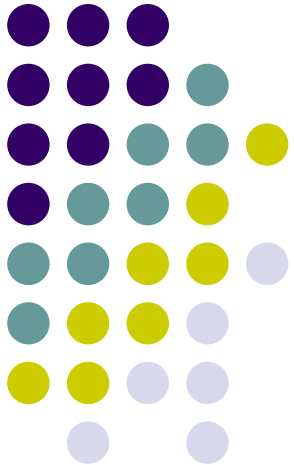
Economic Analysis Alongside Clinical Trials and Observational Studies

AHRQ Workshop
December 6 and 7, 2007
Washington, DC

Deborah Marshall, PhD
Associate Professor, McMaster University and
Vice President, Health Economics, i3 Innovus

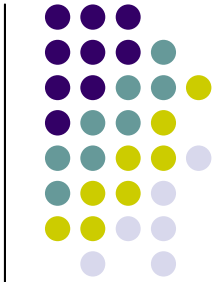
Marg Hux, MSc
Lead Analyst, i3 Innovus



Outline

- Clinical Question vs Health Economic Question
- The Nature of Economic Data
- Comparison of Approaches to Economic Evaluation
- Design and Analysis Issues in Cost-Effectiveness Alongside Trials

The Clinical Question vs The Health Economic Question



	Clinical Trial	Economic Evaluation
Audience	Licensing regulatory authorities and clinicians	Purchasers and payors of health care
Objective	Demonstrate **safety and efficacy**	**'Value for money'** – lowest cost per unit benefit
Outcome Measure	**Efficacy** "Does it work?"	**Effectiveness and Efficiency** "Does it work in real world?" Consider quality of life (QALY)
Comparison	**Choose** Which treatment is better	**Estimate** Incremental cost-effectiveness
Timeframe	Driven by clinical events Intermediate clinical outcome	Long enough to measure 'downstream' consequences Typically longer than clinical study

Clinical vs Economic Data

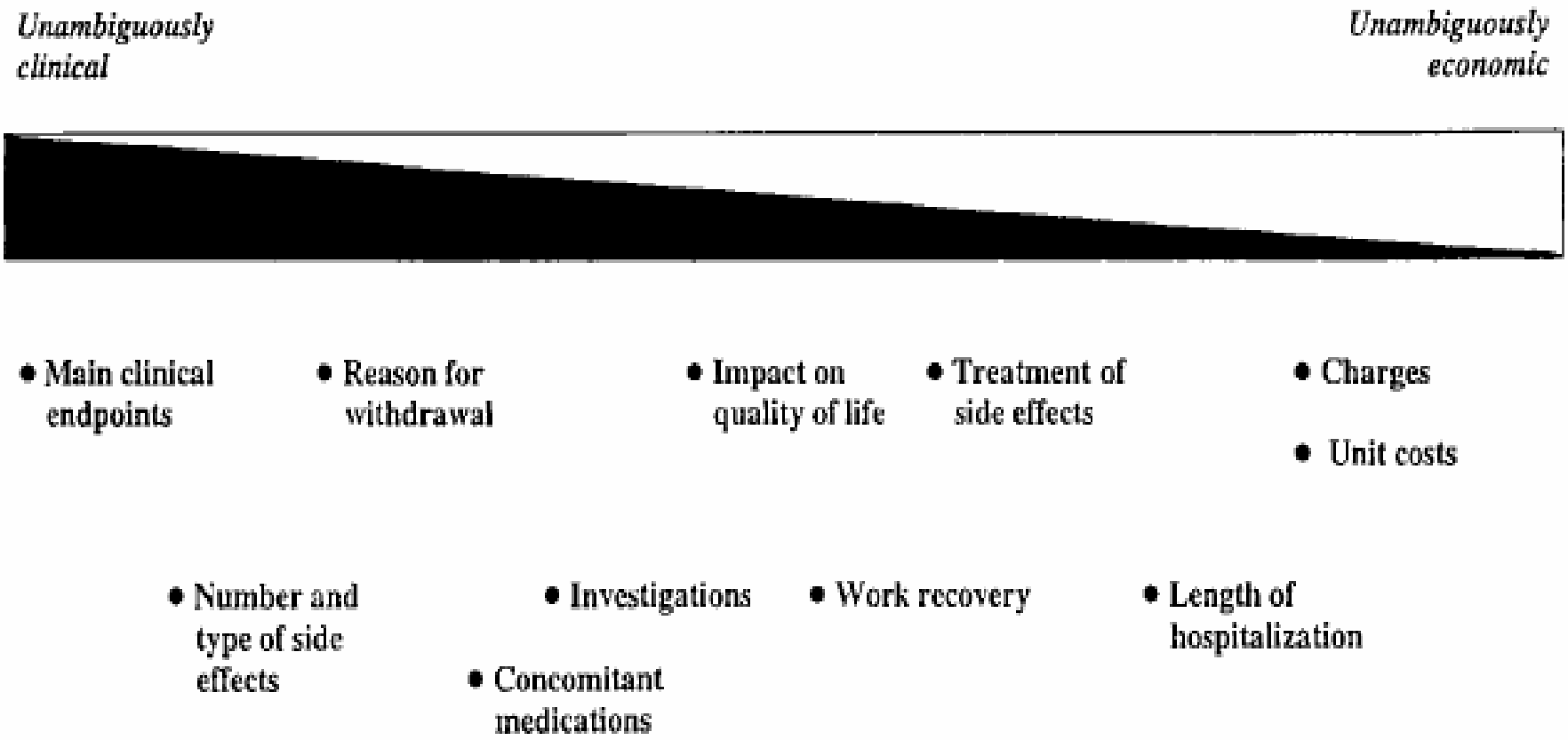
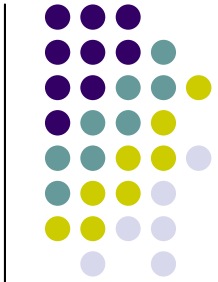


