007	Patented Medicine Prices Review Board (PMPRB)	Guidelines for conducting pharmaceutical Budget Impact Analyses for submission to public drug plans in Canada

Table 2: BIA categories and recommendations of nine national and transnational BIA guidelines.

BIA primary elements	**Perspective**
BIA secondary elements	The recommended perspective is that of the budget holder range from a single payer covering an entire health care system through specific providers
ISPOR (2014)	Yes
Canada (2007)	Yes (Federal, provincial and territorial drug plans, private payers)
Belgium (2012)	Yes (Healthcare payers; patients; provider)
France (2018)	Yes (French statutory social insurance scheme; patient; provider)
Ireland (2018)	Yes (Publicly-funded health and social care system)
Poland (2016)	Yes (Public payers; patients; hospitals)
UK (2017)	Yes (Commissioner; provider)
Australia (2016)	Yes (PBS/RPBS; federal government)
Brazil (2012)	Yes (Public and Private systems; Nation, States or Municipalities)

BIA primary elements	**Technology**	**Target Population Assessment**	
BIA secondary elements	The technology should be described in sufficient detail to differentiate it from its comparators and to provide context for the study.	Definition of patient population	Top-down approach (epidemiology)
ISPOR (2014)		Yes (all patients eligible for the new intervention)	Yes
Canada (2007)		Yes (defined as individuals insured by drug plans of interest)	Yes (epidemiologic)
Belgium (2012)			Yes
France (2018)		Yes (target and expected population)	Yes
Ireland (2018)	Yes	Yes (target population should be defined based on the approved indication for the technology AND also defined as those with a specified disease who may avail of the technology)	Yes
Poland (2016)		Yes (all patients in whom a given health technology can be used in the assessed medical indications)	Yes
UK (2017)		Yes (resident and registered population)	Yes (incidence and prevalence-based approach)
Australia (2016)		Yes (number of patients will be treated and number of unit doses will be dispensed over the time horizon)	Yes (epidemiologic approach)
Brazil (2012)		Yes	Yes

BIA primary elements	**Target Population Assessment**			
BIA secondary elements	Bottom-up (claim-based)	Open population	Subgroups	Catch-up effect
ISPOR (2014)		Yes	Yes	Yes
Canada (2007)	Yes (claim-based)			
Belgium (2012)	Yes	Yes	Yes	
France (2018)	Yes	Yes	Yes	
Ireland (2018)	Yes	Yes	Yes (based on biologically plausible and justified evidence but not based on treatment response)	Yes
Poland (2016)		Yes		
UK (2017)				
Australia (2016)	Yes (market-share approach)		Yes (stratify by beneficiary)	
Brazil (2012)	Yes (claim-based approach)		Yes	

BIA primary elements	**Target Population Assessment**		
BIA secondary elements	Access restrictions	Unit of analysis (per patient or episode)	Off-label indications in the eligible population may also be included.
ISPOR (2014)	Yes		Yes (for the current treatment mix)
Canada (2007)	Yes		No
Belgium (2012)			Yes
France (2018)			Yes
Ireland (2018)		Yes (per patient or per episode of care)	No
Poland (2016)	Yes		
UK (2017)			
Australia (2016)		Yes (per unit dispensed)	
Brazil (2012)	Yes	Yes (per episode)	Yes

BIA primary elements	**Target Population Assessment**	**Comparators**
BIA secondary elements	Degree of implementation of the new intervention (substitution, combination and expansion)	Definition
ISPOR (2014)	Yes	Yes (BIA compares scenarios defined by sets of, rather than specific individual, interventions)
Canada (2007)		Yes (two scenarios, Reference and new drug scenario, should be compared for the treatment-strategy)
Belgium (2012)	Yes	Yes (current situation that would change if the intervention under consideration is introduced in the healthcare system; most cost-effective alternatives)
France (2018)	Yes	Yes (BIA compares sets of interventions (scenarios) rather than individual interventions)
Ireland (2018)		Yes
Poland (2016)	Yes	Yes (the assumptions concerning the "current scenario" and the "new scenario" should be described and justified in the analysis)
UK (2017)		-
Australia (2016)	Yes	Yes (PBS medicines that will be affecting by the proposed listing; mixed treatment comparisons)
Brazil (2012)	Yes	Yes (comparison of two or more scenarios, which are representations of different market conditions)

BIA primary elements	**Comparators**
BIA secondary elements	Current intervention mix for the eligible population
ISPOR (2014)	Yes (the current mix may include no intervention and interventions that replaced by the new one)
Canada (2007)	Yes (Forecasted version of the current market without the new drug)
Belgium (2012)	Yes
France (2018)	Yes (scenarios without the intervention under study)
Ireland (2018)	Yes (baseline scenario that reflects the current mix of technologies and forecasts the situation should the new technology not be adopted)
Poland (2016)	Yes (takes into account the interventions currently used in a given population [including no intervention or interventions used in different conditions)
UK (2017)	
Australia (2016)	
Brazil (2012)	Yes (set of therapeutic options currently available for the treatment of the disease)

BIA primary elements	**Comparators**	**Costs and outcomes**
BIA secondary elements	New intervention mix	Direct cost consequence of implementing NICE guidelines
ISPOR (2014)	Yes (introduction of a new intervention sets in motion various marketplace dynamics)	
Canada (2007)	Yes (new drug scenario is forecasted version of the current market with introduction of the new drug)	
Belgium (2012)	Yes	
France (2018)	Yes (scenarios with the intervention under study)	
Ireland (2018)	Yes (new technology scenario, where the new drug is adopted)	
Poland (2016)	Yes (reflects the market after the introduction of the new technology)	
UK (2017)		Yes
Australia (2016)		
Brazil (2012)	Yes (cost of each intervention included in the analysis will reflect the cost of the entire therapeutic package)	

BIA primary elements	**Costs and outcomes**	
BIA secondary elements	Cost of the current and new intervention mix: Is determined by multiplying the budget holder's price for each intervention by proportion of the eligible population using that intervention	Actual acquisition cost of the intervention for the budget holder (including any discounts, rebates, or other adjustments that may apply).
ISPOR (2014)	yes	Yes
Canada (2007)	Yes (treatment strategy-based approach)	Yes
Belgium (2012)		
France (2018)	Yes	
Ireland (2018)	Yes	Yes
Poland (2016)	Yes	
UK (2017)		
Australia (2016)		
Brazil (2012)		

BIA primary elements	**Costs and outcomes**	
BIA secondary elements	Opportunity costs are the costs that arise when implementing the technology or clinical guidelines that might not being reflected in the "actual costs" at the time of doing BIA analysis	The costs included should be limited to **direct costs** associated with the technology that will accrue to the relevant payer(s)
ISPOR (2014)	Yes	Yes
Canada (2007)		Yes (direct drug cost)
Belgium (2012)		
France (2018)		
Ireland (2018)	Yes	Yes (drug administration costs, the cost of drug wastage and the cost of drug monitoring)
Poland (2016)	Yes (the cost of additional outlays in the health care system, related to the implementation of the assessed technology)	Yes (actual payments and actual savings achieved by a public payer/patient; taking into account the existing Risk Sharing Schemes)
UK (2017)		Yes
Australia (2016)		Yes (direct drug cost)
Brazil (2012)		Yes (costs of the new drug and those directly associated with its use, as adjuvant medications or treatment of adverse events)

BIA primary elements	**Costs and outcomes**	
BIA secondary elements	**Cost of clinical outcomes** and disease complication	**Cost of health care utilization** (e.g., hospital days or physician visits)
ISPOR (2014)	Yes	Yes
Canada (2007)	No	No
Belgium (2012)	No (health outcomes are not included however cost consequences of health outcomes e.g., treatment cost of adverse events are included)	Yes (e.g., cost of treatment of adverse drug reactions)
France (2018)		
Ireland (2018)	Yes (Efficacy, effectiveness and safety, cost off-sets)	Yes (cost off-sets)
Poland (2016)		Yes
UK (2017)	Yes (direct clinical consequences)	
Australia (2016)		
Brazil (2012)		

BIA primary elements	**Costs and outcomes**	
BIA secondary elements	**Indirect costs:** The impact of the new intervention on productivity, social services, and other costs outside the health care system	**Cost of supplies**: The analytic framework should allow for cost-relevant details of how accompanying devices for the proposed medication are used
ISPOR (2014)	No (should not be included routinely in a BIA (Except for the private payers or employers)	Yes
Canada (2007)	No	
Belgium (2012)	Maybe (can be quantified in a separate analysis)	
France (2018)		
Ireland (2018)	No	Yes
Poland (2016)		Yes
UK (2017)	Yes (e.g., productivity cost)	
Australia (2016)		
Brazil (2012)	No	Yes

BIA primary elements	**Costs and outcomes**		
BIA secondary elements	The annual depreciation of any **capital costs** should be included in the analysis	**Labour costs**	Value-added tax
ISPOR (2014)			
Canada (2007)			
Belgium (2012)			
France (2018)			
Ireland (2018)	Yes	Yes	Yes
Poland (2016)		Yes (e.g., staff training cost)	
UK (2017)			
Australia (2016)			
Brazil (2012)			

BIA primary elements	**Costs and outcomes**	
BIA secondary elements	Proposed drug cost based on unit **drug price and average dose** for average duration of time	The BIA should also estimate the impact of **adherence** or persistence on intervention effectiveness and safety if condition-related costs are included in the BIA.
ISPOR (2014)	Yes	yes
Canada (2007)	Yes	
Belgium (2012)		
France (2018)		
Ireland (2018)	Yes (technology cost)	
Poland (2016)	Yes	
UK (2017)	Yes	
Australia (2016)	Yes	
Brazil (2012)	Yes (per patient, per time period)	

BIA primary elements	**Costs and outcomes**	
BIA secondary elements	Calculate both the **global budget impact and separately the budget impact for the different health care payers**	Application of the **therapeutic equivalence method** in the comparison of costs is recommended
ISPOR (2014)		
Canada (2007)		
Belgium (2012)	Yes	
France (2018)		
Ireland (2018)		
Poland (2016)		
UK (2017)		
Australia (2016)	Yes	
Brazil (2012)		Yes

BIA primary elements	**Time horizon**
BIA secondary elements	BIAs should be presented for the time horizons of relevance to the budget holder
ISPOR (2014)	1-5 years
Canada (2007)	3 years
Belgium (2012)	3 years
France (2018)	3-5 years
Ireland (2018)	5 years
Poland (2016)	2 years
UK (2017)	5 years
Australia (2016)	6 years
Brazil (2012)	1-5 years (subjected to budget holder's needs)

BIA primary elements	**Modeling**	
BIA secondary elements	Modelling may be needed to calculate the budget impact for bringing together the best available data from different sources.	Assumptions should be the same as EE
ISPOR (2014)	Yes (if an economic evaluation was performed, the BIA model should be consistent with assumptions in	Yes (a justified comparator in an economic evaluation may be different from the comparator in the BIA)
Canada (2007)		
Belgium (2012)	Yes	Yes
France (2018)	Yes (according to the characteristics and the management of the disease of interest in France)	
Ireland (2018)	Yes (based on the good modelling practice)	Yes
Poland (2016)		
UK (2017)	Yes	Yes
Australia (2016)	Yes	Yes
Brazil (2012)	Yes	

BIA primary elements	**Modeling**	
BIA secondary elements	The computing framework for a BIA can be a simple cost calculator programmed in a Excel- based spreadsheet	More complicated Software
ISPOR (2014)	Yes	Yes
Canada (2007)	Yes	
Belgium (2012)	Yes	Yes (decision tree, Markov model)
France (2018)	Maybe (transparent and accessible to the decision maker)	
Ireland (2018)		No (simplest design)
Poland (2016)		
UK (2017)	Yes (A resource impact template is an Excel spreadsheet)	
Australia (2016)	Yes	
Brazil (2012)	Yes	Yes (Decision Tree, Markov models, Discrete event simulation)

BIA primary elements	**Handling uncertainty and Scenario Analyses**		
BIA secondary elements	**Sensitivity analysis**: Parameter uncertainty in the input values	**One-way and/or multi-way sensitivity analysis**, analysis of extremes	**Probabilistic Sensitivity Analysis (PSA)** is recommended in BIA
ISPOR (2014)	Yes	Yes	
Canada (2007)	Yes	Yes	No
Belgium (2012)			Yes
France (2018)	Yes	Yes	
Ireland (2018)	Yes	Yes	Yes
Poland (2016)		Yes	
UK (2017)			
Australia (2016)			
Brazil (2012)	Yes		

BIA primary elements	**Handling uncertainty and Scenario Analyses**	
BIA secondary elements	**Scenario analysis**: Structural uncertainty introduced by the assumptions made in framing the BIA	**Important parameters** to be assessed in the sensitivity and scenario analyses have been provided in the guidelines
ISPOR (2014)	Yes	Yes
Canada (2007)		Yes
Belgium (2012)	Yes	
France (2018)	Yes	
Ireland (2018)	Yes	Yes
Poland (2016)		Yes (population size [e.g. the degree of possible abuse], costs of use and reimbursement conditions)
UK (2017)		
Australia (2016)	Yes	Yes
Brazil (2012)		Yes

BIA primary elements	**Handling uncertainty and Scenario Analyses**	**Discount rate**
BIA secondary elements	Describe the **direction and magnitude** of the impact of uncertainty on the overall estimates	An attempt should be made for forecasting changes in the value of the currency used the BIA over the time horizon
ISPOR (2014)		Yes
Canada (2007)		Yes
Belgium (2012)		
France (2018)		
Ireland (2018)		Yes (in certain circumstance)
Poland (2016)		
UK (2017)		
Australia (2016)	Yes	
Brazil (2012)		Yes

BIA primary elements	**Discount rate**	**Validation**	
BIA secondary elements	Discounting is generally not required.	The computing framework and input data used for a BIA must be sufficiently valid to credibly inform the budget holder's decisions.	The process of the validation is required
ISPOR (2014)	Yes	Yes	
Canada (2007)	Yes	Yes	No
Belgium (2012)	Yes	Yes (face validity)	
France (2018)	Yes	Yes	
Ireland (2018)	Yes	Yes	Yes (should be documented)
Poland (2016)	Yes		
UK (2017)	Yes		
Australia (2016)	Yes	Yes (The template workbook enables the PBAC to validate the presented estimates)	
Brazil (2012)	Yes	Yes	

BIA primary elements	**Validation**	
BIA secondary elements	Value of the information analyses (the cost of extra data collection vs improved model precision)	The programming created by the developer of the budget impact model to perform the analysis (source code) should be made available for review (on the condition that property rights are
ISPOR (2014)		
Canada (2007)	Yes	Yes
Belgium (2012)		
France (2018)		Yes
Ireland (2018)		
Poland (2016)		
UK (2017)		
Australia (2016)		
Brazil (2012)		Yes

BIA primary elements	**Validation**	
BIA secondary elements	Model code should be provided to reviewers	Post-market re-assessment: the observed costs in a health plan with the current interventions should be compared with the initial-year estimates from a BIA.
ISPOR (2014)		Yes
Canada (2007)	Yes	Yes
Belgium (2012)		
France (2018)		
Ireland (2018)		
Poland (2016)		
UK (2017)		Yes
Australia (2016)		Yes
Brazil (2012)		

BIA primary elements	**Validation**	**Inputs and Data Sources**
BIA secondary elements	Quality assurance and publication	Recommended data sources
ISPOR (2014)		Yes
Canada (2007)		Yes
Belgium (2012)		
France (2018)		Yes
Ireland (2018)		Yes
Poland (2016)		
UK (2017)	Yes (For all resource impact products)	Yes (quite comprehensive list)
Australia (2016)	Yes (Quality use of medicines)	
Brazil (2012)		Yes

BIA primary elements	**Inputs and Data Sources**	
BIA secondary elements	Search strategy; inclusion criteria for data selection and source selection; strengths and weaknesses of the used sources, and methods of analysis should be presented	Use data from another jurisdiction where the intervention has been introduced
ISPOR (2014)		Yes
Canada (2007)		Yes
Belgium (2012)		
France (2018)		
Ireland (2018)		Maybe (might not be realistic in Ireland)
Poland (2016)	Yes	
UK (2017)		
Australia (2016)		
Brazil (2012)		Yes (health systems comparable to the Brazilian system)

BIA primary elements	**Inputs and Data Sources**		
BIA secondary elements	Use estimates of expected market share from the producer	Extrapolate from experience on product diffusion with similar interventions in the budget holder's setting.	Data could be sourced from clinical trials
ISPOR (2014)	Yes	Yes	Yes
Canada (2007)	-	Yes	Yes
Belgium (2012)			
France (2018)			
Ireland (2018)	-		Yes
Poland (2016)			
UK (2017)			
Australia (2016)			
Brazil (2012)			

BIA primary elements	**Inputs and Data Sources**	
BIA secondary elements	Unpublished data sources, such as expert panels	Original cost survey, obtaining primary data, by sampling, involving interviews with health professionals under study
ISPOR (2014)	Yes	
Canada (2007)	Yes	
Belgium (2012)		
France (2018)		
Ireland (2018)	Yes	
Poland (2016)	Yes (taking into account the existing Risk Sharing Schemes)	
UK (2017)		
Australia (2016)		
Brazil (2012)	Yes	Yes

BIA primary elements	**Presenting results**		
BIA secondary elements	The estimated annual total and incremental budget impacts should be reported separately for each year of the time frame	Results should be reported in terms of their natural units and financial cost	Introduction, study design and methods, results, conclusions and limitations
ISPOR (2014)	Maybe (a table should show the total and disaggregated costs for each time period reported in		Yes (very detailed)
Canada (2007)	Only incremental impact		Yes (not described in details)
Belgium (2012)			
France (2018)	Yes		
Ireland (2018)	Yes	Yes	Yes (not described in details)
Poland (2016)	Yes		
UK (2017)			
Australia (2016)	Yes		
Brazil (2012)			

BIA primary elements	**Presenting results**		
BIA secondary elements	All results should be presented in their disaggregated and aggregated forms for each year of the timeframe	Resource impact products: resource planner; resource impact reports and templates; resource impact statement	Inclusion of graphics and figure of the analytical framework, schematic representation of uncertainty analyses
ISPOR (2014)	Yes (results should be presented in a disaggregated manner)		Yes
Canada (2007)	Yes (results should be presented in a disaggregated manner)		
Belgium (2012)	Yes (results should be presented in a disaggregated manner)		
France (2018)	Yes		
Ireland (2018)	Yes		
Poland (2016)	Yes (results should be presented in a disaggregated manner)		
UK (2017)	Yes (results should be presented in a disaggregated manner)	Yes	
Australia (2016)	Yes (according to the PBS and the RPBS, and for beneficiary type)		
Brazil (2012)			

BIA primary elements	**Presenting results**	
BIA secondary elements	Table of assumptions, Tables of inputs and outputs, Appendices and References	The addition of relevant appendices to the main report is encouraged. The Appendices may cover literature search strategies, evidence summaries, intermediate results (e.g., of individual Delphi panel rounds), and the names and addresses of participating experts and investigators, etc.
ISPOR (2014)	Yes	Yes
Canada (2007)		
Belgium (2012)		
France (2018)		
Ireland (2018)		
Poland (2016)	Yes	
UK (2017)		
Australia (2016)		
Brazil (2012)	Yes	Yes

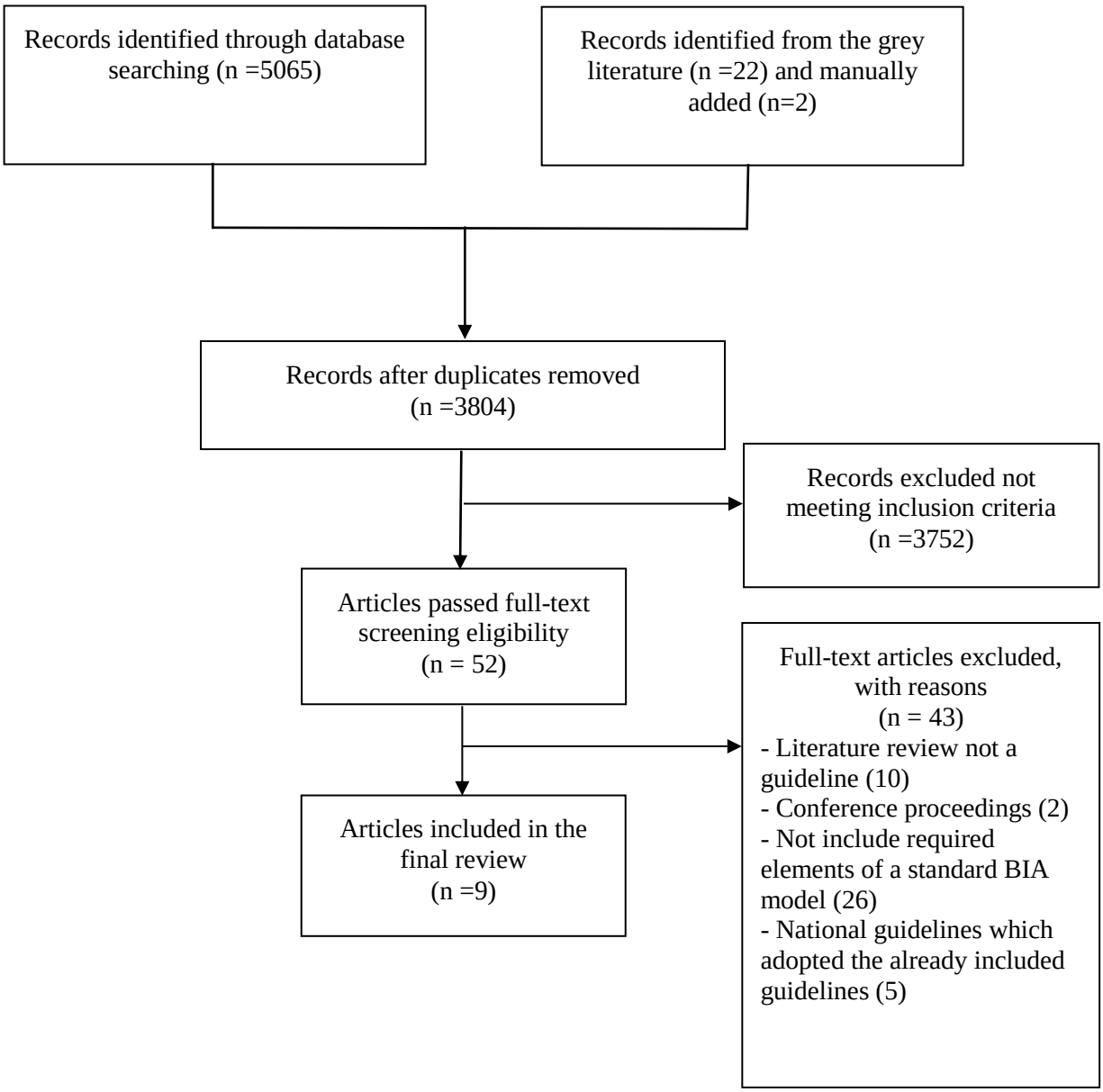

Figure 1: PRISMA flow diagram of search results.

