Economic Analysis Alongside a Clinical Trial

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HERC
Health Economics Resource Center

VA
U.S. Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service

Disclosures

- No financial conflicts of interest
- Worked on multi-site clinical trials funded by VA CSP program
- All errors are my own

Objectives

1. When and why should we measure economic endpoints in clinical trials?

2. Trial design elements

3. Methods for economic analysis

Why measure economic endpoints?

Randomized Trails

- Randomized controlled trials (RCTs) are the gold standard for understanding causation
- Often study proponents are interested in the economic effects
- An economic analysis increases the cost of a clinical trial, but is the added cost worth it?

Why conduct economic evaluations?

- Economics helps inform two common decisions
  - Adoption: Is the treatment effective such that we should adopt it?
  - Implementation: How should we implement this new technology?
- There are many similarities in adoption and implementation trials, although there are some notable differences too.

Added Value of Economic Analysis

- Potential
  - Widely used existing interventions
  - Interventions designed to improve cost-effectiveness
  - Substitutes for another intervention where there are possible gains in outcomes or changes in costs
  - May lead to policy changes

- Unclear
  - Comparisons of close substitutes
  - New intervention not yet shown effective
  - Designed to change clinical behavior

- Unlikely
  - Basic science hypothesis
  - Intervention addresses significant treatment gap (e.g., HCV treatment)
  - Phase 1 or 2 trials

Types of analysis

- Cost-effectiveness analysis (CEA), measured with an incremental cost effectiveness ratio
- Cost analysis
- Resource use analysis
- Employment analysis
- Budget impact analysis

Types of analysis-2

- Many factors can affect the choice of the type of analysis.
- CEA significantly more expensive.
- Especially in VA, budget impact can affect adoption as the facility directors want to know not only what the intervention/therapy will cost, but the timeline of any added costs and savings.

Types of analysis-3

- Bottom line, need to ask why is an economic analysis needed?
- What are the objectives of the economic analysis?
- Answers will drive what type of analysis is needed.

Conditional analysis, regardless of type

- What if the need for an economic analysis will be dependent on the results of the trial?
- For example, if the intervention works, then need an economic analysis, but no need for one if the intervention works.
- One option is to have economic input on the trial design to make sure that the necessary data will be available, but no economic analysis are done until the results of the trial are known.

Bottom line

- Economic analysis can add significant expense to the cost of the trial.
- Further, no point in doing an economic analysis if the results of the economic analysis will have no impact.
- Remember, strong dominance is rare. Economic analysis can inform a decision if an added benefit is worth the extra cost.
- Useful to think about these issues in the trial design phase.