FIGURE 1. Which data items are clinical and which are economic?

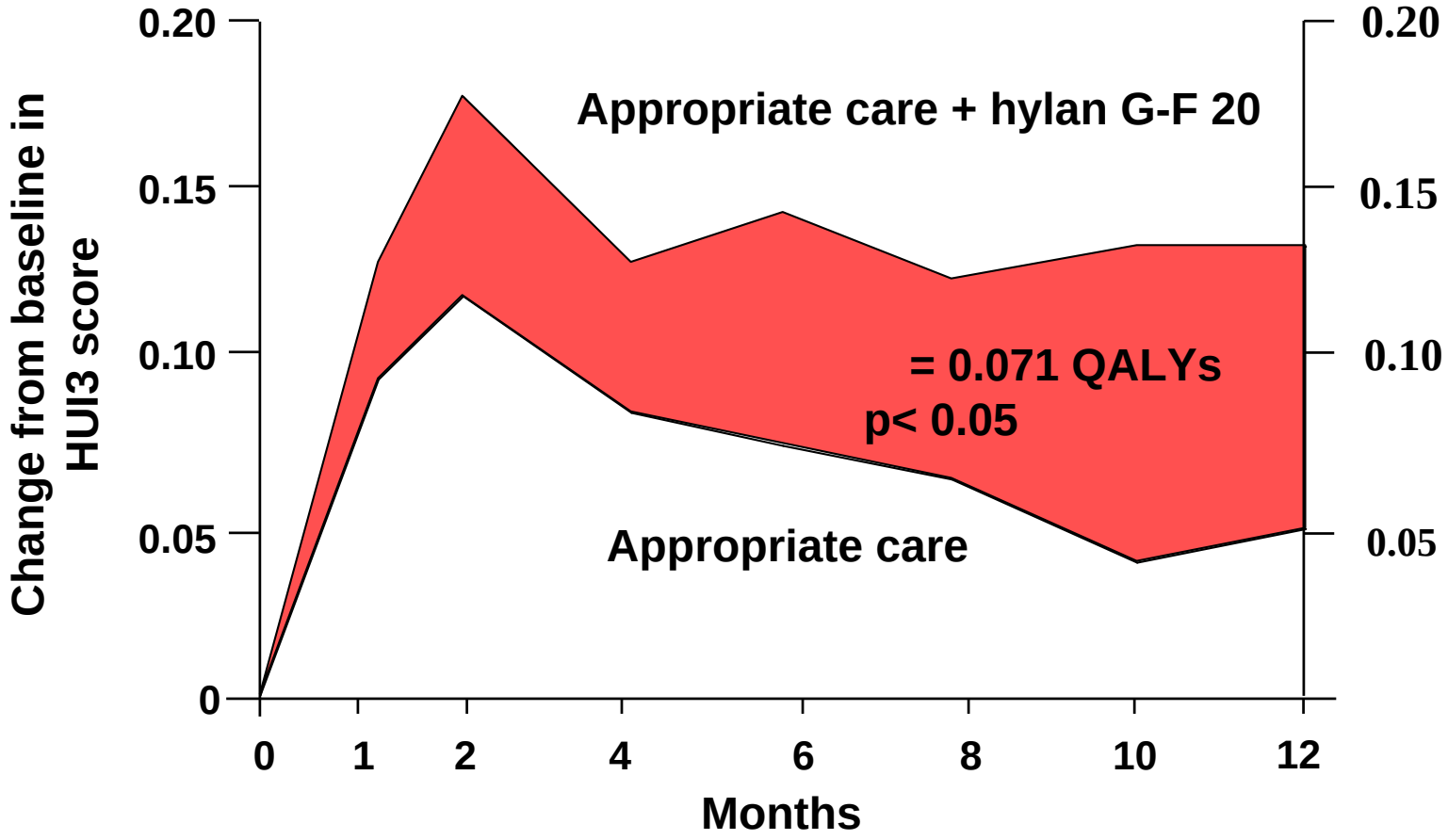
- *Drummond. Med Decis Making 1998;18(2):12-8.*

