CCTG
New Investigator Clinical Trials Course:
Economic Evaluation

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Disclosures

• Merck
• Novartis
• Roche
• Ipsen

• AstraZeneca
• Eisai
• Pfizer
• Astellas

• I am not an economist

• I do listen to economic podcasts

• I am a member of the CCTG Committee on Economic Analysis
1. To understand the current funding process in Canada

2. Review economic analysis concepts

3. Review criteria for inclusion of economic analysis alongside clinical trial
Pineapple on pizza?

Yes… bring on the luau!

Wrong… despite the Canadian origin
What is your discipline?
What exposure have you had to economic analysis?

I have participated in an EA

I have received teaching about EA

I did an EA on the value meal at McDonald's yesterday
Cancer Funding
Economics and Cancer

- Cancer is growing problem – estimated cost of cancer care in US >$210 billion USD  

- New treatments that improve outcome should be adopted

- But with limited resources, economic constraints factor into resource allocation, in order to maximize population health

- 3 pillars of FDA approval of novel interventions:
  - Safety; Mechanism of action; Clinical efficacy
  - 4th pillar (pCODR): cost-effectiveness!

- Cost effectiveness – expression of an intervention’s cost in relation to its benefit
Cost of Health Care and Life Expectancy

% GDP

- USA
- Switzerland
- Canada
- Monaco
- Australia
- Japan
- Spain
- Ireland
- Singapore

Female Life Expectancy (years)

The economic burden of cancer care in Canada: a population-based cost study

Claire de Oliveira MA PhD,* Sharada Weir MA DPhil,* Jagadish Rangrej MSc MMath, Murray D. Krahn MD MSc, Nicole Mittmann MSc PhD, Jeffrey S. Hoch MA PhD, Kelvin K.W. Chan MD PhD, Stuart Peacock MSc DPhil
### Table 4: Total net cost (in constant 2015 dollars) for patients with malignant neoplasms* diagnosed in the past 10 years in Ontario, 2009–2012, by cost category

<table>
<thead>
<tr>
<th>Cost category</th>
<th>Year; net cost (95% CI), $ millions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2009</td>
</tr>
<tr>
<td><strong>Hospital care</strong></td>
<td></td>
</tr>
<tr>
<td>Acute inpatient hospital care</td>
<td>571.3 (547.2 to 595.3)</td>
</tr>
<tr>
<td>Ambulatory hospital care</td>
<td></td>
</tr>
<tr>
<td>Day surgery</td>
<td>48.3 (46.9 to 49.7)</td>
</tr>
<tr>
<td>Emergency department visits</td>
<td>9.5 (8.5 to 10.4)</td>
</tr>
<tr>
<td>Cancer clinics</td>
<td>474.1 (468.5 to 479.8)</td>
</tr>
</tbody>
</table>
Canadian drug approval process
HTA: Health Technology review
pCODR: pan-Canadian Oncology Drug Review Board
NOC: Notice of Compliance
CADTH - CDR = Canadian Agency for Drugs and Technologies in Health - Common Drug Review
PMPRB: Patented Medicine Prices Review Board
pCPA: pan-Canadian Pharmaceutical Alliance

Kirk et al In submission 2019
Where does the most expensive class of cancer drug sit in national ranking of health expenses?

First
Second
Fourth
Sixth
### Table A5  Top 10 drug classes by public drug program spending on males, * 2017