Design Issues

Details of many of the design issues addressed in other lectures in this course

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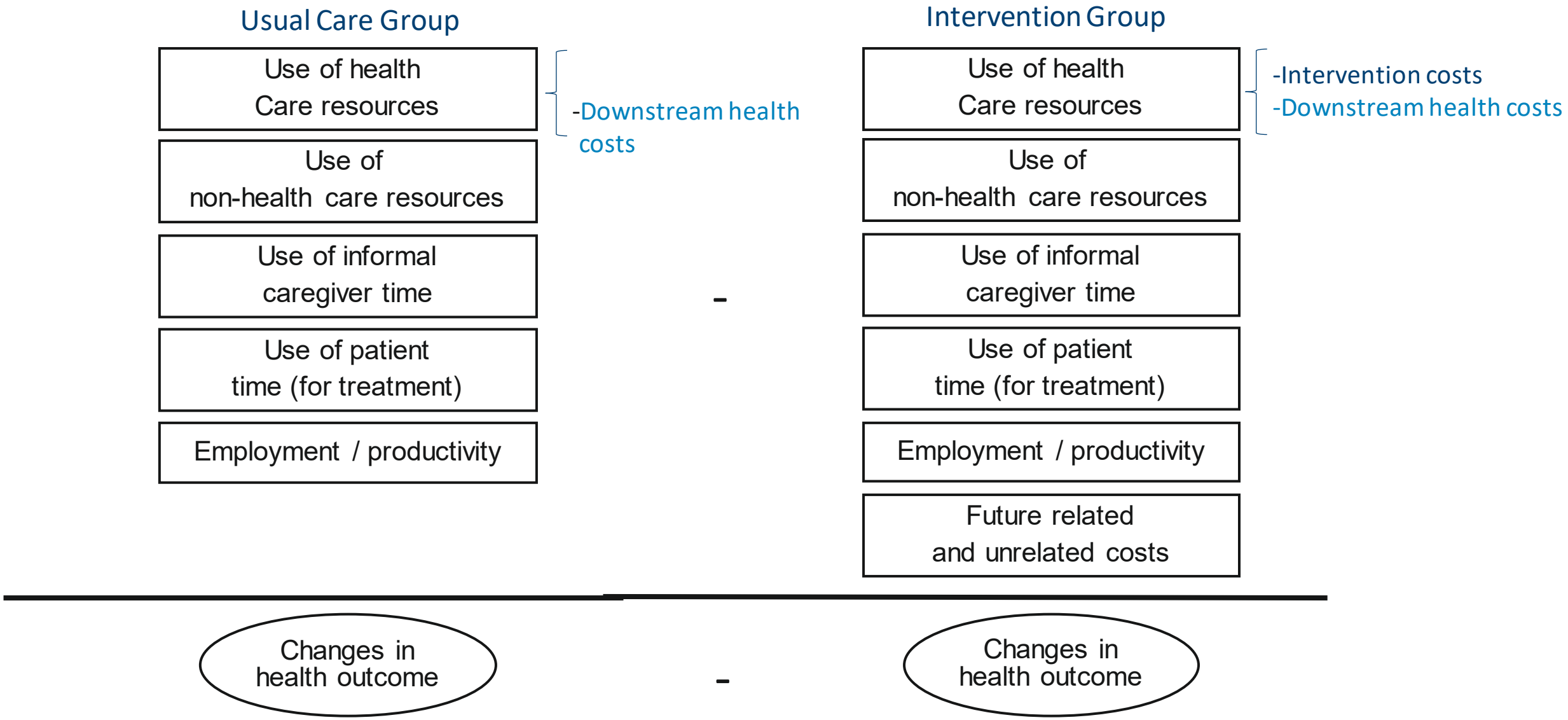
ICER

- CEA, measured with the incremental cost-effectiveness ratio, is a common request

- Compares two or more treatments with regard to gains in outcomes, measured in quality adjusted life years (QALYs) relative to costs.

$$\frac{\text{Ave Cost}_a - \text{Avg Cost}_b}{\text{Ave QALY}_a - \text{Avg QALY}_b}$$

ICER



Adapted from Figure 8.1, Neumann et al 2016

Design Issues

- Strategic issues
  - Perspective
  - Time Horizon
  - Type of analysis

- Operational issues
  - Preplanning— what are the key economic issues
  - Measurement
    - Self-report
    - Administrative data
  - Cost estimation methods

Strategic Issue

- Perspective: whose costs are you going to measure
  - Societal, health care sector, VA perspective
- Time horizon
  - Costs at the end of the trial
  - Modeling beyond the end of the trial
- Type of analysis
  - Cost effectiveness
  - Budget impact
  - Employment effects

Operational: Measurement

- Options
  - VA administrative data
  - Self-report
  - VA Community Care Data
  - Medicare FFS data

Don’t double count

- If you use multiple sources, you need a plan for combining them.

Modeling

- Many clinical trials are short with endpoints measures <1 year
- What about longer term costs and effects?
- In some situations, you might need to develop a Markov model or a micro-simulation to address long-term endpoints.

Timing/Method of Data Collection for Costs/Utilization

- Administrative data.
  - Short lags for VA data
  - Longer lags for Medicare and Medicaid
- What about non-VA healthcare costs?
  - Can ask patients, but there is recall bias, and this varies with recall period.
- Are there other relevant costs that need to be collected? E.g., travel costs, employment effects, etc.

Methods

- Standards exist for CEA alongside a clinical trial.
- HERC has extensive experience with trials.
- We rely heavily on administrative data in VA trials.

