



Canadian Agency for
Drugs and Technologies
in Health



Agence canadienne
des médicaments et des
technologies de la santé

Considering the Cost-Effectiveness of Drugs based on Surrogate Outcomes: recent Canadian experience

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Outline

Considering the Cost-Effectiveness of Drugs based on Surrogate Outcomes: recent Canadian experience

- CADTH's view of surrogate outcomes
 - CADTH Guideline for the Economic Evaluation of Health Technologies: 3rd Edition
 - Common Drug Review Submission Guidance
- Some applied examples
- Recent experience with oncology products

Objectives

Considering the Cost-Effectiveness of Drugs based on Surrogate Outcomes: recent Canadian experience

- To better understand approach to evaluation using surrogate outcomes at CADTH
- To understand broader issues, beyond scientific judgment
- To understand issues regarding the economic evaluation of oncology treatments

Canadian Environment - Guidelines

Canadian Agency for Drugs and Technologies in Health (CADTH)

- A national body that provides Canada's federal, provincial, and territorial health care decision makers with timely, relevant, rigorously derived, evidence-based information to support decision making processes

Developers of Canada's Economic Evaluation Guidelines

- First edition 1994
- Most recent revision 2006

Canadian Guidelines



Identify preferred methods

- Improve reliability and relevance of results
- Reduce the risk of introducing bias

Make economic evaluations more comparable

- Standardize methods and reporting
- Enhance transparency

Canadian Environment – Drug Reviews

Common Drug Review – A single common process for assessing new drugs for potential coverage by F/P/T drug benefit plans in Canada (except Quebec), established 2003

- Review of best available clinical evidence and critique of manufacturer-submitted pharmacoeconomic evaluation
- Listing recommendation from a national expert committee (CEDAC – Canadian Expert Drug Advisory Committee)
- More specific guidance to manufacturers submitting to CDR (CDR Submission Requirements)

CADTH Position on Surrogate Outcomes

CADTH Documents

- CDR guidance is more strictly defined interpretation
- Neither document suggests methods for validation
- Both documents suggest health outcome categories are not mutually exclusive
- Both documents call attention to surrogates that do not reasonably predict clinical outcomes
 - CADTH Guidelines suggest valid if a “strong, independent, consistent association” with an important patient outcome, and there is “evidence from randomized trials that... improvement in the surrogate end point has consistently lead to improvement in the target outcome.” (Bucher, 2005)

CADTH Position on Surrogate Outcomes

Health Economic Evaluation Guidelines

- Outcomes are Final, Important Clinical, or Surrogate
- Final outcomes are related to mortality and quality of life

CDR Submission Requirements

- Outcomes are Final, or Intermediate (surrogate)
- Final outcomes allow health benefits to be expressed in life-years, QALYs, or events (myocardial infarction, stroke, or fracture)

