Economic Analysis In Clinical Research

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Introduction to the Principles and Practice of Clinical Research
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Overview

- Introduction
- Concepts
- Technical and Statistical Issues
- Examples
  - Value of Health
  - Cost of Illness
  - Cost-Benefit Analysis
  - Marginal Analysis
  - Cost Effectiveness Analysis
    - Clinical Trial plus Economic Follow-up
    - Clinical Trial plus Modeling
    - CEA Along Side a Clinical Trial

INTRODUCTION

Purpose of Economic Analysis in Health Care Research

- Policy and program evaluation
- Health care resource allocation decisions
- For understanding determinants of technical and organization efficiency of health care delivery
- For understanding determinants of distribution, access and equity issues in health care delivery

Relationship of Economic Studies to Clinical Trials

- Health Services Research: observational data in community settings or quasi-controlled experimental settings
- Health Economics Modeling: economic modeling combined with results of randomized clinical trials through modeling
- Economic Studies Along-side Clinical Trials: used especially in Pharmaco-economics

CONCEPTS

Some Types of Economic Analysis in Health Care Studies

- **Descriptive Studies**
  - **Economic Value of Health**
  - **Cost-of-Illness Studies**
- **Cost - efficiency Studies - What should it cost?**
- **Cost Evaluation Studies**
  - **Cost Benefit Analysis (CBA)**
  - **Cost Effectiveness Analysis (CEA)**
  - **Cost Utility Analysis (CUA)**

Principles of Cost Evaluation Studies

- All relevant costs and benefits should be counted
- Purpose of evaluation is to compare alternative used of resources
- Measurement is incremental

Cost Benefit Analysis

- All costs and health effects are expressed in monetary terms (i.e., must put a $ value on a year of life)
- Cost Benefit -> all benefits minus all costs, sometimes call Social Return on Investment
- Cost Benefit Ratio -> All benefits divided by all costs, sometimes called Social Rate of Return

Cost Effectiveness Analysis

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

Incremental Cost Effectiveness (or Utility) Ratios

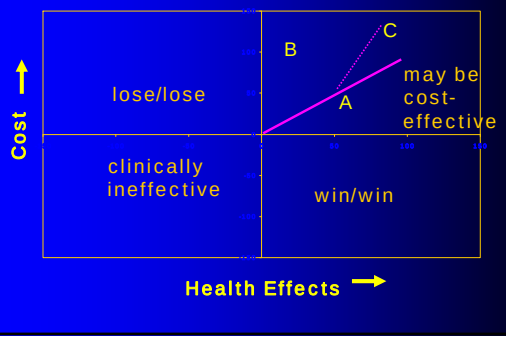
- Let C_a and C_b be the costs of Intervention a and Intervention b;
- Let E_a and E_b be the health effects of Intervention a and Intervention b;
- Intervention a is often defined as status quo or standard treatment.

Incremental Cost Effectiveness Ratio (ICER)

$$ICER = [C_b - C_a] / [E_b - E_a]$$

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

The Cost-Effectiveness Plane



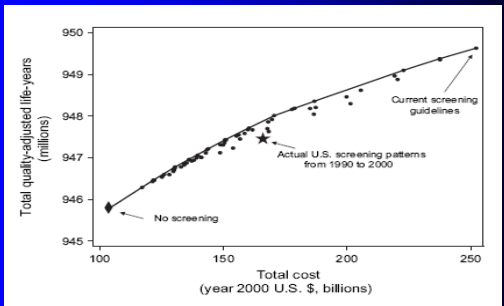
Dominance

- Intervention A produces more health benefits at lower cost than intervention B: A "dominates" B.
- Intervention C produces more health benefits than intervention A, but at higher cost: the ICER of A relative to C can be computed.
- ICER of A relative to C is the slope of the dotted line

Caution

- Sometimes health effects are shown on the vertical axis and costs on the horizontal axis
- Example: Stout et al. examined 64 different breast cancer screening scenarios (starting/stopping ages and screening frequency) for the U.S.
- There are possible scenarios that dominate current U.S. screening practices