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VALUE IN HEALTH

Good Research Practices for Cost-Effectiveness Analysis Alongside Clinical Trials: The ISPOR RCT-CEA Task Force Report

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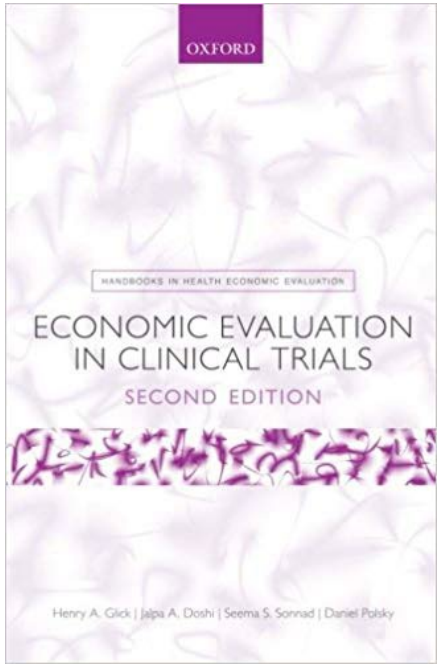

Protocol

- Clinical trials are performed according to a protocol, which is a living document that describes all of the methods
- Many clinical trials publish their protocol
- Most clinical journals will want to review the protocol when you submit the results
  - The main results must be done in accordance with the methods specified in the protocol
  - Promotes transparency
  - Prevents gaming / fishing
- Protocol should detail the economic analysis

Methods

Summary

- Step 1: Identify cost of the intervention relative to usual care
- Step 2: Identify the cost of downstream health care costs
- Step 3: Include other downstream costs that are relevant to your perspective and time horizon
- Step 4: Conduct analysis per protocol
- Step 5: Conduct sensitivity analysis or modeling as needed

Examples: ROOBY

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Five-Year Outcomes after On-Pump and Off-Pump Coronary-Artery Bypass

A. Laurie Shroyer, Ph.D., Brack Hattler, M.D., Todd H. Wagner, Ph.D., Joseph F. Collins, Sc.D., Janet H. Baltz, R.N., Jacquelyn A. Quin, M.D., G. Hossein Almassi, M.D., Elizabeth Kozora, Ph.D., Faisal Bakaeen, M.D., Joseph C. Cleveland, Jr., M.D., Muath Bishawi, M.D., and Frederick L. Grover, M.D., for the Veterans Affairs ROOBY-FS Group*

Costs Five Years After Off-Pump or On-Pump Coronary Artery Bypass Surgery

Todd H. Wagner, PhD, Brack Hattler, MD, Faisal G. Bakaeen, MD, Joseph F. Collins, ScD, G. Hossein Almassi, MD, Jacquelyn A. Quin, MD, Frederick L. Grover, MD, Muath Bishawi, MD, and A. Laurie W. Shroyer, PhD, for the VA #517 Randomized On/Off Bypass (ROOBY) Study Group

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ClinicalTrials.gov identifier NCT00032630

Example: Rheumatoid Arthritis Comparions of Active Therapies (RACAT)

- O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, Lew RA, Cannella AC, Kunkel G, Phibbs CS, Anis AH, Leatherman S, Keystone E, for the CSP551 RACAT Investigators. Therapies for Active Rheumatoid Arthritis after Methotrexate Failure. *New England Journal of Medicine*, 2013;369(4):307-318.
- Bansback N, Phibbs CS, Sun J, O'Dell JR, Brophy M, Keystone EC, Leatherman S, Mikuls TR, Anis A, CSP 551 RACAT Investigators. Triple Therapy Versus Biologic Therapy for Active Rheumatoid Arthritis: A Cost-Effectiveness Analysis. *Annals of Internal Medicine*, 2017; 167(1):8-16.

Key consideration for trial design

- Biologic therapies (e.g., Entanercept) are very expensive.
- Alternative triple therapy with low-cost (off patent) drugs had very similar effectiveness data vs. placebo as biologic therapies.
- Prior from study design is that biologics had slight advantage as patients tended to respond a little bit faster.
- Thus, simple head-to-head comparison, biologics would probably be more effective.
- Study design was essentially to test a strategy of trying the lower-cost options first.

Trial design

- Double-blind, placebo-controlled study.
- All patients randomized to receive on therapy and placebo for the other therapy.
- Patients evaluated at 24 weeks, those that had responded to therapy were continued on initial therapy
  - Those that had not responded to initial therapy, were crossed over to the other therapy, with the blind and placebo-control maintained.
- All patients evaluated at 48 weeks.

Trial design-2

- Essentially a trial comparing initial assignment to biologic vs. trying the low-cost triple therapy first.
- Were there any gains in outcomes from one therapy vs. the other.
- Automatic that triple therapy was lower costs, so question was if the added expense of the biologic was worth that very large additional expense.

