Cost-effectiveness and cost-utility analysis accompanying Cancer Clinical trials

NCIC CTG New Investigators Workshop

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Outline

- Background
- Economic analysis along Clinical trials
- Methods for Economic Evaluation
- Cost-effectiveness Analysis
  -- Analysis of Cost and Effect
  -- Handling of incomplete cost data
  -- Estimate of ICER and Assess the uncertainty
- Cost-Utility analysis
- Relevant issues in analysis and report Cost-effectiveness analysis

Background: Why Economic Evaluation

- Increasing cost in drug development results in high drug cost
- Increasing health care costs
- Regulators, providers, payers, and patients have begun to question the value for the cost of individual medical therapies
- Decision to obtain the greatest Improvement in Health possible with the limited resources available

  - Measure Health gain of the Population via Outcomes

  - Compare Costs and Outcomes in an Effort to Maximize Value

  -- Evidence of cost-effectiveness as part of pricing and reimbursement decision

Economic analysis alongside Clinical trials

- Growing trends in incorporation of economic evaluation within randomized controlled clinical trials of medical therapies (Piggyback evaluation)
- Most often these evaluations are incorporated into the drug development process

  -- When evaluate a drug's safety and efficacy prior to regulatory approval (Phase II and III)

  -- After approval in Phase IV.
- A number of national regulatory bodies have indicated they are comfortable with economic evidence derived from trials (Although asking for it to be tailored to their need)

Methods for Economic Evaluation

Evaluation method	**Outcome Valuation**
Cost-minimization $\Delta_e \sim 0$	Multiple outcomes in natural units – examine cost difference between equivalent therapies.
Cost-effectiveness $\Delta_e > 0$	Evaluate of efficiency/effectiveness of a new therapy– Additional cost per unit of gained benefit (LYs)
Cost-utility $\Delta_e > 0$	Multiple outcomes combined: Additional cost per unit of gained of the adjusted benefit (e.g., QALYs)
Cost-benefit $\Delta_e > 0$	Net monetary benefit (NMB)

Cost Effectiveness Analysis

- Cost Effectiveness Analysis (CEA) is a type of economic evaluation that examine both the costs and outcomes of alternative therapies.
- Costs are expressed in monetary terms

- Benefits are expressed in “natural units” of health outcome, e.g., “cases prevented”, “life-years saved”, etc.

