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# Health Technology Assessment Standards and Practices: How Does Canada Compare with Other Countries?

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## ABSTRACT

Over the past 30 years, many countries including Canada have established agencies and developed policies and programs for health technology assessment (HTA) to inform decision-making regarding public reimbursement coverage of new medicines. Differences exist between agencies in terms of their philosophies, policies, practices and methods in the application of HTA. This study compares the Canadian Agency for Drugs and Technologies in Health (CADTH) with HTA agencies in comparable countries – the Pharmaceutical Benefits Advisory Committee in Australia, the National Institute for Health and Care Excellence in England and Wales, and the Scottish Medicines Consortium in Scotland. The clinical and economic recommendations from the four HTA agencies for 9 new biologic therapies for plaque psoriasis were reviewed. The HTA recommendations demonstrate a distinct difference between CADTH and the other agencies. The agencies in the United Kingdom and Australia found that the majority of the biologics were cost-effective, especially when the manufacturer supported a patient access scheme. In contrast, most of CADTH's recommendations for the biologics had a requirement that the price should not exceed the least costly biologic already covered or the price should result in savings, even though CADTH's role does not include price setting or price negotiation. The oversight of the National Institute for Health and Care Excellence, the Scottish Medicines Consortium and the Australian Pharmaceutical Benefits Advisory Committee is much better than CADTH's. All the agencies made some improvements in transparency over the past decade based on this case study, but CADTH and the Pharmaceutical Benefits Advisory Committee should do more. The participation of all stakeholders, especially patients, must be improved in Canada if CADTH is to put its commitment to inclusivity into practice. The National Institute for Health and Care Excellence and the Scottish Medicines Consortium are closer to complying with the principles of accountability/impartiality, transparency, participation/inclusivity and responsiveness than the Pharmaceutical Benefits Advisory Committee and are decidedly better than CADTH. CADTH needs to demonstrate its independence, rather than being a complicit partner in the federal, provincial and territorial governments' processes to drastically reduce new drug prices.

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## Introduction

Over the past 30 years, Canada and many other countries have established agencies and developed policies and programs for health technology assessment (HTA). HTA is now considered to be a key tool for decision-making in health care policy for reimbursement coverage of new medicines. Its aim is to support the efficient use of resources by achieving value for money. Nevertheless, differences exist between these agencies in terms of their philosophies, policies, practices and methods in the application of HTA.

The international society Health Technology Assessment international (HTAi) defines HTA as "a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle" with the purpose of informing decision-making in order to promote an equitable, efficient and high-quality health care system.[1] Although HTAs for new medicines, especially high-priority or life-saving therapies, are increasingly being started in advance of regulatory approval, many continue to be performed after the drug has received marketing approval. Recommendations resulting from HTAs can vary between jurisdictions, even though the evidence reviewed is frequently the same.

The objectives of this report are to compare:

- HTA key principles and standards by referencing Canada and relevant peer countries and to highlight any differences.
- Clinical and economic recommendations from the Canadian Agency for Drugs and Technologies in Health (CADTH) and the HTA agencies of relevant peer countries for new treatments for a specific disorder brought to market over the past 12 years.

The report is divided into two parts. In part I, HTA processes in Canada and comparable countries are discussed and HTA principles identified. Recommendations from CADTH and agencies in other countries for new therapies for a specific disorder are compared in part II as an illustrative case study.

## Part I: Health Technology Assessment Principles

### HTA in Canada

Created in 1989 by federal, provincial and territorial governments, with the exception of the province of Quebec, CADTH is Canada's almost national HTA agency. CADTH describes itself as an independent, not-for-profit organization responsible for providing health care decision-makers with objective evidence to help make informed decisions about the optimal use of health technologies, including drugs.[2] However, its independence must be questioned.

CADTH's 13-member Board are all appointed by federal, provincial and territorial governments and 10 members (77 percent) hold senior positions in these governments, are employed in administrative positions within the health system, or have a public service background.[3] Only two members represent the public (one a senior business executive and the other a lawyer) and the final member is an academic. Furthermore, CADTH's executive team consists of individuals previously employed in senior roles in Ontario's health system.[4]

Assessments of drugs submitted to CADTH by pharmaceutical manufacturers are performed under a standard, tailored, or cell and gene therapy review. Standard reviews for single medicines or indications are undertaken by one of three expert committees: the pan-Canadian Oncology Drug Review Expert Review Committee (pERC) for oncology medicines, the Canadian Drug Expert Committee (CDEC) for other medicines, and a separate committee for blood and plasma products.

The CDEC, described by CADTH as "an appointed, pan-Canadian advisory body to CADTH composed of individuals with expertise in drug therapy, drug evaluation and drug utilization and public members,"[5] evaluates clinical, economic and patient evidence on drugs and provides reimbursement recommendations based on its evaluations to participating federal, provincial and territorial public drug plans. In December 2020, the CDEC consisted of 15 members of whom six are physicians, six are pharmacists, one is a lawyer/ethicist and two are public members (one is a career industry and community board member and the other holds management and volunteer leadership positions in

charities and non-profits). The Committee presently has no health economics member and does not have patient representatives.

The pERC performs a similar role to the CDEC to evaluate cancer drugs for the provincial and territorial cancer agencies (except Quebec's) and to make recommendations regarding reimbursement. In December 2020, the Committee's 17 members comprised eight oncologists, a non-oncologist physician, a pharmacist, three economists, an ethicist and three patients.[6]

Members of the CDEC and pERC receive expenses and remuneration for leading evaluations.

CADTH's processes for an HTA submission are detailed in an extensive document with numerous bureaucratic templates and checklists.[7] For each standard review, a protocol is developed to identify relevant clinical information on the medicine, populations with the condition being treated, current clinical practice guidelines, availability of comparator drugs, health outcomes, and stakeholder input from patient groups, clinical experts, drug programs and committee members. CADTH also designs and conducts one or more independent systematic literature searches to supplement the material provided by the manufacturer. An additional document on the type of economic evaluations that required by CADTH is available.[8]

However, limited information is available about how submissions are evaluated and recommendations developed. In particular, it is unclear exactly how a medicine's clinical and economic value is assessed by the CDEC and pERC.

The reimbursement recommendations of the CDEC and pERC are not binding upon the federal, provincial and territorial public drug plans or the provincial and territorial cancer agencies. The drug plans and cancer agencies can cover medicines not reviewed by the committees.

## HTA in Other Countries

When performing international comparisons of health care systems, the Canadian Institute for Health Information regards Australia, France, Germany, the Netherlands, New Zealand, Sweden, the United Kingdom and the United States as peer countries because they have "large, developed economies with similar levels of resources to devote to health care."[9] However, when it comes to HTA, few of these countries are suitable comparators.

The HTA systems in France, Germany, the Netherlands, New Zealand and Sweden are inappropriate comparators for CADTH because:

- The approach to HTA in France is centralized, but multiple agencies are involved.[10]
- Germany has a complex system in which all new medicines are reimbursed after marketing approval with the benefit assessment mainly determining the price, rather than the reimbursement status.[11]
- In the Netherlands, the therapeutic value of a new medicine is the most critical criterion for reimbursement, which is not the case in Canada.[12]
- Although need and cost-efficiency are taken into account in assessing new medicines in Sweden, human value is generally the overriding criterion for reimbursement approval.[13]
- In New Zealand, the Pharmaceutical Management Agency makes "decisions on which medicines and medical devices are funded in order to get the best health outcomes from within the available funding"[14] working, uniquely, with a fixed budget. Little information is publicly available about the policies and practices of HTA within the New Zealand system.
- Efforts in HTA in the United States have been described as "erratic."[15] In public programs, such as Medicaid and Medicare, HTA is limited and largely done at the state level. The five largest private health insurance companies in the United States, working with the four largest pharmacy benefits management companies, have significant HTA programs, but the scope and methods are mainly regarded as proprietary and confidential.[16]

In contrast, the HTA processes in Australia, the United Kingdom (England and Wales, and Scotland) are valid comparators for Canada.