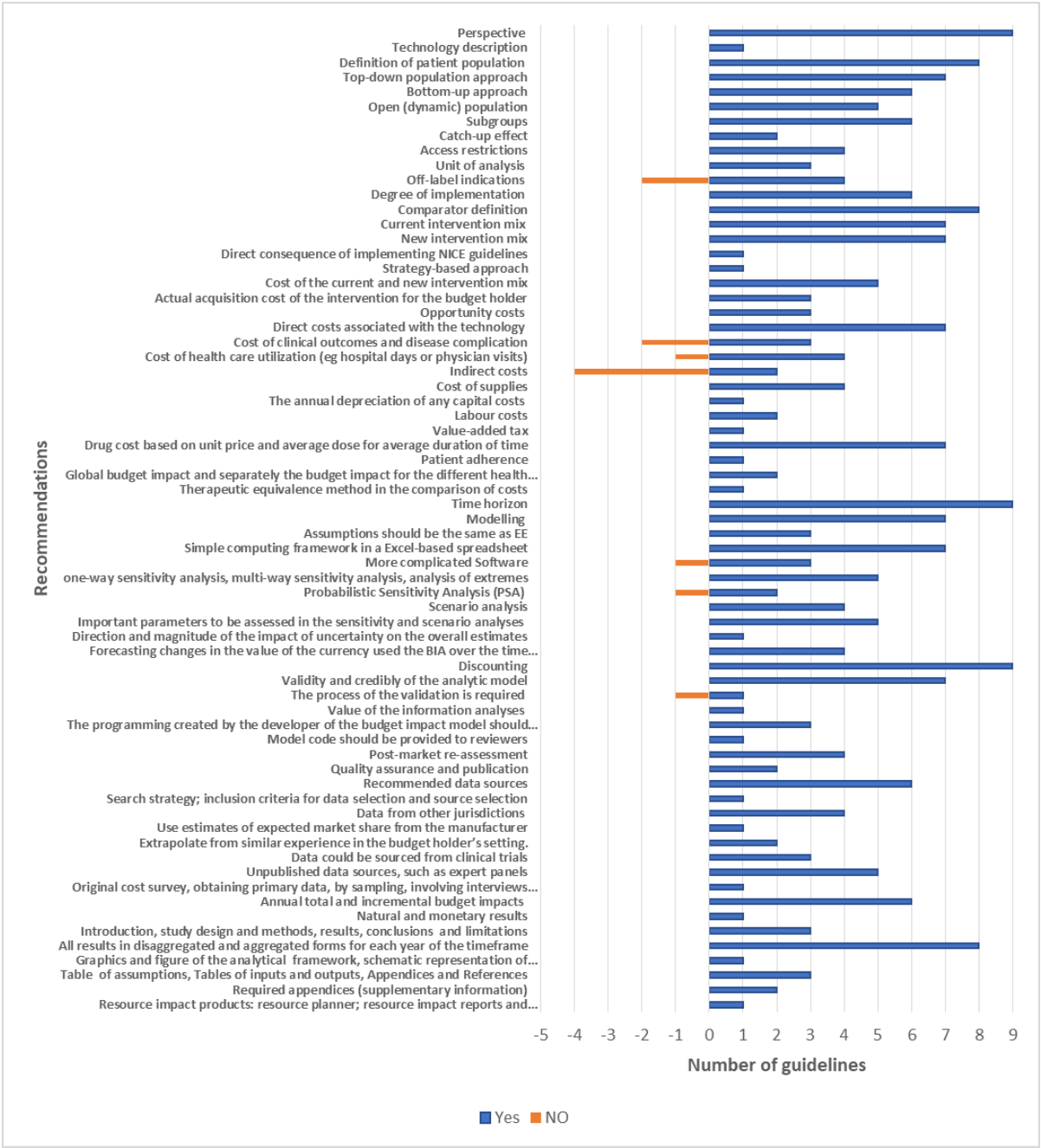

Figure 2: A schematic list of BIA recommendations in the reviewed guidelines. The positive and negative recommendations are illustrated in different colors.

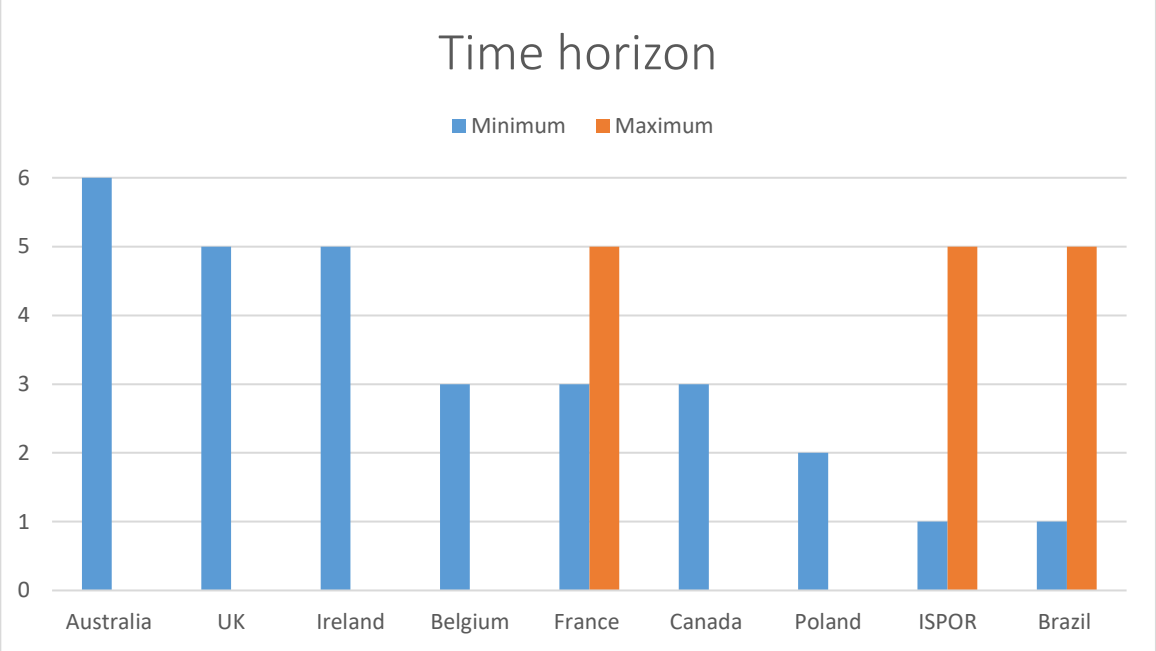

Figure 3: Time horizon recommended by nine reviewed guidelines. A range of time horizon is illustrated (in different color) for the guidelines/countries, if applicable.

Appendix 1: Systematic literature review process

Medline, EMBASE, Cochrane, EconLit, CINAHL, Business source, Ovid Healthstar and the grey literature including INAHTA and non-INAHTA members (e.g. NICE, PHARMAC) as well as EUnetHTA, HTAi, iHEA and ISPOR were searched using a combination of text words and Medical Subject Headings terms and synonyms of budget/ financial analysis, guidelines, and methodology/ modeling. The keywords used for the searches are as following:
Search strategy

MEDLINE:

Budget impact/ budgetary impact/ resource impact/ financial impact analysis/assessment/ studies

1. "budget impact*".m_titl.
2. "budgetary impact*".m_titl.
3. budget impact analy*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4. budgetary impact analy*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5. budget impact stud*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6. financial impact*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7. "economic impact*".m_titl.
8. "economic analy*".m_titl.

Review; guidance; guidelines; methods

9. review.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10. limit 9 to "review articles."
11. "Review Literature as Topic"/
12. "review*".m_titl.
13. "guideline*".m_titl.
14. limit 13 to abstracts
15. "guidance*".m_titl.

16. limit 15 to abstracts
17. Methods/
18. "method*".m_titl.
19. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
20. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
21. 19 and 20

#HITs: 120

The grey literature list

Websites of health technology assessment or regulatory agencies

Country	Agencies
Inter/Multi-National	International Network for Agencies for Health Technology Assessment (INAHTA); Health Technology Assessment International (HTAi); International Society For Pharmacoeconomics and Outcomes Research (ISPOR); WHO Health Evidence Network; European Information Network on New and Changing Health Technologies (EUROSCAN). The University of Birmingham. National Horizon Scanning Centre; European network for health technology assessment (EUnetHTA)
Australia	Department of Health and Aging (https://pbac.pbs.gov.au/)
Austria	Institute of Technology Assessment (ITA); Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Belgium	Federal Kenniscentrum voor de Gezendheidszorg (KCE)
Canada	Canadian Agency for Drugs and Technologies in Health (CADTH) Provincial drug plans: • http://www.health.gov.on.ca/en/pro/programs/drugs/drug_submissions/guideline_templates.aspx • https://www.ab.bluecross.ca/dbl/pdfs/bia-form.docx • https://www.gov.mb.ca/health/mdbif/sub.html • http://www.inesss.qc.ca/fileadmin/doc/INESSS/Inscription_medicaments/Fiches_inscription/en/Submission_guidance_document.pdf
China	National Health Development Research Center (NHDRC); Key Lab of Health Technology Assessment
Denmark	Danish Centre for Evaluation and Health Technology Assessment (DCEHTA); Danish Institute for Health Services Research and Development (DSI)
Finland	Finnish Office for Health Care Technology and Assessment (FinOHTA).

France	L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES). Ministere de la Santé, de la Famille, et des Personnes handicappés; Committee for Evaluation and Diffusion of Innovative Technologies (CEDIT); French National Authority for Health (HAS) Department of Economics and Public Health Assessment
Germany	German Institute for Medical Documentation and Information (DIMDI)
Israel	Israel Center for Technology Assessment in Health Care (ICTAHC)
Netherlands	College voor Zorgverzekeringen/Health Care Insurance Board (CVZ); Health Council of the Netherlands
New Zealand	New Zealand Health Technology Assessment Clearing House for Health Outcomes and Health Technology Assessment (NZHTA)
Norway	Norwegian Centre for Health Technology Assessment (SMM)
Poland	Agency for Health Technology Assessment (AHTAPol)
Sweden	Centre for Medical Technology Assessment (CMT); Swedish Council on Technology Assessment in Health Care (SBU)
Switzerland	Swiss Network for Health Technology Assessment; Institute for Innovation and Valuation in Health Care (INNOVAL)
Thailand	Health Intervention and Technology Assessment Program (HiTAP)/ International Health Policy Program (iHPP)
UK	National Health System (NHS) National Institute for Clinical Excellence (NICE) • https://www.nice.org.uk/about/what-we-do/into-practice/resource-impact-assessment • https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/budget-impact-test • https://www.nice.org.uk/about/what-we-do/into-practice/forward-planner • https://www.nice.org.uk/about/what-we-do/into-practice/forward-planner#view
USA	Agency for Healthcare Research and Quality (AHRQ); ECRI Institute; Institute for Clinical Systems Improvement (ICSI); Blue Cross and Blue Shield Association's Technology Evaluation Center (TEC)

Appendix 2: Countries with developed BIA guidelines and the types of drug programs where they are applied.

1. In Australia, there is a government-run Pharmaceutical Benefits Scheme (PBS) that subsidizes prescription medication, and there is a co-payment for patients at the point of dispensing [1]. The BIA guidelines as a part of the Australian guidelines on the preparation of new drug submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) (2016) is the first full revision of PBAC guidelines since 2006. After 2010, any recommendation by PBAC that has a financial impact on the Federal government's budget is reviewed by the cabinet [2]. There is a close relationship between the estimated financial impact of a drug on the Australian drug budget and the rate of PBAC positive recommendations for reimbursement [3].

2. Belgium has a Bismarck-type social insurance system (multi-payer) in which the insurers, called Sickness Funds, are financed by both employers and employees [4]. In Belgium, since 2002, Health Care Knowledge Centre (KCE) under the supervision of the Minister of Public Health and Social Affairs is in charge of conducting studies that support the political decision making on health care and health insurance [5]. The Belgian guidelines for economic evaluations now include guidance for a BIA in an updated version (2015). The Belgian official HTA [6] institute, KCE,

and Belgian stakeholders from both government and industry contributed to improving their recent national economic evaluations and BIA guideline [5].

3. In Brazil, the Unified Health System (SUS) provides free universal care for all Brazilians as well as vaccinations and pre-natal care. A highly decentralized system has led to complex patterns of funding and service provision with the Federal, State and Municipal governments involved. Brazil's system remains highly privatized with the private sector receiving substantial funds from all levels of government [7]. Brazil [Ministry of Health (CONITEC)] has been developing the necessary analytical instruments for the evaluation of new technologies for health. In this context, the development of national recommendations for budget impact studies in the health area became more important. The methodology for the development of budgetary impact studies in the health area was adapted to the Brazilian needs, through several presentation and discussion sessions among the professionals of the institutions involved [8].

4. Canada is an example of a “National Health Insurance” model. Canada’s publicly funded health care system is called “Medicare” in which ten

provincial and three territorial health care insurance plans share roles and responsibilities for health care services with the Federal government [9]. Drug benefit funding is primarily a composite of provincial/territorial governments and private insurance programs. Federally, the Patented Medicine Prices Review Board (PMPRB) sets ex-factory price ceilings for patented medications [40]. Although a BIA had been required to be submitted to most provincial public drug plans in the 1990's, before 2007, there was no standardized method of conducting a BIA in Canada. In 2005, PMPRB initiated the development of the Canadian BIA Guidelines on behalf of the National Prescription Drug Utilization Information System (NPDUIS), and this was published in 2007 [9].

5. In France, the pharmaceutical reimbursement decision-making process consists of two steps: a) the technical assessment by French national authority for health (HAS) and b) enlisting the drug with price-fixing by the "health care products pricing committee" of the Ministry of health (CEPS). Since January 2016, CEA [10- 11] and BIAs are required to be submitted by manufacturers to HAS and CEPS for highly specialized medicines with an expected 2-year sales revenue more than €50M [10-11]. In France, BIA for new drug submissions should be prepared for the French statutory social insurance scheme. HAS updated the French BIA

guidelines for new drug submissions in Dec. 2017, however, it is not still clear that how BIA results would be applied in the reimbursement price negotiation process.

6. The Republic of Ireland has a new NHS which was launched in 2005 and is controlled by the Health Service Executive (HSE) [12]. The Irish "Health Information and Quality Authority" (The Authority) has the responsibility to evaluate the clinical and cost-effectiveness of health technologies, and provides evidence-based reports to the Minister of Health and HSE and develops guidelines for doing HTA in Ireland. The latest updated version of the Irish BIA guidelines on health technologies was published by The Authority in 2018 [13].

7. Healthcare in Poland is primarily financed by the National Health Fund (NFZ) and state budget or local government budgets. The state budget plays a complementary role in NFZ in the system. The primary role of the local governments is to ensure access to the services, mostly by performing ownership functions towards healthcare institutions. In Poland, the BIA guidelines are a part of the latest updated Health Technology Assessment guidelines which initially issued by the Agency

for Health Technology Assessment and Tariff System (AOTMiT) in 2007 and were updated in 2009 and 2016 [14].

8. National Health System (NHS) in the United Kingdom is an example of a single-payer health care system for a country. In the UK, the National Health Service (NHS) institution in England and Wales pays for medicines if NICE provides a favorable recommendation. NICE published their updated guidelines on the resource impact (budget impact) assessment process on May 2017. It is proposed that a cap called "budget impact test [15]" of £20 million, in any of the first three years, be considered to signal the need for negotiation with manufacturers for special arrangements to better manage the introduction of new technologies recommended by NICE [15]. Moreover, NICE has recently proposed a Fast Track technology Appraisal (FTA) process for the new technologies which fall below an incremental cost-effectiveness ratio of £10,000 per QALY [16]. The budget impact test would be removed as a criterion for entry into the FTA [23] process [21, 24]

References

1. Four healthcare systems divided by the English language: Australia, Canada and Ireland have universal healthcare systems, although run on

different lines to Britain's NHS. And then there is the USA. 2011, The Guardian.

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CHAPTER 3

A comparison of pharmaceutical budget impact analysis (BIA) recommendations amongst the Canadian Patented Medicine Prices Review Board (PMPRB), public and private payers

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Abstract

The Canadian budget impact analysis (BIA) guidelines were published by the Patented Medicine Prices Review Board (PMPRB) in 2007. Some Canadian Federal, provincial and territorial (F/P/T) drug plans have updated their BIA guidelines since then. The aim of the present review was to provide a comprehensive list of the key BIA recommendations in different Canadian F/P/T drug plans and private payer and to highlight the differences between those guidelines and requirements and recommendations in the 2007 Canadian PMPRB BIA guidelines. We searched the websites of fifteen F/P/T public drug benefit programs including the Canadian Agency for Drugs and Technologies in Health (CADTH) and non-insured health benefit programs (NIHB) and 5 private payers' websites. An Excel-based data abstraction form was designed to highlight differences between recommendations relating to the BIA key elements made by different guidelines. Seven F/P/T public and private BIA guidelines (Alberta, British Columbia, Manitoba, Ontario, Quebec, CADTH, Medavie Blue Cross) were reviewed, and a comprehensive list of recommendations was abstracted. Recommendations were similar in terms of time horizon duration; comparators; target population assessment and using direct drug costs in BIAs. Differences were mostly relating to actual acquisition cost such as to include or not to include markups and dispensing fee, patient's perspective, cost of supplies, cost of healthcare utilization, scenario analysis. The recommendations that were not

included in the PMPRB BIA guidelines in 2007 but were subsequently included in at least one of the Canadian F/P/T or private guidelines were related to the inclusion of the patients' perspective (i.e., co-payment), the costing, the handling of uncertainty and the reporting format. The present study is a comparative review of recommendations in the Canadian 2007 PMPRB and F/P/T and private payers' BIA guidelines. The review provides a most up-to-date list of recommendations which could be applied towards a revision of the Canadian BIA guidelines which would apply to both public and private payers BIA requirements for new drug submissions in Canada.

Key Points for Decision Makers

- Only six out of 15 federal, provincial and territorial (F/P/T) drug plans [i.e., those of Alberta, Ontario, British Columbia, Manitoba, Quebec and the Canadian Agency for Drugs and Technologies in Health (CADTH)] have published their budget impact analysis (BIA) requirements for drug submissions on their websites. For private payers, very limited information is available online.
- There was more consistency between the F/P/T BIA requirements and the Patented Medicine Prices Review Board (PMPRB) 2007 BIA guidelines, compared with private payers. Private payers' requirements were not included in the PMPRB 2007 BIA guidelines.
- There is a discordance between F/P/T BIA recommendations and the PMPRB 2007 BIA guidelines, including the cost of health care utilization (e.g., Manitoba), scenario analysis (e.g., Quebec), the patients' perspective (e.g., Alberta), and reporting total, gross and net impact on the budget (e.g., Quebec) in BIAs, which were not discussed in the PMPRB 2007 BIA guidelines.

Keywords: Budget impact analysis, financial impact, resource impact assessment, pharmaceutical, reimbursement, new drug submissions, guidelines

1. Introduction

Canada is among the highest spenders on health care in the Organization for Economic Co-operation and Development (OECD) [1, 2]. In Canada, public insurance covers only 43% of prescription drugs cost, while the remainder is paid by private payers (35%) or patients (out-of-pocket). In the public sector, provincial/territorial programs and federal direct drug subsidy programs are the main payers. In the private sector, payers include private health insurance and either households or individuals paying out of pocket [1, 2].

1.1.Drug pricing and reimbursement in Canada

In Canada to obtain public reimbursement cost-effectiveness reports are prepared by manufacturers in accordance with the Canadian Agency for Drugs and Technologies in Health (CADTH) economic evaluation guidelines [3] (submitted to Common Drug Review (CDR), the pan-Canadian Oncology Drug Review (pCODR) [4]) and/or the Institut national d'excellence en santé et en services sociaux (INESSS) in Québec [5]. Drug submissions that received a positive listing recommendation will be submitted to the pan-Canadian Pharmaceutical Alliance (pCPA) for price negotiations (for the provincial price negotiation including Quebec) [6]. All provinces participating in the pCPA process require the submission of a BIA that applies to their jurisdiction. The federally operated drug programs [i.e., Non-Insured Health Benefits Program (NIHBP)] and private

payers also require BIA reports for new drug submissions.

For patented drugs, since 1988, the Patented Medicine Prices Review Board (PMPRB) regulates and defines the ceiling price, i.e., the non-excessive price. Figure 1 illustrates PMPRB as part of Canada's pharmaceutical regulatory and reimbursement system. In 2005, PMPRB initiated the development of the Canadian BIA Guidelines on behalf of the National Prescription Drug Utilization Information System, and this was published in 2007 [7, 8]. The guidelines were initially developed to provide a standard for BIA accompanying new drug submissions to public drug plans. This was supplemented with an interactive Excel-based template to address provincial differences in drug regulations (e.g., drug prices, markups, professional fees, co-payments, discounts and cost analyses). However, over the last few years some Federal, Provincial and Territorial (F/T/P) drug plans have updated their specific BIA requirements [9-12]. The present study will provide a most up-to-date list of recommendations which could be applied towards a revision of the Canadian BIA guidelines and with the perspective of meeting the BIA requirements for new drug submissions to either public or private drug plans in Canada. We used the results of the present study and our previously published literature review [13] to create a comprehensive list of recommendations relating to three key elements of designing a BIA (i.e., analytical model structure, input and data sources, and

reporting format). The two systematic reviews were complimentary with regard to drafting a consultation proposal for obtaining the Canadian stakeholders' feedback on the BIA recommendations. A standard abstraction form was developed for extracting data from BIA guidelines by Foroutan et al. [13] and was applied for abstracting data from the Canadian public and private plans' BIA guidelines in the current study. The first literature review [13] focused on national and transnational BIA guidelines including Australia [14], Canada[3] [7], United Kingdom (UK) [15], Belgium [16], Ireland [17], France [18], Poland [19], Brazil [20] and ISPOR[4] [21] whereas in the present study we performed a comparative review of the Canadian public, private and PMPRB 2007 BIA guidelines.