Cost-Effectiveness of Mammography Screening in the U.S



Source: Stout et al. J Natl Cancer Inst 2

Transformations of ICER

- ICER may be transformed to:
  - Net Benefit (NB) = $E - (C * 1/V_s)$
  - Net Monetary Benefit (NMB) = $(V_s * E) - C$
- V_s = the Social Value of health (e.g., $100,000 per life-year, but this can also be varied)
- Can be used to synthesize CEA and CBA through "Acceptance Curves"

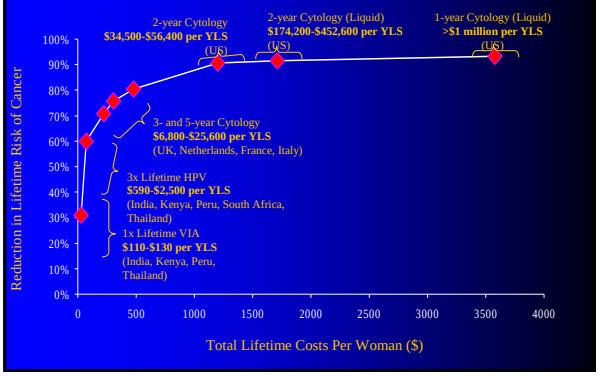
The Social Value of Health

- Two Interpretations
  - Value = "Willingness to Pay"
    - $7 Million per Death Averted (in U.S.)
    - $150,000 per Life-Year (in U.S.)
  - Value Reflects Nation's Healthcare Budget
    - In UK the National Institute of Clinical Effectiveness (NICE) program, V_s= 30,000 pounds per Life-Year
    - WHO Commission on Macroeconomics: V_s= 1X – 3X per capita Gross Domestic Product per Life-Year

What is V_s for the U.S.?

- $50,000 per life-year often cited
- Origin of this is unclear
- Recent analyses suggest that the value of V_s may be much higher, e.g. see: RS Braithwaite et al., Medical Care 2008;46:349-356.

Cost Effectiveness of Cervical Cancer Screening Across National Settings



Comparison of Interventions

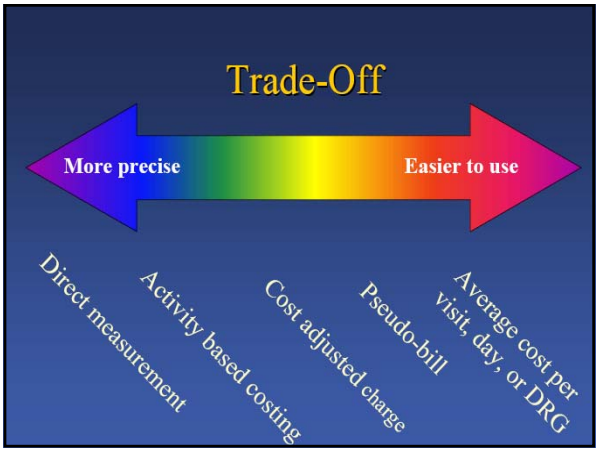
- Micro-analysis – comparison is no treatment or status quo treatment
- Marginal analysis – comparisons are different intensities of the same intervention
- Macro-analysis
  - Comprehensive "league table," e.g. Disease Control Priorities Project
  - Comparison against some value of V_s

Practical Considerations in Cost Evaluation Studies

- Sources of Cost Data
- Technical Economic Considerations
- Statistical Considerations

Potential Sources of Economic Data

- Clinical trial forms/medical record abstraction
- Hospital bills
- Health system cost-accounting systems (e.g. HMOs)
- Administrative claims data (e.g. Medicare, Medstat)
- Patient/provider survey (e.g. MEPS)
- Cost scenario
- Time-motion study
- Engineering study



More on Cost Data

- NCI – AHRQ Workshop Health Care Costs: Standardized Methods & Estimates for Research & Policy Applications
- Presentations at: http://healthservices.cancer.gov/publications/workshops/hcc/
- To be published as supplement to Medical Care, Spring, 2009.