Nature of Health Economic Data



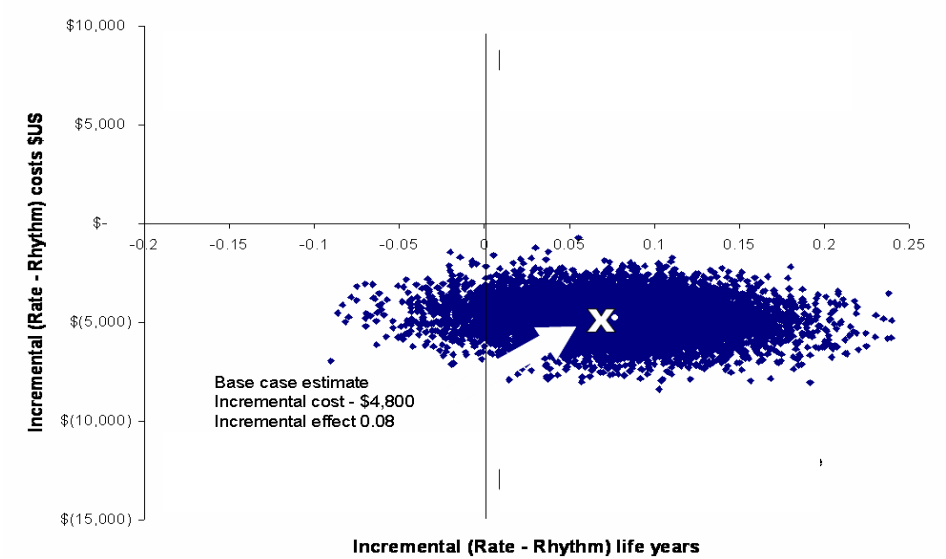
- To Estimate Downstream Effects
  - May need outcomes data beyond trial timeframe
  - May need different outcomes at different frequencies than those in trial (e.g. HRQOL at multiple time points)
- To Estimate Downstream Costs
  - May need resource use data beyond trial timeframe
  - Requires sufficiently detailed information on resource use to estimate total cost (e.g. drug dose, route, frequency)
  - Need to value resource use
- Analysis of Costs
  - Data are usually highly variable and skewed
  - Data are missing
  - Data are censored

Estimating Quality Adjusted Life Years (QALYs)