2. Methods

The websites of CADTH (i.e., CDR and pCODR), pCPA, Canadian F/P/T drug plans (public drug plans which participate pCPA negotiations) and 5 private payers (chosen from a list of private payers for drug submissions in our partner consultant company database) were manually searched (May 2018) for budget impact analysis guidelines, BIA guidance documents or (Excel-based) templates for new drug submissions. The first author also contacted private drug plans to get their BIA templates for new drug submissions. A total of 14 F/P/T public

[3] PMPRB 2007 BIA guidelines
[4] International Society for Pharmacoeconomics and Outcomes Research

drug benefit programs (including Quebec), pCODR (CADTH) and 5 private payers' website were searched (Table 1a and 1b). Where guidelines were available in both English and French, we used the English version for our review. When a BIA guideline was updated, we only included the latest version of the BIA guideline in order to avoid duplication in data abstraction. In the present study, we used our standard Excel-based data abstraction form- which was developed in our previous peer-reviewed systematic literature review of national and transnational BIA guidelines [13]- for data abstraction. Then we highlighted similarities and differences between recommendations related to the BIA key elements provided by the Canadian PMPRB and F/P/T BIA guidelines or templates.

3. Results

BIA guidelines for Canadian publicly funded drug program were from Alberta [11], Ontario [9], Manitoba [10], Quebec [12], British Columbia[5] and CADTH (PCODR) [22] (Table 1a, Appendix 1). Only one BIA checklist for new drug submissions was found for private payers (Table 1b). Some private payers (e.g., Green Shield, Tellus Health Benefits and Payment solutions) in Canada use Academy of Managed Care Pharmacy (AMCP) document (United States) [23] as

[5] British Columbia's BIA requirements are consistent with the standards published in the PMPRB BIA guidelines

their template for BIA (which is adopted ISPOR[6] BIA guidelines).

Table 2 provides a summary of the recommendations relating to the BIA key elements extracted from the reviewed BIA guidelines, highlighting the similarities and differences amongst the recommendations in the PMPRB and Canadian F/T/P and private BIA guidelines/templates. A comprehensive list of recommendations was extracted from eight reviewed guidelines. The following sections provide a synthesis of the key similarities and differences among the eight guidelines.

Analytical model structure

Perspective

The perspective of the healthcare budget holders in Canada (public and private drug plans) should be adopted in conducting a BIA [7, 9-12, 24]. In Manitoba, BIA should be reported for the Manitoba Health, Seniors and Active Living Pharmacare program and additional information may be requested for drugs that significantly impact other Manitoba Provincial Government-sponsored drug programs [10]. In Alberta, "Alberta Health" sponsored drug programs' perspective should be taken for all BIAs [11] (e.g., not the entire health care system). Inclusion of the patients' perspective in addition to the primary payers'

[6] International Society for Pharmacoeconomics and Outcomes Research

perspective (in the case of co-payment) is recommended in the PMPRB BIA guidelines as a supplement to the base-case analysis [7, 24] as per drug plans requirement (i.e., Alberta and Quebec).

Time horizon

The recommended time horizon in the PMPRB and F/P/T and private BIA guidelines is 3 years [7, 9-12].

Modeling

Ontario, British Columbia and the 2007 PMPRB BIA guidelines [7, 9, 24] provided an Excel-based template for reporting BIA results. Only the 2007 PMPRB BIA guidelines [7, 24] recommended testing the face, internal and external validity of the structured BIA model.

Target population

The target population is defined as "all drug plan beneficiaries who are expected to be diagnosed and treated for the conditions of interest and are eligible to use the new drug" [9-12]. For the target population estimation, there are two broad approaches: Top-down or epidemiological and bottom-up or claims-based

(market-share) analyses. An epidemiological approach is usually preferred if the submission indicates a superior therapeutic conclusion in clinical studies, whereas a market-share approach might be preferred if the submission indicates a non-inferior therapeutic conclusion.

The private payer, whose BIA checklist was included in the review, did not explicitly mention anything about the analysis for target population assessment. Private payers who use United States AMCP template, adopt ISPOR BIA guidelines which apply only top-down population assessment approach. In Canada, public plans accept both approaches. In Alberta, in the absence of epidemiologic data (e.g., disease prevalence), claims data could be applied with justification for calculating prevalence in this manner and necessary assumptions and sources appropriately cited [11]. In the epidemiological analysis, disease severity shifts, incidence, and prevalence are required, and it is usually inevitable to use data from different sources [7, 24]. In Manitoba, the prevalence of the disease state and/or indication for which the medication is intended for the total Manitoba population and for the population covered by the Manitoba Pharmacare Program should be provided [10]. A list of all new and currently covered indications for the proposed new medication and shifts in the target population or market expansion is recommended in the Alberta, Ontario and Manitoba BIA guidelines [9-11].

Comparators

According to the 2007 PMPRB BIA guidelines, reference scenario is the current market share distribution of all comparators without new drug, whereas new drug scenario is forecasted market share of same comparators with the inclusion of the new drug [7]. One should note that comparator mix doesn't necessarily always match the comparator mix in the utilization [real world] of the different comparators that private payers see in their database, and that could be due to differences in the public versus private formularies. Choice of the comparators is important which is sometimes consistent with the economic evaluations and sometimes not.

Costing

Clear costing methods description is required in all provincial guidelines, and the inclusion of cost items is directly related to the chosen perspective [9-12, 24]. The costs associated with changes in outcomes, disease complications, adverse drug reactions and resource utilization (e.g., hospitalization, ER admission) are excluded from BIA [9-12]. Manitoba requires reporting any significant impact on health care services (e.g., laboratory testing, diagnostic testing, etc.) if applicable [10]. The BIA should clearly state which unit of analysis is adopted in measuring the outcomes [9-11]. According to Ontario and Manitoba BIA requirements, in the case of medications where recommended duration of use is less than 30 days

(e.g., antibiotics), this should be specified and the cost calculated accordingly [9, 10]. All provincial guidelines require reporting total and incremental impact on the budget in BIAs. Drugs which require reconstitution or dose preparation, the method of dose preparation, dose stability and specifics around potential drug wastage [22]. INESSS and pCODR require the cost of supplies to the manufacturer and the payer, and any cost of companion diagnostic test or medical device should be reported [12, 22].

Some of the BIA guidelines recommend that the cost of the treatment should be adjusted to consider the markups [25], discounts, inventory charges , business-related costs to the pharmacy covered by the drug plans, dispensing fees and/or patient co-payments, as requested by drug plans [7, 10, 12, 24]. Regulations for covering markups (caps) are different across Canadian provinces. For instance, in Ontario, there is a provincial 8% markup cap (6% for high-cost drugs) [25], however markups[7] [25], and dispensing fees should be excluded in BIA reports [9]. In contrast, in Alberta, effective May 2018, the Manufacturer List Price (MLP) is the price published in the Alberta Drug Benefit list plus the wholesaler (3%) and pharmacy (7% up to $100) allowable upcharges and the dispensing fee ($12.5) and if applicable, the Least Cost Alternative (LCA) price for relevant drug comparators is recommended [11]. Also in Manitoba total drug cost/patient/month

[7] "Markup" and "upcharge" are used interchangeably.

should be based on the actual acquisition cost (AAC) of the medication which includes the whole cost borne by the pharmacy; therefore, the AAC may include a wholesaler markup, if applicable [10]. The PMPRB BIA guidelines [7, 24] and Ontario [9] have provided Excel-based templates for reporting BIAs. Other provinces have put a request for submitting BIA results accompanying methods of calculations (spreadsheets).

Only in the PMPRB BIA guidelines and British Columbia [7, 24] using inflation rates permitted if there is justification for being included (e.g., confirmed information on pricing policy, implementation of an approved new policy rule shortly or price changes after patent expiration).

Inflation and discount rates are not applied, however, in the Canadian guidelines, they are permitted in the certain circumstances and if there is justification for being included (e.g., confirmed the information on pricing policy, implementation of an approved new policy rule in the near future or price changes after patent expiration).

Modeling and model validity

All submitted models should be transparent, simple and include confidential prices at the same time. Excel-based electronic models would be preferred if they

have the ability to express results in either contract or fiscal years. In addition, it is recommended that the incident and prevalent patients and patients coming off the excess (if there is one), be shown in the model separately (e.g., in the case of biologics). Face, internal and external validity are recommended to be checked and documented. The model validity and transparency could be assessed using recommendations provided by ISPOR and the Society for Medical Decision Making task force report [26]. The detailed process of the validation is not required in the Canadian BIA. Programming code should be documented, annotated, and undergo quality assurance and control methods for software engineering. The programming created by the developer of the budget impact model to perform the analysis (source code) should be made available for review (on the condition that property rights are respected).

Handling uncertainty

One-way (univariate) deterministic sensitivity analysis or scenario analysis (multivariate) is acceptable for the most critical variables such as prices, population, and market shares. Alberta and Manitoba recommend one-way and/or multi-way sensitivity analyses for direct prescription costs and incremental prescription costs (savings) and an explanation of the methods used to calculate the sensitivity analyses must be included as well as the assumptions used in calculating the values [10, 11]. Sensitivity analysis of drug dosage and duration [9], and cost of supplies for manufacturers [12] are also recommended. Scenario analysis is recommended in Quebec [12].

Input and data sources

Based on our analysis, regarding clinical safety and efficacy and market data (e.g., degree of implementation in the market) it is accepted to use data from other jurisdictions in case of lack of real-world information for a specific disease/ new drug (e.g., rare disease). Epidemiologic data should be captured from Canadian statistics as much as possible. Cost transfers from other jurisdictions are not accepted. In most of the reviewed guidelines including the PMPRB BIA guidelines [7, 24], epidemiologic data (e.g., disease prevalence and incidence) has to be obtained from national and provincial statistics and registries. In Manitoba, data should ideally be Manitoba specific and not simply an extrapolation of Canadian national data or data from other provinces to the Manitoba population. If Manitoba specific data is not available, a justification for why this is so must be provided [10].

The best sources for the claims-based and market research information are the payer database and the manufacturer's marketing department [7, 8]. In the PMPRB, Alberta, and Manitoba BIA guidelines data from foreign markets are accepted if local data are not available [7, 10, 11, 24]. The BIA reports from manufacturers with clear supporting data could also be helpful in the PMPRB,

Alberta, and Manitoba guidelines [7, 10, 11, 24]. Consensus expert opinion is an option when market intelligence for forecasting the new drug market share is not available [7, 8, 24].

Presenting results

There are a few specific requirements for reporting the results mentioned in the reviewed guidelines. In general, total and incremental impact on the primary payer's budget should be presented [9, 10]. Results should be both aggregated and disaggregated in each year of the time horizon [7, 10, 12, 24]. A table of assumptions, inputs, and outputs, a schematic representation of any uncertainty analyses (e.g., Tornado diagram), appendices, references [11] and net[8] and gross[9] impact [12] should be included.

4. Discussion

We conducted a comparative review amongst the Canadian BIA guidelines available from the PMPRB, F/T/P jurisdictions and private drug plans. A comprehensive list of recommendations was abstracted from seven reviewed guidelines. Table 2 summarizes the similarities and differences between the 2007

[8] Net impact: The incremental cost associated with coverage of the drug of interest.
[9] Gross impact: The anticipated sales of the drug of interest for each of the first 3 years after the coverage is granted for it

PMPRB, F/P/T and private payers BIA requirements.

The similarities amongst the different BIA guidelines include a time horizon of 3 years, terminologies used for defining current and new scenarios, the epidemiologic data requirements for the proposed indications, the real-world market analysis information, the market share or market capture estimates for the new drug and comparators, and the direct drug costs to be used in the BIAs. Limited information was available regarding private payers' BIA requirements.

There are differences among provincial BIA guidelines in terms of nature and number of the recommendations provided for analysts to conduct comprehensive BIA reports based on the provincial drug plans' requirements (e.g., actual acquisition cost such as to include or not to include markups and dispensing fee, supplementary patient's perspective, cost of supplies, cost of healthcare utilization, scenario analysis and providing Excel-based templates for cost analysis). To address these differences that were evident also in 2007 [7], the PMPRB BIA guideline was supplemented by an interactive Excel-based template and provided general rules for conducting a BIA that could help policymakers with formulary and reimbursement decisions [7, 8]. The most likely explanation for differences amongst the provinces is the fact that provinces have different

inclusion criteria for the coverage eligibility (target population); access to new drug; pricing regulations for generic and brand drugs, allowable markups (upcharges), dispensing (professional) fees, and patient co-payments [25].

There are also differences among the updated provincial and the 2007 PMPRB guidelines for which the most suitable explanation is the passage of time and the development of more sophisticated BIA guidelines in which the later guidelines capture the inclusion of patient's perspective as supplementary to the base-case analysis, in case of co-payment [11]; clear description for unit of analysis in the population and cost analyses [9-11]; degree of implementation of the new intervention (i.e., substitution, combination and expansion) [9-12]; significant impact on health care services (e.g., laboratory testing, diagnostic testing) [10]; cost of supplies [12]; Least Cost Alternative (LCA) price for relevant drug comparators [11]; scenario analysis [12]; gross and net impact on the budget [12] and detailed recommendations regarding inclusion of graphics and figure of the analytical framework, schematic representation of uncertainty analyses, table of assumptions, tables of inputs and outputs, appendices and references [10, 11].

There are literature reviews as part of the Canadian [7], Belgian [16] and French [18, 27] BIA guidelines. Our review is an update to the literature review published

by Marshall et al. in 2008 [7]. They made a side-by-side comparison between the PMPRB 2007 BIA guidelines [8] and the Canadian provincial, other national and transnational BIA guidelines of that time, i.e., Alberta (2006), Manitoba (2003), Ontario (2006), Poland (2004), Australia (2002) and ISPOR (2007). In their review, they highlighted differences in the BIA costing approach, perspective, time horizon, opportunity cost, the definition of target population and methods for performing sensitivity analysis between the PMPRB 2007 BIA guidelines and the others [7]. When comparing the results obtained in this review with BIA guidelines around the world (Australia [14], United Kingdom (UK) [15], Belgium [16], Ireland [17], France [18], Poland [19], Brazil [20] and ISPOR[10] [21]) we identified that considerable number of recommendations related to BIA key elements including the open (dynamic) population, subgroups analysis in the target population assessment, catch-up effect (for chronic conditions and treatment switch), off-label indications in the eligible population assessment, opportunity costs, cost of clinical outcomes and disease complication, indirect costs, capital costs, staff training costs, applicable tax, patient adherence, total and incremental budget impact for the different health care payers, complicated modelling methods, Probabilistic Sensitivity Analysis (PSA) and scenario analysis for handling the uncertainty were not included or discussed differently in the 2007 PMPRB guidelines. Most of the Canadian provincial recommendations were in line with other reviewed guidelines except for recommendations as following: (1)

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Least Cost Alternative (LCA) price for relevant drug comparators is only mentioned in Alberta [11], (2) sensitivity analysis for drug dosage and duration in Ontario [9], (3) reporting gross impact on the budget is recommended in Quebec [12] and (4) for drugs which require reconstitution or dose preparation, the method of dose preparation, dose stability and specifics around potential drug wastage [22].

There were two important limitations to the current study including (1) only six (out of fifteen) F/P/T drug plans had published their template for BIA on their website and (2) there was limited information for private payers which were found online. Thus we had to contact some private payers to get the required information.

The output from the present Canadian study can be used in conducting a qualitative research project[11] and questionnaire[12] designed to obtain stakeholders' feedback and opinion on the relevance and applicability of the recommendations that were not included or were discussed differently in the 2007 PMPRB BIA guidelines. This would be the next step towards developing a proposal for

[11] For designing the interview guide and a closed survey
[12] Link to the survey: https://www.surveymonkey.com/r/F6KRRTZ

updating the guidelines.

5. Conclusion

The present study has provided a review of the current BIA guideline environment in Canada. It also identified where the PMPRB 2007 guidelines might not have kept pace with the evolution of BIA guidelines over the past decade. The study has provided a foundation for updating those guidelines which will occur after conducting a qualitative study to obtain Canadian stakeholders' feedback and opinion. Future work will also need to address the diversity of BIA needs across the different provincial and territorial programs.

6. Author Contribution

All authors contributed to the conception and planning of the work. Naghmeh Foroutan conducted the database search, data abstraction and the final descriptive analysis with input from Mitchell Levine. She also led the writing of this manuscript and was supervised by Mitchell Levine. All authors participated in the discussion that led to this paper and in the revision of all drafts. All authors approved the final version submitted for publication.

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8. Data Availability Statement

We provided required data as much as possible (in a summarized format) and there is no additional data to be shared.

9. Compliance with Ethical Standards

Conflict of interest: Naghmeh Foroutan, Jean-Eric Tarride, and Feng Xie have no conflicts of interest that are directly relevant to the contents of this article. Mitchell Levine is the chair of Patented Medicines Price Review Board (PMPRB), and Fergal Mills is a director at Innomar Consulting

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Table 1a: Summary of the searched F/P/T drug plans and their BIA guidelines or templates published on their websites.

#	**Federal, Provincial and Territorial Public drug benefit programs**	**Review BIA for new drug submissions***	**Template or guidelines**
1	Alberta (Prescription Drug Programs)	Yes	Budget Impact Assessment for the Alberta Drug Benefit List (Version 9, updated: May 2018) [11]
2	British Columbia (Pharmacare)	Yes	PMPRB BIA Guidelines (2007) [7]
3	Manitoba (Drug Benefits and Interchangeability Formulary)	Yes	Budget Impact Analysis for the Manitoba Health, Seniors and Active Living (Updated: April 2017) [10]
4	New Brunswick (Prescription Drug Program)	Yes	No information
5	Newfoundland (Pharmaceutical Services)	Yes	No information
6	Northwest Territories	No information	No information
7	Nova Scotia (Pharmacare)	Yes	No information
8	Nunavut	No information	No information
9	Ontario (Drug Benefit Program)	Yes	ODB financial impact estimates (2016) [9]
10	Prince Edward Island (Drug Cost Assistance Programs)	Yes	No information
11	Quebec (Prescription Drug Insurance)	Yes	Guidance document for submitting a request to INESSS (Updated: 2018) [12]
12	Saskatchewan (Drug Plan)	No information	No information
13	Yukon	No information	No information
14	Non-Insured Health Benefits Program (Federal Public Drug Benefit Programs)	Yes	No information
15	CADTH	Yes†	pan-Canadian Oncology Drug Review

			Submission guidelines [22]

F/P/T: Federal, provincial and territorial; *based on information found on the website; †non-specific BIA is required in the submission to the pCODR program

Table 1b: List of Canadian private health insurance companies included in this review.

#	**Private payers**	**Review BIA for new drug submissions***	**Template or guidelines**
1	Green Shield	Yes	AMCP‡ document (USA)[23]
2	Great-West Life	No information	No information
3	Express Scripts Canada	No information	No information
4	Medavie Blue Cross	Yes	BIA checklist for new drug submissions*
5	TELUS Health Benefits and Payment Solutions (Pharmacy Benefit Manager)	Yes	AMCP document (USA)[23]

*based on information found on the website or through contacting people who are responsible for reviewing BIAs, ‡AMCP Academy of Managed Care Pharmacy (United States)

Table 2: Summary of abstracted data of PMPRB and Canadian F/P/T BIA guidelines.

