

Challenges with Integrating Early-Stage Cancer Trial Endpoints into Economic Models: Review of Canadian and International HTA Recommendations

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BACKGROUND

How have HTA agencies handled long-term benefit assumptions in economic models for early-stage cancers?

Trials measure intermediate endpoints

Potentially curative adjuvant and neoadjuvant therapies for early-stage cancers often demonstrate early clinical benefit in reducing disease recurrence. Though aspiring to improve survival, such benefits may take years or be challenging to confirm.

Outcomes are estimated over a lifetime in economic models

There is limited evidence at adoption to project outcomes and assume treatment effects or remission are sustained.

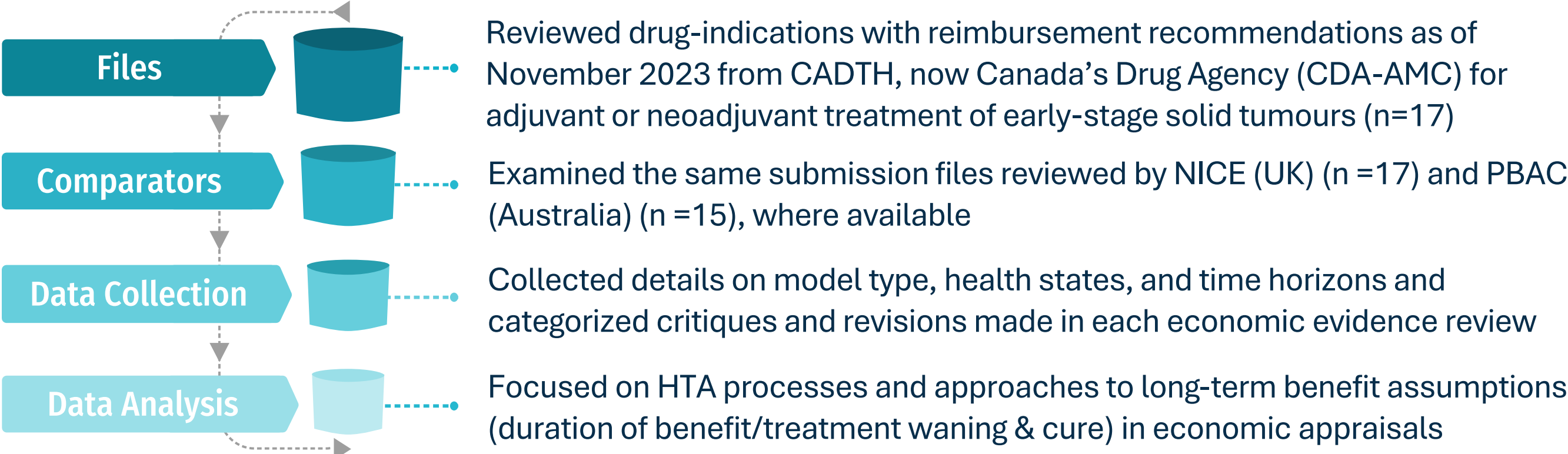
Guidance on modelling long-term benefits are still unclear

Explicit modifications to parametric extrapolations to account for treatment benefit waning or reflect cure require additional assumptions, and best practices have not yet been established.

Reviewing international approaches

We reviewed HTA agencies' appraisal of approaches **modelling long-term clinical outcomes** among potentially curative oncology therapies to identify opportunities for methodological refinement and guidance.

METHODS: WHAT WE DID



What we know: Our prior research in Canada has shown acceptance of early endpoints by HTA with evidence of patient- and trial-level associations supporting surrogacy.

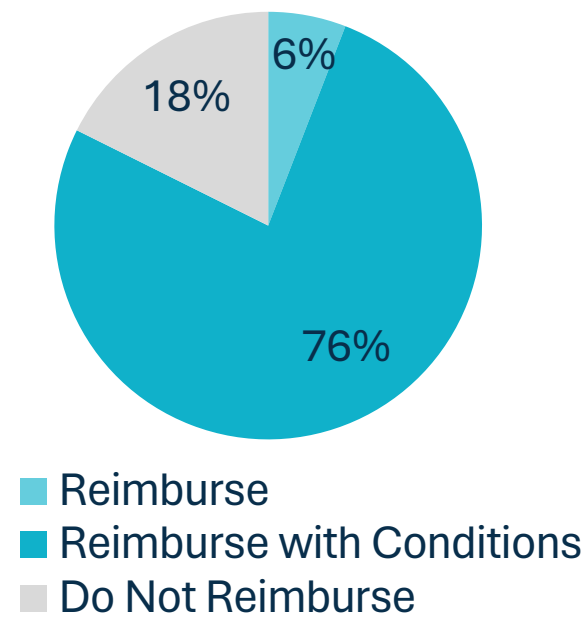
Though in broadly similar health systems, each HTA agency has unique context, processes, and operational differences that affect their appraisals.

Limitations Includes critiques described in publicly available reports, which may not capture all issues. Modelling approaches, HTA processes and reporting standards have also evolved.