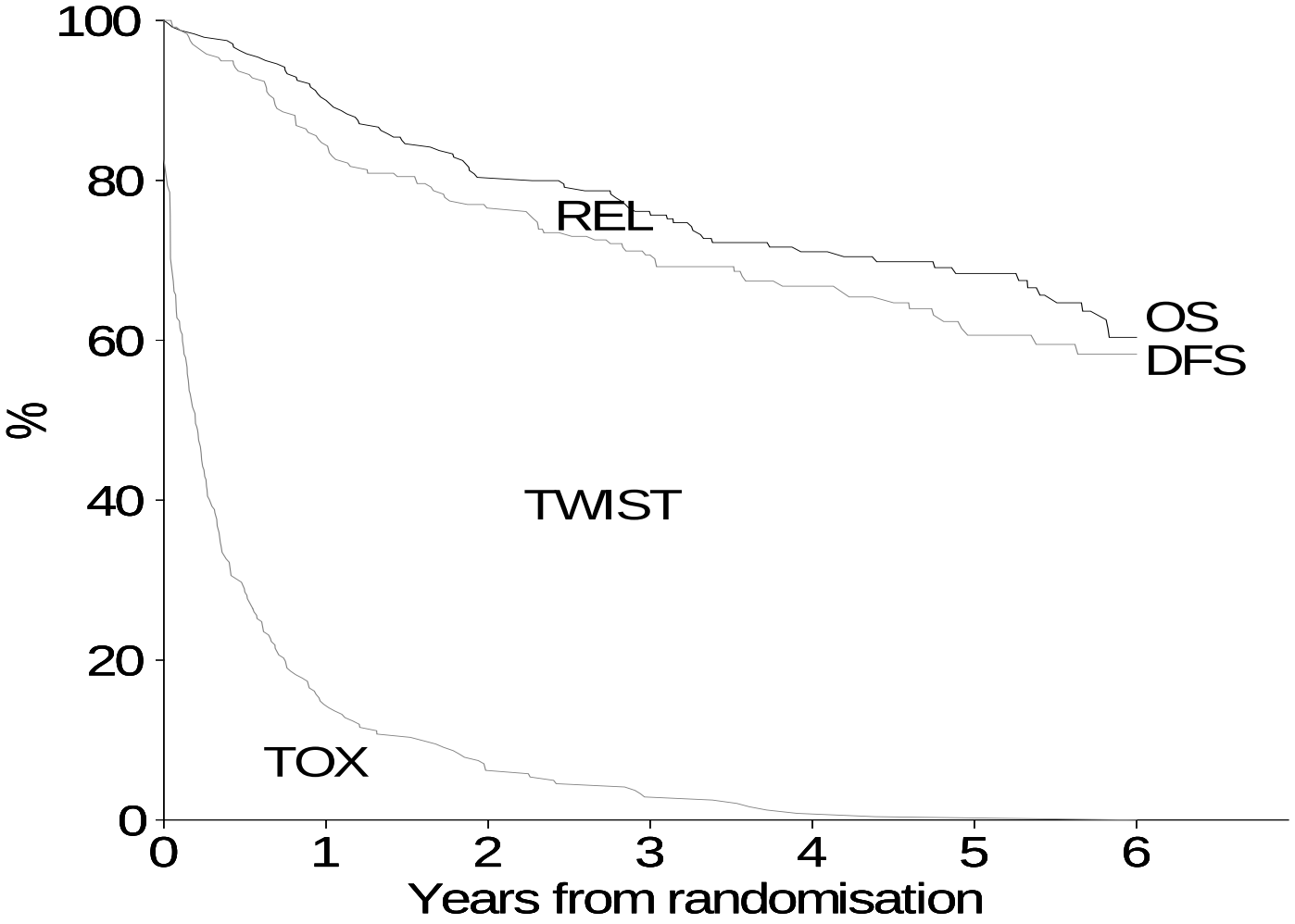
- Measure of cost-effectiveness of new over standard: Incremental Cost Effectiveness Ratio (ICER) -> $\Delta C/\Delta E$; e.g. incremental Cost divided by additional life-years gained (or other measure of benefit)

Cost Utility Analysis

- Costs are expressed in monetary terms
- Benefits are expressed in quality-adjusted "natural units," e.g., quality adjusted life-years
- Incremental Cost Utility Ratio (ICUR) -> Incremental Cost divided by Incremental Quality Adjusted Life Years gained