Some Technical Economic Issues

- Adjusting for price (unit cost) differences
  - For different years
  - For different settings/locations
  - For different countries (currencies) (e.g. DCPP)
- Discounting
- Pricing non-market goods
  - E.g. time

Some Statistical Issues

- Economic data are complex
- Economic data tend to be highly skewed and censored
  - special estimation techniques have been developed
- Trials designed for clinical end-points may be under-powered for economic and/or cost-effectiveness results
- Cost-effectiveness or Cost-utility ratio estimates pose specific problems for analyzing and presenting confidence intervals (regions)
- See presentations from NCI-AHRQ Workshop

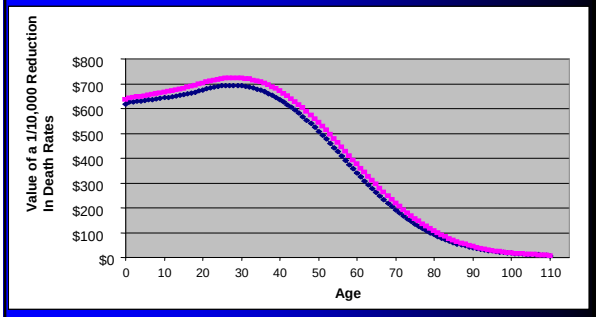
EXAMPLES

DESCRIPTIVE STUDIES

Economic Value of Health

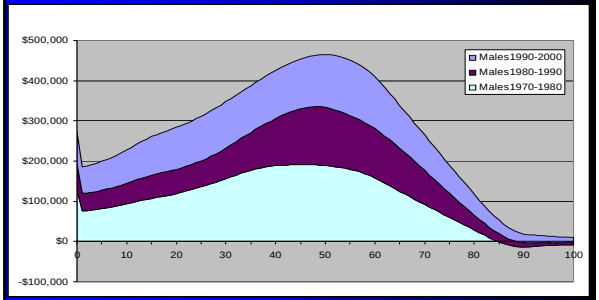
- The benefit side of the Cost-Benefit equation
- Includes all aspects of health in monetary terms
- One way to think about V_s

Economic Value of Health



Source: K.M. Murphy

Economic Gains From Increased Longevity - Males



Source: K.M. Murphy

Economic Value of Health Compared to Healthcare Expenditures: 1970 - 2000

- Economic value of health improvements: $95,345 Billion
- Healthcare expenditures: $34,725 Billion
- Implies a favorable Cost-Benefit Ratio

BUT:

- How much of health improvements are due to healthcare?

Source : K.M. Murphy

Cost Domains

- **Cost domains refers to categories of costs according to whether they are directly or indirectly related to the provision of marketed health care services.**
- **The cost domain may also determine whether accessible and/or high quality cost data is available to the researcher and what degree of effort is required to obtain data.**

Examples of Cost Domains

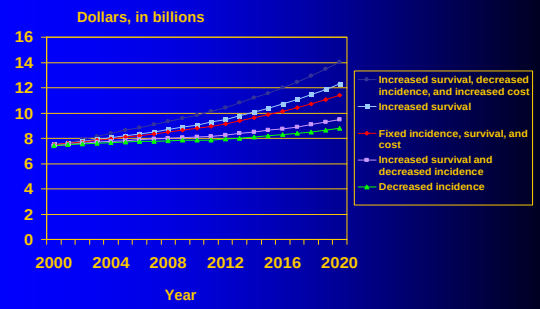
- Direct health care costs (e.g. Medicare payments)
- Direct non-health care costs (e.g., paid child care)
- Patient time costs (e.g., value of time to attend treatment)
- Morbidity costs (e.g., lost productivity due to work disability)
- Mortality costs (e.g., lost productivity due to premature death)