### Australia

In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) is appointed by the federal government to assess applications for each medicine regarding its clinical benefit and value for each indication. In December 2020, the PBAC's 20 members were 15 physicians, a pharmacist, two consumer nominees, a health economist and a pharmaceutical industry representative.[17] The PBAC has two subcommittees covering drug utilization and economics to assist with its work: the former with 13 members (five physicians, two pharmacists, two consumer nominees, a health economist, two academics in data-related areas and an industry representative) and the latter with 18 members (eight physicians, six health economists, a pharmacist, a consumer nominee, a health policy analyst and an industry representative).

PBAC committee members receive a publicly reported annual fee[18] and expenses.

No new medicine can be listed unless the PBAC makes a positive recommendation, but the ultimate decision about listing is made by the Minister of Health. After a positive recommendation, price negotiations can begin with the Department of Health,[19] which may include rebates and risk-sharing agreements.[20]

The manufacturer of a medicine that receives a negative recommendation can resubmit or, if the PBAC allows, seek an independent review.[21] However, the outcome of an independent review cannot overturn the PBAC's recommendation.

### England and Wales

The National Institute for Health and Care Excellence (NICE) provides assessments and recommendations to the National Health Service in England and Wales. Of NICE's programs,[22] the one relevant to this report is the Technology Assessment Program that assesses the clinical benefits and cost-utility of drugs. NICE does not assess every new drug but selects individual drugs or a class of drugs for review based on criteria that include the burden of the disease being treated, their clinical and policy importance, the cost impact on the National Health Service or the public sector, whether there is inappropriate treatment variation in practice, any urgency for the need for guidance, and the likelihood of the assessment having an impact on public health, quality of life or health inequalities.[23]

NICE commonly commissions independent academic centres, called technology assessment groups, to prepare assessment reports for consideration by its Technology Appraisal Committee. The membership of the Committee is drawn from the National Health Service, patient organizations, public nominees, academia and the pharmaceutical industry. All Committee members receive expenses but not remuneration; lay members receive an honorarium.

The Technology Appraisal Committee is the primary decision-making body in the production of recommendations on new health technologies. Based on advice from the Committee, which is intended to be free from any vested interests of its members, NICE makes recommendations to the National Health Service regarding whether medicines should be reimbursed. Originally, NICE recommendations were advisory, and much was left to local discretion in terms of adoption and implementation. However, from 2005 onwards, the National Health Service in England and Wales has been legally obligated to provide funding for medicines recommended by NICE within three months of the date of the recommendation.[24]

NICE has always sought to be transparent in its processes and procedures by publishing all appraised evidence, except commercially confidential information. In addition, NICE encourages extensive stakeholder involvement in HTAs with manufacturers, professional groups, patient organizations and the National Health Service all of which have the opportunity to submit data and comment on recommendations and, if they are unhappy with recommendations, to appeal them. NICE regularly holds public consultations about its work.

### Scotland

The Scottish Medicines Consortium (SMC) is the source of advice on the benefit and value of all new medicines for National Health Service Scotland to ensure that people in Scotland have timely access to medicines that provide most benefit based on best available evidence.[25] Unlike NICE, the SMC assesses all new drugs for every indication. The SMC Committee consists of 25 members with 19 representing the Scottish National Health Service

regions or hospitals and related services, three public members, two pharmaceutical representatives and an academic,[26] all of whom have a vote. SMC Committee members receive expenses but not remuneration.

Each assessment is carried out by a team of pharmacists, health service researchers and health economists, who evaluate evidence provided by the pharmaceutical manufacturer. The evaluation is considered by the New Drugs Committee, which in December 2020 comprised 16 health care providers and National Health Service representatives and two pharmaceutical industry representatives,[27] considers the clinical and economic evidence. New Drugs Committee members receive expenses.

The evidence, together with information from patient groups and voluntary organisations about how people are affected by the condition and the impact of the new medicine on patients and their caregivers, is reviewed by the SMC Committee, which makes the final recommendation. When the SMC accepts a new medicine, National Health Service Scotland regions are expected to make it or an equivalent SMC-accepted medicine available. The boards are also expected to publish updated lists of accepted medicines included and excluded from their formularies together with the reasons for such decisions.

**HTA Principles and Standards in Canada, Australia, England and Wales, and Scotland**

In examining the standards of HTA agencies, some authors have focused on methodological criteria used by the agencies and others on the appropriateness of the evidence incorporated in models used in HTA.[28] However, the intention here is to take a higher-level view of the principles and standards used in HTA in Canada in comparison with the other countries.

Good governance should play a key role in how HTA organizations interact with and relate to their stakeholders and how decisions are taken. Governance has been defined as a process that "determines who has power, who makes decisions, how other players make their voice heard and how account is rendered."[29] Evaluations of governance focus on the framework upon which the process rests. Although no universally agreed governance criteria exist, the United Nations Development Program principles (**Table 1**) are

**Table 1: United Nations Development Program's good governance principles.**

| |
|---|
| ***Accountability***: Decision-makers in government, the private sector and civil society organizations are accountable to the public and institutional stakeholders |
| ***Transparency***: Processes, institutions and information are directly accessible to those concerned with them and enough information is provided to understand and monitor them |
| ***Equity***: Everyone has opportunities to improve or maintain their wellbeing |
| ***Rule of law***: Legal frameworks should be fair and enforced impartially |
| ***Participation***: Everyone should have a voice in decision-making either directly or through legitimate intermediate institutions that represent their interests |
| ***Consensus orientation***: Good governance mediates differing interests to reach a broad consensus on what is in the best interest of the group and, where possible, on policies and procedures |
| ***Responsiveness***: Institutions and processes try to serve all stakeholders |
| ***Effectiveness and efficiency***: Processes and institutions produce results that meet needs while making the best use of resources |
| ***Strategic vision***: Leaders and the public have a broad and long-term perspective on good governance and development, together with a sense of what is needed for such development and an understanding of the historical, cultural and social complexities on which the perspective is based |

commonly used to describe good governance.[30] All processes through which societies, governments and organizations make important decisions should adhere to good governance principles to instil confidence in stakeholders and the general public in the process and its results. HTAs should also comply with these principles to assure all stakeholders that the recommendations are based on the best available evidence of a drug's benefit and cost, not cost-containment objectives alone. The main governance principles of concern to stakeholders are accountability, transparency, participation, consensus orientation and responsiveness. These principles overlap with those developed at a recent meeting of the HTAi Global Policy Forum of which CADTH is a member;[31] these are transparency, inclusivity and impartiality (**Table 2**).[32] The processes for arriving at HTA recommendations in the four countries are examined in the light of accountability and impartiality, transparency, and inclusivity which includes participation and consensus orientation (**Table 3**).

The PBAC, NICE and SMC are held accountable by Acts of Parliament, but CADTH is not similarly answerable. Information regarding the governance and accountability of NICE is available from its website[33] and for the SMC by direct request, but similar documents are not publicly accessible for the other agencies. NICE, the SMC and the PBAC are subject to public and parliamentary accountability including a code of conduct for their Boards and staff containing rules on financial and other conflicts of interest, freedom of information requests and external audit requirements. CADTH's accountability is to the governments that own, fund and manage it. CADTH does appoint an evaluation company through a tendering process every four years to evaluate its relevance and performance. The latest available evaluation was in 2016[34] in which it was reported that fewer than 12 percent of the "key informant interviews" were provided by clinicians, patients or pharmaceutical industry representatives. The rest came from CADTH employees and committee members, government officials and other HTA producers, raising questions about the scope and impartiality of the evaluation.

Meetings of NICE and the SMC are open and all stakeholders, including pharmaceutical companies, patients and the media, have access to all information and discussions related to a drug's review. The PBAC includes industry representatives and lay members but not patients. In Canada, pharmaceutical manufacturers and patient and clinician groups can comment on draft CDEC and pERC recommendations but are unable to participate in discussions or observe at meetings. Manufacturers are also denied access to confidential information (other than their own) discussed at CDEC or pERC meetings, which is shared with observers from the federal, provincial and territorial governments' price negotiating organization at the meetings prior to governments deciding whether and how negotiations will proceed. Consequently, the price negotiating organization has a significant advantage if negotiations are opened.