- *Torrance et al. Osteo Cartilage 2002;10:518-27.*

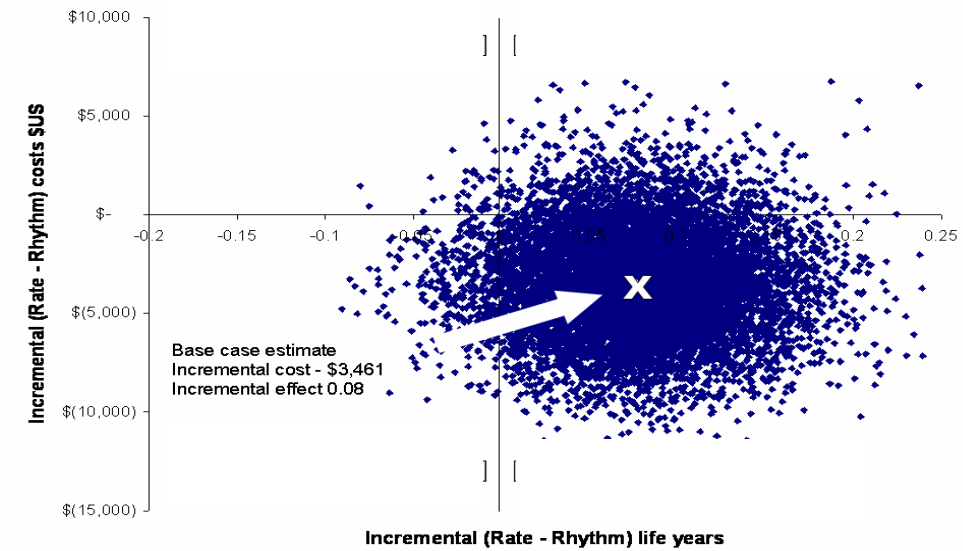
Cost Data are Censored



'Before' – Partial Censoring

Censoring for survival but not costs

Cost = - $4,800



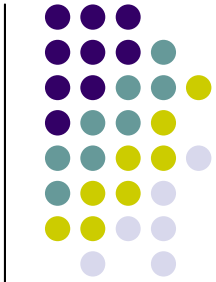
'After' – Full Censoring

Censoring for both survival and costs

Cost = - $3,461

- Fenwick E et al. Value in Health, 2007 (in press).

Incremental Cost-Effectiveness Ratio (ICER) is a Ratio Measure



- Compare treatment (T) and control (C). Adopt T if:

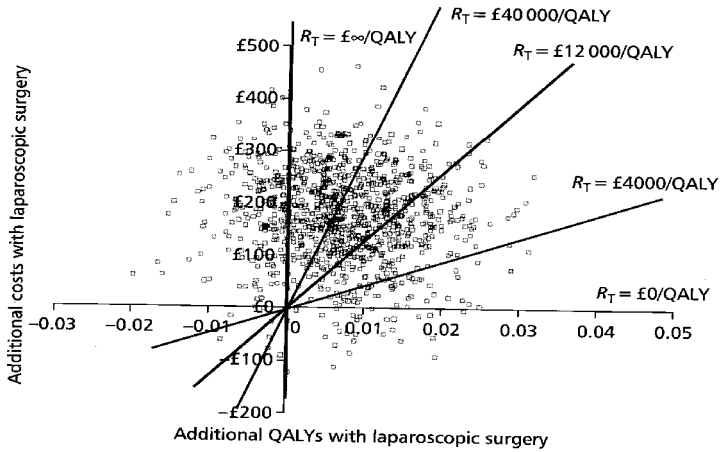
$$ICER = \frac{(C_T - C_C)}{(E_T - E_C)} < \lambda$$

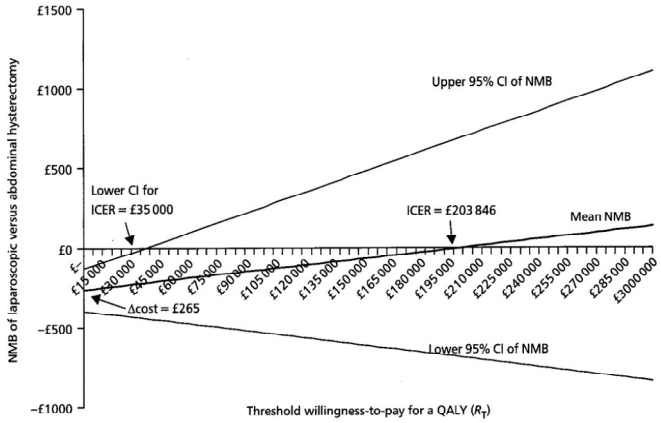
where λ is willingness to pay for one unit of effect