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Common uses</th>
<th>TPS (C$ millions)</th>
<th>Proportion of TPS (%)</th>
<th>Rate of use (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour necrosis factor alpha inhibitors (anti-TNF drugs)</td>
<td>Rheumatoid arthritis, inflammatory bowel disease, Crohn’s disease</td>
<td>534.8</td>
<td>8.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Antivirals for treatment of hepatitis C infections*</td>
<td>Hepatitis C</td>
<td>430.0</td>
<td>6.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Antineovascularization agents*</td>
<td>Age-related macular degeneration, secondary and diabetic macular edema</td>
<td>259.9</td>
<td>3.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Other antipsychotics</td>
<td>Schizophrenia, bipolar disorder</td>
<td>193.8</td>
<td>2.9</td>
<td>2.4</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors (statins)</td>
<td>High cholesterol</td>
<td>192.8</td>
<td>2.9</td>
<td>34.0</td>
</tr>
<tr>
<td>Oral protein kinase inhibitors</td>
<td>Various types of cancer</td>
<td>173.2</td>
<td>2.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Other immunosuppressants</td>
<td>Rheumatoid arthritis, renal transplant, multiple myeloma</td>
<td>150.6</td>
<td>2.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Antivirals for treatment of HIV infections, combinations</td>
<td>HIV</td>
<td>145.8</td>
<td>2.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics</td>
<td>Asthma, emphysema, chronic bronchitis</td>
<td>137.0</td>
<td>2.1</td>
<td>4.3</td>
</tr>
<tr>
<td>Direct factor Xa inhibitors</td>
<td>Venous thromboembolism, stroke prevention, deep vein thrombosis prevention</td>
<td>138.9</td>
<td>2.1</td>
<td>3.4</td>
</tr>
<tr>
<td>Combined top 10</td>
<td></td>
<td>2,354.8</td>
<td>35.8</td>
<td>n/a</td>
</tr>
</tbody>
</table>
What is the most expensive cancer drug? (excluding CAR-T cell therapy)
### Table 2: Top Ten Anti-Cancer Drugs by Cost

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication(s) (NOC or NOC/c)</th>
<th>Route</th>
<th>Schedule</th>
<th>Dose[^1]</th>
<th>Cost per 28 days (CAD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotuzumab ozogamicin</td>
<td>ALL[^1]</td>
<td>IV</td>
<td>Variable</td>
<td>Variable</td>
<td>$43,217.55 to $57,623.40</td>
</tr>
<tr>
<td>Blinatumomab</td>
<td>ALL[^1]</td>
<td>IV</td>
<td>Daily (days 1-28)</td>
<td>Variable</td>
<td>$47,648 to $55,589.33</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>Melanoma</td>
<td>IV</td>
<td>Q21days</td>
<td>3mg/kg</td>
<td>$38,666.67</td>
</tr>
<tr>
<td>Daratumomab</td>
<td>Multiple Myeloma</td>
<td>IV</td>
<td>Variable</td>
<td>16 mg/kg</td>
<td>$7,176.24 to $28,704.96</td>
</tr>
<tr>
<td>Carfilizomib</td>
<td>Multiple Myeloma</td>
<td>IV</td>
<td>Variable</td>
<td>Variable</td>
<td>$15,333.30 to $18,390.96</td>
</tr>
<tr>
<td>Brentuximab vedotin</td>
<td>Hodgkin lymphoma, non-Hodgkin's Lymphoma</td>
<td>IV</td>
<td>Q21days</td>
<td>1.8mg/kg</td>
<td>$16,262.40</td>
</tr>
<tr>
<td>Olaratumab</td>
<td>Sarcoma</td>
<td>IV</td>
<td>Days 1 and 8, Q21 days</td>
<td>15 mg/kg</td>
<td>$13,162.99</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>NSCLC[^3], UC[^4]</td>
<td>IV</td>
<td>Q14days</td>
<td>10 mg/kg</td>
<td>$11,576.90</td>
</tr>
<tr>
<td>Avelumab</td>
<td>MCC[^5]</td>
<td>IV</td>
<td>Q14days</td>
<td>10 mg/kg</td>
<td>$10,600</td>
</tr>
</tbody>
</table>

[^1] Prices reflect pCODR economic analysis. Actual retail price, which include pharmacy retail markup and dispensing fees will vary and may be higher than stated here. Additionally, prices shown accounts for vial wastage.