As the most vulnerable, patients are the stakeholders that should receive priority engagement in drug reimbursement recommendation processes.[35] Patient groups can make written submissions in the HTA process using a standard questionnaire with pre-determined questions and a conflict-of-interest declaration about the impact of the condition for which a drug is indicated, effectiveness of present treatments, and their expectations for a new therapy. Producing an effective submission, rather than an emotional one, is challenging for small patient groups with limited resources. Unlike

**Table 2: HTAi principles for deliberative processes in health technology assessment.**

| |
|---|
| ***Transparency***: Explicitly describe and make publicly available information on the deliberative process and the basis for a recommendation or decision |
| ***Inclusivity***: Bring the right perspectives together so that decision-making has the best chance of reflecting the reality of people impacted by the decision and living up to their values as much as possible |
| ***Impartiality***: The deliberative process used for each decision and those involved in it should be perceived to be free from undue influences, both internal (from the HTA agency) and external |

several other public interest processes in Canada, there is no provision for funding for intervenors in HTAs.

NICE and the SMC have a public involvement program. NICE has a team of 10 staff to support such submissions.[36] CADTH has two or three staff members to provide support to patient groups, resulting in submission support and feedback being limited. PBAC does not have a program, although patients can make submissions.

CDEC meetings exclude patients and, until recently, draft recommendations were only shared with the relevant manufacturer. Patient groups could only comment on the CDEC summary of their written submission included in the draft recommendation report, which has raised uncertainty about how much weight is given to patient

**Table 3: Adherence of health technology assessment processes to good governance principles.**

| Governance principle | CADTH | PBAC | NICE | SMC |
|---|---|---|---|---|
| *Accountability/Impartiality* | | | | |
| **Funded, managed, owned by:** | FPT governments | Federal government | NHS | NHS Scotland |
| **Recommendations** | Non-binding | Non-binding | Binding | Binding |
| **Committee reimbursement** | Fee for each assessment performed and expenses | Annual fee and expenses | Expenses only; honoraria for lay members | Expenses only |
| **Governance documentation** | Not publicly available | Not publicly available | Policies, procedures and code of practice available | Available on request |
| **Held accountable by** | Governance document not publicly available | Act of Parliament, but governance document not publicly available; COI document available | Act of Parliament, code of conduct with financial and other COI rules, FOI requests, audit requirements | Act of Parliament, code of conduct with financial and other COI rules, FOI requests, audit requirements |
| *Transparency* | | | | |
| **Reporting** | Recommendation report. Separate reports on clinical and economic assessments and patient group input | Recommendation report with clinical and economic assessments and consumer comments | Guidance with clinical and economic assessments. Separate patient and professional input | Recommendation report summarizing clinical and economic assessments and patient and caregiver input |
| *Inclusivity/Participation* | | | | |
| **Review committee composition:** | | | | |
| **Health care providers** | Yes | Yes | Yes | Yes |
| **Health system administrators** | No | No | Yes | Yes |
| **Academics** | Yes | Yes | Yes | Yes |
| **Public nominees** | Yes | Yes | Yes | Yes |
| **Patients** | CDEC: No; pERC: Yes | No | Yes | No |
| **Industry representation** | No | Yes | Yes | Yes |
| **Observers at meetings** | FPT governments' price negotiation representatives | No | Public meetings | Public meetings |
| **Patient engagement** | Written submission with limited support | Limited opportunity for stakeholder meetings | Written submission with a support program | Written submission with a support program |
| **Industry engagement** | Written submission | Limited opportunity for stakeholder meetings | Written submission | Written submission |
| **Appeal process** | Reconsideration process | Independent review process | Yes | No |

CADTH: Canadian Agency for Drugs and Technologies in Health; CDEC: Canadian Drug Expert Committee; COI: Conflict of interest; FOI: Freedom of Information; FPT: Federal, provincial and territorial; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PBAC: Pharmaceutical Benefits Advisory Committee; pERC: pan-Canadian Oncology Drug Review Expert Review Committee; SMC: Scottish Medicines Consortium.

input. In contrast, patient representatives participate in pERC meetings and draft reports are shared with all stakeholders including patient groups.[37] However, recent changes to CADTH procedures allow draft recommendations to be shared with patient groups, as well as clinician groups and the manufacturer, for comment.[38]

Like the CDEC, the PBAC and SMC do not include patients in their meetings, only public nominees. However, unlike the CDEC and pERC, meetings of NICE, the SMC and the PBAC all include pharmaceutical industry representatives, and the SMC has a pharmaceutical industry user forum to address technical and process issues.

Only NICE has an appeal process for any stakeholder who is unhappy with a recommendation. In some circumstances, the PBAC will allow manufacturers to have an independent review of a recommendation, but this will not lead to a reversal of the PBAC's recommendation. The CDEC has a process for reconsideration of a recommendation where the manufacturer believes that it is not supported by the evidence,[39] but this process does not provide for additional clinical or patient input and takes place in private.

## Part II: HTA Recommendations in Practice: An Illustrative Case Study

In part II, the clinical and economic recommendations from the four HTA agencies for new treatments for a specific disorder are reviewed. The medicines selected were biologic therapies for plaque psoriasis. These were chosen because a considerable number (nine) have been launched over the past 12 years for a disorder that is common, chronic and incurable for which the effectiveness of earlier therapies in patients with moderate to severe disease is often limited. The new biologics have a variety of mechanisms of action and are considered to be the best choice of therapy in patients with more severe psoriasis.[40]

Nine biologic therapies – adalimumab (Humira), ustekinumab (Stelara), secukinumab (Cosentyx), ixekizumab (Taltz), guselkumab (Tremfya), brodalumab (Siliq), certolizumab (Cimzia), risankizumab (Skyrizi) and tildrakizumab (Ilumya in Canada and Australia; Ilumetri in Europe) – have been brought to the market since 2008 (**Table 4**). Recommendation reports issued by CADTH,[41] NICE,[42] the PBAC[43] and the SMC[44] for these medications present an instructive case study of the evolution of HTAs performed in Canada and the other countries over the past decade in the light of the principles discussed in Part I.

### How do HTA Agencies Present their Recommendation Reports?

HTA recommendation reports from the CDEC have traditionally been brief, which is reflected in the two to six-page reports for the eight biologics reviewed by the Committee. Recommendation reports were the only information publicly available about HTAs until late 2013 when the CDEC began to provide extensive, detailed clinical and pharmacoeconomic reports – the clinical reports for secukinumab, ixekizumab, guselkumab, brodalumab, certolizumab and risankizumab ranged from 70 to 134 pages and the pharmacoeconomic reports from 16 to 32 pages.[45] In late 2014, comparatively short reports of patient group submissions were also added.

For each HTA recommendation in Australia, the PBAC provided a "public summary document" that describes the purpose of the application, the disease and the population impacted, the clinical trial evidence (often in much detail), the economic evidence and the budget implications for the Australian Pharmaceutical Benefits Scheme. The review of the clinical data was often extensive and might not be easily understood by the general reader. Three public summary documents included recommendations ranging from a short comment to over 20 pages of information for listing in the national drug plan.[46]

In England and Wales, NICE produces "guidance" documents describing the medication being reviewed, the disease it is designed to treat and how it is currently managed, a summary of the manufacturer's submission which includes the benefits, risks and economic analysis, and NICE committees' discussions of the evidence on efficacy and safety and the economic assessment, including the assumptions made. Guidance documents were as short as 10 pages and as long as 40. Other documentation on specific facets of assessments,

including patient group input, are available on the NICE website.

Based on the recommendation reports for the nine biologics in Scotland, which summarized efficacy, safety and economic evidence and patient and carer input, SMC documentation has become more extensive over time. Nevertheless, they were relatively short – the report for adalimumab was six pages,[47] while that for risankizumab was 15 pages[48] – and, like NICE guidance documents, are designed to provide a summary of the evidence and SMC Committee discussions, rather than being a scientific report.

Page length is obviously a crude measure of transparency, but it suggested that the agencies, especially CADTH, the PBAC and the SMC, now provide more information than previously. Nevertheless, page length does not indicate whether the contents are useful to stakeholders. Providing the results of the clinical, safety and economic evaluations in a technically detailed manner can simply overwhelm the average reader, whereas a user-friendly, plain-language, shorter report of the type provided by NICE and the SMC can be of greater value to most stakeholders.