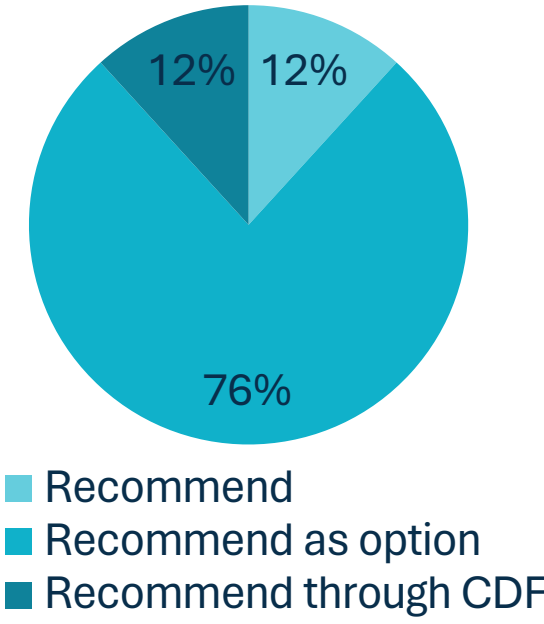
RESULTS: WHAT WE FOUND

HTA outcomes: Most files have been recommended for funding

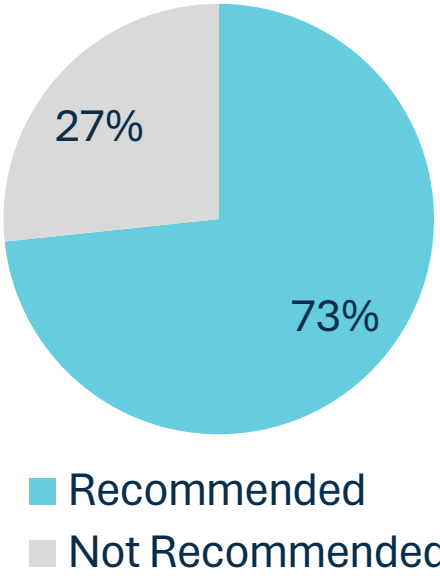
CADTH (CDA-AMC)



NICE

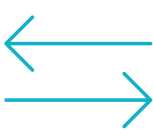


PBAC



Files not recommended by CDA-AMC were also not recommended by PBAC

Processes and objectives of HTA agencies may impact their approach



Dialogue and revision: Multiple opportunities offered by NICE and PBAC for discussion and updates models with sponsors.



Role in Pricing: NICE and PBAC include confidential net pricing in its evaluation; CADTH (now CDA-AMC) does not consider net pricing.



Availability of Information: CDA-AMC has improved transparency; NICE shares all materials and communication. NICE and PBAC redact confidential inputs and report results with ICER ranges.

CDA-AMC reports impact of key factors to inform subsequent negotiations, while NICE and PBAC ensure net price results fall within acceptable range.

Opportunities for dialogue, justification and refinement help facilitate agreement on plausible and moderate approaches.

Acceptable approaches and justifications used by each agency to inform appraisal varied widely

Though broadly similar, we noted some differences in submitted approaches, some variability expected given local preferences, processes and objectives

Markov

Model Types

PSM

Of 49 files, 44 submissions were based on Markov models. 2/17 indications involved different model types submitted between HTA agencies.

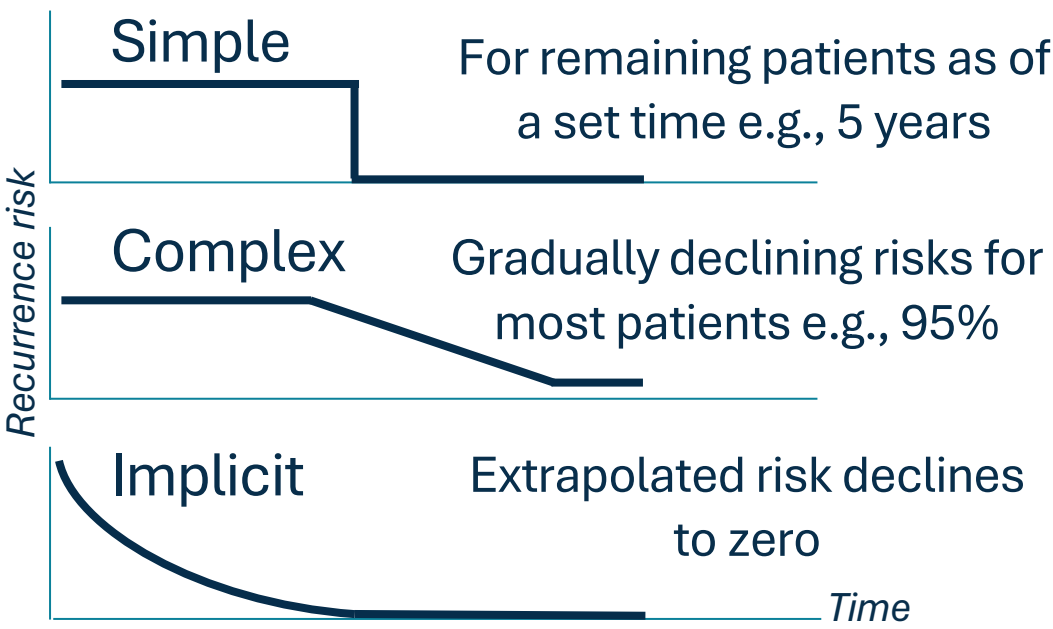
3 — 4 — 5 — Health States — 9

Most submissions included 4 or 5 health states. Different numbers of health states were described between HTA agencies for 7/17 drug-indications.