[^2] Dose per 28 days calculated based on a weight of 70kg and BSA 1.7m[^2]
Components of EA

- Select type of analysis (CUA, CEA, CMA)
- Perspective – Societal; Payer (government), Patient
- Prospective or Retrospective Data Collection
- Costs – direct and indirect medical, lost productivity
- Time Horizon – lifetime; duration of clinical trial
  - What about after trial? Adjuvant – late effects, relapse and treatment
- Outcomes – OS in Phase III trial; (what about PFS in phase II?)
  - How do you value OS with cancer vs. cancer-free? Utilities, QALY
  - What about value of PFS, RR? Time with toxicity?
  - What comparator(s) should be used?
- Discounting – used for valuation of future costs, benefits
- Uncertainty – 95% confidence intervals, sensitivity analyses
Quality Adjusted Life Year (QALY)

- Integrates mortality and morbidity
- QALY = duration of health state * utility score during that health state
- 1 year with disease = fraction of a healthy year
- Considers impact on quality of life
- Considers impact of toxicity
Health Preference (Utility)

- Measure of health preference
  - 1 - perfect health
  - 0 - death
  - Average Canadian 0.92-0.96
  - Changes according to disease state

- Standardized tools available to measure
  - Direct-Time Trade Off, Standard Gamble
  - Indirect-HUI, EQ5D, VAS
Adopting a New Technology

Laupacis et al. CMAJ 1992;146(4):473-81
What do you think is a reasonable ICER ($/QALY)?
Thresholds for Adopting Technology

Laupacis et al. CMAJ 1992;146(4):473-81
Thresholds for Adopting Technology

Oncologists perceive good value at $50K-300K/QALY

Weak: >$100K/QALY

Moderate: $20-100K/QALY

High: <$20K/QALY

Hemodialysis

Laupacis et al. CMAJ 1992;146(4):473-81
Nadler et al. Oncologist 2006; 11(2):90-5
Ubel et al. Health Aff 2012; 31:709-717
## League Table

<table>
<thead>
<tr>
<th>INTERVENTION</th>
<th>COST / life-yr gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow transplant</td>
<td>$220,000</td>
</tr>
<tr>
<td>Inpatient hemodialysis</td>
<td>$54,000</td>
</tr>
<tr>
<td>Neonatal ICU</td>
<td>$30,900</td>
</tr>
<tr>
<td>Automobile airbags</td>
<td>$20,000</td>
</tr>
<tr>
<td>Treatment of mild hypertension</td>
<td>$19,100</td>
</tr>
<tr>
<td>Treatment of severe hypertension</td>
<td>$9,400</td>
</tr>
<tr>
<td>Bypass surgery (left main)</td>
<td>$4,200</td>
</tr>
<tr>
<td>Mandatory smoke detectors</td>
<td>$1,300</td>
</tr>
<tr>
<td>Smoking cessation counselling in men</td>
<td>$705</td>
</tr>
</tbody>
</table>
CEA Criteria for Determining if a Clinical Trial is Appropriate for an Economic Evaluation

- New intervention anticipated to have only a modest therapeutic benefit in a potentially large patient population
- Therapy potentially very costly
- High degree of uncertainty about economic impact of treatment
- Economic evaluation may yield important information in determining routine practice (e.g. equivalence trial)
- Economic data will assist future economic evaluations
- For intergroup trials, suitable number of Canadian patients (100)

Evans et al Chronic Dis Prev 2003
NCIC CTG CO.17: Cetuximab improves survival and quality of life in end-stage advanced colorectal cancer; greatest benefit in KRAS wild type (not KRAS mutant)

A  Entire Study Population (unselected)

No. at Risk
Cetuximab plus best supportive care 287 245 189 136 87 60 37 20 13 4 1
Best supportive care alone 283 235 157 85 58 37 25 11 8 4

B  Wildtype Kras

No. at Risk
Cetuximab plus best supportive care 110 101 88 75 48 32 19 8
Best supportive care alone 105 88 65 34 23 17 12 5

HR 0.77 (95% CI 0.64-0.92) vs. 0.98 (95% CI 0.70-1.37) in KRAS mutation +
Test for interaction p = 0.01

- 69% tumour samples (394/572), similar characteristics to overall population
- 58% KRAS wild type of those tested (230/394), 40% of entire study population