CADTH Position on Surrogate Outcomes

CADTH Documents

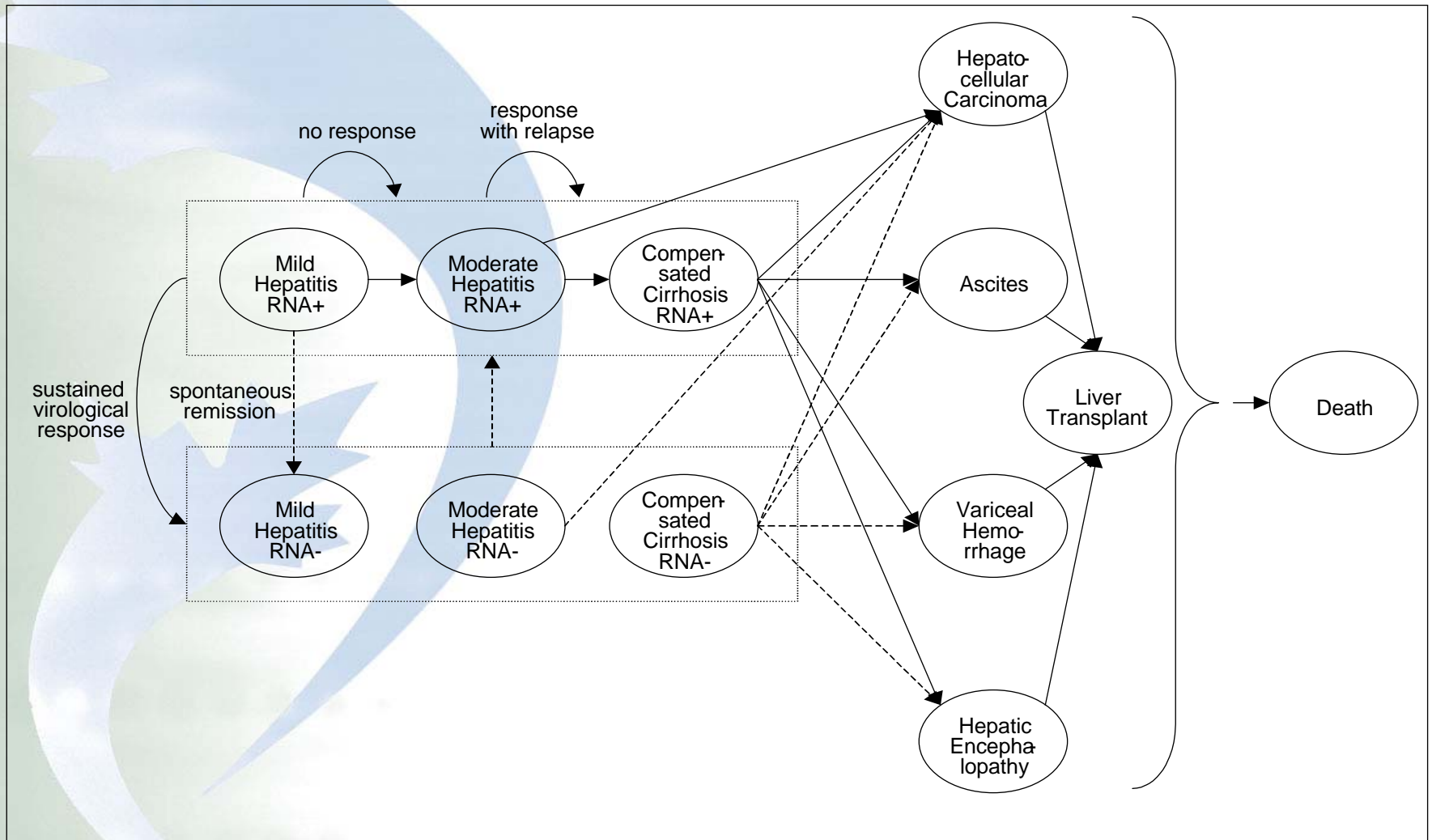
- CADTH Guidelines suggests
 - “Emphasis should be placed on using the relevant and valid outcomes of the highest importance for the health of patients.”
- CDR guidance suggests cost-consequence analysis if surrogate is unproven
 - “believability” of surrogate can be addressed by review and deliberative process
 - Consistent with CADTH Guidelines

Some Examples

Sustained Viral Response

- Treatment of RNA+ virally infected patients with the hope of altering disease prognosis
- Viral clearance is determined by HCV ribonucleic acid (RNA) testing at the end of treatment or six months after the end of treatment (sustained virological response)
- Effects of viral infection will not manifest for decades
- Sustained Viral Response perceived as a clinical cure.
- Brady B, Siebert U, Sroczynski G, Murphy G, Husereau D, Sherman M, Wong W, Mensinkai S, **Pegylated interferon combined with ribavirin for chronic hepatitis C virus infection: an economic evaluation [Technology report no 82].** 2007.
- Husereau D, Bassett K, Koretz R. **Inteferon-based therapies for chronic hepatitis C virus infection: an assessment of clinical outcomes. [Technology report no 47.]** 2004.