BIA primary elements	BIA secondary elements	Canada PMPRB (2007)	British Columbia	Alberta	Manitoba	Ontario	Quebec	CADTH (pCODR)	Medavie Blue Cross
Perspective									
	The recommended perspective is that of the **budget holder** range from a single payer covering an entire health care system through specific providers	Yes	Yes	Yes	Yes	Yes	Yes		
	Co-payment: Inclusion of patient's perspective is complementary to the base-case analysis			Yes					
Population Size and Characteristics									
	Definition of patient population (defined as individuals insured by drug plans of interest and have the condition of interest)	Yes	Yes	Yes	Yes	Yes	Yes		yes
	Top-down population approach: Estimation of the number covered by the locally approved indications	Yes (epidemiologic approach)	Yes (epidemiologic approach)	Yes (epidemiologic approach)	Yes (epidemiologic approach)	Yes (epidemiologic approach)	Yes (epidemiologic approac		

	for the new technology which needs to reflect uptake, and changes in patterns of use.						h)		
	<u>Bottom-up approach</u>: this starts from the number of individuals likely to avail of the technology. It includes the number of individuals that will switch from an existing technology and the number of newly treated patients. These estimates may be informed by existing claims-based data	Yes (claim-based approach)	Yes (claim-based approach)	Yes (claim-based approach)	Yes (claim-based approach)	Yes (claim-based approach)	Yes (claim-based approach)		
	Access restrictions	Yes	Yes						
	Unit of analysis (per patient or episode)			Yes	Yes	Yes			
	Off-label indications in the eligible population may also be included.	No (only in sensitivity analysis)	No (only in sensitivity analysis)						
	Degree of implementation of the new intervention (substitution, combination and expansion)			Yes	Yes	Yes	Yes		

Comparators									
	Definition	Yes (two scenarios, Reference and new drug scenario, should be compared for the **treatment-strategy**)	Yes	Yes	Yes	Yes	Yes		
	Current intervention mix for the eligible population (Forecasted version of the current market without the new drug)	Yes	Yes	Yes	Yes	Yes	Yes		
	New intervention mix (new drug scenario is forecasted version of the current market with introduction of the new drug)	Yes	Yes	Yes	Yes	Yes	Yes		
Costs and outcomes									
	Cost of the current and new intervention mix: Is determined by multiplying the budget holder's price for each intervention by	Yes (treatment strategy-based approach)	Yes (treatment strategy-based approach)	Yes	Yes	Yes	Yes	Yes	Yes

	proportion of the eligible population using that intervention and by the number of people in the eligible population.								
	Actual acquisition cost of the intervention for the budget holder: (including any discounts, rebates, or other adjustments that may apply).	Yes	Yes	Yes	Yes	No (markups and dispensing costs should be excluded)			
	The costs included should be limited to **direct costs** associated with the technology that will accrue to the relevant payer(s)	Yes (direct drug cost)	Yes (direct drug cost)	Yes (direct drug cost)	Yes (direct drug cost)	Yes (direct drug cost)	Yes (direct drug cost)		
	Cost of clinical outcomes and disease complication	No	No						
	Cost of health care utilization (eg hospital days or physician visits)	No	No		Yes [Significant impact on health care services (e.g., laboratory testing, diagnostic testing,				

					etc.)]				
	Indirect costs: The impact of the new intervention on productivity, social services, and other costs outside the health care system	No	No						
	Cost of supplies: The analytic framework should allow for cost-relevant details of how accompanying devices for the proposed medication are used						Yes (in the sensitivity analysis)	Yes	
	Proposed drug cost based on unit **drug price and average dose** for average duration of time	Yes	Yes		Yes (cost adjustment is recommended if the duration of use is less than 30 days)	Yes (cost adjustment is recommended if the duration of use is less than 30 days)			
	Least Cost Alternative (LCA) price for relevant drug comparators is			Yes					

	recommended								
	Drugs which require reconstitution or dose preparation, the method of dose preparation, dose stability and specifics around potential drug wastage							Yes	
Time horizon									
	BIAs should be presented for the time horizons of relevance to the budget holder	3 years	3 years	3 years	3 years	3 years	3 years		3 years
Modeling									
	The computing framework for a BIA can be a simple cost calculator programmed in a Excel-based spreadsheet	Yes	Yes			Yes			
Handling uncertainty and scenario analyses									
	Sensitivity analysis: Parameter uncertainty in the input values	Yes	Yes	Yes	Yes	Yes	Yes		Yes
	One-way and/or multi-way sensitivity analysis, analysis of extremes	Yes	Yes	Yes	Yes	Yes	Yes		Yes
	Probabilistic Sensitivity Analysis (PSA) is	No	No						

	recommended in BIA								
	Scenario analysis: Structural uncertainty introduced by the assumptions made in framing the BIA						Yes		
	Important parameters to be assessed in the sensitivity and scenario analyses have been provided in the guidelines	Yes	Yes			Yes (drug dosage and duration)	Yes (cost of supplies)		
Discount rate									
	An attempt should be made for forecasting changes in the value of the currency used the BIA over the time horizon	Yes	Yes						
	Discounting is generally not required.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Validation									
	The computing framework and input data used for a BIA must be sufficiently valid to credibly inform the budget holder's decisions.	Yes	Yes						
	The process of the validation is required	No	No						

	Value of the information analyses (the cost of extra data collection vs improved model precision)	Yes	Yes						
	The programming created by the developer of the budget impact model to perform the analysis (source code) should be made available for review (on the condition that property rights are respected).	Yes	Yes						
	Model code should be provided to reviewers	Yes	Yes						
	Post-market re-assessment: the observed costs in a health plan with the current interventions should be compared with the initial-year estimates from a BIA.	Yes	Yes						
	Quality assurance and publication								
Inputs and data sources									
	Recommended data sources	Yes	Yes						
	Use data from another jurisdiction where the	Yes	Yes	Yes	Yes				

	intervention has been introduced								
	Use estimates of expected market share from the manufacturer	Yes	Yes	Yes	Yes				
	Extrapolate from experience on product diffusion with similar interventions in the budget holder's setting.	Yes	Yes						
	Data could be sourced from clinical trials	Yes	Yes						
	Unpublished data sources, such as expert panels	Yes	Yes						
Presenting results									
	The estimated annual total and incremental budget impacts should be reported separately for each year of the time frame	Only incremental impact	Only incremental impact	Yes	Yes	Yes	Yes		
	Gross and net impact on the budget [the anticipated sales of the drug of interest for each of the first 3 years after the coverage is granted for it (gross impact) and the net impact]						Yes		

	Introduction, study design and methods, results, conclusions and limitations	Yes (not described in details)	Yes (not described in details)						
	All results should be presented in their disaggregated and aggregated forms for each year of the timeframe	Yes (results should be presented in a disaggregated manner)	Yes (results should be presented in a disaggregated manner)		Yes		Yes		Yes
	Inclusion of graphics and figure of the analytical framework, schematic representation of uncertainty analyses			Yes	Yes				
	Table of assumptions, Tables of inputs and outputs, Appendices and References			Yes	Yes				

F/P/T: Federal, provincial and territorial; BC: British Columbia; AB: Alberta; MB: Manitoba; ON: Ontario; QB: Quebec; PCODR: pan-Canadian Oncology Drug Review; *BC BIA guidelines are consistent with the PMPRB BIA guidelines

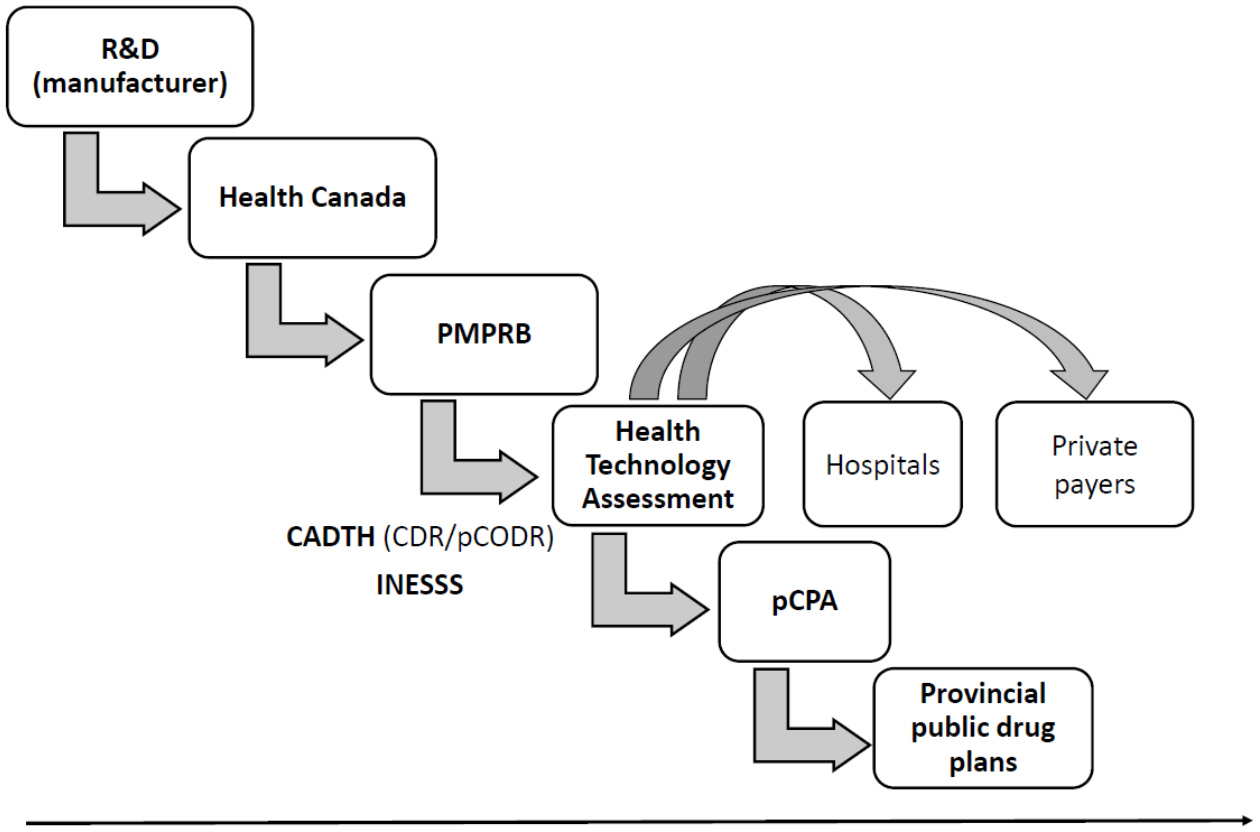

Figure 1: Drug approval and reimbursement process in Canada.

R&D: research and development; PMPRB: Patented Medicine Prices Review Board; CADTH: Canadian Agency for Drugs and Technologies in Health; CDR: Common Drug Review; pCODR: pan-Canadian Oncology Drug Review; INESSS: Institut national d'excellence en santé et en services sociaux; pCPA: pan-Canadian Pharmaceutical Alliance

Appendix 1: Provincial and territorial requirements for manufacturers' submissions for Budget impact analysis

Alberta (Prescription Drug Programs): There is a budget impact assessment form provided for manufacturers[13] [11].

British Columbia (Pharmacare): A provincial budget impact analysis (BIA) for BC that is consistent with the standards published by the Patented Medicines Prices Review Board (PMPRB) [24].

Atlantic Common Drug Review (ACDR): Budget impact analysis for all four provincial plan (Nova Scotia, New Brunswick, Newfoundland and Labrador, and Prince Edward Island) have to be also submitted to ACDR. Submissions to the individual Atlantic provincial drug plans only require their own budget impact analysis.
Note: The Atlantic Common Drug Review (ACDR) assesses the clinical and cost effectiveness of drugs that do not fall under the mandates of the National Common Drug Review (CDR) or the Pan Canadian Oncology Drug Review (pCODR), and provides formulary listing recommendations to the provincially funded drug plans in Atlantic Canada (e.g. new single-source products that do not fall under the CDR mandate, line extensions, resubmissions for products not previously reviewed by CDR and currently listed drugs) [28, 29].

Ontario (Drug Benefit Program): There is a BIA template for new drug submission on their website [9].

Manitoba (Pharmacare Program): The Budget Impact Analysis for Manitoba Health, Seniors, and Active Living should be prepared in accordance with the

[13] https://www.ab.bluecross.ca/dbl/manufacturers.html

template supplied on their website [10].

Northwest Territories: In terms of formulary decisions, the government of the Northwest Territories (GNWT) follows the Non-Insured Health Benefits (NIHB) formulary [30].

Saskatchewan: No information regarding specific requirements for BIA were found on the website [31].

Nunavut: No information regarding specific requirements for BIA were found on the website [32].

Yukon: No information regarding specific requirements for BIA were found on the website [33]. According to the expert opinion, Yukon follows the Non-Insured Health Benefits (NIHB) formulary.

Federal drug plans (Citizenship and Immigration Canada, Correctional Service Canada, Non-Insured Health Benefits (NIHB), National Defense, Veterans Affairs Canada): No information regarding specific requirements for BIA were found on the website. According to the expert opinion, Non-Insured Health Benefits (NIHB) has no specific requirements for BIA, and they review BIA reports prepared for other provinces [34].

CHAPTER 4

Stakeholders' feedback and opinion on the proposed recommendations for updating the Canadian budget impact analysis guidelines for new drug submissions to public and private payers

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Abstract

Introduction: The present study aimed to obtain Canadian stakeholders' feedback on a list of proposed recommendations for updating the Patented Medicine Prices Review Board (PMPRB)'s 2007 budget impact analysis (BIA) guidelines.

Methods: Participants included two stakeholder perspectives (policy-makers and manufacturers). An interview guide and a questionnaire survey were developed based on the list of recommendations related to BIA key elements, which were either not discussed or addressed differently in the PMPRB BIA guidelines of 2007. The list was derived from sixteen BIA guidelines, which were published or updated in Canada or jurisdictions outside Canada over the last decade. We obtained policy-makers' opinion through interviews consisting of ten open-ended and fourteen closed questions. We collected feedback from manufacturers and their consultants using an online questionnaire survey. Seven questions were common to both the interview and the online survey which provided an opportunity for some between-group comparison.

Results: Eight policymakers and twenty-seven individuals from the pharmaceutical industry participated in interviews and the survey, respectively. Participants supported the inclusion of proposed new recommendations into the guidelines pertaining to the use of expert opinions, data extrapolated from the payers' database, scenario analysis, and dynamic population. They did not support

including the patients' perspective, off-label indications, direct non-medical costs and indirect costs, and cost transfers from other jurisdictions. There was no consensus regarding the inclusion of patients' adherence/compliance, the use cost offsets (e.g., cost of clinical outcomes and disease complications) and the reporting total and incremental impact on the budget. We did not observe any difference in the responses between the policy-makers and the manufacturers where data were available from both groups.

Conclusions: The present study has provided sufficient insights to enable the creation of a penultimate version for updating the PMPRB BIA guidelines. This penultimate version will be subject to a broader consultation among stakeholders prior to a final revision and approval.

1. Introduction

In Canada and other developed countries spending on pharmaceuticals is expected to increase significantly with the population aging and the introduction of highly specialized expensive medicines [1]. Health technology assessment and budget impact analysis (BIA) are an important component of the determination of whether a drug will be approved by drug benefit programs. In Canada, the fourth version of the guidelines for the economic evaluation of healthcare technologies has been updated in 2017 and manufacturers must comply with these guidelines when submitting a cost-effectiveness analyses to support the public or private reimbursements of their products. Similarly, manufacturers have to provide a 3-year BIA to reimbursement authorities. The first and only Canadian BIA guidelines have been published in 2007 by the Patented Medicine Prices Review Board (PMPRB) [2]. These BIA guidelines provide recommendations on BIA analytical model structure, data input, and sources and reporting format and have been approved and adopted by most of the Canadian provincial drug plans [3].

Since 2007, many BIA guidelines have been published or updated in several jurisdictions [4, 5] but contrary to the Canadian guidelines for economic evaluation which have been updated three times to incorporate new developments in the conduct of economic evaluations [6], the Canadian BIA guidelines have never been updated. To this end, we conducted a systematic review of BIAs [4, 5]

to identify recommendations from the literature that were either not included or discussed differently in the 2007 PMPRB BIA guidelines. In this paper, we present the results of a qualitative and quantitative (mixed) analysis of Canadian stakeholders' views and feedback on the proposals for updating the Canadian PMPRB BIA guidelines.

2. Methods

2.1.Study design

This study was premised upon the central research question, "What is the Canadian stakeholders' perception of the practicality and relevance of the new proposed BIA recommendations for updating the Canadian BIA guidelines?" This mixed methods study obtained research ethics approval from Hamilton Integrated Research Ethics Board (project number: 2923). The study includes both qualitative and quantitative data collection.

For the qualitative analyses, a semi-structured interview guide was developed collaboratively by the research team to ensure that the questions would address the research objectives of the study [7, 8]. The interview guide was developed based on the discordance we observed between the PMPRB 2007 and the other BIA guidelines that were reviewed [4, 5] (Table 1). These include for example

proposing "dynamic" (vs. closed) population[14], including catch-up effect in the case of chronic conditions, scenario analysis for managing uncertainty and off-label indications in the target population assessment -which are currently in the sensitivity analysis- in the PMPRB 2007 BIA guidelines. Based on this information, we developed a semi-structured interview guide which included 10 interview questions around major themes (i.e., BIA usage in drug reimbursement decisions and price adjustments in Canada, BIA usage in disinvestment decisions, linking incremental cost-effectiveness ratio (ICER) and BIA (affordability) and BIA key elements). In addition, it was agreed that as interviews progressed, interview probes and follow-up questions could be amended given the completion and content of previous interviews and in order to elicit the most comprehensive information possible from the research participants. The interview guide also included 14 closed questions for which a Likert-type ordinal scale was used to rate the responses ranging from 1 to 5 (1 = "strongly disagree," 3 = "neither agree nor disagree", 5 = "strongly agree") (Appendix 1). Appendix 1 presents the semi-structured questionnaire.

All interviews were conducted by the lead author (NF), who had extensive knowledge of the BIA context. The methodological principles of interpretive

[14] patients could be added to or removed from the analysis based on whether they meet the inclusion criteria
or not over time. In some cases, when a drug applies to a well-defined group of patients, the BIA may require a defined closed population.

description were applied to sampling, data collection, and analysis procedures for the interviews [9].

Interviews were mostly conducted in a single meeting using the Google Hangout application (n=6) except for a number of participants where the interview was conducted using a telephone call (n=3). The 30-minute (average) interviews were recorded, and they were completed between March 2018 and September 2018.

In parallel with the interviews, an online written survey consisting of 30 questions was developed using SurveyMonkey (Appendix 2). We converted each BIA recommendations that is not considered or discussed differently in the Canadian BIA guidelines (Table 1) to a question in order to get participants' opinion to assess whether they agreed, disagreed, or neither to include a recommendation in the Canadian BIA guidelines. It was mandatory to answer all the questions, and there was no option to move backward through the survey. The survey was open from May 10 to December 31, 2018.

2.2.Participants

Candidates for the interviews were purposively selected from public drug plans,

the federal ministry of health (Health Canada), PMPRB, CADTH (CDR and pCODR), pCPA, NIHBP, and private payers. For each interview, a maximum of three email invitations were sent to the representatives of these key stakeholder organizations inviting them to participate in the study. The initial email included brief information about the project, the identity of the interviewer (NF), the purpose of the study, the number of questions, the expected interview duration and that the study was voluntary. Recipients were also told that the interview would take place through an online meeting at a time convenient to them. It was stated that their agreement to be interviewed was inferred as their consent to participate in the study. A second reminder was sent two weeks after the initial request, followed by a third reminder which was sent a month later. Those who did not respond to the third reminder were contacted by phone.

For the online survey, we sought participation from pharmaceutical manufacturers and industry reimbursement consultants in order to obtain a pharmaceutical industry perspective. Recruitment was conducted with an invitation and URL link that was sent by email to these stakeholders. Similar to the interview, a second reminder was sent two weeks after the initial request, followed by a third reminder which was sent a month later.

2.3.Data Analysis

To promote the reliability and validity of the semi-structured interview guide, we designed it based on a previously validated survey published by Ellen et al. [10] for obtaining managers' and policymakers' feedback. We conducted pilot interviews with some key informants [11, 12] to determine test-retest reliability, face validity, and technical functioning. We were not concerned with the internal consistency of our survey because we did not measure one attitude or characteristics through different questions. Instead, we were interested in the responses to each item.

With consent obtained prior to the interviews, all interviews were audio-taped and stored in an MP3 format. Two authors (NF and BJ) did the data transcriptions. The interviews, transcription, and analysis were conducted concurrently, allowing the opportunity for new themes to emerge across participants and for further exploration of these themes throughout the remaining interviews [9]. A deductive content analysis that is based on previous knowledge and framework was deemed appropriate for this study [13].

Given that the present study was one of four studies for the author's (NF) doctoral dissertation, NF independently coded, all of the transcripts. Specifically, NF

completed iterative readings of each transcript. This allowed her to gather, label and compare keywords from the text that captured key thoughts and concepts described by the participants, referred to as "codes." The author generated overarching themes among the codes through a process of identifying patterns of coding within and across participants. She generated an initial codebook with definitions of each code and the linking themes. The draft codebook (Excel-based) was refined through the process of theoretical memoing by the author (NF). The online survey data were analyzed using the "results analysis" feature of the SurveyMonkey application.

3. Results

We conducted nine interviews with policy-makers including public and private payers (62% response rate) and collected twenty-seven online surveys from reimbursement experts in the pharmaceutical industry (51% response rate). The audio data for one participant was lost due to an unexpected error in the recording process (although interview notes were still available). Thus, transcripts from eight interviews entered the thematic analysis. The results are reported below in three sections (1) feedback from policy-makers (BIA reviewers) (2) feedback from manufacturers or their consultants (BIA producers) and (3) comparative analysis between policy-makers and manufacturers/consultants.

3.1.Feedback from policymakers

Through a thematic content analysis, we identified the following major themes in the interview results: (1) BIA usage in drug reimbursement decisions and price adjustments in Canada, (2) BIA usage in disinvestment decisions (3) linking incremental cost-effectiveness ratio (ICER) and BIA (affordability) and (4) BIA key elements (e.g., time horizon) including additional recommendations for improving the guidelines.

3.1.1. BIA usage in drug reimbursement decisions and price adjustments in Canada

Most interviewees believed that BIA could be useful in drug reimbursement decisions and price adjustments. This was captured by the following comments: “I would say they are very useful” or “it is the crucial part of assessing the affordability to pay for new technology,..., very important, the most important [part is] when it comes to the reimbursement because it shows the … how the new technology may impact the budget…” The remaining interviewees did not have a strong idea about it due to the fact that they were representing organizations which do not actually review BIAs or do not usually use BIA for price adjustments (e.g., private payers). In the private drug benefit programs, BIA could be helpful in setting insurance premiums, however, according to an interviewee,

premiums tend to be set about 12-18 months in advance of when a BIA arrives, so they usually don't have BIAs in time for setting the premiums. "There [are] sort of two parts … the traditional BIA that we get as part of a submission [which] tends to be a little more directional in nature. There's starting to be a little more attention paid to sort of creating what I call miniature BIAs on pipeline drugs to try and get a better feel for what those BIAs are [going to] be with closer about a 2 or 3 year time horizon, based on what's in the pipeline and what the major drugs are looking like, in terms of what their indications may end up being" according to a private payer representative.

3.1.2. BIA usage in disinvestment decisions

Most participants believed that, at least theoretically, BIA could be helpful in disinvestment decisions (delisting drugs), however, in practice, there are many other factors that would need to be taken into account in delisting a drug (e.g., clinical efficacy and safety, cost-effectiveness, ethical, patient access), which makes it a rare occurrence in the formulary management process. "The way we use it right now is when we look at the BIAs we just generally look at it when we do listing decisions for our formularies at the very front end, when we decide whether or not we list that drug, so we don't ever look at them later to make disinvestment decisions pretty much, but I assume they [BIA] could come in handy" was mentioned by one of the provincial drug plan's representative.

According to the latter interviewee, BIA could be useful in disinvestment decisions in the circumstances that they do consider disinvestment such as when a new more cost-effective drug becomes available and is associated with a considerable cost saving.

3.1.3. Linking incremental cost-effectiveness ratio (ICER) and budget impact

In a *constrained budget*, the higher the budget impact of a new drug, the lower the ICER threshold for appraising the drug for reimbursement [14]. We asked the Canadian stakeholders for their opinion about the use of BIA (affordability) in price adjustments by defining the ICER thresholds. Some found the idea of linking ICER and BIA helpful in the sense that they are complementary to each other and having both pieces together could provide policy-makers with a better understanding of value for money and affordability in assessing a new medication for reimbursement and price adjustments. A few stakeholders preferred keeping them separate (as they are) e.g., "I think keeping it [BIA] separately would make more sense … so it gets down to what the purpose is, and that is to determine the BIA for the drug plan".

3.1.4. BIA key elements and additional comments for improving the

PMPRB BIA guidelines

With regards to the perspective to adopt in a BIA, in addition to the public or private payer perspective, some interviewees believed that asking manufacturers to include the patients' perspective as a complementary component to the BIA base-case analysis would not be practical or feasible. The main concern was that in some jurisdictions "there are so many different scenarios/plans that they could have for co-payments and co-insurance, which makes it really hard for the manufacturers to capture any of that in their submission, or in their BIA"

Participants were asked for their opinion about the advantages and limitations of the current 3-year time horizon in the Canadian BIA guidelines. Some participants believed that a longer time horizon (≥ 3 years) could be more helpful in Canada (e.g., 5 years). The advantages and disadvantages of a 3-year or a longer time horizon are summarized in Table 2. Increasing the uncertainty especially for market size estimation and lack of real-world information was the main concern of most participants on using longer time horizon.