- Problems with ICER:
  1) Negative - uncertainty crosses multiple quadrants
  2) Meaningless – higher costs and lower effects OR lower costs and higher effects – dominant results
  3) Undefined – if difference in effects is zero
  4) Representing uncertainty – need joint estimate of variability

-Drummond MF et al. Methods for the Economic Evaluation of Health Care Programmes, 2005
-Willan AR and Briggs AH. Statistical Analysis of Cost-Effectiveness Data. Wiley, 2006

Representing Uncertainty
Joint Variability for Costs and Effects





1. **Cost-effectiveness plane**

   No significant difference in costs or effects

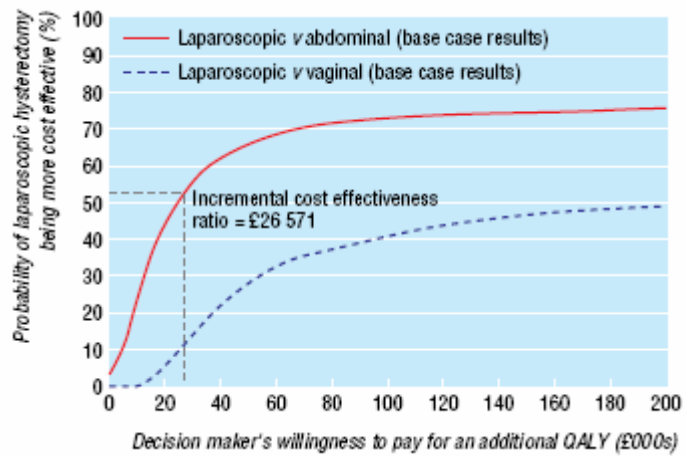
2. **Incremental Net Benefit (INB)**

   Transform ICER into a single metric

$$INB = (E_T - E_C).\lambda - (C_T - C_C)$$

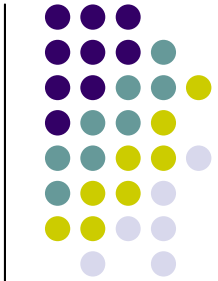
3. **Cost-effectiveness Acceptability Curve (CEAC)**

   Probability cost-effective



- *Sculpher M et al.* BMJ, 328:134-40.
- *Claxton K et al, Health Econ 2005;14:339*

Opportunities for Economic Evaluation using Prospective Data



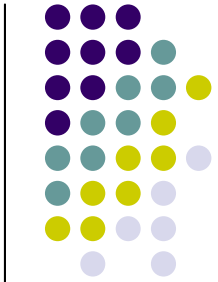
- Observational Study
  - Identify patient cohorts and extract data from existing dataset or collect data prospectively

- Trial-Based
  - 'Piggyback' study - Concurrent evaluation within context of RCT where economic evaluation is secondary objective
  - 'Pragmatic' study - Evaluate effectiveness of intervention under real-world conditions similar to routine practice *(Tunis et al JAMA 2003;290:1624)*

Summary of Prospective Approaches

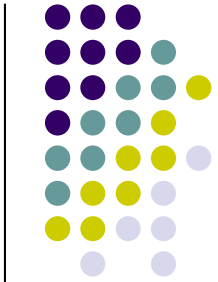
	Observational Study	Pragmatic Economic Trial	Piggyback on Clinical Trial
Context	Database analysis or cohort study	Comparative real-world RCT	Comparative clinical RCT
Design	Prospective or retrospective non-interventional	Prospective interventional	Prospective interventional
Validity	Low internal High external	Medium internal High external	High internal Low external
Research Question	Disease history, practice patterns, burden of illness	Test effectiveness hypothesis	Test efficacy hypothesis
Population and comparator	Cohort(s) defined by patients with a specific disease or receiving a specific treatment	'Usual care' control group in broad patient population and practice settings	Placebo control group with highly selected patients and standardized, intense follow up
Suitable for Economics?	√	√√√	√√

Economic Evaluation Based in Observational Data



1. Identify patient cohorts
   - who receive the treatments of interest
   - within existing administrative or research dataset
2. For each patient, identify
   - relevant measures of effectiveness
   - health care resource use or cost
3. Estimate mean cost and mean effectiveness by group and calculate incremental ratio (ICER)
4. Apply statistical approaches to reduce bias

