Combination regimens: reimbursement challenges and solutions

Research Report and Summary from a Canadian multi-stakeholder workshop

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Introduction

What are combination therapies?

Combination therapy is the use of two or more therapies with the intention of improving patient health (i.e., length and health-related quality, of life) or other useful benefits to health systems or society (e.g., reducing drug resistance, or improve care provider experiences; reducing absenteeism). Combination therapies may be sold as a single preparation (e.g., combined in the same vial, pill, or inhaler, sometimes called fixed-dose combinations), or product (e.g., combined in the same package).

A combination therapy may also be two or more separate products taken together, or in close sequence. These types of combination therapies can be referred to as *combination regimens*, and may require different drug dosing or administration schedules than when individual drugs are used alone (i.e., monotherapy). Combination regimens often involve the introduction of one or more "add-on" therapies to an existing "backbone" therapy or regimen.

Combination therapies are helpful in conditions where it is more difficult to achieve desirable responses with single therapies and where interventions with different, but complementary, mechanisms of action exist. The use of combinations has become commonplace in chronic conditions in areas such as infectious disease, respirology, neurology, ophthalmology, cardiovascular disease, and diabetes.

Combination therapies, and particularly the use of combination regimens, have also become especially relevant in cancer, where the use of targeted therapies with highly selective mechanisms of action (i.e., precision oncology) are increasingly commonplace and where there is an opportunity to improve outcomes (i.e., delayed progression, improved survival or increased response rates) by using more than one mechanism of action.[1]

For physicians and patients, any potential benefits from the use of a combination therapy must be weighed against the risk of harm from additional side effects. Physicians and patients may also weigh the advantages and disadvantages of increasing pill or other burden on patients and complexity of adding a new drug to an existing dosing schedule.

Combination regimens may also be more complex to negotiate pricing and make reimbursement arrangements. Without an adequate framework to address these complexities, providing access to combination regimens may be associated with avoidable delays (or even failures) in access and ultimately have a negative impact on patients and the care community.

1 Joaquin Mateo et al., "Delivering Precision Oncology to Patients with Cancer," Nature Medicine 28, no. 4 (April 2022): 658–65, https://doi.org/10.1038/s41591-022-01717-2.

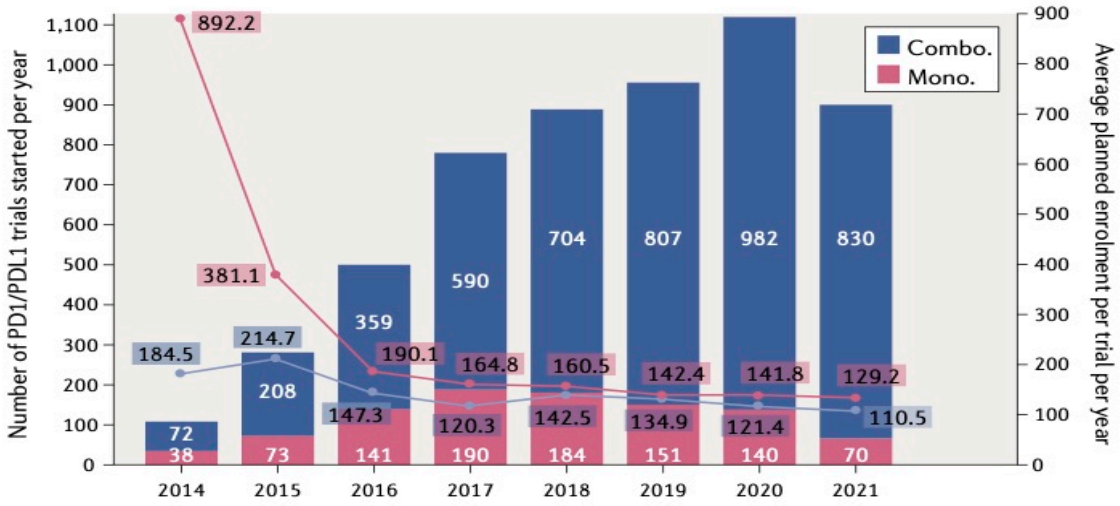
Current and future state

Oncology

Oncology has seen an increasing use of combination therapy, particularly in multiple myeloma, chronic lymphocytic leukemia, and acute myeloid leukemia. This trend is expected to continue as drugs with new mechanisms of action are introduced and combined with existing therapies, including inhibition of phosphoinositide 3-kinase (PI3K) and Bruton's tyrosine kinase ; selective inhibitors of nuclear export (SINEs) cereblon modulators, antibody-drug conjugates, chimeric antigen receptor (CAR)-directed T-cell therapy, and bispecific antibodies.[2]

Solid tumours will also see an increase in combination regimens.[3] Immune checkpoint inhibitors will also continue to be promoted in combination with other agents. Of the more than >5,500 clinical trials currently investigating PD-1/L1 inhibitors, 80% are reported to be in combination with other agents.[4] Monotherapy trials of immune checkpoint inhibitors have also seen a declining trend with 90% of trials starting 2021 investigating combinations (Figure 1). The introduction of combinations for harder-to-treat breast cancer with additional agents such as PARP inhibitors and antibody-drug conjugates are also being explored.[5]

Figure 1 Comparison of monotherapy and combination trials for PD-1/L1 inhibitors [6] .



2 Jing-Zhou Hou et al., "Novel Agents and Regimens for Hematological Malignancies: Recent Updates from 2020 ASH Annual Meeting," Journal of Hematology & Oncology 14, no. 1 (April 21, 2021): 66, https://doi.org/10.1186/s13045-021-01077-3.
3 Nehad M. Ayoub, "Editorial: Novel Combination Therapies for the Treatment of Solid Cancers," Frontiers in Oncology 11 (2021), https://www.frontiersin.org/articles/10.3389/fonc.2021.708943.
4 Murray Aitken, Michael Kleinrock, and Jamie Pritchett, "Global Oncology Trends 2022: Outlook to 2026" (The IQVIA Institute, 2022), https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-oncology-trends-2022/iqvia-institute-global-oncology-trends-2022-forweb.pdf.
5 Rachel M. Webster, "Combination Therapies in Oncology," Nature Reviews Drug Discovery 15, no. 2 (February 2016): 81–82, https://doi.org/10.1038/nrd.2016.3.
6 Samik Upadhaya et al., "Challenges and Opportunities in the PD1/PDL1 Inhibitor Clinical Trial Landscape," Nature Reviews Drug Discovery 21, no. 7 (February 10, 2022): 482–83, https://doi.org/10.1038/d41573-022-00030-4.

Non-oncology

New combination therapies outside of oncology will also create pricing and reimbursement challenges. Anti-VEGF therapies, which have become a mainstay in the management of neovascular age-related macular degeneration are currently being investigated in combination with other novel agents, including anti-platelet derived growth factor (PDGF) therapies, tissue factor therapies, and Tie-2 tyrosine kinase receptor antagonists.[7] These same drugs and combinations are being investigated in other ocular disorders, such as polypoidal choroidal vasculopathy. Other challenging areas for reimbursement and the anticipated use of combination therapies will be in diabetes, autoimmune diseases, and infectious disease.

