Economic Analysis Alongside a Clinical Trial

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Disclosures

- No financial conflicts of interest
- Worked on many multi-site clinical trials funded by VA and NIH
- 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

- 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

Design Issues

Types of analysis

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

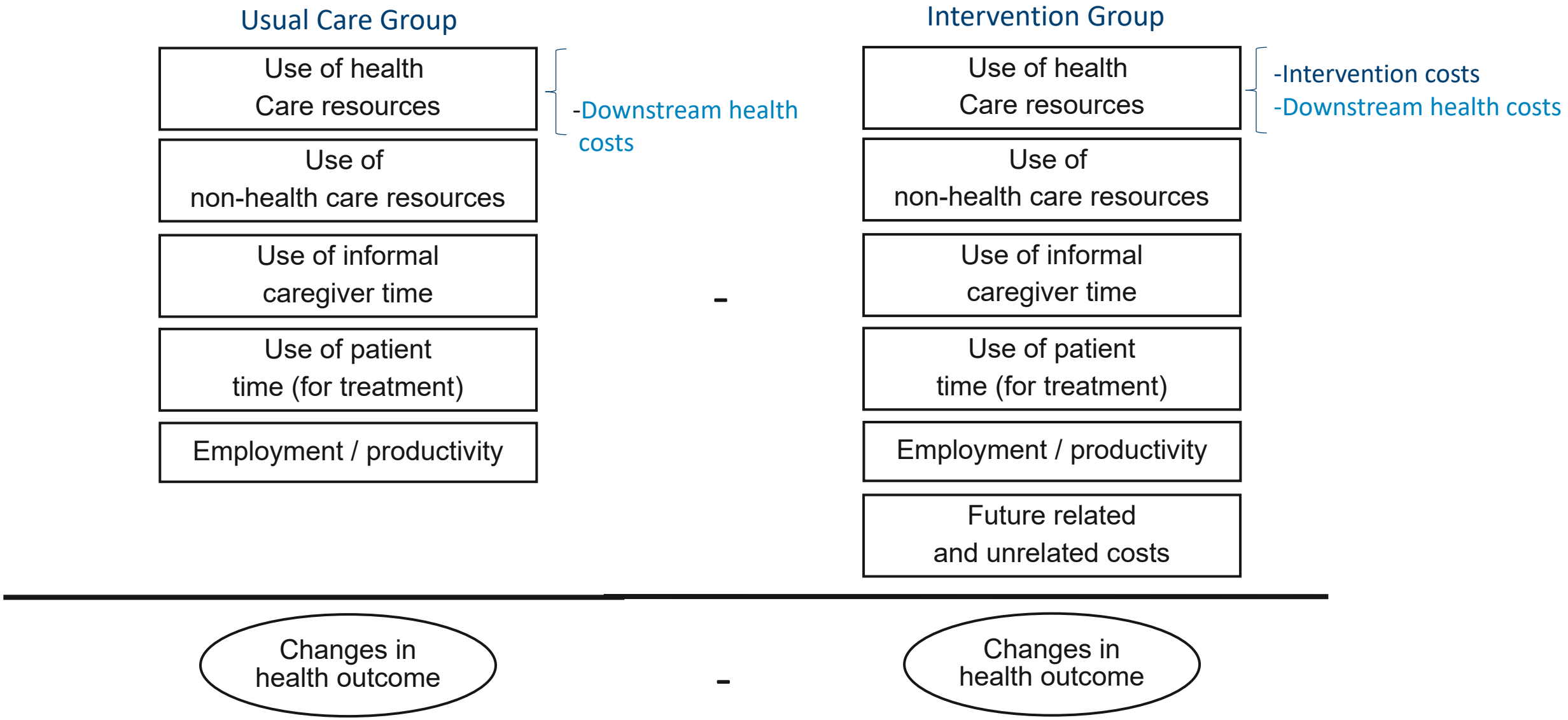
ICER

- 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: Preplanning

- Some large trials start by conduct a value of information analysis (VOI).[1]
- A VOI identifies parameters where more information could influence main outcome
  - Patient subgroups
  - Comparators and endpoints
  - Length of follow up would be most valuable
  - Sample size and power

1. Claxton KP, Sculpher MJ. Using value of information analysis to prioritise health research. Pharmacoeconomics. 2006 Nov 1;24(11):1055-68.

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.

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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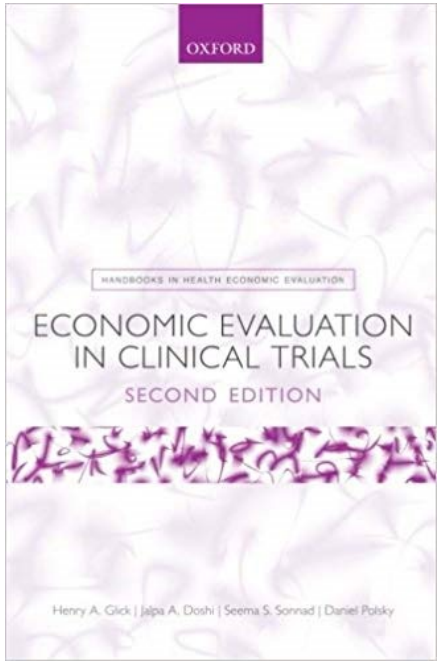


