# The Practice of Cost-Effectiveness Analysis: Designing, Conducting and Interpreting CEA under Non-Ideal Circumstances

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# Overview

- Current Practice of CEA
- Designing and Conducting Your Own CEA
- Interpreting a Published CEA

# Current Practice of CEA

- Academia
  - Reference Case
    - Societal perspective
    - Lifetime Horizon
    - Compare new strategy to gold standard or best alternative
  - TreeAge
- Pharmaceutical-sponsored
  - International Audiences and U.S. MCOs
    - NICE, CADTH, PBAC
    - Third-party payer perspective
    - Non-lifetime horizon
    - Compare new strategy to placebo or to competitor
  - Excel-based

# Designing and Conducting a CEA

# Designing and Conducting a CEA

- Model structure
- Estimating Costs
- Estimating Probabilities
- Obtaining Utility Values
- Sensitivity Analyses

# Model Structure

- Time Horizon
  - Lifetime
  - Long enough to capture the majority of costs & effects
- Perspective
  - Societal
  - Third-party payer
- Markov model
  - Use if patients transition from one health state to another
  - Health states should be collectively exhaustive and mutually exclusive
  - Cycle length should be appropriate for disease in question

# Markov models

- Frequently used in health services or clinical decision making
- Benefit:
  - More reflective of real life; patients do not just stay in one health state
- Drawback:
  - Memory-less quality
  - Does not incorporate the effect of duration of disease
    - - problem with both Markov process and Markov cycle models

  - A patient who had has uncontrolled diabetes for 8 years is more likely to develop diabetic retinopathy than a patient who has had uncontrolled diabetes for 1 year
  - Markov model does not take this into account; would assign singular probability of diabetic retinopathy regardless of the amount of time you have spent in that state
  - Can account for some of this using tunnel states and tracker variables in TreeAge

# Inputs: Estimating Probabilities

- One of the most difficult aspects of a CEA
- Also one of the most important
- Potential Difficulties:
  - Extrapolating beyond time horizon of available data
  - Lack of head-to-head trials
  - Lack of RCT data

# Extrapolating beyond the horizon of existing data

- A clinical trial generally does not have a long enough follow-up to directly populate a CEA
  - E.g., clinical trial lasts for 2 years; your CEA has a a 30-year horizon

- Last Observation Carried Forward (LOCF)
  - Can lead to substantial inaccuracies

- A better approach applies a distribution to derive probability inputs for Years 3-30:
  1. Understand how your data are distributed
     - Normal probability plot, Weibull probability plot, etc
  2. Once you know how your data are organized, you can apply the appropriate distribution to extrapolate beyond the available data

- Run one analysis at the time horizon for which you have observed data inputs, and compare those results to the time horizon that includes the predicted data inputs to see how results vary

# Lack of head-to-head data

- You want to compare Drug A to Drug B
- Evidence exists comparing Drug A to placebo and Drug B to placebo
- It is ill-advised to take Drug A data from one study and Drug B data from another study and plug that directly into your model
- Doing so breaks randomization and introduces bias (e.g., different patient populations)

- Use a Bayesian meta-analysis approach

# Bayesian meta-analysis approach

- Use when you don't have direct comparisons of Drug A to Drug B, but you have an evidence network that links Drug A → common comparator → Drug B

- Use these data and specify a regression model to then compare

  Drug A to Drug B

- This method is sufficiently complex to warrant its own seminar(s)
- Needs the involvement of a Bayesian statistician

# Inputs: Using data from RCTs

- Benefit: Randomization
  - Accounts for observed and unobserved differences in patients across treatment arms
- Drawback:
  - Clinical trial sample often does not reflect the patient population
    - Clinical trials have very strict inclusion/exclusion criteria
  - The clinical trial assesses drug efficacy; the CEA model is evaluating drug effectiveness

# Inputs: Using data from chart review

- Patients not randomized to treatment
- Selection bias
- Propensity scoring can mitigate the effect of selection bias
  - Propensity score: composite variable that minimizes the difference in patient characteristics across groups
    - Use the propensity score to match patients from each group
  - Has its limitations:
    - Need large samples
    - May still have biases – because you are only matching based on observed variables
    - Need a lot of group overlap -- you don't want to compare the worst cases from Group A to the best cases from Group B
- Propensity scoring is not a substitute for randomization!