The information on each HTA varied, e.g. more detailed extensive reports were available from the CDEC and NICE about specific aspects of the assessment, but not from the PBAC and SMC, which complicates comparisons. Consequently, the remainder of this evaluation focuses on the main recommendation reports issued by each HTA agency for the biologics for psoriasis. These reports are probably the only documents reviewed by most stakeholders, with the exception of the manufacturer's staff who likely read every page of each report concerning their product.

**Table 4: Date of marketing approvals and health technology assessment recommendations for biologics for psoriasis in the three countries. ***

| | Canada | | Australia | | United Kingdom | | |
|---|---|---|---|---|---|---|---|
| Biologic | **Marketing approval** | **CDEC recommendation** | **Marketing approval** | **PBAC recommendation** | **Marketing approval†** | **NICE recommendation** | **SMC recommendation** |
| **Adalimumab (Humira)** | Jan 2008 | Oct 2008 | Apr 2008 | July 2008 (negative) Mar 2009 | Sep 2003 | June 2008 | May 2008 |
| **Ustekinumab (Stelara)** | Dec 2008 | June 2009 | July 2009 | Nov 2009 | Jan 2009 | Sep 2009 | Jan 2010 |
| **Secukinumab (Cosentyx)** | Feb 2015 | Oct 2015 | Jan 2015 | Mar 2015 | Jan 2015 | July 2015 | May 2015 |
| **Ixekizumab (Taltz)** | May 2016 | Oct 2016 | Sep 2016 | July 2016‡ | Apr 2016 | Apr 2017 | Mar 2017 |
| **Guselkumab (Tremfya)** | Nov 2017 | Feb 2018 | Mar 2018 | Mar 2018 (negative) July 2018 | Nov 2017 | June 2018 | May 2018 |
| **Brodalumab (Siliq)** | Mar 2018 | June 2018 | Under review? | – | July 2017 | Mar 2018 | Apr 2018§ |
| **Certolizumab (Cimzia)** | Aug 2018 | Nov 2019 | Jan 2010 | Mar 2019 | Jan 2015 | Apr 2019 | Mar 2018 |
| **Risankizumab (Skyrizi)** | Apr 2019 | May 2019 | July 2019 | July 2019 | Apr 2019 | Aug 2019 | Sep 2019 |
| **Tildrakizumab (Ilumya/ Ilumetri)** | Under review since Feb 2019 | Suspended | Sep 2018 | July 2018‡ | Sep 2018 | Apr 2019 | July 2019 |

CDEC: Canadian Drug Expert Committee; NICE: National Institute for Health and Care Excellence; PBAC: Pharmaceutical Benefits Advisory Committee; SMC: Scottish Medicines Consortium. * All recommendations were positive, except where shown, but had clinical and/or cost conditions attached; † From the European Medicines Agency; ‡ Australia has a parallel process for marketing approval and health technology assessment and these drugs were likely processed through this system, but the recommendation would not have been finalized until marketing approval was received; § A submission in December 2017 was rejected without review.

## What do HTA Agencies' Recommendation Reports Include?

The recommendation reports concentrated on two main areas: evidence about the clinical benefit of the medicine and an economic analysis of its value.

### Evidence about Clinical Benefits

The first and usually largest component of the HTAs was the analysis of the clinical evidence in the manufacturer's submission. This was especially reflected in the CDEC recommendation reports and, since 2014, in its clinical reports. However, the real need of HTA agencies was an evaluation of the comparative efficacy and safety of the new drug relative to comparable existing drugs.

The "gold standard" for the evaluation of the efficacy of medications is the randomized controlled trial. In general, the same direct randomized controlled trial evidence was reviewed by the four agencies, although the interpretation of the trial results was not always consistent. The PBAC also reviewed other randomized controlled trial because most submissions included additional published information.

Evidence from randomized controlled trials is what the agencies desire in developers' submissions but, rather than placebo-controlled trials, the agencies prefer head-to-head comparisons that test whether a new medicine has better efficacy than a comparable existing drug. A head-to-head randomized controlled trial is highly useful to the manufacturer of a new drug only if it demonstrates a significant benefit over a current therapy; negative or inconclusive results can have a detrimental effect.

Moreover, the choice of a comparable existing medicine is not always easy and, since trials require time to plan, execute and analyze, the HTA agency may be more interested in a comparison with a different drug than the

**Table 5: Treatment comparisons reported in the health technology assessment recommendation reports for the biologics for psoriasis.**

| | CDEC | PBAC | NICE | SMC |
|---|---|---|---|---|
| Biologic | **Efficacy of biologic** | **Efficacy of biologic** | **Efficacy of biologic** | **Efficacy of biologic** |
| **Adalimumab (Humira)** | > Methotrexate | > Efalizumab | = Etanercept | > Methotrexate |
| **Ustekinumab (Stelara)** | > Etanercept | > Etanercept | > Etanercept | > Etanercept |
| **Secukinumab (Cosentyx)** | > Etanercept | > Adalimumab, etanercept | > Etanercept | > Etanercept |
| **Ixekizumab (Taltz)** | > Adalimumab, etanercept, ustekinumab; = Secukinumab | > Etanercept; = Adalimumab, secukinumab, ustekinumab | > Adalimumab, etanercept, ustekinumab; = Secukinumab | > Etanercept, ustekinumab |
| **Guselkumab (Tremfya)** | > Adalimumab | > Adalimumab = Ustekinumab | > Adalimumab, ustekinumab; = Secukinumab, ixekizumab, | > Adalimumab, ustekinumab |
| **Brodalumab (Siliq)** | > Ustekinumab | Not applicable | > Ustekinumab | > Ustekinumab |
| **Certolizumab (Cimzia)** | > Etanercept | > Etanercept; = Ustekinumab | > Etanercept | > Etanercept |
| **Risankizumab (Skyrizi)** | > Adalimumab, secukinumab, ustekinumab | > Adalimumab, secukinumab, tildrakizumab, ustekinumab; = Guselkumab, ixekizumab | > Adalimumab, ustekinumab; = Guselkumab | > Adalimumab, ustekinumab |
| **Tildrakizumab (Ilumya/Ilumetri)** | Not applicable | > Etanercept; = Adalimumab, ustekinumab | > Etanercept; =Adalimumab, ustekinumab | > Etanercept; =Adalimumab, ustekinumab |

CDEC: Canadian Drug Expert Committee; NICE: National Institute for Health and Care Excellence; PBAC: Pharmaceutical Benefits Advisory Committee; SMC: Scottish Medicines Consortium. > Efficacy significantly better than; = Comparable efficacy.

one selected for the trial by the time the final results are available. For example, the initial submission to the PBAC for adalimumab[49] was rejected because the randomized controlled trial comparator was efalizumab which was withdrawn for safety concerns. Consequently, as the HTA submissions for the biologics demonstrated, clinical evidence is predominantly in the form of placebo-controlled studies.

First proposed over 20 years ago,[50] a technique known as network meta-analysis offers a method to interpret evidence from a set of trials for the same disease and outcomes but with multiple test drugs, including placebo, to derive indirect treatment comparisons in order to assess the relative clinical efficacy of the medications.[51] Network meta-analysis has rapidly become a key method in HTAs for evaluating the relative efficacy of new medicines against existing drugs.

Network meta-analyses were used in the submissions for all the biologics to the PBAC, NICE and SMC. This type of analysis was employed in the submissions to the CDEC for ixekizumab, guselkumab, brodalumab, certolizumab and risankizumab,[52] but not in those for the earlier biologics. This seems to be the result of CADTH's slow acceptance of this methodology – the agency's first guidance document on its use was published in October 2015[53] – and even when used in the submissions, the CDEC was frequently critical of how it was applied.

As **Table 5** demonstrates, the evaluation of the direct and indirect treatment comparisons led to some differences in how the results were understood. Nevertheless, despite criticisms (in some cases, extensive) of the clinical data, all the HTA agencies eventually accepted the benefits and risks of the new biologics for psoriasis for which they received submissions.

**Evidence from Economic Analyses**

The second component of each HTA was an assessment of the economic analysis submitted by the manufacturer. With the exception of the earlier drugs (adalimumab and ustekinumab), all the agencies identified weaknesses, concerns or criticisms of the analyses of all the biologics. However, their concerns were not always consistent. The concerns led to NICE re-analyzing the manufacturers' models for two biologics and the CDEC re-analyzing the submitted models, usually using more restrictive assumptions, for all the drugs except adalimumab and ustekinumab. The PBAC and SMC did not report any re-analyses.

