Economic Analyses in Clinical Trials

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Financial Disclosures

- Research Funding – Novartis
Learning Objectives

- Review concepts including:
  - Cost effectiveness
  - Cost utility
  - Cost minimization
  - Incremental cost effectiveness ratio (ICER)

- Review criteria for inclusion of economic analysis alongside clinical trial

- To understand the impact of molecular testing on design of economic analyses
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
Top-10 Therapeutic Classes by Drug Cost, 2007/08

Cardiovascular Drugs: $1039M
Central Nervous System Drugs: $484M
Gastrointestinal Drugs: $300M
Autonomic Agents: $238M
Hormones & Substitutes: $178M
Anti-Infective Agents: $141M
Antineoplastic Agents: $124M
Blood Formation and Coagulation: $68M
Eye, Ear, Nose & Throat Prep.: $60M
Skin & Mucous Membrane Prep.: $32M

Total Drug Cost: $3.2B

NDFP 2011/2: $449M

48% of Total Drug Cost: $286M

* Does not include New Drug Funding Program (NDFP) expenditures, administered on behalf of the MOHLTC by Cancer Care Ontario (CCO). For 2007/2008 NDFP expenditures = $162.5 million
BCCA: Projected Growth in Provincial Drug Costs ($ Millions)
“First one on when the music stops gets today’s hip operation.”
Types of Economic Evaluation

- **Cost-effectiveness analysis (CEA)** — outcome measured units, e.g. life-years gained or clinical event avoided; sometimes used to refer to all economic evaluations.

- **Cost-utility analysis (CUA)** — outcome measured in terms of health-related preference or value, e.g. quality-adjusted life-years (QALYs).

- **Cost-benefit analysis (CBA)** — values net benefits and opportunity costs in monetary terms.

- **Cost-minimiziation analysis (CMA)** — Outcomes of intervention & alternatives are considered equivalent; alternative with lowest cost is selected.

- **Cost-consequence analysis (CCA)** — costs and outcomes are listed separately in a disaggregated format, (no ICER).
Incremental Cost Effectiveness Ratio (ICER)

- $\Delta$ cost between option A and option B / $\Delta$ benefit
- Treatment A costs $10,000 - B $8,000/A improves survival by 1 year, quality-adjusted survival by 0.8 yrs
- ICER – $2,000/LYG; $2,500/QALY
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
Thresholds for Adopting Technology

New intervention less effective, more costly
New intervention more effective, more costly
New intervention less effective, less costly
New intervention more effective, less costly

Weak CE: >$100K/QALY
Moderate CE: $20-100K/QALY
High CE: <$20K/QALY

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

- **Weak**: >$100K/QALY
- **Moderate**: $20-100K/QALY
- **High**: <$20K/QALY

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

- $50K USD/QALY (1973) Hemodialysis

Laupacis *et al.* CMAJ 1992;146(4):473-81
Earle *et al.* J Clin Oncol 2000;18:3302-17
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>
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</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
NCI C 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)

- 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 Economic Evaluation (resource utilization, HUI 3) 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)

"Tests on rats show that if you pay for these drugs through the nose, the effect increases dramatically."
BR.21: Erlotinib v. Placebo in pretreated advanced NSCLC
Overall Survival

Survival distribution function

Erlotinib
Placebo

<table>
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<tr>
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<th>Erlotinib (n=488)</th>
<th>Placebo (n=243)</th>
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<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>
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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

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<tr>
<th>Category</th>
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<th>Placebo</th>
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<td>Hospitalization</td>
<td></td>
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<td>Investigations</td>
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<td>Clinic Visits</td>
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<td>Toxicity</td>
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CAD$
ICER $94,638 CAD/LYG
(95% CI: $52,359 - $429,148/LYG)
## Forest Plot: Survival in BR.21 by Selected Clinical and Molecular Subgroups

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<tr>
<th>Subgroup</th>
<th>N</th>
<th>HR</th>
<th>ICER (Range)</th>
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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
Everyone agrees to help reduce healthcare costs!

I can't afford that diagnosis. Do you have a cheaper one?