10 — Time Horizons — 40 — 60

The same time horizon was used across HTA submissions for only 1 drug-indication. PBAC submissions frequently involved shorter time horizons.

Assuming cure when patients are no longer at risk of tumour recurrence



Justified with external evidence from longer follow-up or natural history to inform long-term recurrence risks of some files, others relied on clinical opinion of time-to-establish cure, or on precedent. Mixture models not often used due to data immaturity.

Drug-Indication		Cure			Treatment waning		
		CDA-AMC	NICE	PBAC	CDA-AMC	NICE	PBAC
Pert	N						
Pert	A				Earlier		Censored
Nera	A		Modified		Earlier	Added	Earlier
TDM1	A						
Pemb	N				Earlier		Added
Abem	A				Earlier	Earlier	Earlier
Olap	A			Later		Modified	
Nivo	A				Added	Added	Earlier
DabT	A	Modified	Removed	Modified	Earlier		
Pemb	A						
Pemb	A			N/A	Added		N/A
Pemb	A	Added		N/A	Added	Added	N/A
Nivo	A		Later				
Nivo	A	Later	Later	Later			Modified
Osim	A	Modified	Later	Later			
Atez	A	Later	Later	Removed	Earlier		
Nivo	N	Modified	Modified				

Modifications in 2/3 of files

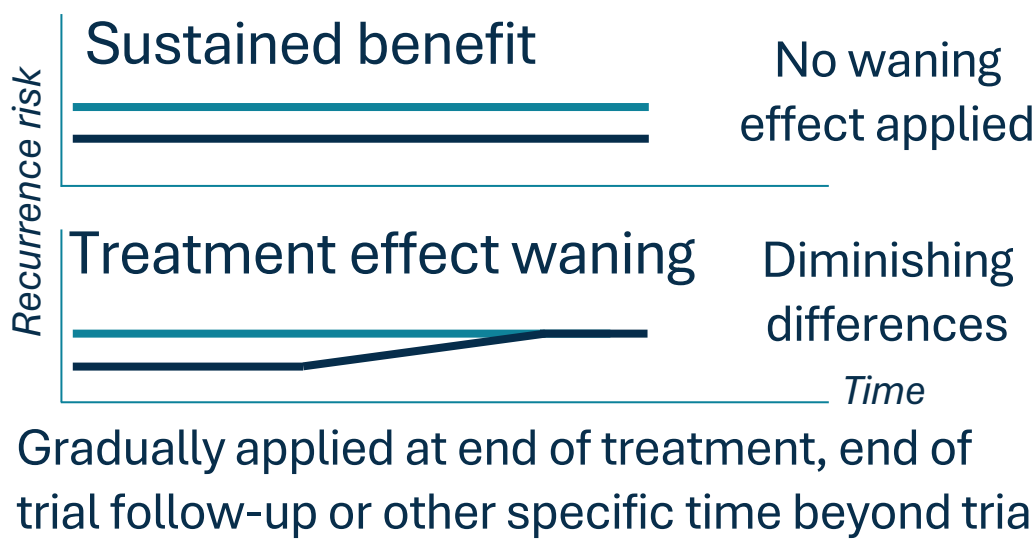
No clear consistency of explicit cure or treatment waning assumptions within files or across agencies.

Wide variation in accepting or modifying assumptions by HTA; primarily initiating waning earlier and cure later.

Cure – simple
Cure – complex
Cure – implicit
Treatment waning included
Cure/waning not included
No mention/no submission

High variability in when or how to apply cure or waning assumptions, and in acceptable justifications based on clinical input, evidence, or prior experience

Assuming waning of treatment effect on risks relative to the comparator



Justified sparingly, often based on precedent. Common to assume sustained benefit especially with cure. A common justification to modify against sustained benefit was made from observing waning in trial time-dependent risks.

Unknown how often either assumptions are implicit in extrapolations

IMPLICATIONS: WHAT COULD WE BE DOING BETTER?

Consistently considering within-trial and **external disease-related evidence** along with clinical input to inform long-term disease risks and risk changes, rather than precedent.

Standardizing reporting to improve terminology and **including visualization of relative hazards** over time to validate need for explicit assumptions and their implications.

Generating and leveraging relevant external data (trials and RWE) with **calibration and integration in extrapolations with flexible methods** beyond cure models.

Developing guidance and consensus on **acceptable principles and evidence needed** to justify treatment waning and cure assumptions within and across jurisdictions, conditions, and treatments.

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