NIH Cost of Illness Report

Disease/Condition	Total Costs	Direct Costs	Indirect Costs
Alzheimer's Disease	$87.9 billion	$13.3 billion	$74.6 billion
Atherosclerosis	$5 billion	$4.4 billion	$0.6 billion
Cancer	$96.1 billion	$27.5 billion	$68.7 billion
Stroke	$43.3 billion	$28.3 billion	$15 billion
Liver Disease	$3.2 billion	$1.2 billion	$2.1 billion
Pulmonary Disease	$37.3 billion	$21.6 billion	$16.2 billion
Diabetes	$98.2 billion	$44.1 billion	$54.1 billion
Heart Disease	$175.3 billion	$97.9 billion	$77.4 billion
HIV/AIDS	NA	$10.3 billion	NA
Homicide	$33.7 billion	$10.4 billion	$23.3 billion
Injury	$338 billion	$89 billion	$248 billion
Kidney Disease	$40.3 billion	$26.2 billion	$14.1 billion
Pneumonia/Influenza	$22.9 billion	$17.5 billion	$5.4 billion
Septicemia	$7.2 billion	$4.9 billion	$2.3 billion
Suicide	NA	NA	$10.2 billion

Source: H. Varmus, Disease Specific Estimates of Direct and Indirect Costs of Illness and NIH Support

Projected Treatment Costs for Colorectal Cancer 2000-2020



Source: Yabroff KR, et al. *Health Economics* 2007.

Time Cost: Initial Treatment for Colorectal Cancer

	Category of Service	Visits		Time (hours)	
		Cases	Controls	Cases	Controls
Initial Phase	Office visits	16.95	5.98	24.62	8.69
	Emergency room visits	0.62	0.35	2.17	1.22
	Chemotherapy	6.61	0.05	22.78	0.17
	Radiation therapy	1.43	0.04	2.34	0.06
	Hospitalization LOS	17.96	1.89	294.90	37.82
	Out-patient surgery	1.17	0.25	6.18	1.30
	Initial Phase Total**			**355.02**	**49.26**

Source: Yabroff et al. Medical Care, 2005.

How do time costs compare to direct costs?

- For colorectal cancer, time costs (valued by average wage rates) during initial treatment were $4655, 20% of direct medical expenditures in that period.

COST BENEFIT ANALYSIS

Using Cost of Illness in a Cost-Benefit Analysis

- COI of Neural Tube Defects at Birth
- Cost-Benefit Analysis of Folic Acid Fortification

COI of Neural Tube Defects

- **Cost Domains Included in COI Estimate:**
  - **Medical care**
  - **Developmental services**
  - **Special education**
  - **Morbidity cost**
- **COI per case:**
  - **Spina bifida: $349,133**
  - **Anencephaly: $485,016**

Source: PS Romano, et al. Folic acid fortification of grain: an economic analysis. AJPH 1995:85:667-676.

Cost-Benefit Analysis of Folic Acid Fortification

- **Cost of low level folic acid fortification = $27.94 million per yr**
- **Note: folic acid fortification can "mask" vitamin B12 deficiency**
- **Cost of surveillance of those with undiagnosed vitamin B12 deficiency- $5 million per year**

Benefits of Folic Acid Fortification

- Proportion of target population with inadequate folate intake - 66%
- Cases of birth defects averted: 191 spina bifida, 113 anencephaly

Folic Acid Fortification: Cost-Benefit Analysis

- Economic benefit of birth defects averted: $121.5 million
- Net benefit of fortification program = $93.6 million
- Benefit/Cost Ratio = 4.3
- Is supplementation a better policy?

Supplementation vs. Fortification

- Cost-effectiveness analysis of folic acid supplementation vs. fortification
- Both found to be cost-savings compared to doing nothing
- Fortification (dominantly) cost-effective relative to supplementation

Source: Kelly AE, et al. Appendix B in Gold, et al. Cost-Effectiveness in Health and Medicine. Oxford U. Press, 1996.

Did the Policy Work?

- Studies of NTD prevalence pre- and post-fortification
- More fortification that anticipated
- Original estimate did not take dose-response into account
- NTDs averted:
  - 520 Spina Bifida
  - 92 Anancephaly
- Net Benefit = $143 million (in 2002$)

Source: Williams et al. Teratology 2002;66:33-39; Waitzman , personal comm.

Additional Benefits of Folic Acid?