Policy challenges with combination therapies

Combination therapies, and particularly combination regimens that involve on-patent individual component therapies from different manufacturers may pose challenges for policymakers and innovators:

- ***Regulators*** must decide whether new combination preparations have a desirable benefit-risk ratio for patients and how marketing a combination may affect product quality and how this is communicated in the product label. They must also consider whether the new labeling should affect the labeling of any of the individual components in the combination, and what rules may govern the promotion of the individual components of the combination product.

- ***HTA bodies*** must assess the value of the combination product to inform decision-making. They may also need to consider how to attribute value to individual components in a combination regimen, if the payer will need this information to negotiate prices.

- ***Drug payers*** must consider whether, and if so how, to reimburse combination therapies, and consider the impact of a new combination on utilization management and expenditure of any existing components in a combination regimen. Fixed-dose combination therapies may also lead to waste and must be managed, as individual component doses cannot be as easily tailored to patients' needs. Some provinces will pay for oral and injectable therapies through different budgets.

- ***Healthcare administrators*** must create new care protocols which may involve operational and clinical logistics around the use of orals and injectable therapies taken at different cycles and having different monitoring needs.

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[7] Sruthi Arepalli and Peter K. Kaiser, "Pipeline Therapies for Neovascular Age Related Macular Degeneration," *International Journal of Retina and Vitreous* 7, no. 1 (October 1, 2021): 55, https://doi.org/10.1186/s40942-021-00325-5.

- ***Product innovators and manufacturers*** must consider how to market combination regimens while being respectful of rules governing anti-competitive practices and tied selling as well as how their individual market activities may impact those of their competition.

It's about the prices….

A larger issue for payers and product innovators is how to pay for combination regimens when one or more of the individual components of the combination are already seen as 'expensive' by payers, or at a maximum level of willingness to pay based on their perceived value/affordability. In Canada, affordable reimbursement levels are achieved through confidential rebates in product listing agreements (PLAs) that contain terms collectively negotiated through the pan-Canadian Pharmaceutical Alliance (pCPA).

The pCPA involves all major public insurers and prioritizes negotiations based on the current coverage landscape and therapeutic gaps, as well as the health technology assessment (HTA) recommendations from the Canadian Agency for Drugs and Technologies in Health (CADTH) and the Institut national d'excellence en santé et en services sociaux (INESSS), impact on budget expenditures, affordability, and jurisdiction-specific needs.[8]

To determine if a price reduction (through rebates) is desirable, payers will use a CADTH price recommendation. The recommendation is based on a value threshold; in simple terms, paying a price beyond the threshold means money is not well spent. It tells the payer that more health for other patients (in terms of their length and related quality of life) could be purchased through investments in other, higher-value drugs or services.

When a new drug is added to an existing one, CADTH recommendations have varied[9]. In several cases, a recommendation for reducing the prices of each (backbone and add-on) component therapy individually has been issued (Figure 2).

A review of CADTH price reduction recommendations for combination therapies between January 2020 and December 2021 found:"

- Four recommendations requested price reduction for the add-on innovative medications only.
- Seven recommendations had price reduction conditions for both constituent parts of the combination.
    - Four recommendations had a single percentage reduction for both the constituent parts of the combination therapy. Notably, three of these recommendations included combinations of two innovative medications,

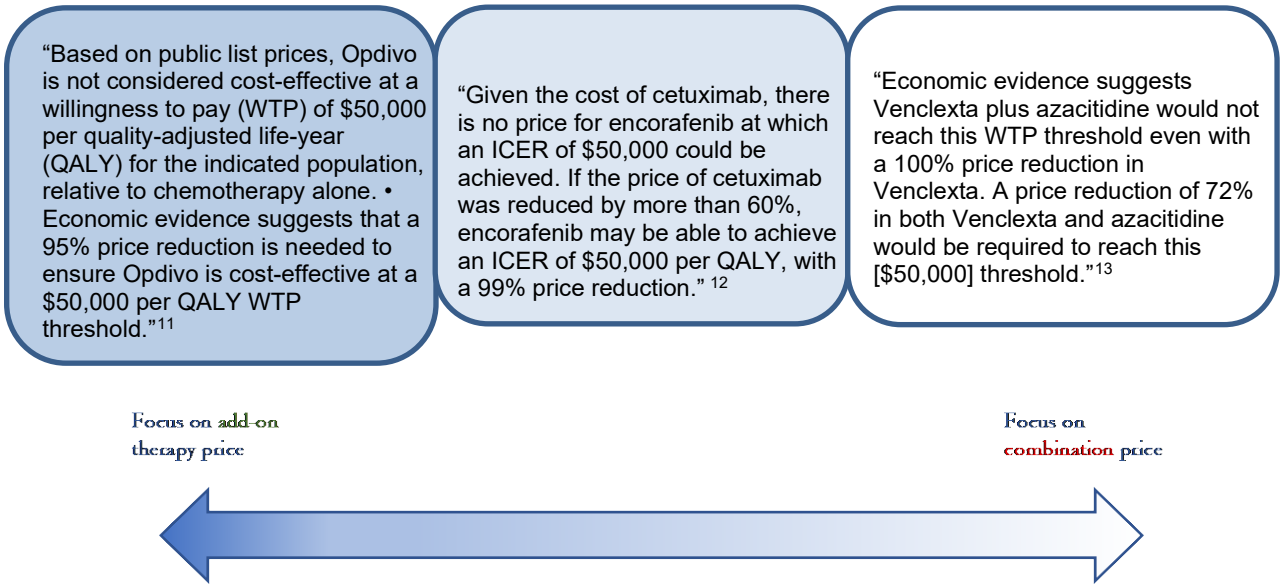
[8] "The Negotiation Process | PCPA," accessed October 26, 2022, https://www.pcpacanada.ca/negotiation-process.

[9] R. M. Rogoza, D. Husereau, and B. Millson, "HTA40 Challenges in Evaluating and Paying for Combination Therapies in Oncology - a Canadian Perspective," *Value in Health* 25, no. 7 (July 1, 2022): S511, https://doi.org/10.1016/j.jval.2022.04.1172.

and one included add-on innovative medication combined with two back-bone medications.