# Inputs: Cost Estimates

DATA INPUTS

| Category | Non-VA |
|---|---|
| Outpatient | Medicare CPT, MEPS |
| Inpatient | DRG, HCUP |
| Pharmacy | Drug Red Book |

- Medical Care supplement, July 2009, is an excellent source of information on costing and cost sources

# Inputs: Utility Values

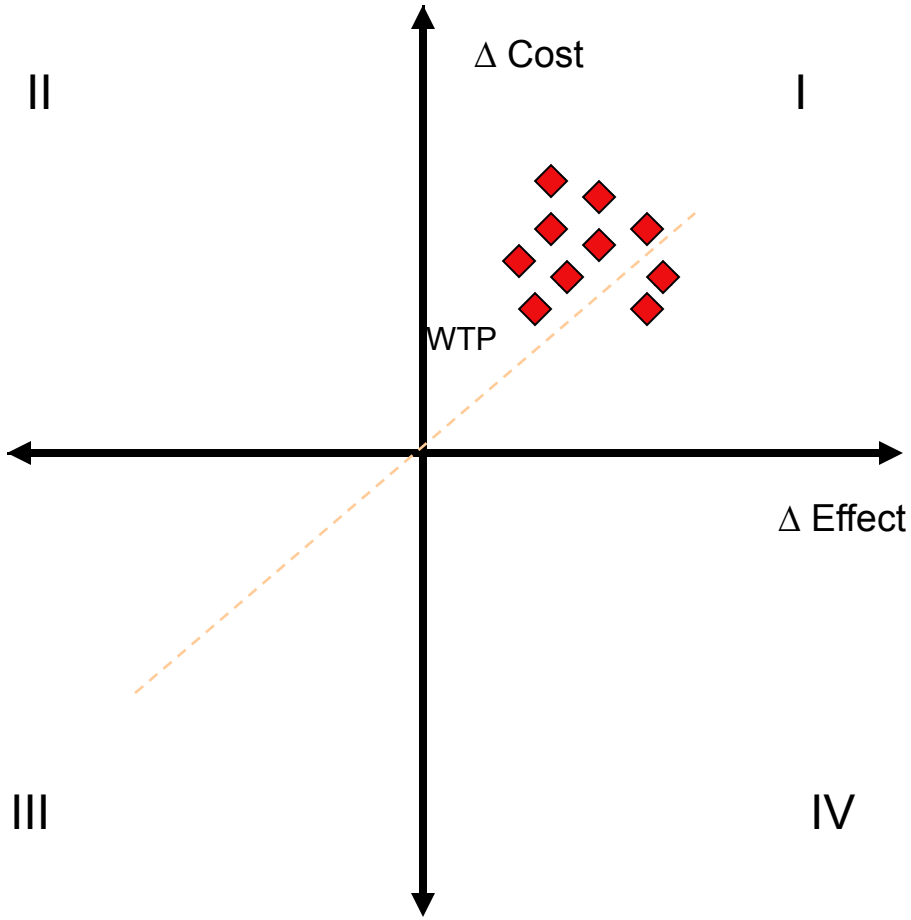
- Utility: patient preference for health
- Disease-specific vs. generic

  - Disease-specific: directly provide utility
    - SG, TTO, VAS
  - Generic: provides HRQoL associated with a general health state; you apply preference weights to derive utility
    - EQ-5D, HUI, QWB, SF-6D
- Patient sample vs. community sample
- Be consistent about whatever method is used to elicit utilities for your CEA

SG: Standard Gamble; TTO: Time Trade-Off; VAS: Visual Analog Scale; HUI: Health Utilities Index; QWB: Quality of Well-Being scale

# CEA Results

- Results come as incremental cost-effectiveness ratios (ICERs) and will fall into one of four quadrants:




Quadrant I: More cost and more effective. May be cost-effective

Quadrant II: More costly and less effective. Do not adopt strategy.

Quadrant III: Less costly and less effective. May be cost-effective

Quadrant IV: Less costly and more effective. Definitely adopt strategy.