Statistical Approaches for Observational Data



- Statistical adjustments for bias because of lack of randomization
  - bias in allocation of treatments
  - sample selection bias
  - confounding effects associated with real world treatment
- Approaches
  - *A priori* stratification in study design
  - Adjustment for imbalance amongst treatment groups using various regression modeling techniques
  - Propensity scores – multiple approaches

However, well-designed observational studies do not systematically overestimate magnitude of treatment effects compared to RCTs

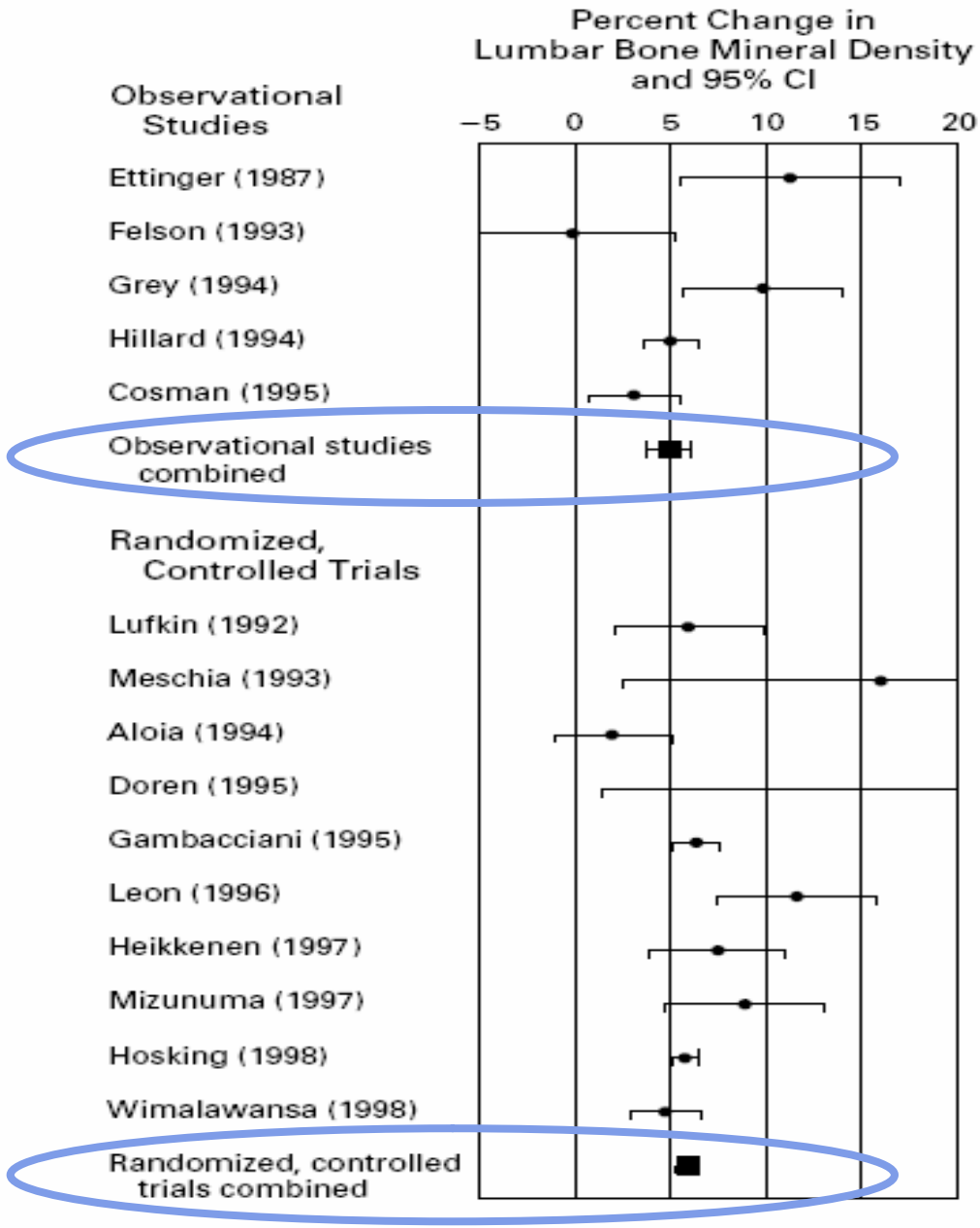


Figure 3. Percent Change in Lumbar Bone Density in Postmenopausal Women Given One to Two Years of Hormone-Replacement Therapy as Compared with Controls.