- The remaining three CTs had different percentage reductions recommended for the constituent parts of the combination. Prices of the add-on innovative medications were recommended to be reduced by 99% on average. However, the back-bone treatments they were combined with were recommended to be reduced by only 60% on average." [10]

Figure 2 CADTH Recommendations – different approaches to price recommendations for combination regimens



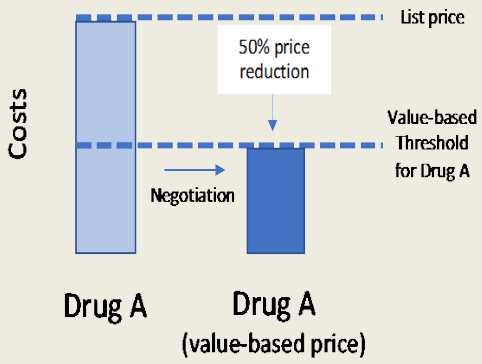
ICER= incremental cost-effectiveness ratio; WTP= Willingness to pay; QALY= quality-adjusted life-year

Some (seemingly) paradoxical recommendations suggest that a drug with life-saving clinical benefit is not cost-effective even if the manufacturer gave it to the payer for free.[14] Figure 3 (next page) provides an illustration of how this occurs.

[10] R. M. Rogoza, D. Husereau, and B. Millson, "HTA40 Challenges in Evaluating and Paying for Combination Therapies in Oncology - a Canadian Perspective," *Value in Health* 25, no. 7 (July 1, 2022): S511, https://doi.org/10.1016/j.jval.2022.04.1172.
[11] Reimbursement Team, "Nivolumab (Opdivo)," *Canadian Journal of Health Technologies* 2, no. 3 (March 22, 2022), https://doi.org/10.51731/cjht.2022.287.
[12] Reimbursement Team, "Encorafenib (Braftovi)," *Canadian Journal of Health Technologies* 1, no. 9 (September 16, 2021), https://doi.org/10.51731/cjht.2021.152.
[13] Team, "Ven Reimbursement Team, "Venetoclax (Venclexta)," *Canadian Journal of Health Technologies* 1, no. 8 (August 23, 2021), https://doi.org/10.51731/cjht.2021.130.
[14] Reimbursement Team, "Venetoclax (Venclexta)," *Canadian Journal of Health Technologies* 1, no. 8 (August 23, 2021), https://doi.org/10.51731/cjht.2021.130.

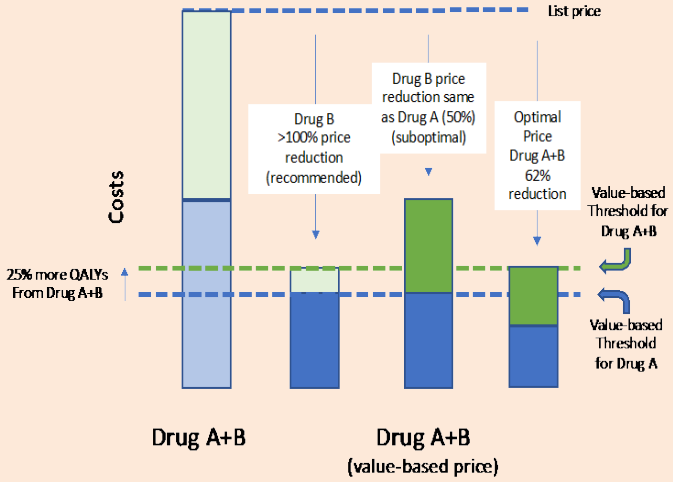
Figure 3 The challenge of establishing a value-based price for combination therapies

Scenario A – New drug A enters market



- Assume there is an existing therapy (Drug A) which has a list price higher than what CADTH determines to be a value-based price, based on a willingness to pay of $50,000 for an extra quality-adjusted life-year (QALY).
- Negotiation through pCPA will ideally result in a confidential net effective price equivalent to (or in the direction of) its value-based price.
- In this example, the manufacturer provides a 50% rebate which implies a 50% net effective price reduction.

Scenario B – New drug B combination therapy with new drug A enters market



- If a second therapy (Drug B) with the same list price is added on to Drug A, the recommendation to lower price of the new, add-on drug is greatly influenced by the cost-effectiveness of Drug A based on its original list price . This can result in a >100% price reduction recommendation.
- If the manufacturer of Drug B is only willing to provide a 50% rebate (as Drug A), then the new net effective price of the combination is still not cost-effective.
- If we assume both drugs contribute equally to the effectiveness of the combination, then the optimal price reduction requires rebates for both component therapies (Drug A+B) of 62%.

Value' in any context is what consumers and producers are willing to give up to get something. Ultimately, the price that payers are willing to pay and drug producers are willing to receive reflects the value of any new intervention. Payers (consumers) typically want to 'get' health benefits (length and quality of life) for patients as well as the ability to fill a therapeutic gap, achieve predictable spend, or improve patient or caregiver experiences. They are willing to give up part of their budget to do so. Producers want sales (and revenues), in turn, and are typically willing to 'give up' a rebate or provide guarantees of predictable spending through price guarantees or volume caps to do so.

What elements of a solution have been proposed?

Different solutions have been proposed in the literature or implemented in other jurisdictions to address the challenge of appropriate pricing and providing access to combination regimens.[15] Some features and components of these solutions include:

- **Changing the evidence base for combination therapy** (i.e., manufacturer-based, clinical development solutions)
    - The use of platform or adaptive trials or other innovative designs to tease out the impact of individual components of a combination or the impact of different dosing regimens on benefits and harms from therapy.
- **Changing how prices are assessed** (i.e., HTA-based solutions):
    - Changes to how costs and benefits are assessed, including subtracting costs associated with extended use of drugs[16], or considering additional dimensions of value.[17]
    - Attribution of value to individual components of therapy and price recommendations for individual components of therapy using a specific approach, or equal attribution according to the number of components.
- **Changing how prices are negotiated** (i.e., PLA-based solutions):
    - Automatic price reductions (rebate increases) for combinations, as in Switzerland and Germany.
    - Re-developing combinations as single products[18]
    - The use of a voluntary arbitration framework to support between-company negotiation, using principles borrowed from merger and acquisition and sharing of confidential information and allowing blended or indication-specific pricing, either between companies or between companies and the payer.[19]
    - The use of a technology platform to aid in multilateral negotiation, between companies and the HTA payer.
    - The use of future-proofing clauses in current PLAs to ensure uncertainty in expenditure from future combination therapies are addressed

While most individual jurisdictions do not have specific approaches to address combination therapies (See Table 1), some are developing approaches. Germany has recently announced a mandatory 20% discount applied to all components of certain combination therapies (excluding drugs that have major/considerable additional benefit).

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[15] "Challenges in Valuing and Paying for Combination Regimens in Oncology Report of an International Workshop Convened by Bellberry, Held on November 18-20, in Sydney, Australia," ScHARR HEDS Discussion Papers. (School of Health and Related Research University of Sheffield), accessed October 26, 2022, https://bellberry.com.au/wp-content/uploads/Meeting-report-final-draft-May-2020.pdf.

[16] Sarah Davis, *Assessing Technologies That Are Not Cost-Effective at a Zero Price*, 2014.

[17] Danko, Blay, and Garrison, "Challenges in the Value Assessment, Pricing and Funding of Targeted Combination Therapies in Oncology."