Cost Utility Analysis

- **Cisplatin + Vinorelbine group**



$Q\text{-}_{TWIST} = U_{TOX}*Tox + TWiST + U_{REL}*REL$

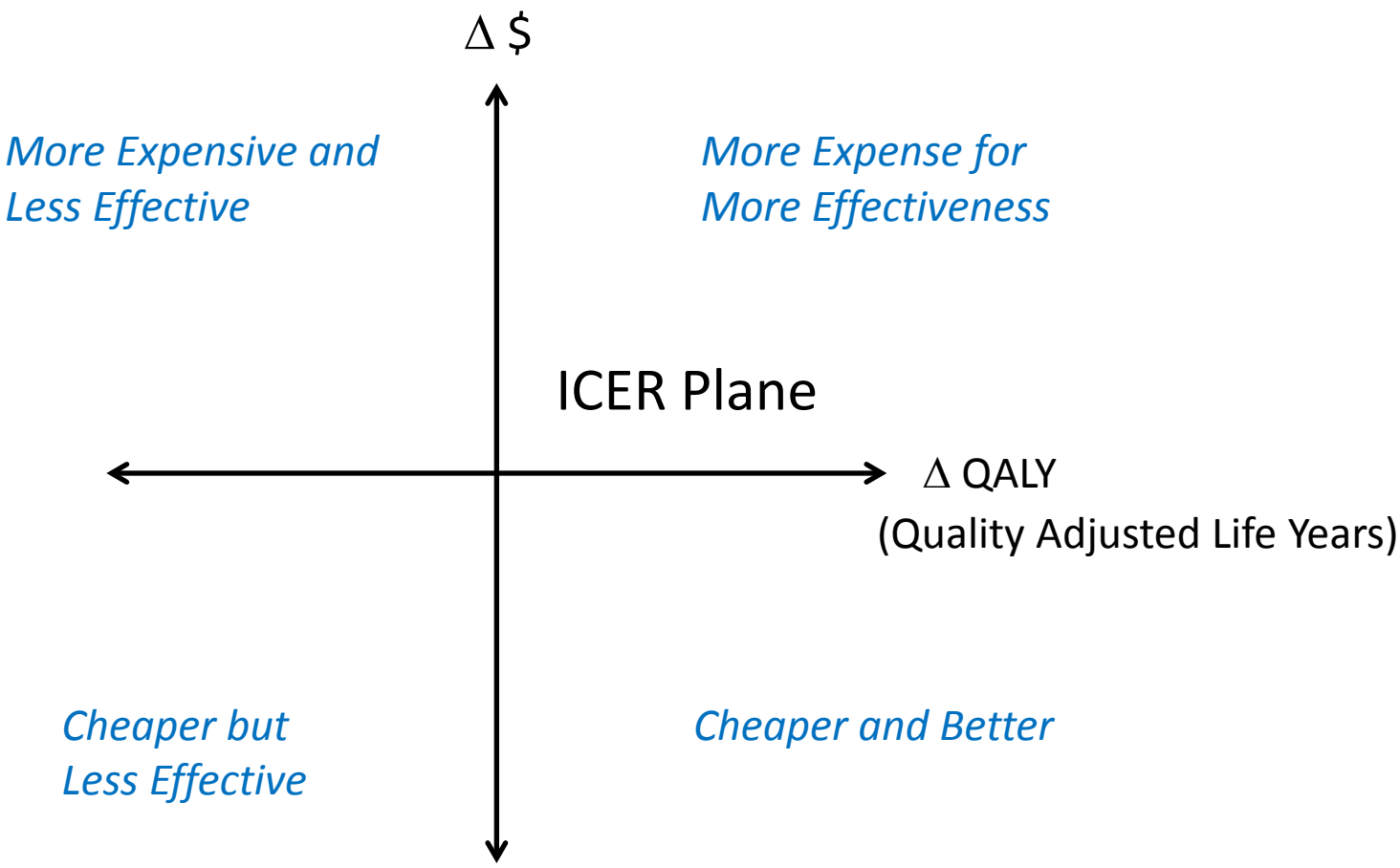
EQ5

Incremental Cost Effectiveness (or Utility) Ratios

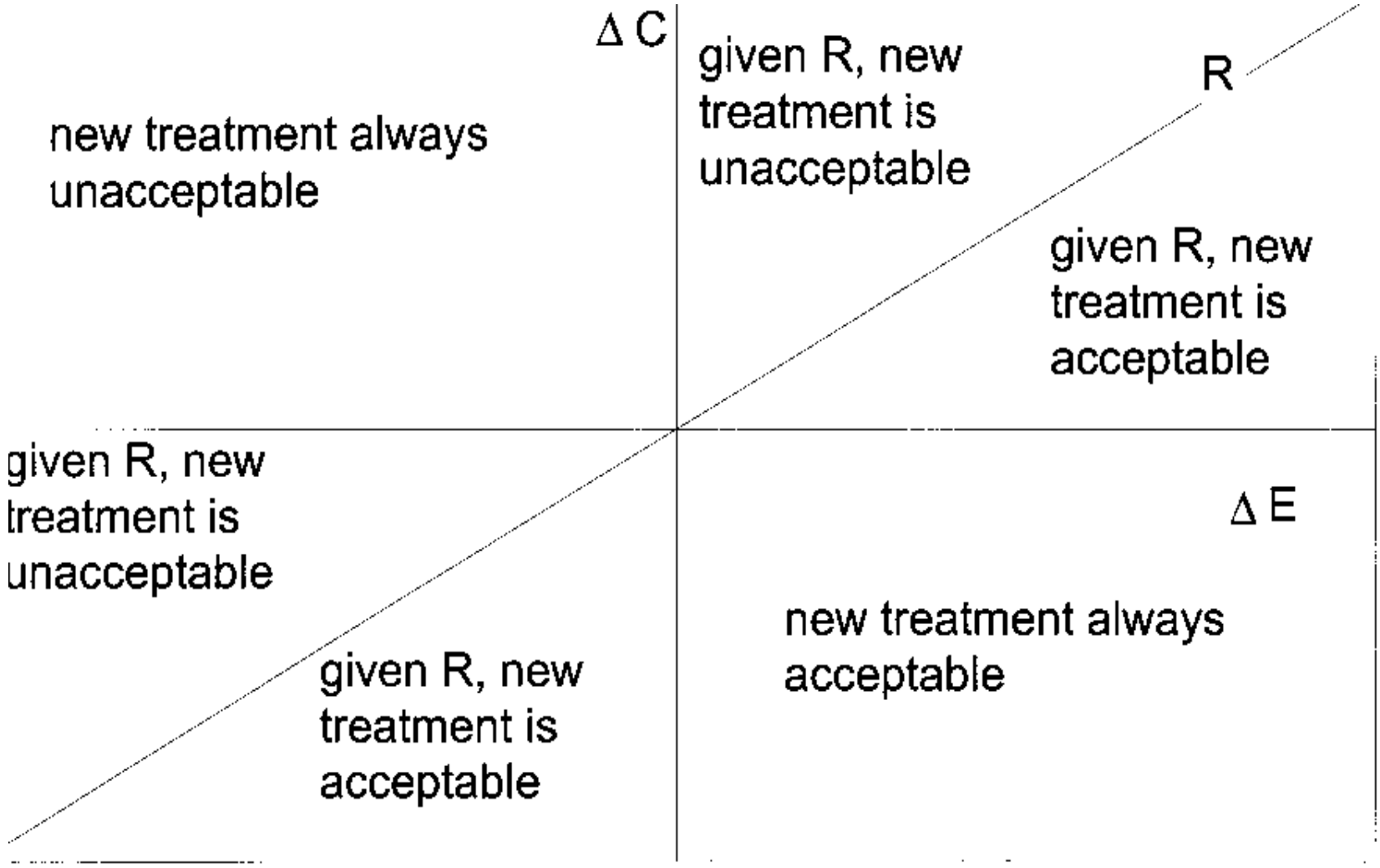
- Let C_a and C_b be the costs of Intervention a and Intervention b;
- Let E_a and E_b be the health effects of Intervention a and Intervention b;
- Intervention a is often defined as status quo or standard treatment.
- $ICER = [C_b - C_a] / [E_b - E_a]$

Note: This is the equation for the slope of a line when E is the horizontal axis and C is the vertical axis

ICER Plane


Δ $
More Expensive and
Less Effective
More Expense for
More Effectiveness
ICER Plane
Δ QALY
(Quality Adjusted Life Years)
Cheaper but
Less Effective
Cheaper and Better

ΔC : ΔE Plane


Δ C
given R, new treatment is unacceptable
R
new treatment always unacceptable
given R, new treatment is acceptable
given R, new treatment is unacceptable
Δ E
new treatment always acceptable
given R, new treatment is acceptable

Advantage of CEA over CBA and CUA

- CBA: assigned dollar values to the outcomes to the new treatment
- CEA is less time- and resource- intensive
- Easy to understand
- More readily suited to decision making

When to use CEA

- Interventions with shared goals, identifying which is more effective
- A specific population: CEA not generalizable to all populations
- Sound evidence of efficacy: CEA justify efficiency of a new trt, provide backing for a switch from one to the other
- Possible Inefficient Treatment: CEA can be used for evidence of a Treatment that are wasting resources.