Cost analysis is directly related to the perspective of the adopted budget holder. If the new drug represents one of a class of drugs, the least cost alternative (LCA) within the class as defined by the drug plan could be used to set the price of the

new comparator. Among public plans “Alberta and British Columbia [use LCA]… Ontario doesn’t” and “it varies by the provinces based on what they deem to be interchangeable.” Private payers have programmed their system “to recognize what the lowest cost is, and [the] price for that [which] generally is the generic [version of the drug], but sometimes it might not be”

From the policy-making standpoint, there may be an opportunity cost associated with introducing new technology, as the new technology may use additional resources that must be taken from the existing services [15]. Having this definition in mind, participants believed that manufacturers could not estimate the opportunity cost, “obviously in terms of specific decisions that provinces make, it's literally impossible for the drug company to know what we would do with the money instead of funding this so… that’s not really something they can answer”.

Modeling may be needed to calculate the budget impact for bringing together the best available data from different sources [1, 3, 15-20]. If there is an economic evaluation (EE) in advance to the BIA, assumptions should be consistent with EE [3, 15-17, 19, 20]. All participants believed that modeling could be helpful as long as is as simple as possible. Using complicated models (e.g., Markov) is not required. One of the participants mentioned that “certainly we try to model out the

condition or population as much as we can, to get to a level that gives us confidence while providing say enough certainty, so that's an extra level of complexity that usually is not needed". One participant brought up the discussion related to BIA models in the US in comparison with the Canadian approach. "I think in the US there's less of a reliance on cost-effectiveness analysis (CEA). So there's a lot of emphasis on BIA, and so they might not be getting some of this additional information regarding some of the complexity of the condition with BIA alone. So I guess it really depends on the purpose of the BIA and from what perspective it being conducted. … if you already have a CEA that accounts for some of this already, and the BIA is completely from a pharmacy perspective or a drug plan perspective then maybe there's not the same level of need to have components of the CEA [as] part of the BIA. But … if you don't have a CEA or the perspective of the BIA needs to be broader, [then it is another story]… it really depends on the question that the BIA is intended for". From a private payer's perspective, sensitivity analysis is a better way to take into account the complexity of the disease (e.g., acute plus chronic conditions). In general, participants believed that the extent of required modeling complexity depends on the disease condition and payers' perspective (e.g., in one province, they are sometimes interested in a more dynamic model if the treatment reduces the disease mortality, disease rate of complications, and when it changes the duration of treatment). Moreover, the idea of reflecting both chronic and acute conditions is more about using incidence and prevalence-based approaches in BIA. A "re-

assessment approach" was also recommended by a payer to determine the long-term consequences of medications in chronic conditions.

All but one participant had read the 2007 PMPRB BIA guidelines (that individual was familiar with the US guidelines for BIA), and all believed that there is a need to update the PMPRB BIA guidelines mainly because they are considered out of date. All participants provided comments for improving the new version of the PMPRB BIA guidelines, which are summarized in Table 3.

Based on the results of the survey component of the interview guide (Appendix 3), a majority of interviewees believed that (1) treatment switches and (2) changes in the rate of mortality and disease progression are important to be captured over the time horizon. Most welcomed the idea of providing a list of acceptable databases as reliable references for input data in BIA calculations in the updated version of the Canadian BIA guidelines. Most also agreed with a cap or threshold for the budget impact of new drugs to signal the need for negotiation with manufacturers for lowering the price. They thought it is important to build in a reassessment process of BIAs in a future real-world post-market environment. The opinions regarding the inclusion of patient adherence and compliance in the target population assessment, and including the cost of adverse events, clinical

outcomes and disease complications in the BIA cost analysis were inconclusive.

3.2.Feedback from manufacturers or their consultants

The results from the online written survey of 27 participants with an industry perspective are summarized in Appendix 4. On the major issue of time horizon, 20 agreed with the 3-year time horizon in BIAs as reasonable in Canada. Only a quarter of respondents (n=7/27) believed that there should be a change in the time horizon in the new PMPRB BIA guidelines. However, there was the sense that flexibility (variability) depending on, e.g., the disease area and patent duration should be considered and justified after 3 years in different cases.

With respect to the target population issue, 11 of 27 (41%) survey participants agreed with conducting subpopulation analysis in addition to an aggregated analysis for the whole population. Thirteen believed that the target population should be dynamic (open) in BIAs, meaning that patients could be added to or removed from the analysis based on whether they meet the inclusion criteria or not over time. Including off-label indications in the target population assessment was not supported by the majority of participants (74%; n=20/27 disagree).

Pertaining to the costs either of comparators or those included in the base-case, using the least cost alternative (LCA) in the cost analysis was acknowledged as appropriate by the majority of the survey participants. Approximately 50% of survey participants disagreed with the inclusion of either indirect or non-healthcare related cost (e.g., training or introduction cost, transportation, productivity, and caregiver related costs), or the taxes, e.g. HST in BIA. Including the cost transfer from other jurisdictions (where there is a lack of real-world data for the proposed medicine) was not acceptable to 70% of survey participants. A majority (62%; n=16/27) supported including the total and incremental impact on the budget (cost analysis for all new and currently covered indications) in the BIA, but that the effects of inflation and discounting should not be included in the BIA.

Most participants disagreed with using Probabilistic Sensitivity Analysis (PSA) in BIA. Scenario or deterministic sensitivity analyses were highly recommended (96% and 85%, respectively). There was support for describing the direction and magnitude of the impact of uncertainty on the overall estimates, but risk-sharing agreements and longer introduction phase were not favored for decreasing model and data uncertainty. A majority of respondents felt that data from manufacturers, clinical data from other jurisdictions, expert opinions, and extrapolating data from similar (or proxy) drug experience on the payers' database could all be considered

reliable sources of data in BIA.

Over 80% of respondents supported reporting the gross and the net impact on the budget based upon the anticipated sales of the drug of interest for each of the first 3 years after the coverage is granted. There was less support for a schematic representation of the uncertainty analysis (e.g., Tornado diagram). Two-thirds felt that aggregated and disaggregated budget impact results should be reported for each year of the time horizon.

The support was 52% for both cost outcomes being presented separately for different payers and for cost outcomes being presented in monetary units. There was no consensus on whether some cost outcomes should be in natural units (e.g. number of unpaid working days) or not.

3.3.Comparative analysis of stakeholders' feedback (policy maker versus pharmaceutical manufacture perspectives)

We performed a comparative analysis between the two groups of stakeholders for seven survey questions. Table 2 summarizes the questions which are in common in the data obtained from both groups. Figure 1 illustrates all survey results

including the comparative results between two groups.

Both groups did not support the inclusion of staff training or introduction costs, non-healthcare related costs or taxes in a BIA. Both groups believed that expert opinions and data extrapolation from the similar drug in the payers' database are reliable sources of data to be used in BIAs where there is a lack of real-world data for the proposed drug. While 62% of industry participants supported that reporting both the total and incremental impact on the budget for a new medication is important in BIA, the results from policymakers were indecisive (38% neither agreed nor disagreed).

4. Discussion

In the present study, the Canadian stakeholders' feedback on the BIA recommendations, obtained through qualitative and quantitative methods, provides additional insight to help define BIA guidelines from a Canadian perspective. This information may also be of value for updating or creating BIA guidelines worldwide. The present study arose upon the results of the literature reviews describing Canadian, international (e.g., France, Australia, Belgium, Ireland, Brazil, and the UK) and transnational (e.g., ISPOR) BIA guidelines and was designed to capture feedback and expert input of the stakeholders (policy-

makers and manufacturers) in the field of pharmaceutical pricing and reimbursement in Canada [4, 5]. The authors identified discrepancies between the PMPRB 2007 BIA guidelines and the more recently published or updated BIA guidelines either in Canada or outside. This generated a list of BIA recommendations, which were not included or discussed differently in the PMPRB 2007 guidelines. While the PMPRB BIA guidelines are clearly intended to serve the interests of the people who will be using them, i.e., the policymakers, we also obtained input from the stakeholders who are charged with creating the BIA documents for submission to the policymakers. On a positive note, for the items where we were able to obtain common data, there was general agreement between these two groups. Nevertheless, had there been disagreement the BIA guidelines would have to reflect the needs of the policymakers or the BIA submissions otherwise the guidelines would be unhelpful in the drug reimbursement regime. While there was consensus on many recommendations, some recommendations will need further input to determine whether they should be included in an updated version of the PMPRB BIA guidelines, especially involving policy-makers from both public and private perspectives (e.g., 3-year or longer time horizon, patient adherence and compliance, cost offsets, reporting total and incremental impact on the budget and providing a list of reliable databases as data sources).

Obtaining stakeholders' feedback was part of the process to create many of the previously published national BIA guidelines [1, 3, 19, 21]. The PMPRB 2007 BIA guidelines were initially developed based on a needs assessment and a literature review and then improved with the input of the NPDUIS Advisory Committee, including drug plan managers from multiple provinces in Canada and a representative from the CADTH [3]. In Poland, the BIA guidelines were initially conducted internally within the Agency for Health Technology Assessment and Tariff System, and then within the Guidelines Update Team. The Guidelines were submitted for public comment and for review by the Minister of Health [21]. In Belgium, the preliminary BIA guidelines were developed based on a literature review and then stakeholders' feedback was obtained involving the Belgian Health Care Knowledge Centre (KCE) and different Belgian stakeholders from both government and industry [19]. In France, as a part of the French BIA guidelines development, a public consultation process was conducted including international expert reviews and approval from the HAS Board and the Economic and Public Health Evaluation Committee of HAS [1]. Unfortunately, the stakeholder analyses that were conducted as part of the above-mentioned guidelines were not published with any methodologic detail. Our study is unique in terms of (1) the rigorous study design (mix methods) (2) the scope (including policy-makers from both public and private drug plans) (3) inclusion criteria (clear definitions for selecting stakeholders) (4) the one-on-one semi-structured interviews providing a rich description of the stakeholders' opinion on improving

the PMPRB BIA guidelines and (5) publishing the stakeholder analysis in the public domain.

There are a number of conclusions that arise from the results of the feedback. Similar to Pearson and Ghabri et al., we found that using the BIA as an affordability factor for ICER[15] threshold adjustments and price cap estimation, especially in the chronic conditions such as hepatitis C virus drugs, is a practical benefit of using BIA in the real-world [1, 21, 22]. Moreover, considering a BIA cap or threshold received positive feedback in our study. There are some examples for using BIA threshold internationally such as a budget impact test of £20million for NHS England since 2017 [23] and a budget impact threshold linked to the growth in the national economy (GDP[16]) in the United States [21]. Similarly, a real-world reassessment process for BIA results (in the post-market surveillance phase) would be recommended, as already used in the UK.

One should note that in the Irish [15] and ISPOR [20] BIA guidelines, opportunity costs are defined as the costs that arise when implementing the technology or clinical guidelines that might not be reflected in the "actual costs" at the time of

[15] Incremental cost-effectiveness ratio
[16] Gross domestic product

doing a BIA, and that is different from the opportunity cost definition in policy-making of "whether the improvement in health outcomes that the proposed new drugs offer exceeds the improvement in health that would have been possible if the resources had, instead, been made available for other health care activities [24]". Based on the results, we concluded that it is not feasible to ask manufacturers to calculate in BIA the opportunity cost of investing in a new drug. Therefore, there is a need for a method to calculate the opportunity cost without relying upon the BIA and an alternative method has been proposed by Ochalek et al. where the opportunity costs in the health care expenditures are represented by the threshold value for the CEA [24].

Regarding time horizon, a minimum of 3 years is favorable in Canada and beyond 3 years should be justified by the manufacturer (e.g., for a specific drug, a disease area or patent duration). In some BIA guidelines such as in France [1], ISPOR [20] and Brazil [25] there is a range for time horizon, e.g., 3-5 years, whereas in the British and Irish guidelines they introduce a punctual time horizon of 5 years. Further stakeholder feedback is required to reach a consensus on the most favored approach for a BIA time horizon in Canada.

The results show that using complicated modeling techniques (e.g., Markov models) are not recommended in BIA, but it is advised that the disease condition be modeled as much as possible to capture the long-term consequence (at least within the adopted time horizon) associated with using the proposed medication in a chronic condition. Providing either incidence- or prevalence-based (or both) models would help to better understand drug costs related to the acute and chronic conditions. This is especially important for responding to a methodological gap which was highlighted by Mauskopf et al. [26].

Different terminology is used in different guidelines/countries to define comparators. In the Canadian context, the multi-drug treatment strategy for defining comparators is called “strategy-based treatment”, which is different from France [1] (treatment set), ISPOR [20] (treatment mix or set) and Australia [16] (treatment mix). In the new version of the PMPRB BIA guidelines using “treatment mix” is suggested to be most consistent with international terminology.

One should note that comparator mix does not necessarily always match the comparator mix in the utilization [real world], e.g., the treatment mix that private payers and public plans see in their database may be different because of inherent differences in their formularies. This type of difference between public and

private payers should be addressed in BIA. It is also recommended that the choice of comparators in BIA should be consistent with the health economic evaluation (e.g. cost-effectiveness study) unless there are clear justifications for not taking the same treatment strategy as the health technology assessment (e.g., in the case of non-drug/surgical alternatives). Similar to the PMPRB 2007 BIA guidelines, our study participants confirmed that Off-label indications should be considered only in the sensitivity analysis (not in the base-case analysis). As recommended in the Irish [15] and ISPOR [20] BIA guidelines, the catch-up effect (treatment switch) is also recommended in BIA in Canada. Mauskopf et al. [26] raised a methodological gap relating to the "treatment switch" or "drug discontinuation", in the chronic conditions, which might not be appropriately addressed in many published BIAs in the United States.

Similar to the PMPRB 2007 BIA guidelines, cost offsets, i.e., costs associated with changes in clinical outcomes, costs associated with clinical consequences/complications (e.g., adverse drug reactions) and resource utilization (e.g., hospitalization, emergency room admission)] are still excluded from the analysis. The impact on indirect costs (e.g., productivity, transport, capacity, and workforce) are not included in a BIA base-case analysis and cost data from other jurisdictions are not acceptable.

Uncertainty in input data is a general concern in BIA. Probabilistic Sensitivity Analysis (PSA) is used in the Irish and Belgium guidelines [9, 10] whereas it is not recommended in Canada. In contrast, scenario (for structural uncertainty) or deterministic (for input data uncertainty) sensitivity analyses are highly recommended in Canada. A methodological review of US budget impact models [26] showed that sensitivity and scenario analyses presented in published BIAs are "typically too limited to allow a budget holder to assess the likely budget impact for their health plan." We would expect that the gap would be covered by recommending scenario and sensitivity analyses being included in the PMPRB BIA guidelines for dealing with uncertainty. Risk sharing agreements and longer introduction phase for decreasing the uncertainty in new drug submissions, as they are recommended in Australia [16] and the UK [17], are not favored in Canada.

There are a number of limitations to the present study. There was a limited sample size for interviews providing the qualitative data. Nine policy-makers agreed to participate in an interview, and the audio data for one participant was lost. As well, two participants from the same province were interviewed at the same time. While the sample size was limited, we were able to obtain data from representatives of different jurisdictions across Canada and a similarity in their

responses was noted suggesting that new themes or ideas might not have been forthcoming even if the sample size was larger. Nevertheless, in order to make any meaningful comparison between the opinions of public and private payers' (subgroup analysis) we would have required substantially larger numbers.

5. Conclusion

We obtained Canadian stakeholders' opinion on a list of recommendations prepared based on a comparative literature review of national and ISPOR BIA guidelines using a mixed methods approach. A mandate for submitting a companion CEA/CUA along with a BIA in a new drug application in Canada, could be a reason for some observed differences between the Canadian stakeholders' perspective and recommendations from other jurisdictions (e.g., ISPOR) especially with respect to the inclusion of cost offsets (e.g., clinical outcomes) and complicated modelling techniques in BIA.

The present study is an integral step towards creating a proposal for updating the PMPRB BIA guidelines. The present study aimed to gain initial Canadian stakeholders' feedback and opinion on potentially new recommendations. A penultimate revised PMPRB BIA guidelines will be developed based on the results of the present study. In Canada, when guidelines are proposed by a

government agency or board there is a mandatory comprehensive consultation process with stakeholders. The results generated by the current study will form the template for the new draft guidelines document that the PMPRB will produce. PMPRB will then conduct a broader consultation with stakeholders that could be achieved in this study. After that step, there will be a final revision and subsequent adoption of updated BIA guidelines.

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Table 1: List of recommendations, which are not included or discussed differently in the 2007 Canadian PMPRB guidelines. These recommendations were the basis of developing interview and survey questionnaires.

#	**BIA secondary elements**	**Canada PMPRB (2007)**
Perspective		
1	In the case of co-payment, the inclusion of the **patient's perspective** is complementary to the base-case analysis	Not discussed
Technology		
2	The **technology** should be described in sufficient detail to differentiate it from its comparators and to provide context for the study.	Not discussed
Target population		
3	**Open (dynamic) population**	Not discussed
4	**Subgroups** in the target population assessment are recommended.	Not discussed
5	**Catch-up effect** which applies to the chronic conditions for patients who switch to the new drug	Not discussed
6	**Unit of analysis** (per patient or episode)	Discussed differently
7	**Off-label indications** in the target population assessment (base-case analysis) are recommended.	Discussed and only included in the sensitivity analysis
8	**The degree of implementation** of the new intervention (substitution, combination, and expansion)	Not discussed
Comparators		
9	**Terminology**	Different definitions
10	**Choice of comparators**	Discussed differently
Costing		
11	**Opportunity costs** are the costs that arise when implementing the technology or clinical guidelines that might not be reflected in the "actual costs" at the time of doing BIA analysis	Not discussed
12	**Cost of clinical outcomes** and disease complication	Discussed and excluded
13	**Cost of health care utilization** (e.g., hospital days or physician visits)	Discussed and excluded
14	**Indirect costs:** The impact of the new intervention on productivity, social	Discussed and excluded

	services, and other costs outside the health care system	
15	**Cost of supplies**: The analytic framework should allow for cost-relevant details of how accompanying devices for the proposed medication are used	Not discussed
16	The annual depreciation of any **capital costs** should be included in the analysis	Not discussed
17	**Labor costs**	Not discussed
18	**Applicable tax**	Not discussed
19	The BIA should also estimate the impact of **adherence** or persistence on intervention effectiveness and safety if condition-related costs are included in the BIA.	Not discussed
20	Calculate both the **global budget impact and separately the budget impact for the different health care payers** (This implies that potential transfers of budgets between different levels of governments and/or patients)	Not discussed
21	**Cost transfer** from other jurisdictions is allowed in BIA	Discussed and not allowed
22	**Least Cost Alternative (LCA) price** for relevant drug comparators is recommended	Not discussed
23	Drugs which require reconstitution or dose preparation, the method of dose preparation, dose stability and specifics around potential drug wastage	Not discussed
Modeling		
24	**Modeling** may be needed to calculate the budget impact for bringing together the best available data from different sources.	Not discussed
25	Assumptions should be the same as EE	Not discussed
26	**More complicated Software**	Not discussed
Validation		
27	The process of the validation	Discussed and excluded (not required)
28	Quality assurance and publication of the BIA results	Not discussed
Handling uncertainty and Scenario Analyses		
29	**Probabilistic Sensitivity Analysis (PSA)** is recommended in BIA	Discussed and excluded (not allowed)

30	**Scenario analysis**: Structural uncertainty introduced by the assumptions made in framing the BIA	Not discussed
31	Describe the **direction and magnitude** of the impact of uncertainty on the overall estimates	Not discussed
Data input and reporting format		
32	Search strategy; inclusion criteria for data selection and source selection; strengths and weaknesses of the used sources, and methods of analysis should be presented	Not discussed
33	**Original cost survey**, obtaining primary data, by sampling, involving interviews with health professionals under study	Not discussed
34	The estimated **annual total and incremental budget impacts** should be reported separately for each year of the time frame	The only incremental impact is required
35	**Gross and the net impact** on the budget [the anticipated sales of the drug of interest for each of the first 3 years after the coverage is granted for it (gross impact) and the net impact]	Not discussed
36	Results should be reported in terms of their **natural units** and financial cost	Not discussed
37	The inclusion of graphics and figure of the analytical framework, the schematic representation of uncertainty analyses	Not discussed
38	The addition of relevant appendices to the main report is encouraged. The appendices may cover literature search strategies, evidence summaries, intermediate results (e.g., of individual Delphi panel rounds), and the names and addresses of participating experts and investigators, for example)	Not discussed
39	Resource impact products: resource planner; resource impact reports and templates; resource impact statement	Not discussed

Table 2: Advantages and disadvantages of time horizon ≥3 years in BIA based on the thematic analysis of the interview results (n=8)

Time Horizon= 3 years	Advantages (n=3)	"three year period is easier to project because it's a kind of short-term projection or forecast." "If it's less than three years, you start losing relevance, and if you make it longer than three years, there's just way too much uncertain." "…three years is good."
	Disadvantages (n=1)	"often the three-year budget impact is assumed as a long-term time horizon however it usually takes at least 3 years before the drug reaches steady state (plateau) in the market. So the three-year budget impact is "grossly" underestimate the long-term budget hit which provinces will be ultimately settled with"
Time horizon> 3 years (e.g., 5 years)	Advantages (n=2)	"For 5 or 6 years, it is harder to project what will happen in the market, especially it is hard to project the market trends and what would happen." "[One could] see when the drug will reach its peak sales. For example, many drugs today, they might not reach their peak sales after three years, they will go further and further. So the impact on the budget may not be complete… because it shows lower shares of market uptake after three years, after that, it doesn't go up and show the full extent of the impact."
	Disadvantages (e.g., 5 years) (n=2)	"For a longer TH, many manufacturers don't feel that they can secure market assumptions based on what they submit. So as you increase the time horizon, you increase the likelihood that something is going to be generic or [there will be] struggle through the market…I think the past three years is a little bit too much for us [in Canada]" "The one limitation I think that went for [a] longer BIAs is, right now a lot of things can change during that time period, so three years is good."

n= the frequency of discussions about that specific issue (e.g., advantages of TH=3)

Table 3: Comparative results from surveys (written survey and interview survey)

		Interview survey (N=9)			**Written survey (N=27)**		
		Policy-makers			**Manufacturers/consultants**		
#	Recommendations	Agree	Neither agree nor disagree	Disagree	Agree	Neither agree nor disagree	Disagree
1	Do you agree with including staff training or introduction costs for a new medication (if applicable) in a BIA?	25%	13%	63%	18.5%	14.8%	66.7%
2	Do you agree with including direct non-healthcare related costs (e.g. transportation) or indirect non-healthcare related costs (e.g. productivity) in the PMPRB BIA guidelines?	38%	0%	63%	14.8%	29.6%	55.6%
3	Do you agree with including appropriate rate of value-added tax (e.g. HST)?	0%	25%	75%	11%	11%	77.8%

4	Do you agree with using costs and tariffs data from other jurisdictions (other countries) in the absence of local information?	25%	25%	50%	7.4%	22%	70.4%
5	Do you agree with considering expert opinions as a reliable source of data in BIAs?	88%	13%	0%	63%	37%	0.00%
6	Do you agree with using market-share (or claim-based) data extrapolated from similar drug experience on the payers' database in case of lack of real-world data for the proposed medicine?	100%	0%	0%	74%	22%	3.7%
7	In addition to an incremental impact on the budget for a new medication reported in BIAs, how important is to also report "**total impact**" which includes previous expenditure plus the	25%	38%	25%	63%	3.7%	33%

	costs related to the newly proposed indications for that drug in BIAs						

Table 4: Additional comments for improving PMPRB BIA guidelines, which were addressed by the interview participants.

