Economic Analysis In Clinical Research

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Overview

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

Flyer for Disease Control Priorities Project

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

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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

Demonstration of cost and health effects plane

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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

Graph showing cost-effectiveness of mammography screening in the U.S.

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

Graph showing 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

Arrow showing “Trade-off” from more precise to easier to use.

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

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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

Chart showing economic value of health

Source: K.M. Murphy

Economic Gains From Increased Longevity – Males

Graph showing economic gains from increased longevity in 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

Four column list showing various NIH cost of illness report

Source: H. Varmus, Diseases Specific Estimates of

Direct and Indirect Costs of Illness and NIH Support
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Projected Treatment Costs for Colorectal Cancer
2000-2020

Graph showing projected treatment costs for colorectal cancer 2000-2020

Source: Yabroff Kr, et. al. Health Economics 2007.

Time Cost:
Initial Treatment for Colorectal Cancer

Chart showing demonstration

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

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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 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

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

Graph showing results on cost effectiveness of CABG vs. PTCA 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 tern 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

Graph showing data fro study related to CEA of Hormonal Treatment Confidence Region

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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

Graph showing data for study related to CEA of Hormonal Treat Confidence Region.

Cost-Effectiveness Acceptability Curve for Hormonal Treatment of Prostate Cancer

Graph showing 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