- New evidence that folic acid prevents cardiovascular disease and colon cancer [but next slide!]
- Cost-effectiveness estimates of fortification at 140, 350 and 700 mcg per 100 grams of grain
- 700 mcg most cost effective – 322,940 QALYs gained, $4.4 billion saved per year

Source: Bentley et al. Abstract, 2006 Society for Medical Decision Making

Economic Evaluation (Like All Good Science) Never Ends!

- Are there un-discovered harms from folic acid fortification?
  - Negative results of folic acid prevention trial for adenomas (Cole BF, et. al. JAMA 2007;297:2351-9)
  - Association of increased colon cancer incidence (above trend) with start of folic acid fortification (Mason, et. Al. Ca Epi Bio Prev 2007;16:1325-9)

Cost Evaluation Studies and Clinical Trials

- Clinical Trial with Economic Follow-up
- Economic Modeling Combined with Clinical Trial Results
- Linking to HMO Computerized Data on Patient Care Costs
- Analyzing the Confidence Region for the Cost-Effectiveness Ratio

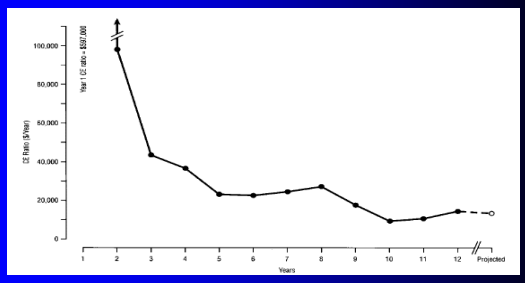
Clinical Trial with Economic Follow-up

- Hlatky MA, et al. Medical costs and quality of life 10 to 12 years after randomization to angioplasty or bypass surgery for multi-vessel coronary artery disease. Circulation 2004;110:1960-1966.
- Bypass Angioplasty Revascularization Investigation (BARI) trial
- Study of Economics and Quality of Life (SEQOL) follow-up study

BARI / SEQOL Study

- BARI Study
  - Randomization: 1988-1991
  - Follow-up through 1996
- SEQOL Study
  - Sub-sample follow-up through 2001
  - Medical costs
  - Quality of life measures

Cost-Effectiveness of CABG vs. PTCA by Year of Follow-up



Source: Hlatky et al. Circulation 2004

Lesson of the BARI/SEQOL Study

"The improvement in the cost-effectiveness ratio over time was largely because of the narrowing of the cost differential between the 2 procedures, with the remainder resulting from a small survival advantage among CABG patients. These observations underscore the importance of a long-term perspective in economic evaluation, as an initially costly procedure may prove cost-effective over the long term if it either provides extended clinical benefits or the initially higher cost can be offset by preventing subsequent hospitalizations."

Economic Modeling Combined With Clinical Trial Results

- **Berthelot JM et al. Decision framework for chemotherapeutic interventions for metastatic non-small-cell lung cancer. Journal of the National Cancer Institute, 2000 Aug 16;92(16):1321-9**
- **Combining trial data with a modeling approach to costs and longer term outcomes**

CEA of Lung Cancer Treatment

- CEA of chemotherapy vs. best supportive care for advanced stage lung cancer
- Survival benefits of treatment based on survival curves modeled (out to 48 months using Weibull survival function) from RCT results and community survival data
- Costs based on Canadian cost scenarios (POHEM model)

Results for stage IV NSCLC

- Total cost of best supportive care = $25,904
- Total cost of chemotherapy = $25,105 - $41,576 depending on regimen
- Hospital/Clinic costs are higher for best supportive care compared to chemotherapy – e.g. intervention results in down-stream cost savings
- ICER of chemotherapy ranges from cost-savings to $37,800 / quality adjusted life year

CEA From Patient Level Data in a Clinical Trial

- Statistical modeling of long-term outcomes and costs
- Accounting for stochastic uncertainty in the measurement of health outcomes and costs – Bootstrap Confidence Interval
- Assessing CEA as a function of the Social Value of health – the Cost Effective Acceptability Curve

CEA of Hormonal Treatment for Prostate Cancer

- **Cost-effectiveness analysis of adding early hormonal therapy to radiotherapy for locally advanced prostate cancer**
- **Clinical Trial – EORTC 22863**

Source: Neymark et al, Health Economics 2002;11:233-248.