BIA key elements	**Comments**
Analytical model structure	One of the participants believed that "the [BIA] methodology is quite comprehensive in the PMPRB BIA guidelines, but for some parameters such as time horizon, the guidelines could be updated to a longer period, or just given opportunity to basically consider it for some of the technologies."
Time horizon	The comment raised by the private payers highlighting the fact that time horizon should be long enough to capture seasonality in pharmacare provinces where there is a deductible season- a part of the year where there is basically no claims as people in that province are working towards the deductible.
Target population assessment	• Two participants mentioned that the target population assessment is always a challenge (e.g., in the hospital setting in Quebec, the billing data for the comparators is not always available for manufacturers and thus it is hard to validate the population size for the BIA

	calculations for RAMQ[17]). So, there are always more data available for public drug plans but not manufacturers which result in differences in the BIA estimations. Also, there is heterogeneity in the epidemiologic data coming from different sources of literature from different jurisdictions. All together the final population could be uncertain, and sometimes it is hard to find good Canadian relevant data. • Another participant raised the issue that manufacturers can predict the eligible population. However, they cannot know how many people would actually start that medication even if their physicians have prescribed them the medication. • Moreover, it is good to make it clear in the BIA guidelines that in what cases the analysis should be incidence-based or prevalence-based or both to make the analysis more consistent. • Furthermore, a concern regarding new (versus old) indications raised highlighting the fact that many drugs are indicated in different disease categories, which are all considered in the BIA. The consideration for continuing (or discontinuing) the coverage for some indications should be highlighted in the guidelines. For example, if a drug is commonly used as the second line in a disease category and in the new application, it becomes the first line in a new indication, then it may not be covered as a second line therapy anymore.
Comparators	Choice of the comparators is important which is sometimes consistent with the economic evaluations and sometimes not. Comparator mix does not necessarily always match the comparator mix in the utilization [real world] of the different comparators that private payers see in their database, and that could be due to differences in the public vs. private formularies.
Costing	Markups and professional fees are different in public and private plans, and it is recommended to be considered in an interactively updated model template for BIA.
Modeling techniques	All submitted models should be transparent, simple and include confidential prices at the same time. Excel-based electronic models would be better if they have the ability to express results in either contract years or fiscal years. In addition, it was recommended that the incident and prevalent patients and patients coming off the patient excess (if there is one), be shown in the model separately (e.g., in the case of biologics).

[17] Régie de l'assurance maladie du Québec

Input and data sources	It is very difficult to come up with solid parameter estimates, particularly around market growth and market penetration of the new drug, target population assessment (market size estimation). Uncertainty is a big issue related to input data according to the participants: "there's not really good evidence of what it's going to be so, it is just judgment [subjective]."
Uncertainty	Robust methods for sensitivity analysis are required to adequately address the issue of uncertainty.
Reporting format	Currently, most BIA reports are providing results in a disaggregated format for each year of time horizon, whereas, provinces need BIA reports in fiscal years. It should be helpful to be reflected in the guidelines.

Figure 1: Summary of written survey results of all participated stakeholders (n=36). Note: Gold refers to" policy-makers" and "Blue bars" represent Manufactures/consultants.

Appendix 1: interview guide

Part 1 of the interview: open-ended questions

Semi-structured interview: We asked the participant's personal opinion on some of the important issues related to BIA methodology and guideline. The questionnaire was developed for stakeholders from different perspectives (e.g., Federal and provincial levels), some questions may not apply on everyone's perspective and position.

A) Open ended questionnaire for interviews (version#1)

Question Number	Question
1	In general, how useful are the BIA reports for new drug reimbursement decisions and price adjustments?
2	Do you think BIA can help in disinvestment decisions? How?
3	Do you think it would be more helpful for decision-making to link CEA and BIA together than keeping BIA separately? Why?
4	Do you think BIA should take into account the complexity of the disease/ condition under study or of the treatment (e.g., acute plus chronic treatments)? Do you prefer to do it through more complex modeling techniques (e.g., Markov models) or sensitivity analysis?
5	What is your opinion about increasing the time horizon to more than 3 years (e.g., 6 years)?
6	Do you think one could require the pharmaceutical company to calculate the opportunity cost of paying for new technology in your province? How practical it is?
7	If applies on you, could you briefly explain the generic versus brand drug pricing or price negotiation process in your province? What happens after PCPA negotiation?
8	If applicable, do you use Least Cost Alternative (LCA) price for relevant drug comparators in your province?
9	Have you ever used or reviewed PMPRB BIA guidelines? Do you believe that there is a need for an update to the PMPRB BIA guidelines?
10	In your view, what are the most important methodological gaps and challenges in the provincial BIA reports for new drug submissions?

BIA: budget impact analysis; CEA: cost-effectiveness analysis; pCPA: pan-Canadian Pharmaceutical Alliance; LCA: Least Cost Alternative; PMPRB: Patented Medicine Prices Review Board

Note: question#6 were replaced to the following question after 6 interviews mainly because we received the same answer from participants repeatedly: "In the case of co-payments, the new recommendations indicate that the patient

perspective should be considered complementary to base-case analysis. What are your thoughts about this recommendation? What do you consider are the benefits of including the patient perspective? What do you consider are the limitations to including the patient perspective?"

B) Open ended questionnaire for interviews (version#2)

Question Number	Question
1	In general, how useful are the BIA reports for new drug reimbursement decisions and price adjustments?
2	Do you think BIA can help in disinvestment decisions? How?
3	Do you think it would be more helpful for decision-making to link CEA and BIA together than keeping BIA separately? Why?
4	Do you think BIA should take into account the complexity of the disease/ condition under study or of the treatment (e.g., acute plus chronic treatments)? Do you prefer to do it through more complex modeling techniques (e.g., Markov models) or sensitivity analysis?
5	What is your opinion about increasing the time horizon to more than 3 years (e.g., 6 years)?
6	In the case of co-payments, the new recommendations indicate that the patient perspective should be considered complementary to base-case analysis. What are your thoughts about this recommendation? What do you consider are the benefits of including the patient perspective? What do you consider are the limitations to including the patient perspective?
7	If applies on you, could you briefly explain the generic versus brand drug pricing or price negotiation process in your province? What happens after PCPA negotiation?
8	If applicable, do you use Least Cost Alternative (LCA) price for relevant drug comparators in your province?
9	Have you ever used or reviewed PMPRB BIA guidelines? Do you believe that there is a need for an update to the PMPRB BIA guidelines?
10	In your view, what are the most important methodological gaps and challenges in the provincial BIA reports for new drug submissions?

Part 2 of the interview: a closed survey

We used Likert-type ordinal scales to rate the responses ranging from 1 to 5 (were: 1 = "strongly disagree," and 5 = "strongly agree") with a middle neutral category (3 = "neither agree nor disagree"). Please answer the questions by

choosing a number between 1 and 5.

1. **In your opinion, how important is to include the <u>treatment switch</u> in the target population assessment in BIAs?**

Completely irrelevant	Not necessary	Neutral	Important	Highly important
1	2	3	4	5

2. **In your opinion, how important is to include <u>patient adherence</u> in the target population assessment in BIAs?**

Completely irrelevant	Not necessary	Neutral	Important	Highly important
1	2	3	4	5

3. **In your opinion, how important is to capture changes in the rate of <u>mortality</u> and disease progression over time horizon in BIAs?**

Completely irrelevant	Not necessary	Neutral	Important	Highly important
1	2	3	4	5

4. **Do you agree with including staff training or introduction costs for a new medication (if applicable) in a BIA?**

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
1	2	3	4	5

5. **Do you agree with including direct non-healthcare related costs (e.g., transportation) or indirect non-healthcare related costs (e.g., productivity) in Canadian BIA guidelines?**

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
1	2	3	4	5

6. **Do you agree with including the cost of adverse events, clinical outcomes and disease complications in BIA cost analysis?**

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
1	2	3	4	5

7. Do you agree with including the appropriate rate of value-added tax (e.g., HST)?

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
1	2	3	4	5

8. Do you agree with using costs and tariffs data from other jurisdictions (other countries) in the absence of local information?

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
1	2	3	4	5

9. Do you agree with considering expert opinions as a reliable source of data in BIAs?

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
1	2	3	4	5

10. Do you agree with using market-share (or claim-based) data extrapolated from <u>similar drug experience</u> on the payers' database in case of lack of real-world data for the proposed medicine?

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
1	2	3	4	5

11. Do you think BIA guidelines should provide a list of acceptable databases as reliable references for input data in BIA calculations?

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
1	2	3	4	5

12. In addition to an incremental impact on the budget for a new medication reported in BIAs, how important is to also <u>report "total impact"</u> which includes previous expenditure plus the costs related to the newly proposed indications for that drug in BIAs?

Completely irrelevant	Not necessary	Neutral	Important	Highly important
1	2	3	4	5

13. Do you agree with considering a cap or threshold for the budget impact of the new drugs to signal the need for negotiation with manufacturers for instance decrease prices or set risk-sharing agreements?

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
1	2	3	4	5

14. In your view, how important is to build in a reassessment process of BIAs in a future real-world post-market environment?

Completely irrelevant	Not necessary	Neutral	Important	Highly important
1	2	3	4	5

Appendix 2: Survey Monkey

Link to the survey: https://www.surveymonkey.com/r/F6KRRTZ

Appendix 3: Interview survey results as part of the interview process; policy-makers' feedback (N=9)

#	Recommendations	Agree	Neither agree nor disagree	Disagree
1	In your opinion, how important is to include the treatment switch in the target population assessment in BIAs?	100%	0%	0%
2	In your opinion, how important is to include patient adherence in the target population assessment in BIAs?	38%	63%	0%

3	In your opinion, how important is to capture changes in the rate of mortality and disease progression over time horizon in BIAs?	75%	0%	25%
4	Do you agree with including staff training or introduction costs for a new medication (if applicable) in a BIA?	25%	13%	63%
5	Do you agree with including direct non-healthcare related costs (e.g., transportation) or indirect non-healthcare related costs (e.g., productivity) in Canadian BIA guidelines?	38%	0%	63%
6	Do you agree with including the cost of adverse events, clinical outcomes and disease complications in BIA cost analysis?	38%	25%	38%
7	Do you agree with including appropriate rate of value-added tax (e.g. HST)?	0%	25%	75%
8	Do you agree with using costs and tariffs data from other jurisdictions (other countries) in the absence of local information?	25%	25%	50%
9	Do you agree with considering expert opinions as a reliable source of data in BIAs?	88%	13%	0%
10	Do you agree with using market-share (or claim-based) data extrapolated from similar drug experience on the payers' database in case of lack of real-world data for the proposed medicine?	100%	0%	0%
11	Do you think BIA guidelines should provide a list of acceptable databases as reliable references for input data in BIA calculations?	75%	25%	0%
12	In addition to an incremental impact on the budget for a new medication reported in BIAs, how important is to also report "total impact" which includes previous expenditure plus the costs related to the newly proposed indications for that drug in BIAs?	25%	38%	25%
13	Do you agree with considering a cap or threshold for the budget impact of the new drugs to signal the need for negotiation with manufacturers for instance decrease prices or set risk-sharing agreements?	63%	25%	13%
14	In your view, how important is to build in a reassessment process of BIAs in a future real-world post-market environment?	75%	13%	13%

Appendix 4: Summary results of the written survey (N=27)

#	Questions	Agree	Neither agree nor disagree	Disagree
1	In the case of co-payment, the inclusion of a patient's perspective is recommended as complementary to the base-case analysis.	40.74%	7.41%	51.85%
2	Do you agree with the current time horizon of 3 years in the Canadian BIA guidelines?	55.56%	18.52%	25.93%
3	Open or dynamic populations (patients can enter or leave the cohort based on their inclusion eligibility over the time horizon) should be used in the target population assessment.	48.15%	40.74%	11.11%
4	Subpopulation analysis should be conducted in addition to an aggregated analysis for the whole population.	40.74%	22.22%	37.04%
5	Off-label indications should be included in the base-case analysis (in the Canadian BIA guidelines 2007, off-label is only recommended in the sensitivity analysis).	14.81%	11.11%	74.07%
6	Training or introduction cost should be included in the BIA.	18.52%	14.81%	66.67%
7	Transportation, productivity and caregiver related costs should be included in the BIA.	14.81%	29.63%	55.56%
8	Opportunity cost estimation in BIAs should be provided by the manufacturers.	14.81%	3.70%	81.48%
9	An appropriate rate of tax (e.g., HST) should be applied to the applicable costs.	11.11%	11.11%	77.78%
10	Cost transfer from other jurisdictions (in case of lack of real-world data for the proposed medicine) should be included in the BIA.	7.41%	22.22%	70.37%
11	The total and incremental impact on the budget (cost analysis for all new and currently covered indications)	62.96%	3.70%	33.33%

	should be included in the BIA.			
12	Least Cost Alternative (LCA) price for relevant drug comparators should be used in the BIA.	70.37%	22.22%	7.41%
13	The effects of inflation should NOT be included in the BIA.	66.67%	33.33%	-
14	Discounting should NOT be included in the BIA.	70.37%	29.63%	-
15	Aggregated and disaggregated budget impact results should be reported for each year of the time horizon	66.67%	33.33%	0.00%
16	There should be reporting of the gross and net impact on the budget.	81.48%	14.81%	3.70%
17	Outcomes should be presented separately for different payers.	51.85%	22.22%	25.93%
18	Outcomes should be presented in natural units (e.g., a number of unpaid working days).	29.63%	37.04%	33.33%
19	Outcomes should be presented in monetary units.	51.85%	40.74%	7.41%
20	There should be a schematic representation of the uncertainty analysis (e.g., Tornado diagram).	48.15%	29.63%	22.22%
21	The impact of uncertainty (quantifying the precision of the results) should be presented in the BIA.	85.19%	7.41%	7.41%
22	Data from the manufacturer can be considered as a reliable source of data.	66.67%	33.33%	0.00%
23	Data from other jurisdictions can be considered a reliable source of data.	59.26%	37.04%	3.70%
24	Expert opinions can be considered a reliable source of data.	62.96%	37.04%	0.00%
25	Extrapolating data from similar (or proxy) drug experience on the payers' database can be considered as a reliable source of data.	74.07%	22.22%	3.70%
26	A BIA should use scenario analysis for dealing with uncertainty.	96.30%	3.70%	0.00%
27	A BIA should use deterministic sensitivity analysis (e.g., one-way, multivariate) for dealing with uncertainty.	85.19%	11.11%	3.70%
28	A BIA should use	25.93%	11.11%	62.96%

	probabilistic sensitivity analysis for dealing with uncertainty.			
29	A BIA should include a proposed risk sharing agreement for dealing with uncertainty.	11.11%	11.11%	77.78%
30	A longer introduction phase should be used with early BIAs to address issues of uncertainty.	11.11%	51.85%	37.04%

CHAPTER 5

Conclusion

The core of this Ph.D. thesis rests in the development of a proposal for updating the 2007 Canadian PMPRB BIA guidelines in accordance with the most up-to-date national and transnational practices, along with the inclusion of a Canadian perspective. The secondary objective of this thesis was to provide other national or transnational bodies a framework for conducting pharmaceutical BIA worldwide. To reach the aforementioned goals, we initially sought to answer four questions:

1. What are the national and transnational pharmaceutical BIA guidelines published over the last 20 years? (since 1998)
2. What Canadian federal, provincial and territorial (F/P/T) BIA guidelines have been published/updated since 2007?
3. What are the differences between recommendations that were listed in the 2007 PMPRB BIA guidelines compared with BIA guidelines used by either Canadian F/P/T groups, or outside of Canada? What is not discussed or recommended differently in the 2007 PMPRB BIA guidelines?
4. What should be included in a proposal for updating the 2007 PMPRB BIA guidelines based upon Canadian stakeholders' feedback on an expanded list

of recommendations?

The first question was addressed through a systematic review of national and transnational BIA guidelines that were published or updated since 1998 (Chapter 2) [1]. This review, which assessed a broad range of bibliographic resources with no limitations of language, resulted in a transnational framework for developing or updating BIA guidelines worldwide. The outputs from this review assisted in making a comparison between the 2007 PMPRB BIA guidelines recommendations with the recommendations used by the rest of the world (outside Canada).

The second question was addressed by performing a comparative literature review of Canadian F/P/T and 2007 PMPRB BIA guidelines to identify recommendations adopted in various jurisdictions across Canada since the publication of the 2007 PMPRB BIA guidelines (Chapter 3). The third question was answered by the results obtained in chapters 2 and 3. We then prepared a comprehensive and detailed list of recommendations which were either not discussed or were mentioned differently in the 2007 PMPRB BIA guidelines when compare with Canadian F/P/T and other national and transnational BIA guidelines (Appendix 1)

In order to answer the fourth question, we obtained Canadian stakeholders' feedback on the expanded list of recommendations (which was developed through the two literature reviews). The stakeholder input was obtained through a mixed method study (qualitative and quantitative analyses) (Chapter 4).

In this concluding chapter, we provide a proposal for updating the PMPRB BIA guidelines incorporating the stakeholders' feedback regarding the use of BIA in policy-making, the appropriateness of BIA key elements, the assessment of gaps in the 2007 PMPRB BIA guidelines, and any other recommendations for improving the guidelines.

There are four important contributions from this thesis:

A) This was the first systematic review of national and transnational BIA guidelines published with sufficient details to enable the reader to assess similarities and differences between jurisdictions [2-9]. The list of the key recommendations related to the analytical model structure, input and data sources, and reporting format of BIA guidelines can be of use to anyone interested in building or updating a BIA guideline.

B) The second literature review (chapter 3) provides a Canadian perspective of BIA guidelines, acknowledging differences across provinces as well as the private payers. This information provides the foundation for updating the Canadian PMPRB BIA guidelines. It is also of value to potential drug sponsors that would require a BIA submission in support of a formulary listing for reimbursement in Canada.

C) The Canadian stakeholder feedback on the BIA recommendations, obtained through the use of qualitative and quantitative methods, provides additional insight from a Canadian perspective to help define an appropriate set of BIA guidelines. This information may be of preliminary value for updating or creating a BIA guideline worldwide.

D) The final contribution from this thesis is the presentation of a proposal (below) for updating the PMPRB BIA guidelines. While this proposal incorporates two literature reviews and Canadian stakeholder input, the latter input was limited in scope. Thus one should view the proposal as the penultimate version, which with more comprehensive stakeholder input would generate the final version. Hence this thesis has generated the “white paper” that will be disseminated broadly prior to the final revisions and formal

adoption by the PMPRB.

The process of developing the final "proposal" document for updating the PMPRB 2007 BIA guidelines

Through two comparative reviews of the Canadian, national and transnational BIA guidelines, thirty-nine recommendations were identified which were not included or discussed differently in the PMPRB 2007 BIA guidelines (Chapter 4, Table 1). Our stakeholder analysis showed support for the inclusion of 56% of the proposed recommendations into the guidelines pertaining to the use of expert opinions, data extrapolated from the payers' database, scenario analysis, and dynamic population. Thirty percent of the recommendations such as off-label indications in the base-case scenario, indirect costs, and cost transfers from other jurisdictions were not approved. There was no consensus with respect to the inclusion of cost offsets and patient adherence and compliance.

Ultimately, the proposed penultimate revised version of the PMPRB BIA guidelines was developed based on (1) PMPRB 2007 BIA guidelines; (2) the list of recommendations which were not included or discussed differently in the PMPRB 2007 BIA guidelines compare with other reviewed guidelines; and (3) Canadian stakeholders' feedback and recommendations.

The proposal- consisting of 72 recommendations, half (49%; n=35) are identical with the PMPRB 2007 BIA guidelines. Thirty-six percent of recommendations (n=26) are new and the remainder (15%; n=11) have been modified from the original version. Table 1 summarizes (1) the recommendations from the literature review which included in the stakeholder analysis; (2) the stakeholders' feedback on those recommendations and (3) the "proposal" recommendations for updating the PMPRB BIA guidelines. We defined three categories for the "proposal" recommendations: "new", "modified" and unchanged (no adjective used) when the recommendation was the same as the PMPRB 2007 guidelines and took the following systematic approach for including recommendations in the proposal:

1. If a recommendation was not included in the PMPRB 2007 BIA guidelines and was supported by the stakeholders, we included it in the proposal as a "new" recommendation (e.g., open or dynamic populations and scenario analysis).

2. If a recommendation was included in the PMPRB 2007 BIA guidelines but discussed differently compare with the other reviewed guidelines (at least one), and was supported by the stakeholders, we included it in the

proposal as a "new" or "modified" recommendation based on the extent of change we made to the original recommendation (e.g., inclusion of gross and net impact on the budget, reporting both aggregated and disaggregated results and inclusion of model validation documentation).

3. If a recommendation was neither included in the PMPRB 2007 BIA guidelines nor supported by the stakeholders, we did not include it in the proposal (e.g., tax application and opportunity cost).

4. If a recommendation was included in the PMPRB 2007 BIA guidelines but discussed differently compare with the other reviewed guidelines (at least one), and the new version of the recommendation was not supported by the stakeholders, we kept the recommendation "the same" as the PMPRB 2007 BIA guidelines (e.g., Off-label indications, inclusion of indirect costs).

5. If a recommendation was not included or discussed differently in the PMPRB 2007 BIA guidelines compare with the other reviewed guidelines (at least one), and also was not included it in the stakeholder analysis, an

internal decision was made by the authors regarding its inclusion in the proposal (e.g., technology description and comparator definition).