The figure is based on data from 15 articles.[43-57] CI denotes confidence interval.

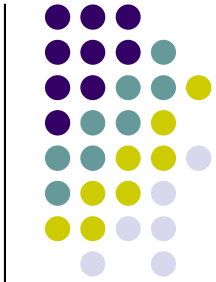
- *Concato J. NEJM 2000;342:1887-92*
- *Benson K. NEJM 2000;342: 1878-86*

Trial-Based Economic Evaluation

1. Obtain clinical effectiveness outcomes
   - Randomized comparative clinical trial
   - Consider if trial reflects ‘real-world’ treatment
2. Collect health care resource use data
   - Supplemental items to clinical data depending on perspective
3. Value resource use
   - At time of analysis, calculate total cost for each patient (microcosting, unit costs or gross costs)
4. Estimate mean cost and mean effectiveness by group and then calculate ICER
5. Estimate variability around ICER (e.g. bootstrap)

-Ramsey S et al. ISPOR RCT-CEA Task Force Report. Value in Health 2005;8(5):521-33.

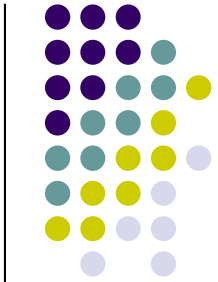
Design and Analytical Considerations in Trial-Based Economic Evaluation



1. Choice of comparison therapy
2. Gold standard outcome measure
3. Intermediate vs. final health outcomes
4. Limited time horizon and sample size
5. Protocol-driven costs and outcomes
6. Geographic transferability of trial data

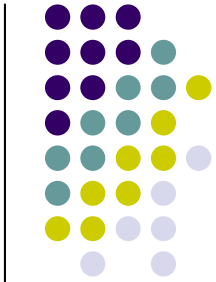
- *O'Brien B. Med Care 1996;34(12):DS99-108*
- *Drummond MF. Med Decis Mak 1998;19(2):12-8*
- *O'Sullivan AK, Thompson D, Drummond MF. Value in Health 2005 8(1): 67-79.*

Issue #1 - Choice of Comparison Therapy



- Placebo comparisons
  - Required for licensing but only relevant to economics if new treatment is adjunct, not substitute
- Active comparator for economic evaluation
  - Compare new drug against most widely used current therapy or standard of care E.g. Enoxaparin trials vs. heparin, but relevant comparison is warfarin
  - Current therapy can be non-drug (e.g. surgery)

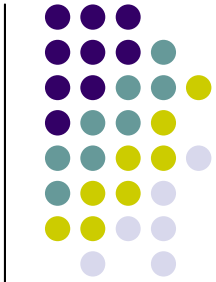
Issue #2 - Gold Standard for Health Outcomes



- Gold Standard outcome used in trials to reveal the 'truth' - but are these used in routine practice?
- Often need to model beyond the trial data; incorporate the costs and consequences of diagnostic errors
  - Example 1 - Trials of DVT prophylaxis
    - Venography used in trials (invasive, expensive, painful), but not first line in real world
  - Example 2 - Trials of ulcer drugs
    - Ulcer recurrence by endoscopy at fixed follow-up times in RCT vs. symptoms in routine practice

- O'Brien et al. CMAJ, 1994;150:1083-172

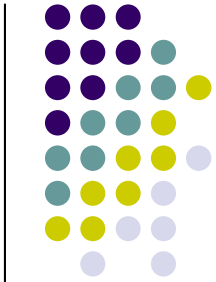
Issue #3- Intermediate vs. Final Health Outcomes



- Trials sometimes report intermediate outcomes but need additional final outcomes for economic evaluation
  - Example 1 - Trials of Cholesterol Lowering
    - Report LDL and HDL levels
    - Sample size too large for MI or death outcome
    - Use epidemiologic modelling studies to project final outcomes using Framingham equations
  - Example 2 - Trials of Treatment for Osteoporosis
    - Report % change in bone density
    - Project fractures prevented with model

-Oostenbrink JB et al. PharmacoEconomics. 2003; 21(15):1103-12.