Prospective Cost-Effectiveness Analysis of Cetuximab in Metastatic Colorectal Cancer: Evaluation of National Cancer Institute of Canada Clinical Trials Group CO.17 Trial

Prospective Economic Evaluation (resource utilization, HUI3) of Cetuximab Therapy in the entire study population and KRAS wild type subgroup

ICUR $300,000/QALY

ICUR $187,000/QALY

Entire study population  (n=572)

KRAS wild type  (n=230)

BR.21: Erlotinib v. Placebo in pretreated advanced NSCLC

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Erlotinib (n=488)</th>
<th>Placebo (n=243)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival (mo)</td>
<td>6.7</td>
<td>4.7</td>
</tr>
<tr>
<td>1-year survival (%)</td>
<td>31.2</td>
<td>21.5</td>
</tr>
</tbody>
</table>

RR 8.9%, improved QL

HR=0.70 (95% CI, 0.61-0.86)*

P<0.001†

*From Cox regression model.
†From 2-sided log-rank test.
HR = hazard ratio.

Shepherd et al, Erlotinib in Previously Treated Non-small-Cell Lung Cancer, NEJM, 353;2; 123-132
Mean Costs per Treatment Arm

CAD$

- Erlotinib
- Hospitalization
- Investigations
- Clinic Visits
- Toxicity

Erlotinib vs Placebo
ICER $94,638 CAD/LYG
(95% CI: $52,359 - $429,148/LYG)
# Forest Plot: Survival in BR.21 by Selected Clinical and Molecular Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>HR</th>
<th>ICER $ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>731</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>146</td>
<td>0.42</td>
<td>$39,487 ($29,963-$68,018)</td>
</tr>
<tr>
<td>Current/Exsmoker</td>
<td>545</td>
<td>0.87</td>
<td>$504,911 (-$3,149,228-$3,122,895)</td>
</tr>
<tr>
<td>1 prior regimen</td>
<td>364</td>
<td>0.76</td>
<td>$67,844 ($39,220 - $330,026)</td>
</tr>
<tr>
<td>2 prior regimens</td>
<td>367</td>
<td>0.75</td>
<td>$110,411 (-$816,326 - $1,245,117)</td>
</tr>
<tr>
<td>EGFR mutation</td>
<td>34</td>
<td>0.55</td>
<td>$138,168 (-$1,125,890-$1,377,049)</td>
</tr>
<tr>
<td>EGFR wild type</td>
<td>170</td>
<td>0.74</td>
<td>$87,994 (-$833,900-$706,634)</td>
</tr>
<tr>
<td>EGFR high copy</td>
<td>61</td>
<td>0.43</td>
<td>$33,353 (-$91,232-$384,569)</td>
</tr>
<tr>
<td>EGFR low copy</td>
<td>98</td>
<td>0.80</td>
<td>$109,792 (-$834,935-$831,854)</td>
</tr>
<tr>
<td>KRAS mutation</td>
<td>30</td>
<td>1.67</td>
<td></td>
</tr>
<tr>
<td>KRAS wild type</td>
<td>176</td>
<td>0.69</td>
<td>$76,657 (-$470,406 - $645,461)</td>
</tr>
</tbody>
</table>
Economic analysis of a randomized phase III trial of gemcitabine plus vinorelbine compared with cisplatin plus vinorelbine or cisplatin plus gemcitabine for advanced non-small-cell lung cancer (Italian GEMVIN3/NCIC CTG BR14 trial)

M. Neil Reaume *,1,2,3, Natasha B. Leigh1,2,4, Nicole Mittmann2,5, Doug Coyle2,6, Vera Hirsh2,7, Lesley Seymour2, Dongsheng Tu2, Frances A. Shepherd2,4, Barbara Graham2, Cesare Gridelli8, Francesco Perrone8, Massimo Di Maio8, Penelope A. Bradbury2, William K. Evans2,9