All the recommendation reports from the SMC and five from NICE mentioned a manufacturer patient access scheme that lowered the price to the National Health Service (**Table 6**) – these seemed to be developed collaboratively. These schemes improve the cost-effectiveness of the medicines to the respective healthcare systems. None of the CDEC or PBAC reports referred to any similar programs, but the public summary documents for five of the eight biologics assessed by the PBAC noted that they were cost-effective.

In contrast, the CDEC recommendations for secukinumab, guselkumab, brodalumab, certolizumab and risankizumab all had a pricing condition that the public drug plan cost should not exceed that of the least costly biologic for psoriasis covered by the plan or the price should lead to a saving. In addition, the report for ixekizumab had a condition that its price should be reduced by an unspecified amount but likely between 4 and 23 percent.[54] HTAs from the CDEC and pERC frequently report the need for a price reduction to improve a medicine's value. It is not CADTH's role to set drug prices or to negotiate prices with manufacturers, but it appears that CADTH is extending its role into influencing the price negotiating process.

**Patient Group Input**

Patient and caregiver groups have the opportunity to submit information to the HTA agencies about the disease, its impact on their lives, and what benefit they think the drug might bring to them, but only the SMC provided a brief summary of these submissions in its recommendation reports for each biologic. Since late 2014, the CDEC added short reports of patient group submissions to its website. NICE included brief comments about the experience of patients with psoriasis in its guidance reports, with a specific section on this topic in the reports on brodalumab, certolizumab and tildrakizumab; more information on patient group submissions were available in committee papers on its website. The PBAC public summary documents did not include information from patient group submissions and they were not available on its website.

## Discussion

### What are HTAs Designed to Achieve?

HTAs are intended to provide an evaluation of the clinical benefits of a drug and to set that against its cost to be able to make an assessment of its value to the health care system and patients or to society in general. How is this done?

When a new medicine receives marketing approval, limited evidence is available about its benefits, risks, cost and eventual place in the therapeutic armamentarium. Unless post-launch information is available from other countries and accepted by an HTA agency, its benefits and risks are only evaluated from pre-marketing studies which, for virtually all HTA agencies, means randomized controlled trials. Most HTA agencies claim to assess clinical effectiveness, but randomized controlled trials

**Table 6: Economic evidence reported in the health technology assessment recommendation reports for the biologics for psoriasis.**

| | CDEC | | PBAC | | NICE | | SMC | |
|---|---|---|---|---|---|---|---|---|
| Biologic | **Analysis type** | **Economic condition** | **Analysis type** | **Economic comment** | **Analysis type** | **Economic comment** | **Analysis type** | **Economic comment** |
| **Adalimumab (Humira)** | CUA | None | CEA and CMA | Difference of opinion regarding modeling | CUA | Concern about reliability of modeling | CEA | Sufficiently robust modeling |
| **Ustekinumab (Stelara)** | CUA | None | CUA | Cost-effective | CUA | Cost-effective | CUA | PAS improves cost-effectiveness |
| **Secukinumab (Cosentyx)** | CUA | Drug plan cost should not exceed cost of least costly biologic covered | CMA | No basis for price advantage over adalimumab | CUA | Cost-effective; company to provide drug via PAS | CMA | PAS improves cost-effectiveness |
| **Ixekizumab (Taltz)** | CUA | Reduced price | CMA | – | CUA | Company to provide drug via PAS | CUA | PAS improves cost-effectiveness |
| **Guselkumab (Tremfya)** | CUA | Drug plan cost should not exceed least costly biologic covered | CMA | Cost-effective | CUA | Choose least costly | CMA | PAS improves cost-effectiveness |
| **Brodalumab (Siliq)** | CUA | Drug plan cost should not exceed least costly biologic covered | – | – | CUA | Cost-effective; company to provide drug via PAS | CUA | PAS improves cost-effectiveness |
| **Certolizumab (Cimzia)** | CUA | Drug plan cost should result in savings compared with least costly biologic covered | CMA | Cost-effective | CUA | 200mg dose only cost-effective in certain patients | CUA and CMA | PAS improves cost-effectiveness |
| **Risankizumab (Skyrizi)** | CUA | Drug plan cost should not exceed least costly biologic covered | CMA | Cost-effective | CCA | Company to provide drug via PAS | CUA and CMA | PAS improves cost-effectiveness |
| **Tildrakizumab (Ilumya/ Ilumetri)** | – | – | CMA | Cost-effective | CUA | Cost-effective; company to provide drug via PAS | CUA | PAS improves cost-effectiveness |

CDEC: Canadian Drug Expert Committee; CCA: Cost-comparison analysis; CEA: Cost-effectiveness analysis; CMA: Cost-minimization analysis; CUA: Cost-utility analysis; NICE: National Institute for Health and Care Excellence; PAS: Patient access scheme; PBAC: Pharmaceutical Benefits Advisory Committee; SMC: Scottish Medicines Consortium.

only provide data on efficacy, i.e. the extent to which an intervention provides a beneficial result under the ideal conditions of a randomized controlled trial.[55] Trial participants are selected based on pre-determined inclusion and exclusion criteria and typically exclude children, seniors, pregnant women and individuals with multiple health issues.

Effectiveness – the extent to which an intervention when deployed in the field in routine circumstances does what it is intended to do for a specified population,[56] i.e. not under the carefully monitored conditions of a trial – is the measure that HTA organizations would like to be able to incorporate into their analyses. Furthermore, pre-marketing trials include relatively few patients, compared with the number likely to eventually use the medicine, which means they are unlikely to identify rare, idiosyncratic adverse effects. Few randomized trials are head-to-head comparisons and network meta-analysis techniques are required to synthesize and maximize the information available in trials included in HTA submissions.

In addition to the limitation about the measurement of a drug's benefit, HTAs are commonly performed with the medicine's cost represented by the developer's list price. Manufacturers do not make discounted prices publicly available in HTA submissions because maintaining price confidentiality is important in a globally competitive marketplace. If a drug receives a positive HTA recommendation, large public and private insurers have considerable power to negotiate a significantly discounted price with the drug's manufacturer. Consequently, the price used in the HTA is unrepresentative of the real world.

HTA results are dependent on the perspective taken in each assessment. Some HTAs are limited to the medicine's value to the relevant health care system, whereas others take a broader societal viewpoint and include the product's potential impact on the patient's and caregivers' life situation, e.g. their ability to be productive and out-of-pocket costs. Most HTA agencies take a health system viewpoint, not a societal one.

It is also important to be aware that HTAs are modelling analyses built on numerous assumptions about how the medicine will be used in ordinary clinical practice – for example, whether the medicine is made available to all patients with the disorder or only those with more severe disease, or whether the medicine is to be used after other treatments have been tried or as initial therapy. Such modelling may not represent the real-life use of the medicine in clinical practice.

Consequently, the evidence incorporated into HTAs should be comprehensive and as unbiased as possible and the analytical methods used should not be based on invalid assumptions. Since this is not always the case, it should not be surprising that HTA agencies can be inconsistent in their recommendations regarding the same medicine.

Under these conditions, it is critical that the good governance principles of accountability and impartiality, transparency and inclusivity (**Tables 1 and 2**) are upheld. All the agencies consider themselves to be independent, but since they are funded by their respective government health systems, their level of independence is questionable. This is especially the case for CADTH and the PBAC where appointed committee members receive not only travel and other out-of-pocket expenses for their work but also fees.

Open HTA meetings that include all stakeholders, including patient representatives, foster participation, inclusivity and public understanding and acceptability, and should lead to responsiveness. Increased transparency and confidence in accountability and impartiality are inspired by governance or terms of reference documents with appropriate and publicly available policies regarding accountability, rules on conflicts of interest, freedom of information and external audit reviews, as well as the publication of all non-commercially confidential information reviewed and analyzed in HTAs.

NICE, the SMC and the PBAC are subject to public and parliamentary accountability including a code of conduct for their Boards and staff members containing rules on financial and other conflicts of interest, freedom of information requests and external audit requirements. In contrast, CADTH is protected by its legal structure from freedom of information requests, Auditor General of Canada reviews, ombudsman or integrity commissioner inquiries and investigations, and public or parliamentary scrutiny.