[18] Latimer and Pollard, "Pre-Read Document 1."

[19] Tanja Podkonjak et al., "Voluntary Arbitration Framework for Combination Therapies A Proposed Process by the Voluntary Arbitration Working Group" (Takeda, September 2021), https://www.takeda.com/4a81d5/siteassets/en-gb/home/what-we-do/combination-treatments/voluntaryarbitrationframeworkforcombinationtherapies_takedawhitepaper_september2021.pdf.

Table 1 Jurisdiction-specific approaches to combination therapies, Adapted from OECD[20]

Country	Approaches to attribute value to constituents
Australia	This is highly context specific. First, the cost-effectiveness of the combination is determined based on the price proposed. Attributing value to the constituent parts will be influenced by relevant factors, including: • whether used concomitantly at all times, whether used in an overlapping way (e.g. use of one medicine extended as "maintenance"), or whether used entirely in sequence • whether one medicine is already listed for the target population and thus has an already established price, and if so, whether this price is likely to change in the near future • whether the constituent medicines are supplied by the same company, or by competing companies. Relevant factors such as these influence first the PBAC deliberations in deciding whether to recommend listing, and subsequently the government negotiations and decisions about whether to implement the PBAC's recommendation to list.
Belgium	No specific approach. In general if a company applies for coverage of its product B to be used with A, it will be expected to cover the cost of A, whose price is unlikely to change.
Canada	The HTA body assesses the combination therapy to issue a recommendation for public plans. The review looks at the product as a combination and does not focus on the constituent parts individually, to develop a funding recommendation. Typically, economic analyses by the Canadian Agency for Drugs and Technologies in Health (CADTH) [recommend] that public plans are not paying more than the aggregate of the current costs of the individual components.
Chile	No approach to attribute value to individual constituents of the combination. Budget impact is taken into account in price negotiations, which typically consider volumes rather than value.
France	The HTA body assesses the application for coverage of B, used in association with A and determines the added therapeutic benefit of A+B over the comparator (which might be A alone). The pricing committee then negotiates the price of the combination - If the combination has a minor added benefit (level IV), the cost of (A+B) must be = previous cost of A. - If the combination has a greater added benefit (from moderate III to major I), the cost of (A+B) may be = to the cost of A + 10% or more. In all cases, both prices must be negotiated. Treatment costs are based on net cost if any rebate. The price negotiation is done for each indication. Authorities do not attribute a share of the 'value' to constituents; the pricing committee negotiates with individual companies separately and may use confidential discounts.
Germany	The comparator therapy is the basis to determine the benefit for a new medicinal product and negotiate price if needed. There is a new, mandatory 20% reduction on all components of certain combination therapies.
Hungary	Based on cost-effectiveness analysis and budget impact analysis and recommendations of Therapeutic Committee (financing protocols).

[20] "Addressing Challenges in Access to Oncology Medicines - OECD," accessed October 26, 2022, https://www.oecd.org/health/health-systems/addressing-challenges-in-access-to-oncology-medicines.htm.

Italy	AIFA negotiates the price of a new product, regardless of its use in combination with other medicines. However, different types of managed entry agreements can be applied to the product used in combination with other medicines, through the implementation of a patient monitoring registry. In such cases, the net price (i.e. list prices minus any agreed discounts) of the combination regimen may be different from the price of the single components used in other indications. When one of the medicines in the combination regimen is already reimbursed by the national health service, its price is generally considered a fixed parameter (although price negotiations can occur) and the price of the second part of the combination is defined so that the total cost of the combination reflects its added value. This approach is not mandatory for pricing decisions made by the Pricing and Reimbursement Committee.
Latvia	If both products are from the same company, the price is set for the combination and reimbursement restrictions may be applied stating that the products are reimbursed only if used in combination. If the new product is added to an existing therapy (which is the comparator) the price of a new product is approved based on cost-effectiveness data.
Lithuania	The combination is assessed as it would be for a monotherapy
Norway	No specific approaches used to valuing constituent parts of combination treatment regimens.
Sweden	The Dental and Pharmaceutical Benefits Agency (TLV) is currently working on the development of a method to price combinations therapies, with consultation in relevant stakeholders, including regions and industry.
Switzerland	Comparison of the combination therapy with the existing Standard of Care. For clinically relevant additional benefits, an innovation premium can be considered (max. 20 % over the price of the comparator). The cost-effective price per month of progression-free survival is used to calculate the price of the combination and then the payback for single agents.
United Kingdom (England)	NICE does not undertake value attribution between constituents of combination therapies; this needs to be established prior to appraisal submission to NICE. Along with the Department of Health and Social Care, NHS England and NHS Improvement, NICE expects to support ABPI's efforts to enable companies to engage with one another where health-improving combination therapies face challenges coming to market, and ensure that the aggregate cost of combinations can be developed for NICE appraisal, within the standard NICE threshold, and in line with competition law.

What are the key challenges with implementing these solutions?

Some key challenges **from the literature** include:

- A focus on add-on therapy will typically lead to higher incremental cost-effectiveness ratios (ICERs) which could, in turn, delay negotiation and time to patient access.
- There is no evidence that society is willing to pay more for combinations as compared with single treatments offering comparable benefits; therefore, the current HTA approach to valuing the overall price of a combination (based on economic evaluation) appears to be valid.[21]
- Many who have looked at this issue conclude that to negotiate prices acceptable to all parties it will be necessary in many situations to have separate (at least notionally) prices for constituent therapies in a particular combination when used in that combination and when on their own or in other combinations. This could in theory be achieved through blended or multi-indication specific pricing, but this may be challenging in some jurisdictions.[22]
- In addition, there are legal and practical barriers to re-negotiating prices with manufacturers of the original therapy or multilateral negotiation with all manufacturers in some jurisdictions.[23]
- Combination therapies can create additional fiscal pressure beyond their price, when the utilization of a backbone regimen increases due to changes in dosing or more prolonged use due to improved survival or reduced rates of progression[24]
- In some situations, negotiation of acceptable prices for the components of a combination may depend upon attribution of the total value of the combination to the separate components, but as yet there is no agreed methodology for this.[25]
- There appears to be a growing consensus that a framework for assessment and reimbursement of a new combination needs a) to include review and negotiation of the price of existing components when used in this combination, as well as negotiation of the price of new combined components and b) that without some form of usage-specific (or blended) pricing manufacturers are likely to resist this.

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[21] N. R. Latimer, A. Towse, and C. Henshall, "Not Cost-Effective at Zero Price: Valuing and Paying for Combination Therapies in Cancer," *Expert Review of Pharmacoeconomics & Outcomes Research* 21, no. 3 (June 2021): 331–33, https://doi.org/10.1080/14737167.2021.1879644; N. R. Latimer et al., "Challenges in Valuing and Paying for Combination Regimens in Oncology: Reporting the Perspectives of a Multi-Stakeholder, International Workshop," *BMC Health Services Research* 21, no. 1 (May 2021): 412, https://doi.org/10.1186/s12913-021-06425-0.