# Sensitivity Analyses

Sensitivity analyses:

- One-way
- Multiple-way
- Tornado diagrams

Overall Robustness of Model Results

- Probabilistic Sensitivity Analyses
  - Uncertainty about model parameters, uncertainty about probability estimates

# Interpreting Published Cost-Effectiveness Analyses

# Important Factors to Critique

- Boundaries of the CEA
- Extrapolation Beyond the Evidence Base
- Estimation of Costs
- Estimation of Utilities
- Presentation of Results
- Assessing whether Model Results are Robust

# Boundaries of the CEA: Time Horizon

Short-term:

- Pros:
  - Smaller impact of assumptions regarding clinical estimates
  - Memory-less capacity of Markov models not as much of a problem
- Cons
  - Results may change with a longer time horizon
  - Example: Drug A saves more lives than Drug B, and is also less costly
    - Drug A is cost-saving compared to Drug B in a 2-year horizon
    - Drug A is cost-effective compared to Drug B in a 3-year horizon
  - At 2 years, patients in both arms were living, and Drug A costs less, so it was cost-saving
  - At 3 years, some patients on Drug B began to die. They now incur no treatment costs. Drug A now costs more than Drug B. However, it is still cost effective because it is saving more QALYs than Drug B

# Boundaries of the CEA: Patient Characteristics

- What are the characteristics of the average patient entering the model?
  - Do these characteristics have good face validity?
  - How common are these characteristics in the overall patient population?
  - Would results be different in another population?

# Boundaries of the CEA: Model Perspective

- Is the perspective of the model really what the authors state it is?
  - E.g., a model that does not consider direct non-medical costs does not have a societal perspective

- Models with a non-societal perspective
  - Consider how results would change if direct non-medical or indirect costs were included
    - E.g., Alzheimer's disease -- excluding direct non-medical costs (caregiver costs) would underestimate costs.
    - E.g., Multiple Sclerosis -- excluding indirect costs (productivity) would substantially underestimate costs

# Excluding certain costs

## Direct non-medical (informal caregiver costs)

- If both treatments have roughly the same effect on patients' ability to be independent and patients in each arm live for a similar amount of time, then ICER will not be much affected
- If one treatment results in sig. improvement in patients' ability to be independent, then ICER will be affected, and the exclusion of direct non-medical costs is problematic
  - E.g., Treatment for DME -- Tx A reverses vision loss, Tx B halts vision loss

## Indirect (economic productivity)

- CEAs should include these when
  - The average patient in the model is 18+ or < 65
    - The age of the patient in the model is far younger than retirement age
  - Disease or tx impacts patient productivity at work
  - Disease or tx requires that patient skip work (e.g., chemo, MS)

# Estimating Costs: Present Value

Inflation Adjusting

- Authors should note the base-year of the cost estimate
- If there is a substantial time between the base-year and the inflation-adjusted year (e.g., 2000 to 2009), ask yourself whether the rate of medical inflation in this time period can reasonably apply to this good or service
    - e.g., actual price of good may have decreased the over time

# Extrapolating beyond the empirical base: clinical information

- Clinical Trials as source of information
  - Does the CEA model have a longer time horizon than the clinical trial?
    - Did authors use Last Observation Carried Forward?
    - Did authors specify a distribution?
      - If so, how did they decide on the distribution?
- Chart review as source of information
  - Did they authors use propensity scoring?
  - Was this warranted?

# Estimating beyond the empirical base: Treatments of Interest

If authors used clinical trials as the source of information, did a head-to-head trial exist comparing Treatment A to Treatment B?

- If not, how different are the patient populations in the source data?

# Estimation of Utilities

- Was the measure appropriate?
  - If generic method was used, is it sensitive enough to capture the difference in different health states used for the CEA?
  - If a disease-specific method was used, has it been validated?

- Was the measure consistent?
  - All generic or disease-specific
  - Was a consistent methodology used?
    - All generic: was the same instrument used?
      - All EQ-5D, all HUI, all QWB, all SF-6D
    - All disease-specific:
      - All SG or all TTO or all VAS?
  - Patient or community sample

# Interpreting the results of a CEA: Description of Conclusions

- Results should be couched in terms of comparator
  - Incorrect: Drug A is cost-effective
  - Correct: Drug A is cost-effective compared to Drug B

- Results should be interpreted in light of “average patient” of model
  - Incorrect: Drug A is cost-effective compared to Drug B
  - Correct: Drug A is cost-effective compared to Drug B in the treatment of hypertension in an elderly male U.S. population

# Assessing whether model results are robust

- Was a probabilistic sensitivity analysis preformed?
  - What parameters were varied?
    - How much were these parameters varied?

- Are results robust to the probabilistic sensitivity analysis?

# Conclusion

- CEA can be a very useful tool, but the results of the model depend very much on its assumptions and the way in which model inputs were calculated

- Methods used to create model structure and derive model inputs should be evaluated with a critical eye before the assessing the validity of results

Questions?