Steps in Economic evaluation

- Quantify the Cost of care
- Quantify outcomes
- Assess whether and by how much average costs and outcomes differ among the treatment groups
- Estimate and Compare magnitude of difference in costs and outcomes and evaluate “value for cost” (e.g. a cost-effectiveness ratio)
- Evaluate sampling uncertainty and perform sensitivity analysis
- Assessing ICER as a function of the Social Value of health – the Cost Effective Acceptability Curve

Quantify the Cost of care

- Cost ((in term of amount of money)

  -- Direct medical costs (Drugs, Hospitalization, Physicians and other medical care givers, Lab testing, et al.)

  -- Direct Non-medical costs (Travel and accommodation, family care, et al.)

  -- Indirect Costs: Cost of lost or reduced productivity resulting from morbidity or premature mortality due to a medical condition or treatment (Work loss, lost productivity at work, premature death)

  -- Intangible costs: Cost assigned to amount of suffering due to the disease or treatment (Pain, inconvenience, suffering et al.)

Quantify the Cost of care

- Discounting of Costs

-- A procedure used in economic analysis to express as “present values” those costs and benefits that will occur in future years

1. Individuals prefer to receive benefit today rather than future

2. Resource invested today in alternative programs could earn a return over time

3. Range from 0 to 10%, 3% and 5% are commonly used

Analysis of Costs

- Cost data

  -- Common feature of cost data is right-skewness (i.e., long, heavy, right tails)

  -- Data tend to be skewed because:

  1. Can not have negative costs

  2. Most severe cases may require substantially more services than less severe cases

  3. Certain events, which can be very expensive, occur in a relatively small number of patients

  4. A minority of patients are responsible for a high proportion of health care costs

  -- Implication: Non-normality of data pose problems for common parametric tests and estimation.

Policy-relevant Summary statistic of Costs

- Summary Statistic of Interest: Arithmetic Means of Costs
- The arithmetic mean is the important summary statistic for CEA from both the budgetary and social perspective

  – Budgetary: Allows decision makers such as hospitals, private insurers, or governments to calculate the total cost of adopting a therapy and the total effect received in return for incurring this cost

  – Social: Minimization of the arithmetic mean cost and maximization of the arithmetic mean effect yields social efficiency

  -- The difference in the sample means is an unbiased estimate of the parameter of interest.

Quantify outcomes (Effects)

- Primary endpoint of clinical trials: Practice changing outcomes.
- Different disease setting with different outcomes

  -- e.g. Cancer clinical trial, overall survival, Disease relapse free survival, et al.
- Summary statistic of efficacy (relative difference) used in Clinical trial may be different that of effect (Absolute difference) in economic evaluation.
- Summary statistic for economic evaluation: Mean in unit of effectiveness.(Restricted mean, AUC of K-M curves for OS)

Summary statistic of effectiveness

- Summary statistic for economic evaluation:

  Mean of effectiveness.
- Composite endpoints: e.g. time to event /Binary endpoint with fatal and nonfatal events

  -- Different outcomes are rarely of equal importance: Weighting endpoints, weighted average
- QALYs: Weighting the time in different health states: e.g. Cancer clinical trial, time with toxicities, time without toxicities and disease progress, time with progressed disease. Summary statistic for economic evaluation: Weighted (Utility index, EQ5) average of time in each health state.

Comparison of costs and outcomes between the treatment groups

- Starting point: t-test and 1–way ANOVA

-- Lack of normality of cost data does not necessarily rule out use of t-tests, ANOVA, and regression analysis

– In large samples t-tests have been shown to be robust to violations of this assumption when:

  - Samples are of similar size and skewness
  - Skewness is not too extreme

Test the difference in total costs, in restricted mean life/QALYs, etc.

- Adopt test of arithmetic means that avoid parametric assumptions.

-- Bootstrap method

1. Estimate the distribution of the observed difference in mean costs
2. Check how likely the mean difference is different from 0 (by evaluating the probability that the observed difference in means is significantly different from 0).