[22] Ulf Persson and J. M. Norlin, "Multi-Indication and Combination Pricing and Reimbursement of Pharmaceuticals: Opportunities for Improved Health Care through Faster Uptake of New Innovations," *Applied Health Economics and Health Policy* 16, no. 2 (April 2018): 157–65, https://doi.org/10.1007/s40258-018-0377-7.

[23] N. Latimer and D. Pollard, "Pre-Read Document 1 : Challenges in Valuing and Paying for Combination Regimens in Oncology," Monograph (School of Health and Related Research, University of Sheffield, November 6, 2019), https://eprints.whiterose.ac.uk/157793/.

[24] D. Danko, J. Y. Blay, and L. P. Garrison, "Challenges in the Value Assessment, Pricing and Funding of Targeted Combination Therapies in Oncology," *Health Policy* 123, no. 12 (12AD): 1230–36, https://doi.org/10.1016/j.healthpol.2019.07.009.

[25] "Why We Need a New Outcomes-Based Value Attribution Framework for Combination Regimens in Oncology," February 2, 2021, https://www.ohe.org/news/why-we-need-new-outcomes-based-value-attribution-framework-combination-regimens-oncology.

Some key challenges **from discussion with industry and payers in Canada** include:

- Combination therapy negotiation is definitely viewed as more complex than monotherapy negotiation and can create challenges for payers and manufacturers in the Canadian setting.
- CADTH price reduction recommendations for combination regimens have varied in approach (See Section “It’s About the Prices” and accompanying Figure 2).
- These recommendations are also based on list prices; this results in even greater reductions in recommended rebates for add-on therapy (Figure 3); this price recommendation is seen as a hinderance to productive and rapid negotiation by new drug manufacturers.
- The pCPA has sometimes negotiated with the manufacturer of the add-on drug only, or sometimes with two or more manufacturers.

Manufacturers and payers both recognized the lack of a single framework or approach to negotiation with combination regimens and that this could lead to avoidable delay. From a manufacturer perspective, there is a perception that inconsistency in the approach to implementation makes it more difficult to plan or make necessary business decisions regarding how, and when to provide access for new combination regimens in Canada ahead of negotiation. These difficulties may in turn delay negotiation, or product access and result in avoidable health losses to patients.

Payers acknowledged that negotiation with different manufacturers simultaneously is plausible through revisiting existing PLA arrangements. While this can usually be done given current provisions for re-negotiation, a manufacturer of a backbone therapy that does not have an existing PLA or little commercial or strategic interest in re-negotiating an existing one could (intentionally or unintentionally) delay negotiation and ultimately, access to patients. Payers in Canada also recognized that while they may be able to negotiate with both manufacturers independently, they must prioritize negotiations and may be less incented to do so, given the added time and resource use. They may also be protected from expenditure increases (with the original backbone therapy) through the existence of price-volume caps written into previous PLAs.

What options look most promising for Canada?

Any solution disrupts the *status quo*. A systematic solution will first require wider scale acceptance that combination therapies require a specific pricing and reimbursement framework. In the Canadian context, some elements of a solution are very long-term and potentially infeasible. Changing the types of clinical trials used to demonstrate effectiveness requires buy-in from regulators and compliance by manufacturers; HTA rules for assessing economic value are unlikely to be changed; redeveloping combination regimens as single products (if feasible) is also a long-term solution requiring multiple actors. All are longer-term solutions, but may be of less help in the short term.

Any solution will require multiple components. While HTA bodies can change their focus towards value-based prices for combination therapies (versus add-ons), this might be less helpful if payers do not have the ability to conduct effective multilateral negotiation. It also raises the question about how much value to attribute to individual components, or whether value should be divided equally among components in the absence of supportive evidence.

Renegotiation of existing (backbone) therapy also requires voluntary compliance by manufacturers or a mechanism of mandating rebate increases (through future-proofing existing PLA agreements). While Canada generally uses a blended pricing approach across indications, any multiple indication pricing proposal could benefit from real-world data that captures indication specific usage.

As a practical step forward, based on what appears to be feasible in Canada, the general approaches believed to merit discussion at the multi-stakeholder workshop were the use of prior agreements and between-company proposals

These are illustrated in Figure 4 (next page).

Figure 4 General forward-looking approaches to pricing and reimbursement of combination therapies discussed at the Multi-Stakeholder Workshop

1: Prior agreements:

Description: *Assessment of reduction in price of each component by the HTA body coupled with automatic price reductions or price protections for backbone therapies based on prior agreement.*

This requires HTA to consistently recommend price reductions for regimen components; it does not require HTA to change rules of economic evaluation or willingness-to-pay thresholds. Prior agreement might be established through PLAs or an all-encompassing agreement (e.g., such as the tiered pricing framework) to compel manufacturers of backbone therapies to automatic price reductions based on the indication.

- Considerations with this approach include: the role of indication-specific pricing and use of increased volumes to drive price considerations; the simplicity of approach and capacity for PCPA to revisit prices.

2: Between-company proposals:

Description: *Manufacturer pricing proposals for combination regimens based on between-company agreements***--**

In this scenario, manufacturers promoting a combination regimen must be prepared to negotiate a collective combination regimen price based on discussion and agreement with other manufacturers. This could involve a voluntary arbitration framework or a technology platform to aid in multilateral negotiation, between companies and the HTA payer.

- Considerations with this approach include: feasibility and legal barriers to this; the simplicity or complexity of approach and capacity for PCPA to revisit prices.

Deliberative approach to identifying practical solutions to pricing and reimbursing combination products in Canada

The Institute of Health Economics (IHE) hosted a virtual, half-day workshop on November 23, 2022. The agenda is shown in Appendix A – Agenda and Participants. The invitational forum was organized by the IHE and was supported by and developed in partnership with Pfizer Canada ULC, Amgen Canada Inc., GlaxoSmithKline Inc. (GSK Canada), AbbVie Corporation, and J&J/Janssen. The views expressed herein do not necessarily represent the official position of any of the individual participants and organizations who participated in this work.

Invited participants were drawn from those currently involved with the value-based pricing and reimbursement of new combination products in Canada, providing perspectives from health technology assessment (HTA), payers and industry. The forum was conducted under the Chatham House Rule (i.e., "participants are free to use the information received, but neither the identity nor the affiliation of the speaker(s), nor that of any other participant, may be revealed") and moderated by Dr. Chris Henshall. Participants were first provided information from the previous section (1. Introduction) in summary slides and were then asked to address the following questions in open discussion.