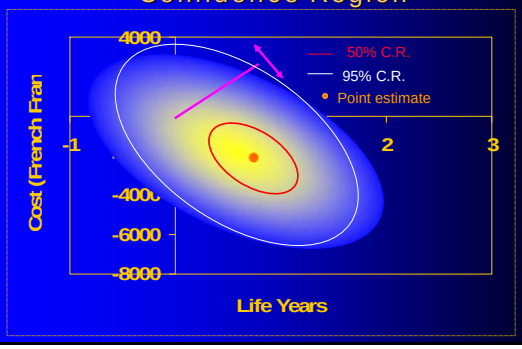
Methods

- Direct medical resource use obtained of 90 subjects for up to 11 years of follow-up
- Unit costs based on based on standard national French tarrifs
- Method of Lin et al. used to adjust for censoring in longitudinal cost data
- Mean survival estimated using the restricted means method

Construction of 95% Confidence Region

- Using standard Monte Carlo simulation methods, (sampling with replacement) 5000 replications of the Incremental Cost Effectiveness Ratio, were calculated

CEA of Hormonal Treatment Confidence Region



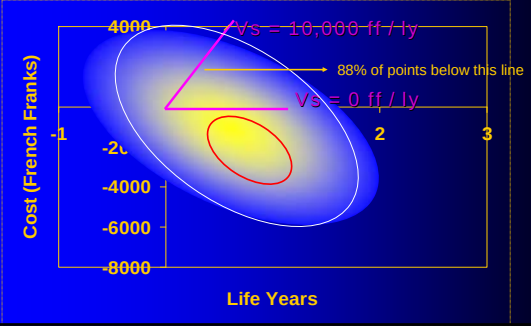
Cost Effectiveness Acceptability Curves

- 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)
- Calculate probability that: CER < V_s

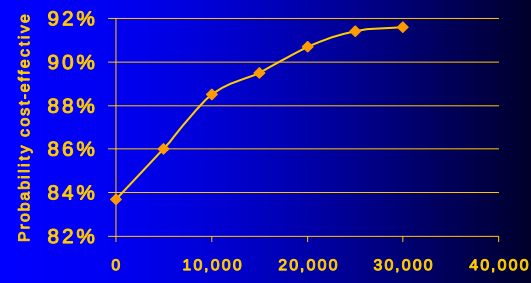
Graphical Analysis

- E.g., Rotate pink cost-effectiveness line – this is equivalent to varying the value of V_s
- Assess what proportion of confidence ellipse lies beneath the line

CEA of Hormonal Treatment Confidence Region



Cost-Effectiveness Acceptability Curve for Hormonal Treatment of Prostate Cancer



Alternative Methods for Estimating Confidence Regions

- Monte Carlo simulation (assumes symmetrical confidence region)
- Fieller's Theorem (assumes a joint normal distribution)
- Empirical likelihood (makes no prior assumption about distribution, but is computationally intense)
- See: AH Briggs, et al. Ann Rev Public Health 2002;23:377-401; Owen AB. Empirical Likelihood. 2001; and ML Brown, et al. Health Economics, forthcoming.

Net Benefit Analysis and Cost Effective Acceptability Curves

- Cost Effectiveness Acceptability Curves can also be derived directly from Net Benefit (NB) Regression
- NB regression can adjust for confounding variables
- See: JS Hoch, et al. Health Economics, 2002;11:415-430 and JS Hoch, JD Blume, J Health Economics 2008;27:476-495.

Sources of Uncertainty in Economic Evaluation

- Parameter Uncertainty
  - biological, demographic, epidemiological, medical and economic parameters (as in example just shown)
- Model Uncertainty
  - Choice of model type and structure
- Methodological Uncertainty
  - Choice of CBA, CEA, CUA, perspective, time horizon, etc.

Source: Brisson et al. Med Decis Making 2006;26:434-446