General comment

- The design of economic analysis, or even the need for economic analysis very much affected by the study question and the details of the trial design.
- HERC was involved from the initial planning meeting.
- Decision was made to conduct a full economic analysis as the expected finding was that that there would be very little gain from the more expensive biologic therapy. Want to have the case as convincing as possible, given the politics.

Methods for RACAT

- VA, non-VA US, and Canadian sites. 353 patients randomized

- Participants were followed by study team through 1 year

Quality of Life

- Disease-specific quality measure DAS
- Overall QAL measured with EQ-5D

Costs from 2 Different Systems

- Couldn’t just use VA administrative costs as not available from Canadian sites.
- Study forms to track RA-relevant utilization (visits, procedures, medication use).
  - Also tracked absences from paid and non-paid work.
- Applied costs from Medicare Fee Schedule.
  - Rx costs from VA drug costs
  - Average wages for lost labor

Why Only Measure RA-relevant Utilization for Study Period?

- Study was a relatively small comparison of alternate drug therapies.
  - If included other costs, rare expensive events could affect the results.
- RA treatment relatively isolated from other healthcare costs/utilization.

Lifetime Effects.

- Canadian economic team had already developed and validated a lifetime model for specific for patients with RA.
- Used this model to estimate lifetime effects.

Track Costs and Utilization

- Most readers want to know why costs differ. Was it hospitalizations, use of medications?

- In the data extraction, you should consider simple counts
  - Number of admissions
  - Days of inpatient care
  - Number of outpatient visits
  - ED visits
  - Rx fills

Separate Treatment Costs from Follow-up Costs

- Need to separately measure the treatment costs from follow-up costs
- Surgical trials and drug trials are relatively simple; can be more complex for other types of interventions
- Timing of follow-up should be consistent
  - For example, 365 days after date of index surgery
  - Follow-up timing should not vary; e.g., it should not be based on date of discharge
- Separate follow-up costs from intervention costs (some interventions last a period of time)

Analytical steps with VA data

- Cross check utilization reported on study forms with VA administrative data
- Double check missing data, death and attrition
- Balance across study arms
- Examine treatment costs

Extensions

1. Self report data
2. Heterogenous treatment effects / sensitivity analysis
3. More complicated treatment costs
4. Administrative follow-up on clinical endpoints
5. Patient outcomes and net benefit

Self-Report Data

- If your clinical trial only collected self-reported utilization, you need to value (in $) the utilization data.
  - Medicare payments
  - Medicaid payments
  - VA costs
  - Cost-adjusted charges

- These methods are relatively easy, but bias the variance in costs
- Need to consider recall bias effects

Administrative Follow-up

- VA has great mortality data
- Administrative follow-up for procedures (e.g., revascularizations) is possible.
- Follow-up on diagnostic related events is really hard without a clinical adjudication panel
  - Stroke
  - AMI

Quin JA, Hattler B, Shroyer AL, Kemp D, Almassi GH, Bakaeen FG, Carr BM, Bishawi M, Collins JF, Grover FL, Wagner TH. Concordance between administrative data and clinical review for mortality in the randomized on/off bypass follow-up study (ROOBY-FS). Journal of cardiac surgery. 2017 Dec;32(12):751-6.

RACAT Study Results-Quick Summary

- Main outcome; triple therapy non-inferior to biologic therapy.
  - 24-week response rates essentially identical
  - Among non-responders at 24 weeks, 48-week response rate essentially identical for alternative therapy.
  - Patients with biologic had 0.004 QALY gain at 24 weeks, and 0.016 QALY gain at 48 weeks.

RACAT Study Results-Quick Summary-2

- With very large difference in Rx costs
  - 24-week ICER $2,672,575
  - 48-weeks ICER $977,805
- These were using the VERY low VA drug costs (Canadian costs for Entanercept about twice the VA costs).
- Lifetime ICER $521,520

Summary

- Increasingly popular to include economic endpoints in clinical trials
- With some planning (and luck), you will have great information to inform adoption and/or implementation questions.
- The majority of this talk was focused on studies designed to address adoption. If you are interested in questions about implementation, I'd recommend a later talk on BIA.

Questions?

For more information visit the HERC website at www.herc.research.va.gov

Email us at HERC@va.gov

Call us at (650) 617-2630

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