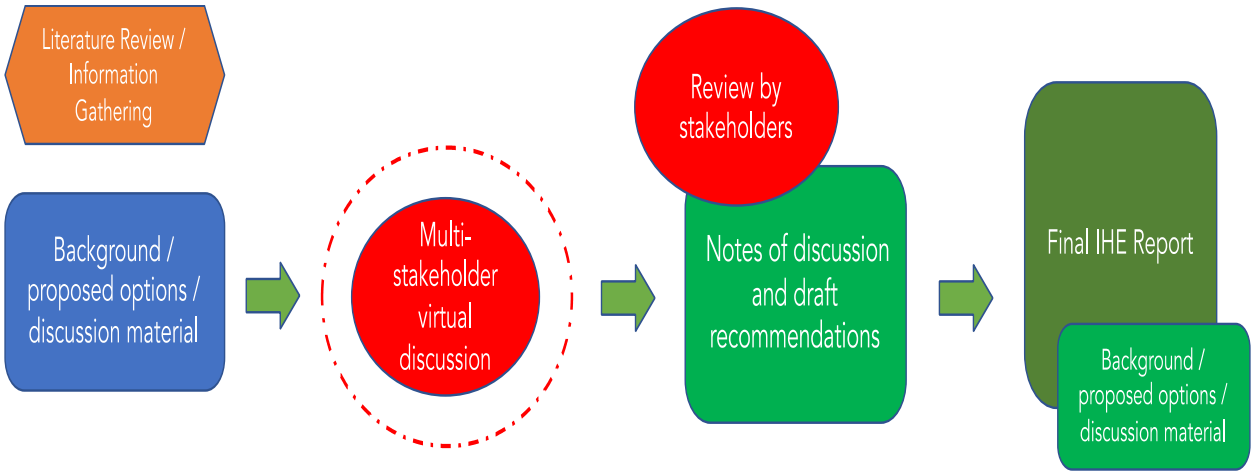
- Is there agreement as to the extent and urgency of the problem?
- Are the general solutions identified appropriate and feasible?
- What are the key issues that need to be resolved?
- Has anything been missed?

Following this, participants were divided into three multistakeholder groups to discuss answers to the following questions:

- What are the conditions or elements of a feasible solution to the pricing of combination therapies?
    - What conditions are essential?
    - What conditions are nice to have?
- What needs to be done to achieve this and who (organizations, individuals) in Canada needs to be involved?

A summary of the subsequent discussion and recommendations were then developed and re-circulated to participants for comment. Figure 5 provides an overview of the process.

Figure 5 Deliberative approach to developing recommendations to improve the pricing and reimbursement of new combination products.



The remainder of this report is organized as follows:

- Summary of the themes emerging through the discussion
- Recommended next steps for Canada, with a description of specific actions and an identification of who should take these on.
- **Appendix A** is a description of the Workshop agenda and attendees.

Reflections from the 2022 Multistakeholder Workshop Discussions

The background and options described in Sections 1 were presented and discussed at an Institute of Health Economics, Virtual Multi-Stakeholder Workshop held on November 23, 2022. Workshop Participants (n=24, See Appendix A –Agenda and Participants). A summary of reflections and observations is provided in point-form.

Summary of open discussion

The high-level discussion of the nature of the problem and its urgency, along with preliminary issues that require resolution led to the following observations:

Is there agreement as to the extent and urgency of the problem posed by combination therapies?

- Participants provided a range of opinions on this: Some felt it was not much of a problem at all, and others more so; of the participants in attendance, it appears that this area is potentially most problematic for some manufacturers, but less so for payers and other manufacturers. Some expressed concerns did exist from some patient groups in relation to potential access to therapies.
- There was general acknowledgment that it is an issue but not the most urgent one facing manufacturers and the health system at present. Participants observed:
- Not all combination therapies are the same – and combination therapies have been available in cancer care a very long time.
- The problem really seems to lie with new sole source (i.e., branded) therapies from two or more different companies. There was acknowledgement that differing levels of urgency will depend on the price of the regimens and their perceived affordability.
- Despite this, it is still anticipated that combinations will play an increasing role, particularly in oncology.
- Oral/injectable combinations could also introduce issues, as in some provinces these come from separate budgets, which could increase the complexity of negotiation.
- Non-transparent net prices also contribute to this challenge (as per Figure 3), however, CADTH has not received any direction to change their approach to using list prices.

What are the key issues that need to be addressed/resolved?

- While there was acknowledgment that WTP thresholds coupled with ICERs reflecting the value of combinations are important, CADTH price reduction recommendations for combination regimens have generally been based on the ICER of the add-on therapy, using list prices and not the ICER of the combination product as a whole and price reduction recommendations for all constituents (see Figure 3).

- Although attributing value to individual components of the combination therapy was seen as a promising approach, participants observed there is no agreed formal methodology for value-attribution to component therapies.
- Using an approach that attributes value-based prices to the individual components, even if feasible, of the combination therapy products does not get around the 'list' price issue (as per Figure 3).
- Ideally, a framework for assessment, pricing, and reimbursement of a new combination regimen will need to include:
  - A review and negotiation of the price of existing components (i.e., backbone therapies) when used in this combination, as well as negotiation of the price of the new entrant, to be appealing to payers; AND
  - Usage-specific (or blended) pricing based on utilization, to be appealing to manufacturers.
- Blended or multi-indication specific pricing which may be a key factor of fair price negotiation for combinations may be challenging in some jurisdictions, where the data required may not be readily available.
- There may be legal and practical barriers to re-negotiating prices with manufacturers of the original therapy or multilateral negotiation with all manufacturers in some jurisdictions.

What are some general solutions to the issues that may be appropriate and feasible in Canada?

- A framework that helps payers to understand the value of the combination (i.e., not simply the value of the add-on therapy) coupled with an approach to adjusting prices of the individual components would be required.
- Most participants felt we already had the right tools (e.g., CADTH, INESSS, the pan-Canadian pharmaceutical alliance (pCPA), and product-listing agreements) but they would require modification.
- There have already been instances where manufacturers who sell individual components of a combination therapy have provided price discounts (through confidential rebates); however, the current approach relies on their willingness to do so. This has led to a "hit or miss" approach where in some cases price adjustment of the individual components of a combination has occurred, while in other cases, it has not.

Simply adjusting the willingness-to-pay threshold commonly used by CADTH (i.e., $50,000 per quality-adjusted life-year gained) on an exceptional basis for combination regimens does not appear to be a practical solution. Participants felt that society is unlikely to be willing to pay more for combination therapies beyond the additional value created through their impact on quality-adjusted life-years, and the willingness to pay for these, as reflected in the incremental cost-effectiveness ratios (ICERS) provided by CADTH.

Summary of breakout/plenary discussion

What are the conditions of a feasible solution to the pricing of combination therapies?

Breakout group discussion followed the open discussion and assumed that a viable framework must help payers to understand the value of the combination (i.e. not simply the value of the add-on therapy) and be coupled with an approach to adjusting prices of their individual components. Participants discussed what elements of this type of framework are essential, what elements might be nice to have, and who might be responsible for these.

What elements are essential?