One should note that there are recommendations which are common among BIA guidelines and should be included in any updated BIA guidelines. We did not ask stakeholders about those recommendations for their inclusion in the proposal.

6. If a recommendation was not included or discussed differently in the PMPRB 2007 BIA guidelines compare with the other reviewed guidelines (at least one) and the stakeholder feedback was not conclusive (maybe), we included it in the proposal (as "new" or "the same") with a requirement for further broader stakeholder feedback analysis (e.g., inclusion of cost offsets, total and incremental impact on the budget and patient adherence and compliance)

In the following section, the proposal for updating the PMPRB 2007 BIA guidelines will be discussed in full details.

Proposal for recommendations to be included in an updated PMPRB BIA guideline

1. Analytical Model Structure

1.1. Perspective

1.1.1. Recommendation:

The perspective used in the BIA should be that of the drug plan.

This is the same recommendation as to the 2007 PMPRB BIA guidelines.

In the case of co-payments, including the patients' perspective is not necessary unless it is required by the payer. Some jurisdictions request that a patient perspective be included (e.g., Alberta [10]) Relating to co-payments, but this is not customary.

1.2. Technology

*1.2.1. Recommendation-**new**:*

The technology should be described in sufficient detail to differentiate it from its comparators and to provide context for the study.

The description should include details regarding how the new technology

compares to existing treatments. The specific characteristics that should be addressed in this section are:

Indication (based on the product monograph), formulation, onset of action, efficacy, side effects, serious adverse events, intermediate outcomes, adherence/compliance, and a brief summary of the clinical trials should also be provided in this section, including information on the design, study population, follow-up period, and clinical outcomes. This summary may be provided in a tabular format if desired.

1.3. Objectives

1.3.1. Recommendation:

The objective(s) of the BIA should be clearly stated.

This is the same definition previously used in the 2007 PMPRB BIA guidelines.

These objectives should state the population for which reimbursement is being sought, the time horizon being reported and the perspective used within the report. A clear statement of any limitations in the analysis should also be included. An example of the latter is that if the new drug will not affect current drug utilization patterns (i.e., market share distribution) but will decrease the need for specific

health care resources, it should be noted that savings to the health care system have not been included due to the use of a drug plan perspective.

1.4. Time horizon

*1.4.1. Recommendation-**modified**:*

3-year time horizon is recommended.

This is the modified version of the recommendation in the 2007 PMPRB BIA guidelines.

A note should be added regarding the consideration for more flexibility (or variability) in the time horizon depending on factors such as the disease area or patent duration. A time horizon beyond 3 years should be considered if it can be justified. This topic is controversial, and further consultation from different policy-making perspectives is required to reach a consensus regarding the most favorable BIA time horizon in Canada. At present, a 3-year time horizon is most favored in Canada.

1.5. Target population assessment

1.5.1. Definition

1.5.1.1. Recommendation:

In the Canadian context, the target population in pharmaceutical BIA should be defined as "all drug plan beneficiaries who are expected to be diagnosed and treated for the condition(s) of interest and who are eligible to use the new drug should be included in the BIA."

This is the same definition previously used in the 2007 PMPRB BIA guidelines.

Eligibility for drug use is defined by the population specified by the manufacturer's drug label/ monograph.

1.5.2. Subpopulation analyses

*1.5.2.1. Recommendation-**new**:*

Subpopulation analyses are to be included with the base-case analysis.

1.5.3. Open (dynamic) population

*1.5.3.1. Recommendation-**new**:*

The population should be considered dynamic, meaning that patients can be added or removed from the analysis based on whether they meet the inclusion criteria or not over time.

Mortality and disease progression (e.g., for chemotherapies) are also important in modeling a BIA analysis which is the nature of a dynamic target population.

1.5.4. Off-label indications

1.5.4.1. Recommendation:

Off-label indications should not be included in the base-case analysis but should be included in the sensitivity analysis, especially if there is robust cost-effectiveness evidence for the indication, or more importantly, it is required by the payer.

This is the same definition previously used in the 2007 PMPRB BIA guidelines.

1.5.5. Local regulations and legislation (access restrictions)

1.5.5.1. Recommendation:

Any planned local regulations and legislation that would limit new drug access in a subpopulation should be considered.

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

As not all new drug submissions obtain or seek a formulary listing that is without restrictions, it is important to include budget projections that reflect the scenario

under which access to the new drug may be restricted by one or more conditions. To accomplish this, the market size should be reduced based on available data. For example, if only seniors who are both female and have experienced a fracture are to be considered in an analysis, then only the population data for that desired demographic profile, i.e., females over 65 years of age who had experienced a fracture, would be considered [4, 7, 9, 11].

1.5.6. Market-share estimation

*1.5.6.1. Recommendation-**modified**:*

Either a top-down (epidemiological) or a bottom-up (market-share or claims-based analyses) approach is recommended in market size analysis.

This is the modified version of the recommendation in the PMPRB 2007 BIA guidelines.

Top-down (epidemiological) (Figure 1): An epidemiological approach is usually preferred if the submission indicates a superior therapeutic conclusion in clinical studies [3]. Bottom-up (market-share or claims-based analyses) (Figure 2): a market-share approach might be preferred if the submission indicates a non-inferior therapeutic conclusion [3].

When developing a claims data-based analysis, the number of claims dispensed for a given indication should be determined. Such estimates should be obtained through a database that provides detailed claims-based information for drug plans (e.g., IQVIA database). The number of claims used in the model for the baseline year should reflect the number of claims filed for all relevant comparators. In cases where the new and existing drugs are used for multiple indications, claims-based data should only be used if the distribution of claims between the two or more distinct indications can be made for each comparator. In the event that this is not possible, a population-based model is recommended. This is because the population-based model allows analysts to define their population(s) of interest based on specific criteria. Claims data-based models are used to calculate the number of active beneficiaries. This should be done when performing a claims-based BIA to validate the reasonableness of the claims estimates and to provide drug plans with an idea of the number of beneficiaries that are currently being treated for a given indication. The number of active beneficiaries can be estimated by dividing the annual number of claims for each primary treatment by the average annual number of claims filed per person. As each claim filed is specific to a particular patient, there should be no double-counting of patients when using this method of estimating the number of active beneficiaries. In addition to the general limitations of using active beneficiaries in BIAs, the estimates calculated using this approach cannot be subdivided by age or gender and thus age- and gender-specific prevalence data cannot be used for forecasting purposes.

*1.5.6.2. Recommendation-**new**:*

The degree of implementation (i.e., full replacement or partial substitution of existing technologies, or shifts in the target population, market growth or expansion) is essential in market size estimation.

Market growth should be based on standard population growth if the availability of the new drug is not anticipated to affect the size of the market (e.g., affect disease incidence or treatment switch) (Figure 1).

1.5.6.3. Recommendation:

For listing a new competing treatment, the market share growth of the new treatment should mirror that of the proposed new drug.

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

1.5.6.4. Recommendation:

For treatment discontinuation, the market share held by the removed drug should be split amongst the remaining treatments proportional to the size of the market

held by each comparator.

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

For example, a treatment that held 80% of the market would be expected to capture 80% of the market share of the treatment that was removed from the marketplace.

*1.5.6.5. Recommendation-**new**:*

For patients who switch to the new drug, a catch-up effect, which applies to the chronic conditions, should be included.

Market growth should be based on both standard population growth and growth due to the new drug if the availability of the new drug is anticipated to affect the size of the market (e.g., the effect on the treatment) (Figure 1).

1.5.6.6. Recommendation:

Forecast changes in the Reference Scenario market

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

Analysts should:

- Avoid forecasting data using computer applications other than the application in which the budget impact model was developed.
- Use published forecasts, whenever possible.
- Access available databases to determine the current distribution of treatment strategies.
- Develop forecasts that take into consideration anticipated changes (e.g., listing of a new competing treatment or treatment discontinuation) to the market over the time horizon.

1.5.6.7. Recommendation:

Calculate the market share of the new drug

This is the same recommendation as the PMPRB 2007 BIA guidelines.

The factors that should be used may include:

- Percentage of users of competing treatments who are eligible to use the new drug.
- Percentage of physicians who are aware of the new drug.
- Percentage of physicians who are willing to prescribe the new drug.
- Percentage of users of competing treatments who are aware of the new drug.

- Percentage of users of competing treatments who are likely to switch to the new drug (refer to "treatment switch" recommendation).
- Percentage of those who try and fail to respond to the new drug.

1.5.6.8. Recommendation:

Forecast changes in the New Drug Scenario market

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

Analysts should:

- Apply the general rules detailed for the forecasting of the Reference Scenario.
- Consult drug-specific data from markets where the new drug is currently reimbursed whenever possible (because of concerns regarding the reliability of market data from other jurisdictions). In the case where there is a lack of real-world data for the proposed medication alternate markets are acceptable.
- Consider and appropriately reference current market intelligence on how the reimbursement of the new drug will affect the market.

*1.5.6.9. Recommendation-**new**:*

In the situation where a drug's indications are evolving this issue needs to be addressed in the BIA.

The consideration for continuing (or discontinuing) the coverage for some indications should be highlighted in the guidelines. For example, if a drug is commonly used as the second line in a disease category and in the new application it becomes the first line in a new indication, then it may not be covered as a second line therapy anymore.

1.5.7. Patient adherence/compliance

*1.5.7.1. Recommendation-**new:***

The impact of patient adherence or compliance should be reported if cost offsets (e.g., cost of clinical outcomes and complications) are included in the BIA.

1.6. Comparators

1.6.1. Definition

1.6.1.1. Recommendation:

The reference scenario is the current market share distribution of all comparators excluding the new drug, and the new drug scenario is the forecasted market share of same comparators with the inclusion of the new drug.

This is the same definition previously used in the 2007 PMPRB BIA guidelines.

Reference Scenario

1.6.1.2. Recommendation:

In the Reference Scenario, the composition of the marketplace is forecasted for the time period of interest assuming that the new drug would not be added to the F/P/T drug formulary.

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

The composition of the forecasted market over the time horizon is based on the current market's competitive landscape as well as data and supportable assumptions regarding the discontinuation and/or adoption of new therapeutic options.

1.6.2. New Drug Scenario

*1.6.2.1. Recommendation-**new**:*

"Treatment mix" rather than "strategy-based treatment" should be the terminology for defining concomitant medications of comparators.

Unlike the Reference Scenario, the New Drug Scenario assumes that the new drug becomes listed on the drug formulary of the F/P/T drug plan of interest. In this scenario, the composition of the marketplace is forecasted for the duration of the time period of interest (Figures 1 and 2). The composition of the forecasted market over the time horizon is based on the current market's competitive landscape, data and supportable assumptions related to how the introduction of the new drug will change the market, and the discontinuation and/or adoption of new therapeutic options. This is suggested that in order to be consistent with international terminology. Previously in Canada, the multi-drug treatment strategy for defining comparators has been called "strategy-based treatment", which is different from ISPOR (treatment mix or set) and France (treatment set), and Australia (treatment mix). One should note that comparator mix does not necessarily always match the comparator mix in the utilization [real world], e.g., the treatment mix that private payers and public plans see in their database may be different because of inherent differences in their formularies. This type of difference between public and private payers should be addressed in this section.

1.6.2.2. Recommendation:

All assumptions made to develop a given scenario should be explicitly stated and supporting references provided.

This is the same recommendation as the PMPRB 2007 BIA guidelines.

*1.6.2.3. Recommendation-**modified**:*

The choice of comparators in BIA should be an accurate reflection of the existing therapeutic options for the condition(s) of interest and preferably be consistent with the health economic evaluation (e.g., cost-effectiveness study) unless there are clear justifications for not taking the same treatment strategy as the related economic evaluation/health technology assessment (e.g., in the case of non-drug/surgical alternatives)

This is the modified version of the recommendation in the PMPRB 2007 BIA guidelines.

Comparators should be categorized and studied by indication to provide F/P/T drug plan managers with the overall impact of reimbursing the new drug and the effect of this reimbursement by indication.

In summary, to select relevant comparators for a budget impact model, analysts should:

- Group drug comparators by indication
- Identify treatment strategies that can be compared to the new drug
- Seek adequate input (e.g., published studies, market research, expert opinion) to identify comparators and their use

1.7. Costing

*1.7.1. Recommendation-**modified**:*

The BIA should identify all medicines likely to be affected by the new drug. In Canada, BIA cost analysis is based on the treatment mix (including adjunct therapies).

This is the modified version of the recommendation in the PMPRB 2007 BIA guidelines.

*1.7.2. Recommendation-**modified**:*

Cost offsets [e.g., costs associated with changes in clinical outcomes, costs associated with clinical consequences/complications (e.g., adverse drug reactions) and resource utilization (e.g., hospitalization, emergency room admission)] should be excluded unless there are substantial costs related to the resource utilization and are directly required by drug plans (e.g., Manitoba, private payers).

This is the modified version of the recommendation in the PMPRB 2007 BIA guidelines.

From the private payers' perspective cost offsets are important and therefore, patient adherence and compliance should be taken into account (according to the ISPOR BIA guidelines).

1.7.3. Recommendation:

The impact on direct and indirect non-healthcare related costs (e.g., productivity, transport, capacity, and workforce) and capital cost are not included in a BIA base-case analysis.

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

1.7.4. Recommendation:

Cost/price data from other jurisdictions are not acceptable.

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

The price used within the BIA should be derived from sources specific to the F/P/T plan being evaluated. For example, a BIA for the province of Ontario should use Ontario costs and not costs for the province of Alberta. The cost sources used should be clearly documented. If the amount of information regarding the price of the unlisted comparator is limited, the price of the comparator should be set to the price of the drug for which the BIA is being submitted.

*1.7.5. Recommendation-**new**:*

Least Cost Alternative (LCA) price for relevant drug comparators is recommended.

1.7.6. Recommendation:

The cost of treatment should be adjusted to consider mark-ups, discounts, inventory allowance business-related costs to the pharmacy covered by the drug plans, and dispensing fees as requested by drug plans in Canada.

This is the same recommendation as the PMPRB 2007 BIA guidelines.

Markups and professional fees are different in public and private plans, and it is recommended to be considered in an interactively updated model template for BIA [2, 7, 9].

1.7.7. Recommendation:

Patient co-payments should not be included in the base-case analysis unless is required by the drug plan.

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

1.7.8. Recommendation:

Drug prices should be obtained from provincial formulary websites, public drug plan databases and manufacturers' market access department for preparing BIA reports.

This is the same recommendation as the PMPRB 2007 BIA guidelines.

- When estimating the cost of the drugs to be included in a BIA for a given F/P/T drug plan, drug prices specific to the F/P/T drug plan should be used.
- The amount reimbursed for each drug by an F/P/T drug plan should be clearly presented and should be specific to the chemical and dose of interest.
- It is recommended that uncertainties regarding the drug reimbursement price should be targeted through a sensitivity analysis [7].

1.7.9. Recommendation:

For unlisted drugs that are expected to obtain a listing in the future, the price of the drug should be estimated using the available data.

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

If there are data to suggest that the drug will be launched at a specific price, these data should be used. If the drug represents a lower dose version of an existing treatment, the price of the existing treatment should be used. This is because of the likelihood that the new treatment will be more expensive than the existing treatment is low. If the new drug represents one of a class of drugs, the least cost alternative (LCA) within the class as defined by the drug plan should be used to

set the price of the new comparator. If the amount of information regarding the price of the unlisted comparator is limited, the price of the comparator should be set to the price of the drug for which the BIA is being submitted. This should be done to minimize bias in the analysis. Any assumptions made about the price of drug comparators should be reported within the BIA report and tested using DSA[18] (refer to "Characterizing the uncertainty").

1.7.10. Recommendation:

Inflation and discount rates are not applied.

This is the same recommendation as the PMPRB 2007 BIA guidelines.

In the PMPRB 2007 BIA guidelines, they are permitted in the certain circumstances and if there is justification for being included (e.g., confirmed information on pricing policy, implementation of an approved new policy rule in the near future or price changes after patent expiration).

[18] Deterministic sensitivity analysis

*1.7.11. Recommendation-**modified**:*

In the case of medications where recommended duration of use is less than 30 days (e.g., antibiotics), this should be specified and the cost calculated accordingly.

This is the modified version of the recommendation in the PMPRB 2007 BIA guidelines.

*1.7.12. Recommendation-**new**:*

Drugs which require reconstitution or dose preparation, the method of dose preparation, dose stability and specifics around potential drug wastage should be clearly mentioned.

*1.7.13. Recommendation-**new**:*

Cost of supplies to the manufacturer and the payer and any cost of companion diagnostic test or medical device should be reported.

*1.7.14. Recommendation-**modified**:*

The BIA should clearly state which unit of analysis is adopted in measuring the outcomes.

This is the modified version of the recommendation in the PMPRB 2007 BIA guidelines.

There are two possible units of analysis: per patient or episode of care. Specified interventions may range from once-only, repeated, periodic or continuous interventions; it needs to be clear the number of times or the length of time people might experience the intervention or how many treatment events might arise" [2, 3, 11].

In the PMPRB 2007 BIA guidelines, unit of analysis is called as "estimation of therapeutic equivalencies." When determining the cost per prescription or the patient cost per year within a BIA, it is important to accurately and transparently evaluate therapeutic equivalences. "Therapeutic equivalences" refers here to equivalence in use, not equivalency in therapeutic efficacy. For example, a therapy that is taken once a month and a therapy that is taken once a day cannot be fairly compared by looking at the unit prices alone. Instead, the frequency of drug use should also be factored into the comparison of the two treatments.

1.7.15. Recommendation:

Considering time to refill data to determine the number of times that dispensing fees are paid for each drug and also determining the patient compliance is optional.

This is the same recommendation as the PMPRB 2007 BIA guidelines.

In summary, when calculating the cost to the F/P/T drug plan, BIAs should:

- Consider treatment strategies rather than the cost of each individual drug.
- Include the expected reimbursement price for all treatment strategies
- Include the price of the new drug.
- Include the price of all relevant comparators as reimbursed by the F/P/T drug plan.
- Include the price of all relevant concomitant medications as reimbursed by the F/P/T drug plan.
- Adjust all drug costs according to the F/P/T drug plan's requirements for BIA submissions.
- Determine the most current values to be used for all required mark-ups, inventory allowances, dispensing fees and patient co-payments.
- Add all required mark-ups, inventory allowances and dispensing fees to drug costs.

- Subtract patient co-payments from drug costs, when required by the F/P/T drug plan.
- Exclude premiums and deductibles.

1.8. Modeling techniques and validity

1.8.1. Recommendation:

Be designed in a manner that meets with the needs of the end users (policymakers)

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

1.8.2. Recommendation:

Explicitly state all choices and assumptions made by the authors of the model.

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

1.8.3. Recommendation:

All submitted models should be transparent and simple.

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

Excel-based electronic models would be preferred if they have the ability to express results in either contract years or fiscal years.

*1.8.4. Recommendation-**new**:*

Markov models are not recommended; however, it is advised that the disease condition should be modeled as much as possible to capture the long-term consequence (at least within the taken time horizon) of using the proposed medication in chronic conditions.

Providing either incidence- or prevalence-based (or both) models would help to better understand drug costs related to the acute and chronic conditions.

*1.8.5. Recommendation-**new**:*

Model validity has to be checked and documented.

The model validity and transparency could be assessed using recommendations provided by ISPOR and the Society for Medical Decision Making task force report [16]. The detailed process of the validation is not required in the PMPRB

2007 BIA guidelines.

1.8.6. Recommendation:

Programming code should be documented, annotated, and undergo quality assurance and control methods for software engineering.

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

The programming created by the developer of the budget impact model to perform the analysis (source code) should be made available for review (on the condition that property rights are respected).

1.9. Characterizing the uncertainty

*1.9.1. Recommendation-**new**:*

Describe the direction and magnitude of the impact of uncertainty on the overall estimates.

*1.9.2. Recommendation-**modified**:*

Robust methods for sensitivity analysis are required to adequately address the issue of uncertainty.

There are two types of uncertainty in a BIA:

- Parameter uncertainty in the input values used (e.g., efficacy estimates for the current and new interventions) which is dealt with through sensitivity analysis (e.g., DSA)
- Structural uncertainty introduced by the assumptions made in framing the BIA (e.g., changes in expected intervention patterns with the availability of the new intervention and restrictions for use) which is addressed through scenario analysis.

Note: Limitations to both approaches: (1) Due to limited data for many of the parameters, much of the parameter uncertainty of BIAs cannot be meaningfully quantified, and thus standard approaches such as one-way and probabilistic sensitivity analyses cannot be carried out fully, (2) Much of the uncertainty is structural and not easily parameterized.

*1.9.3. Recommendation-**modified**:*

Provide deterministic sensitivity analysis (DSA) (i.e., one-way, multi-way and analysis of extremes) to inform decision-makers of the sensitivity of the model to specific assumptions

This is the modified version of recommendation in the PMPRB 2007 BIA guidelines.

Provide reasonable and/or cited information regarding the range of uncertainty associated with each assumption. Sensitivity analysis is recommended for data obtained from clinical trials [3], drug dosage and price, market data from other jurisdictions, changes in the market size over the time horizon (including restriction to subgroups and clinical criteria identified by CADTH, as well as uncertainty regarding future/expanded indications, the utilized population forecasts, and off-label use estimates from relevant sources), market share distribution amongst the new drug and its comparators (including the evaluation of the impact of assumptions regarding the future reimbursement of potential comparators and/or concomitant medications), price of any comparators and/or concomitant medications for which uncertainty exists (e.g., are not currently reimbursed but are anticipated to be granted reimbursement status between the time of BIA submission and the end of the modeled time horizon.

*1.9.4. Recommendation-**new**:*

Scenario analyses should be undertaken by changing selected input parameter values and structural assumptions to produce plausible alternative scenarios.

In case patient adherence and compliance are included, their impact could be assessed in scenario analysis, and the related assumptions should be based on database studies or prospective studies applicable to the budget holder.

1.9.5. Recommendation:

Probabilistic sensitivity analysis (PSA) should not be used in the Canadian BIA guidelines.

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

1.9.6. Recommendation:

Access to uncertainty analyses is essential to effective decision-making as it demonstrates the range of reasonable values that F/P/T drug plans can expect to pay if they choose to reimburse the new treatment).

This is the same recommendation as the PMPRB 2007 BIA guidelines.

*1.9.7. Recommendation-**new**:*

A reassessment process of BIAs in a future real-world could be helpful in assessing the reliability of the BIA results.