## What Do the HTA Recommendations for the Biologics for Psoriasis Demonstrate?

The extensive focus of the HTA organizations on efficacy means that they are repeating work already done by their regulatory agencies. HTA agencies need comparative efficacy and this information usually has to be derived from placebo-controlled randomized controlled trials using network meta-analyses to arrive at indirect treatment comparisons, which CADTH was slow to embrace. The recommendations for the biologics for psoriasis and other work[57] demonstrate that, if an HTA agency has doubts about the clinical benefit of a new drug – regardless of the regulatory agency's evaluation – a positive recommendation is unlikely.

The other focus in the HTAs is the economic analysis, but as already noted, the modelling utilized requires numerous assumptions frequently using less than ideal, incomplete data. Sophisticated methods have been developed in an attempt to overcome these issues. For instance, most agencies, including the four here,[58] prefer cost-utility analyses that use quality-adjusted life-year (QALY), which is a generic measure of disease burden that includes the quality and quantity of life lived. QALYs use a linear scale between zero and one with zero and one being arbitrary values for death and full health, respectively, which is a simplistic, one-dimensional and inadequate measure of health[59] that, in reality, is a complex, multi-faceted and non-linear physical, psychological and social state. QALYs also fail to fully capture the social value of a medicine.[60]

The PBAC also requires its submissions to include a cost-minimization analysis[61] and this type of analysis has been shown to be strongly associated with a positive recommendation from the SMC.[62] Since no international consensus on guidelines for the generation and use of utility data for HTA exists, it should be no surprise that different agencies with different preferences arrive at varying reimbursement recommendations about the value of a drug, which results in a lack of predictability for pharmaceutical manufacturers.

The recommendations for the biologics demonstrate a distinct difference between CADTH and the other agencies. The PBAC, NICE and the SMC found that, with some concerns about the economic modeling employed in the submission for adalimumab, the drugs were generally cost-effective, especially when the manufacturer supported a patient access scheme. In contrast, CADTH's recommendations for the biologics from 2015 onwards included a requirement that the price should not exceed the least costly biologic already covered or the price should result in savings (**Table 6**), even though CADTH's role does not encompass price setting or price negotiation.

Although several of the recommendation reports included comments about the experience of patients, they were generally brief. HTAs concern multiple stakeholders, but patients should be key participants[63] as decisions made on HTA recommendations impact their quality and quantity of life. However, the HTA reports considered in this analysis demonstrate that patient group input is either relegated to supporting documentation or briefly summarized. Given this situation, patient groups naturally question the impact that their submissions make and raise concerns about paternalism or tokenism.[64] One would hope that the reluctance HTA agencies seem to have in including patient members is not one of health professional or bureaucratic paternalism such that they know what is best for patients and the health system because, in the 21st century, this undemocratic perspective should have been eliminated long ago.

Only NICE and the pERC include patient representatives at their meetings so that it is evident that "getting to the table" is a major challenge.[65] NICE has recently proposed a number of changes in its processes including involving patients in the selection of outcomes measures in the evaluation of medicines.[66] All the agencies should take action to change their culture so that patients are integrated into HTA processes at every step.[67] The HTAs of the biologics and the ensuing recommendations make it abundantly clear that the perspective each agency takes is one of the health systems within they are embedded. Although not surprising,[68] it means any social benefits that may result from the use of new drugs are ignored as are social deficits such as out-of-pocket expenses and life disruptions born by patients and caregivers.

The work of the PBAC, NICE and SMC has much greater oversight than CADTH does. Moreover, although a positive recommendation requires the Minister of Health's approval in Australia and approval from the

National Health Service in the United Kingdom before listing, these approvals are normally forthcoming and they result in a drug being covered nationally by their socialized health systems.

### What Happens After a Positive HTA Recommendation?

A positive recommendation from the PBAC and approval from the Minister of Health leads to price negotiations in Australia, which if successful results in listing in the country's national formulary. In England and Wales and Scotland, positive recommendations from NICE and the SMC obligate the National Health Service to provide funding for medicines which are accessible by all residents. In contrast, a positive recommendation from CADTH is non-binding and just a step in the process of getting a medicine listed in Canadian government drug plans. The next stage is entering the federal, provincial and territorial governments' pricing negotiation process, the pan-Canadian Pharmaceutical Alliance (pCPA).[69] Manufacturers do not submit applications for this but are invited to negotiate. CADTH and the pCPA have been aligning their processes over the past decade. This is reflected in the change seen in CDEC recommendations from 2012 onwards in which the probability of a new drug receiving a negative recommendation due to a high price dropped to zero, while the probability that a drug, especially costly ones such as those for rare disorders,[70] receives a positive recommendation with a price reduction condition increased to virtually 100 percent.

This development was also seen in the recommendation reports for the biologics for psoriasis after 2014. The change has allowed the CDEC to increase its positive recommendation rate and to rid itself of a reputation for not recommending costly drugs by passing on the role to the pCPA. CDEC pricing conditions, which for some drugs has been a price decrease of 60 to 97 percent to achieve cost-effectiveness,[71] establish an opening bargaining position for the pCPA. Negotiations with the pCPA have been successfully completed for secukinumab, guselkumab, brodalumab and risankizumab, while certolizumab is under active negotiation. No agreement was reached between the pCPA and the developer of guselkumab. Not being invited to a pCPA negotiation or having an unsuccessful negotiation usually locks out a drug from provincial coverage – no province covers guselkumab. On the other hand, a positive HTA recommendation and a successful pCPA negotiation does not guarantee coverage by every provincial drug plan. Currently, British Columbia and Alberta do not cover brodalumab and Prince Edward Island does not cover risankizumab. This situation again raises issues of a lack of predictability for manufacturers and access for patients. In fact, the only predictable aspect of the Canadian pharmaceutical environment is its unpredictability.

Barriers to obtaining coverage for new medicines in Canada's public plans are likely to increase. Health Canada, CADTH and the pCPA are working to align their processes, which may be advantageous for governments but, for drug developers and patients, is more likely to increase the difficulties of getting drugs listed on provincial formularies. In addition, new regulations for the federal tribunal that sets ceiling prices for new medicines in Canada – the Patented Medicine Prices Review Board – are due to come into place in July 2021. These have the potential to drastically reduce drug prices. Even before coming into force, the changes have diminished Canada's attractiveness as a country in which to launch new drugs. The consequence will be delayed or, even worse, denied access to new beneficial medicines for Canadians.[72]

## Conclusion

The accountability of all of the agencies in this analysis are to their respective health systems, but the oversight of NICE, the SMC and the PBAC is much better than CADTH's. All the agencies have improved transparency, although CADTH and the PBAC should do more. The participation of all stakeholders, especially patients (not just public representatives), must be improved in Canada if CADTH is to put its commitment to the principle of inclusivity[73] into practice. No HTA agency has the ideal system. NICE and the SMC are closer to complying with the principles of accountability/impartiality, transparency, participation/inclusivity and responsiveness than the PBAC and are decidedly better than CADTH. CADTH needs to demonstrate its independence, rather than being a complicit partner in the federal, provincial and territorial governments' processes to drastically reduce new drug prices. Canadians' lives depend on access to new beneficial medicines.

## References


[1] HTAi (2020). Welcome to the HTA Glossary. http://htaglossary.net/HomePage.

[2] CADTH (2020). About CADTH. https://www.cadth.ca/about-cadth.

[3] CADTH (2020). Board of directors. https://www.cadth.ca/about-cadth/who-we-are/board-of-directors.

[4] CADTH (2020). Executive team. https://www.cadth.ca/about-cadth/who-we-are/executive-team.

[5] CADTH (2020). Canadian Drug Expert Committee (CDEC). https://www.cadth.ca/collaboration-and-outreach/advisory-bodies/canadian-drug-expert-committee-cdec.

[6] CADTH (2020). The pCODR Expert Review Committee (pERC). https://www.cadth.ca/collaboration-and-outreach/advisory-bodies/pcodr-expert-review-committee-perc

[7] CADTH (2020). CADTH procedures for drug reimbursement reviews. https://www.cadth.ca/cadth-drug-reimbursement-reviews/cadth-procedures-drug-reimbursement-reviews.