NCIC Clinical Trials Group, 10 Stuart Street, Kingston, Ontario, K7L 3N6, Canada
<table>
<thead>
<tr>
<th></th>
<th>GEMVIN</th>
<th>PG</th>
<th>PV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Entire study (n=246)</td>
<td>Canadian subset (n=43)</td>
<td>Entire study (n=123)</td>
</tr>
<tr>
<td>Mean number of cycles</td>
<td>3.9</td>
<td>4.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Drug Costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>$4420</td>
<td>$4873</td>
<td>$3500</td>
</tr>
<tr>
<td>2013</td>
<td>$720</td>
<td>$794</td>
<td>$684</td>
</tr>
<tr>
<td>Treatment Administration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>$1710</td>
<td>$1885</td>
<td>$1531</td>
</tr>
<tr>
<td>2013</td>
<td>$2047</td>
<td>$2190</td>
<td>$1806</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>$406</td>
<td>$448</td>
<td>$396</td>
</tr>
<tr>
<td>2013</td>
<td>$418</td>
<td>$576</td>
<td>$465</td>
</tr>
<tr>
<td>Toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>$332</td>
<td>$453</td>
<td>$937</td>
</tr>
<tr>
<td>2013</td>
<td>$397</td>
<td>$521</td>
<td>$1116</td>
</tr>
<tr>
<td>Total cost</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>$6868</td>
<td>$7659</td>
<td>$6363</td>
</tr>
<tr>
<td>2013</td>
<td>$3583</td>
<td>$4081</td>
<td>$4071</td>
</tr>
<tr>
<td>Incremental cost per cycle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>$537</td>
<td>$416</td>
<td>$451</td>
</tr>
<tr>
<td>2013</td>
<td>$132</td>
<td>$189</td>
<td>$19</td>
</tr>
<tr>
<td>Total incremental cost</td>
<td>$2218</td>
<td>$2336</td>
<td>$1713</td>
</tr>
</tbody>
</table>

GEMVIN = gemcitabine + vinorelbine. PV = cisplatin + vinorelbine. PG = cisplatin + gemcitabine.

Raymond Ng, Baktiar Hasan, Nicole Mittmann, Marie Floescu, Frances A. Shepherd, Keyue Ding, Charles Andrew Butts, Yvon Cormier, Gail Darling, Glenwood D. Goss, Richard Inculet, Lesley Seymour, Timothy L. Winton, William K. Evans, and Natasha B. Leigh
5yr Incremental survival gain 15%
ICER $7175/LYG

Fig 2. Tornado plot of sensitivity analysis of incremental cost-effectiveness ratio (ICER) based on 20% addition/discount.
CEA Initiative to Consider Cancer as a “Special Case” in Health Technology Assessment

- Specific challenges are often encountered in oncology economic evaluations
  - choice of outcome to be used (e.g., overall survival [OS] versus other measures of disease control, such as progression-free survival);
  - the best method to estimate survival gain (e.g., mean survival, median survival, area under the curve);
  - time horizon, especially because most clinical trials report early results;
  - which toxicities to include in the resource utilization data (e.g., mild versus severe);
  - which perspective to take (e.g., the perspective of the payer in a publicly funded federal/provincial/territorial health care system versus a societal perspective).
Why Interventions Fail Economics 101…

- Cost: ICER, budget impact too high (>70-100K/QALY)
- Benefits – not enough clinical benefit (survival); sometimes not enough advocacy…
- Methodologic/Process Issues
  - Pharmacoeconomic submission poor quality
  - Clinical data hard (for non-oncologists) to interpret
    - outcome not OS but surrogate (PFS, RR) – how to value?
    - Trial design – Phase II not III, crossover allowed, outdated/wrong comparator
    - Unpublished data or abstract/ASCO presentation only
Economic Analyses in Clinical Trials

- Important addition to strengthen, complement results of ongoing clinical trials
- Helps clinicians, patients and policy-makers interpret value of novel interventions
- Critical part of Canadian oncology drug funding process (pan Canadian Oncology Drug Review)
- Timely economic evaluation of CTG interventions may facilitate uptake of novel therapies
Thank you
Questions?
nreaume@toh.ca
@NeilReaumeMD