Hepatitis C Disease Progression



Sustained Viral Response

- Treatment effect by patient characteristic interaction
 - People with poorer prognosis less likely to have surrogate outcome response of viral clearance

“The worst-case scenario is that none of the responders were ever at risk of developing end-stage liver disease... As discomfoting as it may appear, the only way we will know if IFN (or any other agent that relies on the same intermediate end points) should be used is to perform the large, lengthy trial. Outside of Wonderland, the verdict (data from randomized trials) must come before the sentence (decision regarding use)”

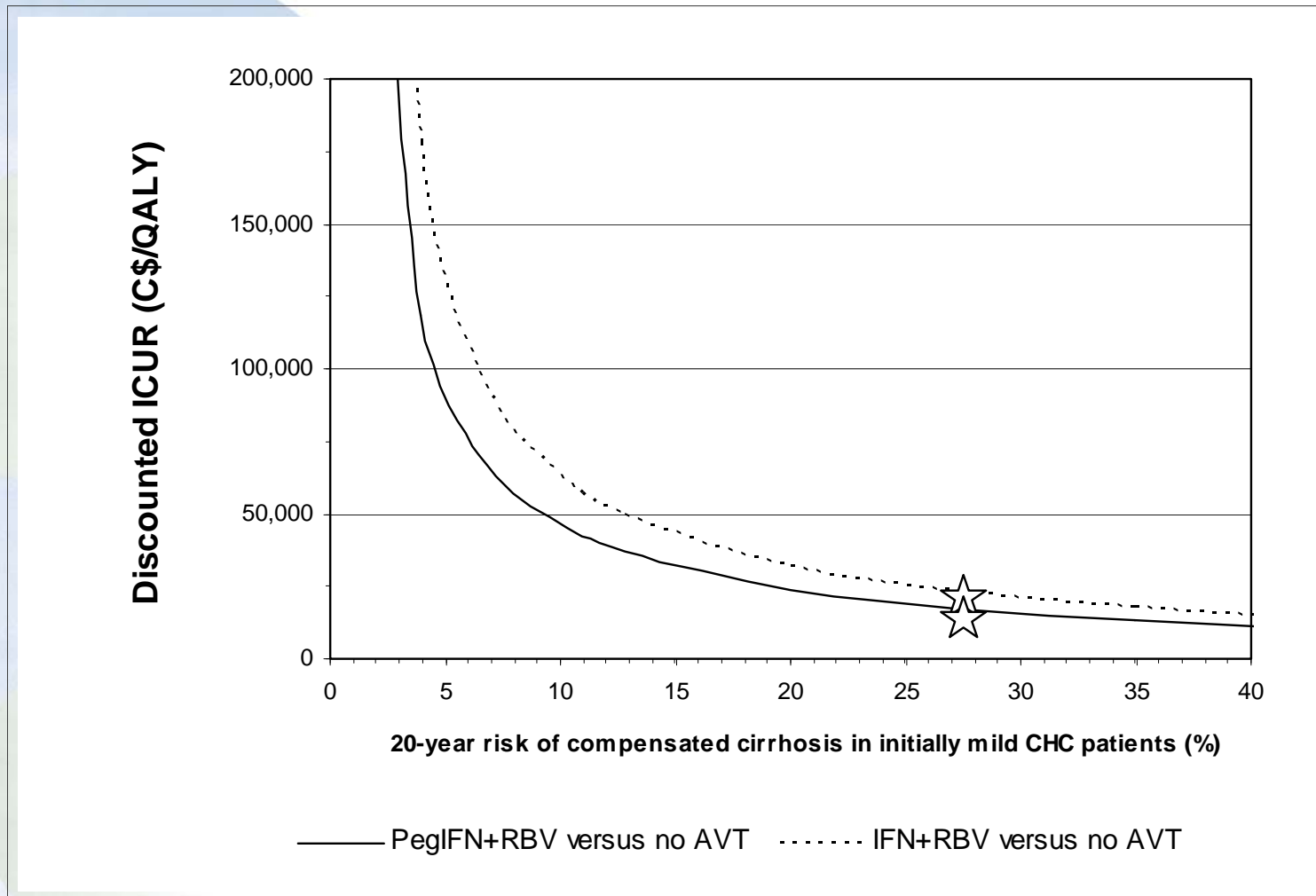
Koretz RL, Interferon in Wonderland. Gastroenterology, 1998 Oct, 115(4); 1027-9

Sustained Viral Response

“In most untreated, infected patients, decompensated cirrhosis will never develop. Moreover, the predictive factors for achieving sustained virologic responses are often similar to those that predict a lower likelihood that cirrhosis will develop. In patients with sustained virologic responses, decompensated end-stage liver disease or hepatocellular carcinoma can still develop. **We lack evidence to support the use of these potential surrogate outcomes.** We need proof that hepatitis C treatment, with its associated morbidity and cost, is efficacious.