[8] CADTH (2017). Guidelines for the economic evaluation of health technologies: Canada. https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf.

[9] CIHI (2020). OECD interactive tool: international comparisons – peer countries, Canada. https://www.cihi.ca/en/oecd-interactive-tool-peer-countries-can.

[10] Allen N, Liberti L, Walker SR, Salek S (2017). A comparison of reimbursement recommendations by European HTA agencies: is there opportunity for further alignment? *Front Pharmacol* 8: 384.

[11] Fricke FU, Dauben HP (2009). Health technology assessment: perspective from Germany. *Value Health* 12 (suppl 2): S20-7; Perleth M, Gibis B, Göhlen B (2009). A short history of health technology assessment in Germany. *Int J Health Technol Assess Health Care* 25 (suppl 1): 112-9; Angelis A, Lange A, Kanavos P (2018). Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries. *Eur J Health Econ* 19: 123-52.

[12] Angelis A, Lange A, Kanavos P (2018). Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries. *Eur J Health Econ* 19: 123-52.

[13] Angelis A, Lange A, Kanavos P (2018). Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries. *Eur J Health Econ* 19: 123-52.

[14] PHARMAC (2020). Our place in the health system. https://www.pharmac.govt.nz/about/your-guide-to-pharmac/factsheet-03-our-place-in-the-health-system.

[15] Luce B, Cohen RS (2009). Health technology assessment in the United States. *Int J Health Technol Assess Health Care* 25 (suppl 1): 33-41.

[16] Sullivan SD, Watkins J, Sweet B, Ramsey SD (2009). Health technology assessment in health-care decisions in the United States. *Value Health* 12 (suppl 2): S39-44.

[17] Australia (2020). Pharmaceutical Benefits Advisory Committee (PBAC) membership. https://www.pbs.gov.au/info/industry/listing/participants/pbac.

[18] Australia (2020). Federal Register of Legislation. Remuneration Tribunal (remuneration and allowances for holders of part-time public office (determination 2020). https://www.legislation.gov.au/Details/F2020C00933.

[19] Wonder M, Milne R (2011). Access to new medicines in New Zealand compared to Australia. *NZ Med J* 124: 12-28; Taylor C, Wonder M (2015). Exploring the implications of a fixed budget for new medicines: a study of reimbursement of new medicines in Australia and New Zealand. *Aust Health Rev* 39: 455-61.

[20] Streat S, Munn S (2012). Health economics and health technology assessment: perspectives from Australia and New Zealand. *Crit Care Clin* 28: 125-33.

[21] Australia (2019). Independent review (PBS) – information for applicants seeking independent review. https://www.pbs.gov.au/info/general/independent-review/independent-review-pbs-info-for-applicants.

[22] Akehurst R (2010). Health technology assessment in the United Kingdom. *Value Health* 13 (suppl 1): S4-5.

[23] Drummond M, Sorenson C (2009). Nasty or nice? A perspective on the use of health technology assessment in the United Kingdom. *Value Health* 12 (suppl 2): S8-13.

[24] Drummond M, Sorenson C (2009). Nasty or nice? A perspective on the use of health technology assessment in the United Kingdom. *Value Health* 12 (suppl 2): S8-13.

[25] SMC (2020). A guide to the Scottish Medicines Consortium. https://www.scottishmedicines.org.uk/media/3574/20180712-a-guide-to-the-scottish-medicines-consortium.pdf.

[26] SMC (2020). A guide to the Scottish Medicines Consortium. https://www.scottishmedicines.org.uk/media/3574/20180712-a-guide-to-the-scottish-medicines-consortium.pdf.

[27] SMC (2020). Who we are. https://www.scottishmedicines.org.uk/about-us/who-we-are/.

[28] Philips Z, Bojke L, Sculpher M, Claxton K, Golder S (2006). Good practice guidelines for decision-analytic modelling in health technology assessment. *Pharmacoeconomics* 24: 355-71; Zechmeister-Koss I, Schnell-Inderst P, Zauner G (2014). Appropriate evidence sources for populating decision analytic models within health technology assessment (HTA): a systematic review of HTA manuals and health economic guidelines. *Med Decis Making* 34: 288-99.

[29] Institute on Governance. 2003. Defining governance. https://iog.ca/docs/2003_August_policybrief15.pdf.

[30] Rawson NSB, Adams J (2017). Do reimbursement recommendation processes used by government drug plans in Canada adhere to good governance principles? *Clinicoecon Outcomes Res* 9: 721-30.

[31] CADTH (2020). Principles for deliberative processes in health technology assessment. https://www.cadth.ca/news/principles-deliberative-processes-health-technology-assessment#:~:text=The%20Global%20Policy%20Forum%20members,for%20deliberative%20processes%20in%20HTA.

[32] Bond K, Stiffell R, Ollendorf DA (2020). Principles for deliberative processes in health technology assessment. *Int J Health Technol Assess Health Care* 36: 445-52.

[33] NICE (2018). Framework agreement between the Department of Health and the National Institute for Health and Care Excellence 2018. https://www.nice.org.uk/Media/Default/About/Who-we-are/NICE-framework-agreement.pdf.

[34] Science-Metrix (2016). Evaluation of CADTH: final report. https://www.cadth.ca/sites/default/files/pdf/2016%20CADTH%20Evaluation.pdf.

[35] Wale J, Scott AM, Hofmann B, Garner S, Low E, Sansom L (2017). Why patients should be involved in health technology assessment. *Int J Health Technol Assess Health Care* 33: 1-4; Wale JL, Thomas S, Hamerlijnck D, Hollander R (2021). Patients and public are important stakeholders in health technology assessment but the level of involvement is low – a call to action. *Res Involv Engagem* 7: 1.

[36] NICE (2020). Public involvement programme. https://www.nice.org.uk/about/nice-communities/nice-and-the-public/public-involvement/public-involvement-programme.

[37] Rocchi A, Chabot I, Glennie J (2015). Evolution of health technology assessment: best practices of the pan-Canadian Oncology Drug Review. *Clinicoecon Outcomes Res* 7: 287-98.

[38] CADTH (2020). CADTH procedures for drug reimbursement reviews. https://www.cadth.ca/cadth-drug-reimbursement-reviews/cadth-procedures-drug-reimbursement-reviews.

[39] CADTH (2020). CADTH procedures for drug reimbursement reviews. https://www.cadth.ca/cadth-drug-reimbursement-reviews/cadth-procedures-drug-reimbursement-reviews.

[40] Sbidian E, Chaimani A, Garcia-Doval I, Do G, Hua C, Mazaud C, Droitcourt C, Hughes C, Ingram JR, Naldi L, Chosidow O, Le Cleach L (2017). Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database Syst Rev* 12: CD011535.

[41] CADTH (2008). Adalimumab. https://www.cadth.ca/adalimumab-48; (2009). Ustekinumab. https://www.cadth.ca/ustekinumab-13; (2015). Secukinumab. https://www.cadth.ca/secukinumab-4; (2016). Ixekizumab. https://www.cadth.ca/ixekizumab; (2017). Guselkumab. https://www.cadth.ca/guselkumab; (2018). Brodalumab. https://www.cadth.ca/brodalumab; (2019). Certolizumab pegol. https://www.cadth.ca/certolizumab-pegol-19; (2019). Risankizumab. https://www.cadth.ca/risankizumab.

[42] NICE (2008). Adalimumab. https://www.nice.org.uk/guidance/ta146; (2009). Ustekinumab. https://www.nice.org.uk/guidance/ta180; (2015). Secukinumab. https://www.nice.org.uk/guidance/ta350; (2017). Ixekizumab. https://www.nice.org.uk/guidance/ta442; (2018). Guselkumab. https://www.nice.org.uk/guidance/ta521; (2018). Brodalumab. https://www.nice.org.uk/guidance/ta511; (2019). Certolizumab pegol.

https://www.nice.org.uk/guidance/ta574; (2019). Risankizumab. https://www.nice.org.uk/guidance/ta596; (2019). Tildrakizumab. https://www.nice.org.uk/guidance/ta575.