- Create a more compelling argument for change.
- Challenges around time to patient access need to be codified and outlined. Participants acknowledged that the impact on patients from delays with the existing framework could be very serious - (i.e., patients could die waiting for access to a combination therapy for oncology). There is overarching agreement that time to patient access is important and it is important to support this with evidence and analysis of the current impact on patients.
- Negotiating lower prices may not be commercially feasible or desirable under the current framework for manufacturers of backbone therapies. There needs to be a clear understanding of incentives for payers and manufacturers.
- Gathering further understanding from previous cases and of the broader commercial community will be necessary.

Dialogue and engagement framework

- Participants observed better communication, planning and prioritization is needed – there is an opportunity to formalize the current *ad hoc* system in a better way.
- At its core, cross-stakeholder engagement and discussion coupled with joint problem solving is required. This includes heightened engagement across involved stakeholders earlier in the process.
    - There are few opportunities for this type of dialogue currently, and stakeholders should work toward sustainable, longer-term platforms of exchange and deliberation for developing pharmaceutical policy.
- CADTH as a provider of value-based advice.
    - Participants recognized that CADTH will continue to play a fundamental role within any new combination therapy framework; even if CADTH is unable to access net confidential prices, it must still provide clear signals toward the negotiation process about how much added value any new combination strategy is providing.
    - There was general agreement that small changes could be made to the existing CADTH approach including:

        - Providing a value-based price of the total combination as well as the value of the add-on therapy.
        - Communicating (and possibly engaging with) backbone manufacturers early in the HTA process so they are aware of the evaluation and can prepare.
        - Continuing to flag those combinations which may have significant budget impact and in line with current CADTH processes to flag the feasibility of adopting combinations associated with significant additional expenditure.
- Creating separate agreements with individual manufacturers.
    - There was general recognition that there must be a mechanism in place to revisit prices with individual manufacturers of a combination product; however, this will require incentives for all manufacturers to participate.
    - One approach is to use existing pCPA letter-of-intent processes and PLAs to outline a set of future conditions relating to combination therapies that may apply to the agreement.
        - Participants observed that existing terms in PLA agreements do recognize "market-driven events" as a condition for revisiting agreements and that this could be adjusted to accommodate combination therapies; however, there was some acknowledgement that even with a change this may still not be readily enforceable.
        - Payers observed that building new PLA terms in would require considerable work in each jurisdiction separately and would require justification through a more detailed forecasting of the issue.
        - Tiers and volume-based caps are another solution that might compel re-negotiation. In some particular cases, PLA agreements have employed these approaches. This in turn has triggered pricing changes which have benefitted payers when adopting combination therapies.
        - Participants felt any solution will still rely on CADTH assessments and negotiation and are unlikely to be an "automatic" adjustment.

What elements are not essential but “nice to have”?

- The ability to track indication-specific utilization will be helpful:
    - Participants observed there will be some challenges to track indication-specific utilization in some jurisdictions. An example provided was monotherapy versus combination therapy using the same drug in the same indication – while this is feasible in some provinces it is not in others. Some products, such as oral oncology drugs may also pose a problem for jurisdictions that use different programs to fund these products.
    - Participants also observed data from prior authorization information for differential rebates within the pharmacy payment delivery system can be utilized in some cases.

  - Even if tracking is technically possible, it may still be infeasible for some jurisdictions given limited capacity and infrastructure.
  - Industry capacity could also be a problem, especially as more companies are involved and complexity and volume of files increases. Some capacity issues could be addressed through pan-Canadian collaboration.
  - As provinces develop health data strategies, they should consider how indication specific pricing can be embedded into existing information systems.
- Value attribution would also be helpful:
  - While a mechanism to attribute value to the individual components of a combination strategy was believed to be nice to have, participants felt it would be difficult to assess based on the evidence that currently is seen at an HTA level.
  - As already noted, there is also no agreed framework for attributing value to individual components of a combination therapy.

Who needs to act toward creating and enabling these conditions?

CADTH

- CADTH (and potentially other HTA bodies, such as INESSS) responsibilities may include:
  - Shift toward systemic reporting value of the combination therapies as a basis for negotiation of value-based prices.
  - Communicating and engaging with all manufacturers implicated in a combination therapy throughout the HTA process.
  - Providing further analyses of discounting scenarios for individual products within a combination rather than a strict focus on the add-on therapy.
  - Attributing value to individual components of therapy if feasible, based on the evidence provided.

pCPA

- Changes to the pCPA process should be a key focus for any proposed approach moving forward:
  - Creating a separate "combination therapies" stream is a starting point. However, the full intention of creating a separate stream with combinations will need to be clarified for all stakeholders.
  - Participants observed that within the current pCPA framework, the first negotiation of a new product typically creates a precedent; a key question to be addressed is how to incent and enforce re-negotiation (or pre-negotiation)?
  - Participants observed that key changes to the existing framework must also address utilization-specific pricing.
- Incenting re-/ pre-negotiation:
  - While feasible, this process may be unenforceable – it may require each province to have legislation. Alternatively, a “Master contract” could be employed.

However, it was felt this would require a lot of work on behalf of both payers and manufacturers (whose legal counsel must look and approve)

- Utilization-specific pricing:
    - Most felt this would be very complex. A blended pricing approach is much easier for jurisdictions to manage. There may also be a way to automate some of the current processes that might address adjudication rather than using person power for things which are less routine.

Manufacturers

- All manufacturers must agree and provide input into any conditional future-proofed PLAs or any proposed framework.
- Manufacturers must be ready to work with other manufacturers in this process early in approval processes.
- Manufacturers should explore a shift toward a “safe harbour” approach; this was felt to be feasible as some participants observed there are precedents in other sectors (such as information sharing in corporate mergers and acquisitions).
    - While some manufacturers fear it could be perceived as anti-competitive, discussion at this meeting led to a conclusion it might not be, as manufacturers are working together toward a goal of improving the health of Canadian patients. It was acknowledged that it will be difficult for any individual company to go to without precedence or assurance that it is not anti-competitive.

Recommendations for feasible next-steps toward a combination therapy framework

Given the reflections from the exchange of perspectives and ideas in the previous section, the IHE has developed the following recommendations to advance pharmaceutical policy in this area:

Recommendation 1: EXPLORE INDUSTRY AND PAYER BUY-IN:

- As an increasing number of manufacturers will be exposed to this issue, and no one manufacturer may be exempt in theory, a logical starting point would be to explore willingness among manufacturers (through industry associations or surveys) to be open to a process for the negotiation of high-cost branded combinations across separate manufacturers.
    - Exploration of "backbone' therapy manufacturers' willingness to engage, or perceived barriers, would be an important step, at minimum.
    - Similarly, the wider payer community should be surveyed. The intent of a process and potential barriers to the approach will need to be further clarified through this ask.