Koretz RL, Gluud C. N Engl J Med. 2009 Mar 12;360(11):1151;

Sensitivity Analysis



Intra-Ocular Pressure

- High intraocular pressure (IOP) is recognized as the most important risk factor contributing to the development and progression of glaucoma
- Elevated IOP is neither necessary nor sufficient to cause glaucoma because an estimated 90% of patients with elevated IOP [>21 millimetres of mercury (mm Hg)] never develop glaucoma
- This chronic condition is characterized by slow and progressive damage to the optic nerve, usually causing gradual loss of vision.
- The goal of current glaucoma treatment is to lower IOP, the only modifiable risk factor for glaucoma progression..
- Hodge W.G, Lachaine J, Steffensen I, Murray C, Barnes D, Foerster V, Ducruet T, Mensinkai S. **Prostaglandin analogues for ophthalmic use: analysis of clinical and cost-effectiveness** [Technology report no 89. 2007.

Intra-Ocular Pressure

- Consultation with researchers suggested transforming IOP to meaningful disease burden measures (final outcomes) would be difficult.
- Consultation with pharmaceutical formulary plan managers suggested clinical and formulary decisions would be made using IOP
- Cost/ Average Reduction in IOP (mmHg) used as outcome measure

Parathyroid hormone and serum calcium

- Hyperparathyroidism secondary to hypocalcemia or hyperphosphatemia in patients with chronic kidney disease
- Conventional treatments are oral phosphate binders and oral or parenteral vitamin D analogs
- Cinacalcet is a calcimimetic that can control PTH release from parathyroid glands without increasing calcium and phosphorus levels.
- Clinically important outcomes are quality of life, symptomatic bone disease, (bone pain, fractures), hospitalization, cardiovascular disease or mortality
- CEDAC Recommendation on Reconsideration and Reasons for Recommendation. CINACALCET (Sensipar – Amgen Canada). March 23, 2005

Parathyroid hormone and serum calcium

- CEDAC recommended drug plan managers “Do Not List” this agent on public drug plan formularies
- “There was insufficient evidence in [nine double-blind randomized controlled trials] that cinacalcet has any effect on clinically important outcomes”
- “The additional medication cost of adding cinacalcet to the management regimes of patients with chronic kidney disease is between \$4000 and \$23,500 per patient per year...”

Insulin-like Growth Factor I (IGF-I)

- Acromegaly is a clinical syndrome due to the overproduction of growth hormone by a pituitary tumour resulting in tissue and organ overgrowth.
- Conventional treatments are dopamine agonists and somatostatin analogues
- Pegvisomant is a growth hormone receptor antagonist for patients inadequately responding to other treatments.
- Clinically important outcomes are quality of life, complications. Acromegaly is a chronic condition.
- CEDAC Recommendation on Reconsideration and Reasons for Recommendation. PEGVISOMANT (Somavert – Pfizer Canada). August 2, 2006

Parathyroid hormone and serum calcium

- CEDAC recommended drug plan managers “Do Not List” this agent on public drug plan formularies
- “The committee is concerned that ... pegvisomant has only been assessed in a 12 week RCT, though acromegaly is a chronic condition”
- No differences in quality of life based on an SF-36 were detected
- “Pegvisomant costs \$60,000 to \$80,000 per year...The economic analysis submitted by the manufacturer [assumed] pegvisomant would ... increase survival, that QoL would be significantly improved, and that pegvisomant would be used without concomitant use of somatostatin analogs”

Oncology products

- “Adaptation of the CADTH Economic Guidelines for Oncology Products”
- Basis for more consistency in
 - submissions to Cancer programs
 - design of Clinical trials
- Consensus guideline development process

Oncology products

- “In oncology, the ultimate goal of a therapeutic intervention is to cure disease. Failing that, the goal is to prolong Overall Survival (OS) and/or to improve patient symptoms and quality of life.”
- “In the Reference Case, QALY and LYG are the recommended outcomes for oncology economic evaluations in both the curative/adjuvant and palliative settings.”
- “Extrapolation from surrogate outcomes to QALY and LYG must be accompanied by appropriate justification based on best available evidence.”



Questions?

For More Information



CADTH web site: www.cadth.ca