[43] Australia (2008). Adalimumab. https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2008-07/pbac-psd-adalimumab-july08; (2009). Adalimumab. https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2009-03/pbac-psd-adalimumab-march09; (2009). Ustekinumab. https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2009-11/pbac-psd-Ustekinumab-nov09; (2015). Secukinumab. https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2015-03/secukinumab-cosentyx-psd-03-2015; (2016). Ixekizumab. https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2016-07/ixekizumab-psd-july-2016; (2018). Guselkumab. https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2018-03/Guselkumab-psd-march-2018; (2018). Tildrakizumab. https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2018-07/Tildrakizumab-psd-july-2018; (2019). Certolizumab pegol. https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2019-03/certolizumab-psd-march-2019; (2019). Risankizumab. https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2019-07/risankizumab-injection-75-mg-in-0-83-ml-pre-filled-syringe.

[44] SMC (2008). Adalimumab. https://www.scottishmedicines.org.uk/medicines-advice/adalimumab-humira-fullsubmission-46808/; (2010). Ustekinumab. https://www.scottishmedicines.org.uk/medicines-advice/ustekinumab-stelara-fullsubmission-57209/; (2015). Secukinumab. https://www.scottishmedicines.org.uk/medicines-advice/secukinumab-cosentyx-fullsubmission-105415/; (2017). Ixekizumab. https://www.scottishmedicines.org.uk/medicines-advice/ixekizumab-taltz-fullsubmission-122317/; (2018). Guselkumab. https://www.scottishmedicines.org.uk/medicines-advice/guselkumab-tremfya-fullsubmission-134018/; (2018). Brodalumab. https://www.scottishmedicines.org.uk/medicines-advice/brodalumab-kyntheum-resubmission/; (2019). Certolizumab pegol. https://www.scottishmedicines.org.uk/medicines-advice/certolizumab-pegol-cimzia-fullsubmission-smc2132/; (2019). Risankizumab. https://www.scottishmedicines.org.uk/medicines-advice/risankizumab-skyrizi-full-smc2196/; (2019). Tildrakizumab. https://www.scottishmedicines.org.uk/medicines-advice/tildrakizumab-ilumetri-full-smc2167/.

[45] CADTH (2015). Secukinumab. https://www.cadth.ca/secukinumab-4; (2016). Ixekizumab. https://www.cadth.ca/ixekizumab; (2017). Guselkumab. https://www.cadth.ca/guselkumab; (2018). Brodalumab. https://www.cadth.ca/brodalumab; (2019). Certolizumab pegol. https://www.cadth.ca/certolizumab-pegol-19; (2019). Risankizumab. https://www.cadth.ca/risankizumab.

[46] Australia (2015). Secukinumab. https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2015-03/secukinumab-cosentyx-psd-03-2015; (2018). Guselkumab. https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2018-03/Guselkumab-psd-march-2018; (2019). Risankizumab. https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2019-07/risankizumab-injection-75-mg-in-0-83-ml-pre-filled-syringe.

[47] SMC (2008). Adalimumab. https://www.scottishmedicines.org.uk/medicines-advice/adalimumab-humira-fullsubmission-46808/.

[48] SMC (2019). Risankizumab. https://www.scottishmedicines.org.uk/medicines-advice/risankizumab-skyrizi-full-smc2196/.

[49] Australia (2008). Adalimumab. https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2008-07/pbac-psd-adalimumab-july08.

[50] Bucher HC, Guyatt GH, Griffith LE, Walter SD (1997). The results of direct and indirect treatment comparisons in in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 50: 683-91.

[51] Mills EJ, Thorlund K, Ioannidis JPA (2013). Demystifying trial networks and network meta-analysis. *BMJ* 346: f2914.

[52] CADTH (2016). Ixekizumab. https://www.cadth.ca/ixekizumab; (2017). Guselkumab. https://www.cadth.ca/guselkumab; (2018). Brodalumab. https://www.cadth.ca/brodalumab; (2019). Certolizumab pegol. https://www.cadth.ca/certolizumab-pegol-19; (2019). Risankizumab. https://www.cadth.ca/risankizumab.

[53] Richter T, Lee KM (2015). Guidance document on reporting indirect comparisons. CADTH. https://www.cadth.ca/sites/default/files/pdf/MH0003_Guidance_on_IDC_Reporting.pdf.

[54] CADTH (2016). Ixekizumab. https://www.cadth.ca/ixekizumab.

[55] Rawson NSB (2001). “Effectiveness” in the evaluation of new drugs: a misunderstood concept? *Can J Clin Pharmacol* 8: 61-2.

[56] Rawson NSB (2001). “Effectiveness” in the evaluation of new drugs: a misunderstood concept? *Can J Clin Pharmacol* 8: 61-2.

[57] Janoudi G, Amegatse W, McIntosh B, Sehgal C, Richter T (2016). Health technology assessment of drugs for rare diseases: insights, trends, and reasons for negative recommendations from the CADTH Common Drug Review. *Orphanet J Rare Dis* 11: 164.

[58] Rowen D, Zouraq IA, Chevron-Severac H, van Hout B (2017). International regulations and recommendations for utility data for health technology assessment. *Pharmacoeconomics* 35 (suppl 1): S11-9.

[59] Prieto L, Sacristán JA (2003). Problems and solutions in calculating quality-adjusted life years (QALYs). *Health Qual Life Outcomes* 1: 80.

[60] Rowen D, Zouraq IA, Chevron-Severac H, van Hout B (2017). International regulations and recommendations for utility data for health technology assessment. *Pharmacoeconomics* 35 (suppl 1): S11-9.

[61] Australia (2016). Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee. https://pbac.pbs.gov.au/.

[62] Charokopou M, Majer IM, de Raad J, Broekhuizen S, Postma M, Heeg B (2015). What factors enhance positive drug reimbursement recommendation in Scotland? A retrospective analysis 2006-2013. *Value Health* 18: 284-91.

[63] Scott AM, Wale JL (2017). Patient advocate perspectives on involvement in HTA: an international snapshot. *Res Involve Engagem* 3: 2; Wale J, Scott AM, Hofmann B, Garner S, Low E, Sansom L (2017). Why patients should be involved in health technology assessment. *Int J Health Technol Assess Health Care* 33: 1-4; Wale JL, Thomas S, Hamerlijnck D, Hollander R (2021). Patients and public are important stakeholders in health technology assessment but the level of involvement is low – a call to action. *Res Involv Engagem* 7: 1.

[64] Santesso N, Dooley A (2006). Consumer involvement in decision making for health care policy and planning. https://www.cadth.ca/media/symposium_pdfs/cadth_symposium06_ppt_Santesso-Dooley.pdf.

[65] Boothe K (2019). "Getting to the table": changing ideas about public and patient involvement in Canadian drug assessment. *J Health Polit Policy Law* 44: 631-63.

[66] NICE (2020). Reviewing our methods for health technology assessment: consultation. https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/chte-methods-consultation.

[67] Wale JL, Thomas S, Hamerlijnck D, Hollander R (2021). Patients and public are important stakeholders in health technology assessment but the level of involvement is low – a call to action. *Res Involv Engagem* 7: 1.

[68] Rawlins MD (2012). Crossing the fourth hurdle. *Br J Clin Pharmacol* 73: 855-60.

[69] pCPA (2020). Pan-Canadian Pharmaceutical Alliance. https://www.pcpacanada.ca/.

[70] Rawson NSB (2017). Health technology assessment of new drugs for rare disorders in Canada: impact of disease prevalence and cost. *Orphanet J Rare Dis* 12: 59; Rawson NSB (2020). Alignment of health technology assessments and price negotiations for new drugs for rare disorders in Canada: does it lead to improved patient access? *J Popul Ther Clin Pharmacol* 27: e48-64.

[71] Rawson NSB (2020). Alignment of health technology assessments and price negotiations for new drugs for rare disorders in Canada: does it lead to improved patient access? *J Popul Ther Clin Pharmacol* 27: e48-64.

[72] Rawson NSB, Adams J (2020). Access to new medicines: what Ottawa should learn from COVID-19. Macdonald-Laurier Institute for Public Policy. https://www.macdonaldlaurier.ca/covid19-weakness-new-medicines/.

[73] CADTH (2020). Principles for deliberative processes in health technology assessment. https://www.cadth.ca/news/principles-deliberative-processes-health-technology-assessment#:~:text=The%20Global%20Policy%20Forum%20members,for%20deliberative%20processes%20in%20HTA.