2. Input and data sources

Important note: it is very difficult to come up with solid parameter estimates, particularly around market growth and market penetration of the new drug (market size estimation). Uncertainty is a serious concern related to input data.

2.1. Recommendation:

National statistics and registries are recommended sources for epidemiologic data (e.g., disease prevalence and incidence)

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

Statistics related to the size of the decision maker's population and the demographic composition of this population (e.g., age, gender, race, and ethnicity) and Canadian prevalence data are used to determine the number of people covered by the F/P/T drug plan that would have the condition of interest. It is assumed that the prevalence of the disease in the population of eligible

participants (by age, gender, race, and ethnicity) is the same as that of the Canadian population, and so the prevalence statistics are applied to the population of the F/P/T drug plan. This represents a less than the ideal alternative and should only be used when appropriate data are not available.

2.2. Recommendation:

Use of prevalence data for the province, territory, or population of interest (e.g., Aboriginal Canadians, not including Métis) in combination with population data for the F/P/T drug plan.

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

Statistics related to the size of the decision maker's population and the demographic composition of this population (e.g., age, gender, race, ethnicity) and prevalence data for the related jurisdiction are used to determine the number of people covered by the F/P/T drug plan that would have the condition of interest (e.g., use of prevalence data for Canada's Aboriginal peoples, excluding the Métis population, and eligible participant statistics for the NIHBP[19]). It is assumed that the prevalence of the disease in the population of eligible participants is the same as that of the general population, and so the prevalence statistics are applied to the

[19] Non-insured health benefits program

population of the F/P/T drug plan. This represents the best alternative to using actual prevalence data for the F/P/T drug plan.

2.3. Recommendation:

Use of prevalence data from a province, territory, or population that is similar to the population of interest in combination with population data for the F/P/T drug plan

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

Statistics related to the size of the decision maker's population and the demographic composition of this population (e.g., age, gender, race, ethnicity) and prevalence data for a jurisdiction that is known to be similar to the region of interest are used to determine the number of people covered by the F/P/T drug plan that would have the condition of interest (e.g., use of Nova Scotia prevalence data and population statistics for those eligible for reimbursement under the Prince Edward Island Drug Cost Assistance Programs). It is assumed that the prevalence of the disease in the population of eligible participants (by age, gender, race, and ethnicity) is the same as that of the population used as a source of prevalence data, and so the prevalence statistics are applied to the population of the F/P/T drug plan. This represents less than the ideal alternative and should only

be used when appropriate data are not available.

*2.4. Recommendation-**new**:*

It is recommended that some reliable data sources be listed in the new version of the PMPRB BIA guidelines for providing manufacturers with more robust epidemiologic and claims-based data.

2.5. Recommendation:

The best sources for the claims-based and market research information are the payer database and the manufacturer's marketing department.

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

2.6. Recommendation:

Market and clinical data from other jurisdictions are acceptable if local information is not available.

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

2.7. Recommendation:

The BIA reports from manufacturers with clear supporting data could also be a helpful source of information.

This is the same recommendation as to the PMPRB 2007 BIA guidelines.

2.8. Recommendation:

Consensus expert opinion is an option as a reliable data source when market intelligence for forecasting the new drug market share is not available.

This is the same recommendation as the PMPRB 2007 BIA guidelines.

*2.9. Recommendation-**new**:*

Extrapolating data from similar drug experience can also be considered as a reliable source of data.

*2.10. Recommendation-**new**:*

Original cost survey, obtaining primary data, by sampling, involving interviews with health professionals under study could also be an option for obtaining required data.

3. Reporting format

3.1. Calculation of budget impact

*3.1.1. Recommendation-**modified**:*

Estimates from the Reference Scenario and the New Drug Scenario should be used to determine the incremental cost (or savings) realized by a drug plan. The value of each scenario is equal to the sum total of the annual cost of each treatment strategy. Estimation of the annual cost of a treatment strategy is dependent on the type of BIA performed by the analyst.

If a population data-based model has been used, the annual cost of a treatment mix is equal to:

$$\boldsymbol{Treatment\ cost = Unit\ cost\ per\ patient \times population\ size}$$

$$\boldsymbol{Budget\ impact = Net\ Cost = Treatment\ cost}\ new - \boldsymbol{Treatment\ cost}\ current$$

In the case where a claims data-based model has been used, the annual cost of a treatment mix is equal to:

Annual number of claims for the treatment mix (for the indication of interest) × Drug cost per claim

The budget impact is equal to the difference between the value of the New Drug Scenario and the value of the Reference Scenario (i.e., New Drug Scenario value minus Reference Scenario). A positive budget impact value indicates that the introduction of the new drug will result in increased expenditures for the drug plan, while a negative value indicates that the drug plan will save money by adopting the new drug. Figures 1 and 2 schematically illustrate BIA calculation using epidemiologic and claim-based approach.

Incremental prescription drug costs should be calculated for each of the three years of the time horizon. In addition, the cumulative incremental prescription drug costs for the time horizon should be evaluated. Summary calculations for the total direct drug costs in each year (Year 1, Year 2 and Year 3) and for all years (Years 1-3) (aggregated and disaggregated impact), should be presented by scenario to allow reviewers to understand how the budget impact was calculated.

3.2. There are specific requirements for reporting the results in the reviewed guidelines:

*3.2.1. Recommendation-**new**:*

Search strategy; inclusion criteria for data selection and source selection; strengths and weaknesses of the used sources, and methods of analysis should be presented.

*3.2.2. Recommendation-**new**:*

Total and incremental impact on the budget for multiple indications of the proposed medication (covered by the payer) is recommended in BIAs.

The 2007 PMPRB BIA guidelines only require an incremental impact on the annual budget [7]. This will provide the payer with a full understanding of how much they will pay for the drug for its all listed indications after providing coverage for the new indication.

*3.2.3. Recommendation-**new**:*

Results should be both aggregated and disaggregated in each year of the time horizon.

Currently, most BIA reports are providing results in a disaggregated format for each year of time horizon [2, 3, 6].

*3.2.4. Recommendation-**new**:*

Gross (absolute) and the net impact on the budget should be reported.

Gross Impact is the anticipated sales of the drug of interest for each of the first 3 years after the coverage is granted for it and Net Impact is the annual incremental cost.

*3.2.5. Recommendation-**new**:*

The budget impact should be presented in monetary units and not in natural units (e.g. number of sick days)

*3.2.6. Recommendation-**modified**:*

A table of assumptions, inputs, and outputs, a schematic representation of any uncertainty analyses [e.g., Tornado diagram], appendices and references should be included.

*3.2.7. Recommendation-**new**:*

Budget impact results should be presented separately for different payers.

*3.2.8. Recommendation-**new**:*

A cap or threshold for budget impact could be considered for recognizing "substantial" budget impact of the expensive (or highly specialized) medications.

3.2.9. Recommendation:

A conclusion that summarizes the key information presented in the report should be included.

This is the same recommendation as the PMPRB 2007 BIA guidelines.

Suggestions for future research

Further research is required for obtaining policymakers' feedback on the following issues:

- Assessing the differences between public and private payers' perspective and BIA requirements.
- Developing a conclusive recommendation on the BIA time horizon in Canada: A 3-year time horizon is marginally passed in our stakeholder analysis and we believe that involving more policymakers in the analysis would make the recommendation more conclusive regarding the appropriate time horizon in Canada

- Developing a conclusive recommendation on the inclusion of cost offsets (e.g., cost of clinical outcomes, disease complications, and adverse drug reactions) and patients' adherence/compliance consequently. Cost offsets are more important to private payers than public payers. Further feedback from both public and private organizations is required to reach a consensus on these recommendations. For example, we may decide to include these recommendations only for private payers.

- Developing a conclusive recommendation on the inclusion of reporting both total and incremental impact on the budget for a new medication which is not finalized in our stakeholder analysis for policymakers; and

- Developing a conclusive recommendation on including a list of acceptable databases[20] in BIA for public and private payers in Canada: Input data uncertainty is an issue and finding Canadian relevant data can be difficult. Discordance between prescribing practices, dispensing activities and patient adherence further complicates the analyses. This recommendation would help to decrease the extent of input data uncertainty in BIA reports.

Moreover, we suggest further research for a review of the terminology used in the BIA literature internationally.

In conclusion, the present Ph.D. thesis has provided a penultimate revised PMPRB BIA set of guidelines. Broader consultation and stakeholder input of this version will follow and should be conducted by the PMPRB. Then there will be an opportunity for further revision and the eventual adoption of a fully updated set of BIA guidelines for Canada.

[20] Although we got a conclusive results from our stakeholder analysis, however, we would suggest to continue asking policy-makers how much they believe this recommendation would be feasible in Canada.

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Table 1: A summary of (1) the recommendations from the literature review which included in the stakeholder analysis, (2) the stakeholders' feedback and (3) the recommendations in the "BIA guidelines update proposal"

Recommendations included in the stakeholder analysis	**Stakeholders' feedback**	**"Proposal" recommendation**	**Category of the proposed recommendation**
A 3-year time horizon is recommended	Maybe	Recommended	Modified
Open or dynamic populations should be used in the target population assessment	Recommended	Recommended	New
Subpopulation analysis should be conducted	Recommended	Recommended	New
The total and incremental impact on the budget should be included in the BIA	Maybe	Recommended	New[21]
Least Cost Alternative (LCA) price for relevant drug comparators should be used in the BIA	Recommended	Recommended	New
The effects of inflation should NOT be included in the BIA unless in the certain circumstances and if there is justification for being included (e.g., confirmed the information on pricing policy, implementation of an approved new policy rule in the near future or price changes after patent expiration)	Recommended	Recommended	The same as PMPRB 2007
Discounting should NOT be included in the BIA	Recommended	Recommended	The same as PMPRB 2007
Aggregated and disaggregated budget impact results should be reported for each year	Recommended	Recommended	New
There should be reporting of the gross and net impact on the budget	Recommended	Recommended	New

[21] This recommendation was not included in the PMPRB 2007 BIA guidelines and therefore we updated the recommendation to "new" for further stakeholder analysis.

Outcomes should be presented separately for different payers	Recommended	Recommended	New
Outcomes should be presented in monetary units	Recommended	Recommended	New
There should be a schematic representation of the uncertainty analysis	Recommended	Recommended	Modified
The impact of uncertainty (quantifying the precision of the results) should be presented in the BIA	Recommended	Recommended	New
Data from the manufacturer can be considered as a reliable source of data	Recommended	Recommended	The same as PMPRB 2007
Market/clinical data from other jurisdictions can be considered as a reliable source of data	Recommended	Recommended	The same as PMPRB 2007
Expert opinions can be considered as a reliable source of data	Recommended	Recommended	The same as PMPRB 2007
Extrapolating data from similar drug experience can be considered as a reliable source of data	Recommended	Recommended	New
A BIA should use scenario analysis for dealing with uncertainty	Recommended	Recommended	New
A BIA should use deterministic sensitivity analysis for dealing with uncertainty	Recommended	Recommended	Modified
Treatment switch should be considered in BIAs	Recommended	Recommended	New
Rate of mortality and disease progression should be considered in BIA	Recommended	Recommended	New
Cost of ADRs, clinical outcomes, and disease complications should be included in BIA (cost offsets)	Maybe	Not Recommended	The same as PMPRB 2007[22]
A cap or threshold for budget impact should be considered	Recommended	Recommended	New

[22] The recommendation remained the same as the PMPRB 2007 BIA guidelines.

A reassessment process of BIAs in a future real-world should be considered	Recommended	Recommended	New
In the case of co-payment, the inclusion of a patient's perspective is recommended in the base-case analysis	Not recommended	Not recommended	The same as PMPRB 2007
Off-label indications should be included in the base-case analysis	Not Recommended	Not Recommended	The same as PMPRB 2007
Training or introduction cost should be included in the BIA	Not Recommended	Not Recommended	The same as PMPRB 2007
Transportation, productivity and caregiver related costs should be included in the BIA	Not Recommended	Not Recommended	The same as PMPRB 2007
Opportunity cost estimation in BIAs should be provided by the manufacturers	Not Recommended	-	Not included in the proposal
An appropriate rate of tax (e.g. HST) should be applied to the applicable costs	Not Recommended	-	Not included in the proposal
Cost transfer from other jurisdictions is allowed	Not Recommended	Not Recommended	The same as PMPRB 2007
Outcomes should be presented in natural units (e.g. number of unpaid working days)	Not Recommended	-	Not included in the proposal
A BIA should use probabilistic sensitivity analysis for dealing with uncertainty	Not Recommended	Not Recommended	The same as PMPRB 2007
A BIA should include a proposed risk sharing agreement for dealing with uncertainty	Not Recommended	Not Recommended	Not included in the proposal
A longer introduction phase should be used with early BIAs to address issues of uncertainty	Not Recommended	Not Recommended	Not included in the proposal
Patient adherence/compliance should be included in BIAs	Maybe	Recommended	New[23]

[23] This recommendation was not included in the PMPRB 2007 BIA guidelines and therefore we updated the recommendation to "new" for further stakeholder analysis.

BIA guidelines should provide a list of acceptable databases	Maybe	Recommended	New[24]

[24] This recommendation was not included in the PMPRB 2007 BIA guidelines and therefore we updated the recommendation to "new" for further stakeholder analysis.

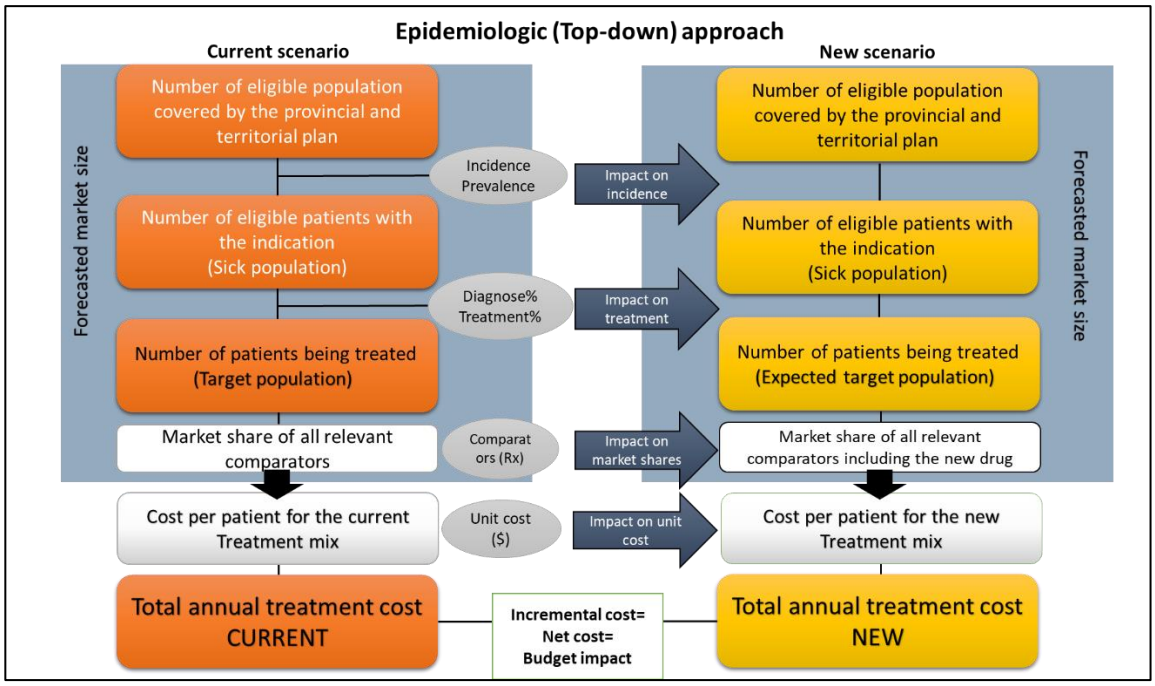

Figure 1: BIA schematic: Epidemiologic or Top-down approach.

Adapted from Value in Health, 17, Sullivan, S.D., et al. Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force, 5-14, 2014. et al. [9]

Note: The figure is adapted for the Canadian perspective from the ISPOR BIA guidelines. Revised features are eligible population covered by the drug plan (rather than total population), market size and market share of all comparators (for Canada), cost of treatment mix (Rx) (rather than health resource utilization, e.g., hospital and ambulatory costs), total annual treatment cost (rather than cost of illness)

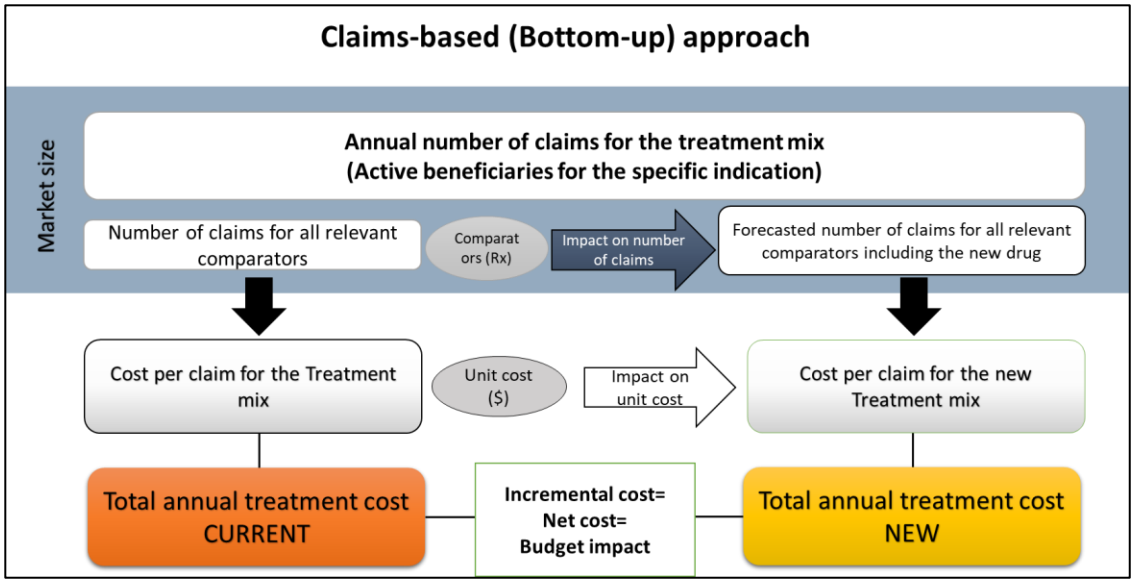

Figure 2: BIA schematic: Claim-based or Bottom-up approach.

Appendix 1: List of recommendations which are not included or discussed differently in the 2007 Canadian PMPRB guidelines.

These recommendations were the basis of developing interview and survey questionnaires.

#	**BIA secondary elements**	**Canada PMPRB (2007)**
Perspective		
1	In the case of co-payment, the inclusion of the **patient's perspective** is complementary to the base-case analysis	Not discussed
Technology		
2	The **technology** should be described in sufficient detail to differentiate it from its comparators and to provide context for the study.	Not discussed
Target population		
3	**Open (dynamic) population**	Not discussed
4	**Subgroups** in the target population assessment are recommended.	Not discussed
5	**Catch-up effect** which applies to the chronic conditions for patients who switch to the new drug	Not discussed
6	**Unit of analysis** (per patient or episode)	Discussed differently
7	**Off-label indications** in the target population assessment (base-case analysis) are recommended.	Discussed and only included in the sensitivity analysis
8	**The degree of implementation** of the new intervention (substitution, combination, and expansion)	Not discussed
Comparators		
9	**Terminology**	Different definitions
10	**Choice of comparators**	Discussed differently
Costing		
11	**Opportunity costs** are the costs that arise when implementing the technology or clinical guidelines that might not be reflected in the "actual costs" at the time of doing BIA analysis	Not discussed
12	**Cost of clinical outcomes** and disease complication	Discussed and excluded
13	**Cost of health care utilization** (e.g., hospital days	Discussed and

	or physician visits)	excluded
14	**Indirect costs:** The impact of the new intervention on productivity, social services, and other costs outside the health care system	Discussed and excluded
15	**Cost of supplies**: The analytic framework should allow for cost-relevant details of how accompanying devices for the proposed medication are used	Not discussed
16	The annual depreciation of any **capital costs** should be included in the analysis	Not discussed
17	**Labor costs**	Not discussed
18	**Applicable tax**	Not discussed
19	The BIA should also estimate the impact of **adherence** or persistence on intervention effectiveness and safety if condition-related costs are included in the BIA.	Not discussed
20	Calculate both the **global budget impact and separately the budget impact for the different health care payers** (This implies that potential transfers of budgets between different levels of governments and/or patients)	Not discussed
21	**Cost transfer** from other jurisdictions is allowed in BIA	Discussed and not allowed
22	**Least Cost Alternative (LCA) price** for relevant drug comparators is recommended	Not discussed
23	Drugs which require reconstitution or dose preparation, the method of dose preparation, dose stability and specifics around potential drug wastage	Not discussed
Modeling		
24	**Modeling** may be needed to calculate the budget impact for bringing together the best available data from different sources.	Not discussed
25	Assumptions should be the same as EE	Not discussed
26	**More complicated Software**	Not discussed
Validation		
27	The process of the validation	Discussed and excluded (not required)
28	Quality assurance and publication of the BIA results	Not discussed
Handling uncertainty and Scenario Analyses		

29	**Probabilistic Sensitivity Analysis (PSA)** is recommended in BIA	Discussed and excluded (not allowed)
30	**Scenario analysis**: Structural uncertainty introduced by the assumptions made in framing the BIA	Not discussed
31	Describe the **direction and magnitude** of the impact of uncertainty on the overall estimates	Not discussed
Data input and reporting format		
32	Search strategy; inclusion criteria for data selection and source selection; strengths and weaknesses of the used sources, and methods of analysis should be presented	Not discussed
33	**Original cost survey**, obtaining primary data, by sampling, involving interviews with health professionals under study	Not discussed
34	The estimated **annual total and incremental budget impacts** should be reported separately for each year of the time frame	The only incremental impact is required
35	**Gross and the net impact** on the budget [the anticipated sales of the drug of interest for each of the first 3 years after the coverage is granted for it (gross impact) and the net impact]	Not discussed
36	Results should be reported in terms of their **natural units** and financial cost	Not discussed
37	The inclusion of graphics and figure of the analytical framework, the schematic representation of uncertainty analyses	Not discussed
38	The addition of relevant appendices to the main report is encouraged. The appendices may cover literature search strategies, evidence summaries, intermediate results (e.g., of individual Delphi panel rounds), and the names and addresses of participating experts and investigators, for example)	Not discussed
39	Resource impact products: resource planner; resource impact reports and templates; resource impact statement	Not discussed