Evaluate the “value for costs”

- ICER = $[C_b – C_a] / [E_b – E_a]$

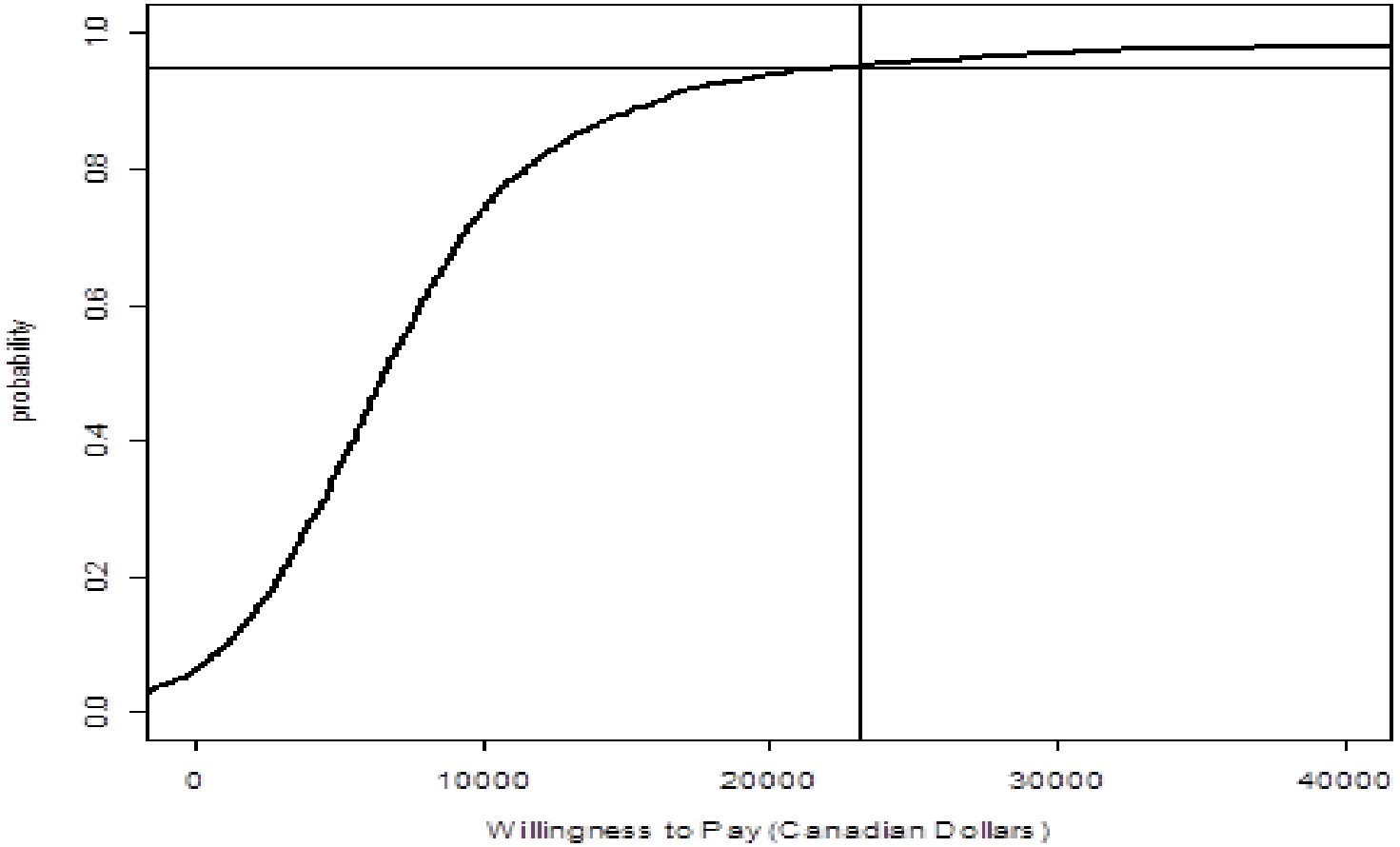
-- Test if the ICER is greater than reference values for social value of health, say, 100’000 for per LYs or QALYs.