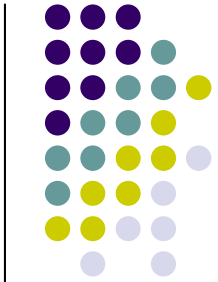
Issue #4 - Restricted Follow-up and Sample Size



- Restricted Follow-up
  - Trial follow-up terminates with clinical event (e.g. stroke or renal failure), but want costs to treat these events
  - Observed trial data for short-term but need to project long-term (e.g. acute MI, recurrence of ulcers)
- Sample size
  - Resource use and costs typically more heterogenous than clinical data - to test for differences in cost, may need larger sample or longer follow-up

- *Briggs A. Economic evaluation and clinical trials: size matters. BMJ 2000;321:1362-3*

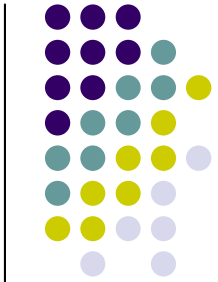
Issue #5 - Protocol-driven Costs And Outcomes



- Additional resources are consumed for trial purposes that would not typically be consumed in standard clinical practice
  - More intense resource consumption (visits, tests, treatment) in trial setting compared to real work which limit ability to extract relevant resource use
  - More frequent monitoring leads to ‘case finding’ that may not have been discovered in the absence of the protocol
  - Patient compliance is actively encouraged and typically higher in trial setting
  - Sites that participate in trials are typically large, urban, academic teaching centres with unique practice patterns

- *Coyle D et al. IJTAHC. 1998 14(1), 135-44.*
- *Revicki DA and Frank L. PharmacoEconomics. 1999, 15(5): 423-34.*

Issue #6 - Geographic Transferability of Evidence



- Trend towards prospective economic analysis as part of multi-country mega-trials
- Treatment effects typically do not vary by country, but resource use depends on practice patterns and can vary tremendously
- Furthermore, there may be correlations between outcomes and costs

- *ISPOR RCT-CEA Task Force, 2005 and Task Force on Transferability, 2007.*
- *Drummond M, Pang F. In: Economic evaluation in health care. 2001; 256-76.*

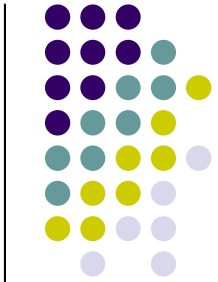
Example of Geographic Variation

Cost-effectiveness Ratio Overall and by Country

	Cost per Death Averted	
	Country-specific utilization	Trial-wide utilization
	Country-specific prices	Country-specific prices
Country 1	5,921	46,818
Country 2	91,906	57,636
Country 3	90,487	53,891
Country 4	93,326	69,145
Country 5	Cost saving	65,800
Overall	45,892	45,892

- *Willke RJ, et al. Health Econ 1998; 7(6): 481-93*

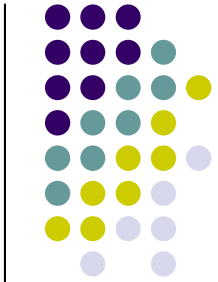
Approaches to CEA within Multinational Studies



Approach	Description
1. Pooled Analysis	• Apply country-specific unit costs to pooled resource use; limited and may not be adequate
2. Test for Interaction	• If significant, apply multivariate regression analysis with treatment-country interaction term to estimate country-specific ICER
3. Homogeneity test	• Statistically significant heterogeneity will indicate if overall results of studies are generalisable and data can be pooled into a single analysis
4. Multilevel random effects models	• Hierarchical regression model to estimate location-specific measures of cost-effectiveness and correct quantification of uncertainly by adjusting standard errors to reflect variability both within and between locations

- *Willke RJ, et al. Health Econ 1998; 7(6): 481-93*
- *Cook et al. Stat Med 2003; 22: 1955–1976*
- *Manca A and Willan A. Pharmacoeconomics 2006;24911):1101-19*

Conclusions



- Economic question fundamentally different from clinical question
- Prospective collection of patient-level resource use data alongside trials can be an excellent basis for concurrent economic evaluation
- Observational studies require careful design and statistical adjustments to reduce bias
- Special design and analytical considerations for trial-based economic evaluation and estimation of cost-effectiveness