Recommendation 2: ESTABLISHING A BACKGROUND CASE AND GATHERING BASELINE INFORMATION TO CHARACTERIZE AND ADDRESS THE ISSUE

- Until feasible solutions are developed some common baseline information would be useful. Health Canada, CADTH , and other pharmaceutical policy research organizations (e.g., PMPRB, IHE) can play a helpful role in quantifying the magnitude of the issue and preparing stakeholders for a future of combination therapies through:
    - Communicating to all implicated manufacturers when regulatory or HTA dossiers with combination therapies have been received and/or are under consideration.
    - Tracking and reporting the number of new and expected branded combinations (e.g., through horizon scanning and manufacturer survey) approved in Canada and internationally to help inform discussions about the magnitude of the issue.
    - Independent assessment/benchmark study on Canadians comparative access to new combination therapies should be conducted to inform ongoing policy discussions.
    - An examination of the current timelines for patient access to combination products in Canada, when compared to similar non-combinations.
    - Consultation on the IHE report should be conducted to identify any barriers to advancing these discussions and what would be required policy levers/incentives/concerns.

Recommendation 3: CREATING A SAFE SPACE TO DEVELOP A MUTUALLY RECOGNIZED PROCESS

- If there is general agreement across payers and manufacturers that a combination-specific process is needed, a first logical step will be to create a forum for multistakeholder deliberation about a new approach, including the prioritization process and approach to negotiation of new combinations (below).
- CREATING A PRIORITIZATION FRAMEWORK
    - Stakeholders need to agree under what specific conditions, a separate process for combination therapy will be required.
- EXPLORE NEGOTIATION APPROACHES
    - Stakeholders will need to decide whether a PLA-based approach, that includes enforceable legal conditions to compel pre-/re-negotiation OR a “safe-harbour” approach are most feasible in the Canadian context or whether a feasible solution combines elements of both.

Recommendation 4: EXPLORE OTHER PRACTICAL AREAS REQUIRING ADAPTATION:

- The current product listing protocols/agreements should be explored and draft clauses be developed for potential inclusion that would anticipate opening pricing negotiations given combination therapies.
- CADTH should revisit its existing value-based pricing framework and whether it is fit for purpose to address multiple products/conditions.
- Develop case studies from existing products where differential value attribution has been conducted.
- Develop a case example in indication specific tracking to inform reimbursement. This could include usage specific versus blended pricing models scenarios.

Appendix A –Agenda and Participants

Combination regimens: reimbursement challenges and solutions

November 23rd – 2022 – 9:30pm – 12:30 ET

Time	Item	Presenters/ Discussants
9:00	Participants can sign in.	
9:30	Welcome and introductions	Chris Henshall
9:45	Opening comments and overview of meeting structure ***What can we achieve with discussion?*** Possible points to include: • Multistakeholder *deliberation* is always a challenge in Canada and more so in the era of COVID. We are all here because we believe challenges involving multiple stakeholders necessitate some level of collaboration and exchange. • There have been discussions in other jurisdictional contexts. The challenges and solutions uncovered there may or not apply here. • We must be mindful that not all stakeholders are at this meeting and that some companies (and payers) have more to gain or lose depending on their pipeline (and formulary). • While there are a lot of options that have been proposed, as per the background paper we will focus on those that appear to be most relevant in the Canadian context.	Chris Henshall
9:55	Overview of key findings in the background paper and from interviews	Don Husereau
10:15	Open discussion • Is there agreement as to the extent and urgency of the problem? • Are the general solutions identified appropriate and feasible? • Has anything been missed? • What are the key issues that need to be resolved?	Chris Henshall
10:50	Break	All
11:00	Breakout / Brainstorming Session • Based on the open discussion and previous background information and interview, we will focus on 2-3 key questions regarding approach. Questions may be: • What are the pros and cons of feasible solutions? • What are the specific details and considerations required for the solutions proposed? • How should the roles /responsibilities of CADTH, manufacturers and the PCPA change to ensure timely negotiation? (who needs to do what?) • What else can we do to ensure timely access?	John / Don (breakout moderators)
11:25	Discussion	Chris Henshall
11:50	Summing it up	Chris Henshall

PARTICIPANTS INVITED:

Payers

- Darryl Boehm, Darryl Boehm, Director, Oncology Pharmacy Services, Saskatchewan Cancer Agency
- Scott Gavura, Director, Provincial Drug Reimbursement Programs
- Chad Mitchell, Assistant Deputy Minister - Pharmaceutical and Supplementary Benefits at Government of Alberta
- Mitch Moneo, Assistant Deputy Minister, Pharmaceutical Services Division, BC Ministry of Health
- Lynne Nakashima, Senior Director, Provincial Pharmacy at BC Cancer

HTA

- Sylvie Bouchard, Directrice, INESSS
- Brent Fraser, Vice-President of Pharmaceutical Reviews, CADTH
- Stuart Peacock, Co-Director, Canadian Centre for Applied Research in Cancer Control (ARCC)

Ex-HTA/Payers

- Matthew Brougham, Consultant, former Chief Executive, New Zealand Pharmaceutical Management Agency (PHARMAC); former Vice President, Products and Services, CADTH
- Jaclyn Beca, Consultant, former Health Economist and Manager, Pharmacoeconomics Research Unit, Cancer Care Ontario
- Tim Buckland, Senior Project Manager at Cancer Strategic Clinical Network - Alberta Health Services
- Sang-Mi Lee, Consultant, former Senior Manager, pan-Canadian Pharmaceutical Alliance
- Michael Mayne, Consultant, former Deputy Minister of health, PEI
- Judy McPhee, Consultant, former Executive Director Pharmaceutical Services & EHB, Department of Health and Wellness
- Glenn Monteith, Consultant, former Executive Director, Pharmaceuticals and Life Sciences

Manufacturers

- Stephane Barakat, Lead, Market Access & HEOR Oncology at AbbVie
- Coral Fairhead, Market Access Manager, Oncology at GSK
- Kevin Harrington, Market Access and Government Affairs Manager AbbVie
- Oliver Johnston, Senior Manager Patient Access and Government Relations - Oncology
- Bonnie Kam, Director, Health Technology Assessment at Janssen, Pharmaceutical Companies of Johnson and Johnson
- Phu Vinh On, Senior Manager Access at Pfizer
- Ben Peacock, Director, Value & Access (Health Economics & Market Access) at Amgen
- Raina Rogoza, Health Economics & Market Access Senior Manager at Amgen
- Luigi Formica, Market Access Lead – Oncology, GSK

Breakout groups

Group A

Bonnie	Kam
Stephane	Barakat
Tim	Buckland
Brent	Fraser
Chad	Mitchell
Judy	McPhee
Lynne	Nakashima

Group B

Coral	Fairhead
Raina	Rogoza
Michael	Mayne
Mitch	Moneo
Sang Mi	Lee
Scott	Gavura
Stuart	Peacock
Phu Vinh	On

Group C

Kevin	Harrington
Luigi	Formica
Oliver	Johnston
Darryl	Boehm
Jaclyn	Beca
Matthew	Brougham
Glenn	Monteith
Sylvie	Bouchard
Ben	Peacock