-- assessment of uncertainty, C.I. (bootstrap method)

Assessment of uncertainty: Cost Effectiveness Acceptability Curves

- Conduct bootstrap simulation
- Examine all results that fall within 95% confidence intervals for the cost effectiveness ratio
- Compare to reference values for social value of health (V_s) (The value that a society willing to pay for one extra unit of health. It reflects the a society's level of economic wealth and the relative distribution of that wealth to the health sector)
- Calculate probability that: ICER < V_s

Cost Effectiveness Acceptability Curves



Assessment of uncertainty: Sensitivity analysis

- To ascertain how the model depends upon the information fed to it.
- Changing efficacy values (Use Discounted LYs, QALY instead of LYs, or reduce the LYs by certain percentage) and costs (Increase or decrease certain proponent of costs at certain percentage) to see whether change had a significant effect on ICER (point estimate, and 95% C.I.). Identify driving force for ICER.

Other relevant issues

- Analysis population: Intention to treat.

  -- Economic questions relate to treatment decisions (e.g., whether to prescribe a therapy), not whether the patient received the drug prescribed nor whether, once they started the prescribed drug, they were switched to other drugs – Implication: costs and effects associated with these later decisions should be attributed to the initial treatment decision.
- Analytic Time Horizon: The period over which costs and outcomes associated with the intervention accrue. A within-trial assessment of costs and outcomes should be conducted.
- A common real discount rate should be used for future costs and outcomes.
- Subgroup analysis: Prespecified subgroups, factors with significant interaction with treatment
- Missing and/or censored

Missing and/or censoring

- The problem: Missing/censored data pose threats to estimation of costs and efficacy.
- -- Missing/Censoring mechanisms can be:

  * Completely at random: the censored data represent a random sample of all of the data observed in the experiment

  * At random: the censored data represent a random sample of a predictable subsample of the data observed in the experiment

  * Non-ignorable: the censored data are not a random sample of either all of the data or a predictable subsample of the data (i.e., additional data -- most likely from outside the experiment -- are needed to estimate the missing data)

Missing and/or censoring

- Recent methodologic developments - A number of authors have proposed methods for addressing issues posed by missing data

  -- General strategy: Identify observations without censored data that are "similar" to observations with censored data, and use data from the former to represent (censored) data from the latter

  -- Some most cited approaches:

  Lin DY, Feuer EJ,et al. Estimating medical costs from incomplete follow-up data. Biometrics. 1997;53:113-28.

  Bang, H. and Tsiatis, A.A. (2000). Estimating medical costs with censored data, Biometrika, 87, 329-343.

  (methods for data that are missing completely at random).

  2. Lin DY. Linear regression analysis of censored medical costs. Biostatistics. 2000;1:35-47.

  (methods for data that are missing at random).

  -- An alternative approach for imputing data that are missing at random is described by: Lavori PW, Dawson R, Shera D. A multiple imputation strategy for clinical trials with truncation of patient data. Stat Med. 1995;14:1913-25.

Missing and/or censoring

- Different proportion of censoring and /or survival distribution have implication on bias of estimate.
- For high censoring data or heavy tailed survival distribution , regression method yields less biased estimate of mean of costs.

Other issues

- Sample size
- Extrapolation, Projection of Costs and Effects beyond the Time Horizon of the Trial
- Transportability: multination trials, explore the heterogeneity of country's effect
- Multivariable analysis; Adjusted analysis

Elements for reporting a CEA

- A clear study perspective, time frame and analytic time horizon
- An explicitly defined study question
- Relevant assumptions underlying the study
- Detailed description of patients population and the interventions
- Existing evidence of the interventions' efficacy
- Proper identification of all relevant cost

  -- whether include or exclude productivity losses

  -- apply appropriate discount rate

  -- Cost included are relevant to perspective

Elements for reporting a CEA

- An appropriate choice of outcome:

  -- calculate suitable ICER

  -- Report ICER

  -- Conduct sensitive analysis

- A comprehensive discussion of the results:

  -- Deal with issues of concern

  -- address implications of underlying assumptions.

- Ref: Consolidated Health Economic Evaluation Reporting Standards (CHEERS)

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