Protocol

- 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

VA Palo Alto Health Economics Resource Center, Menlo Park, California; Department of Surgery, Stanford University, Palo Alto, California; Eastern Colorado Health Care System, Department of Veterans Affairs, Denver, Colorado; University of Colorado School of Medicine at the Anschutz Medical Campus, Aurora, Colorado; Department of Thoracic and Cardiovascular Surgery, Cleveland Clinic, Cleveland, Ohio; Cooperative Studies Program Coordinating Center, Veterans Affairs Medical Center, Perry Point, Maryland; Veterans Affairs Medical Center, Milwaukee, Wisconsin; Department of Cardiothoracic Surgery, Medical College of Wisconsin, Milwaukee, Wisconsin; VA Boston Healthcare System, West Roxbury, Massachusetts; Division of Cardiovascular and Thoracic Surgery, Duke University Medical Center, Durham, North Carolina; and Northport VA Medical Center, Northport, New York

ClinicalTrials.gov identifier NCT00032630

Specific Aims

- Questions have been raised about the relative costs and outcomes for patients receiving on vs. off-pump coronary artery bypass surgery (CABG)

- We compared quality-adjusted life years and costs at 1 year and costs at 5 years for patients randomized to on-pump versus off-pump CABG

Methods for ROOBY

- 18 VA centers consented and randomized 2,203 participants to on-pump (n = 1,099) versus off-pump (n = 1,104) CABG
- Participants were followed by study team through 1 year and administratively after one year
- Analytical sample of 2,203

Quality of Life

- Utility scores were measured using the Veterans' version of the SF-36 (i.e., VR-36)

- The scores ranged from 0 (worst health) to 100 (best health) and, when combined with mortality, yielded quality-adjusted life years (QALYs)

Costs in VA Administrative Data

- The study team, with consent, obtained SSN, date or randomization, date of surgery
- We matched that information to VA administrative records.
- We chose to extract costs from the VA Managerial Cost Accounting database.
  - This is an activity based cost accounting system.
  - Activities are matched with unit costs. Very precise, but errors are possible
  - Validation is important

Data Extraction and Transformation

- Index surgery is the treatment
- We extracted all VA utilization and cost data for the participants.
- Exclusions
  - All VA inpatient records where the discharge date was before date of index surgery
  - All VA outpatient records were visit day < date of index surgery

Transform the Data

- We wanted to measure costs starting with time of surgery
- We excluded costs in the index admission for days of care prior to index surgery
- We transformed the data into annualized costs
  - If patients were in the hospital at the end of the year, we allocated their costs proportionately based on length of stay
  - www.herc.research.va.gov/include/page.asp?id=implementation-tools-resources

Transformations

- Daily
  - Allocate all costs to a specific day. 365 records per person per year
  - Complicated, but powerful.[1]
- Monthly (30 day)
  - Allocate all costs to a specific month. 12 records per person per year.
  - My current default; can be summarized to annual
- Annual (365 day)
  - 1 record per person per year
  - Analytical easy, but can't break into 30 day periods.
- Data sets should be filled (rectangularized) until death
  - Costs are 0 in period with no utilization
  - Costs are missing (.) in periods after death

1. Mor V, Wagner TH, Levy C, Ersek M, Miller SC, Gidwani-Marszowski R, Joyce N, Faricy-Anderson K, Corneau EA, Lorenz K, Kinosian B. Association of expanded VA hospice care with aggressive care and cost for veterans with advanced lung cancer. JAMA oncology. 2019 Jun 1;5(6):810-6.

Cost Subtotals

- Depending on the study, we usually create subtotals based on treating specialty and clinic stops
  - Medical surgical costs
  - Skilled nursing facility costs
  - Outpatient mental health costs
  - Pharmacy costs

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 – not sure it is worth it

Separate Treatment Costs from Follow-up Costs

- Need to separately measure the treatment costs from follow-up costs
- Surgical trials are relatively simple
- 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
  - Cost of the index surgery
  - Costs after index surgery through 1 year.

Validate treatment costs?

- We often conduct validation studies to make sure that we're accurately estimating treatment costs

- For CABG, we did some validation work and then triangulated the VA costs with Medicare

Wagner TH, Cowgill EH. Updating the HERC Average Cost Method: Use of 2009 Medicare Data and an Analysis of CABG Surgery. Technical Report 27. Menlo Park, CA. VA Palo Alto, Health Economics Resource Center; 2012. https://www.herc.research.va.gov/files/RPRT_699.pdf

Construct Validity

- Surgical time and surgical costs increased with the number of grafts.
  - Compared with people with 1 to 2 grafts, a third graft took 38 minutes longer and cost $3,358 more
  - A fourth or more graft took 73 minutes longer and cost $3,854 more (all $P < .01$).
  - So: each graft past 2, adds about 35-40 minutes and $3500
  - Postoperative use of red blood cells and fresh-frozen plasma significantly increased the cost of the index hospitalization.
- Results gave us confidence in the MCA data

Wagner TH, Sethi G, Holman W, Lee K, Bakaeen FG, Upadhyay A, McFalls E, Tobler HG, Kelly RF, Crittenden MD, Thai H. Costs and quality of life associated with radial artery and saphenous vein cardiac bypass surgery: results from a Veterans Affairs multisite trial. The American Journal of Surgery. 2011 Nov 1;202(5):532-5.

Comparability

Average LOS (days)	ROOBY Total	ROOBY post-op	HCUP (2008) Total
	10.9	8.0	9.2

Cost (2010)

	ROOBY	HCUP*	Medicare*	Published Lit.
Facility	Inc.	Inc.	Inc.	Inc.
Physician	Inc.	--	--	Inc.
Total	$36,473	$38,882	$38,941	$35,373 - $59,619

* Costs based on cost-adjusted charges

Analytical steps with VA data

- Double check missing data, death and attrition
- Balance across study arms
- Examine treatment costs
- Examine follow-up costs
- Examine net costs (treatment+ follow-up)

- Non-VA costs
  - VA Community Care
  - Medicare
  - Self-report[1]

1. Bhandari A, Wagner T. Self-reported utilization of health care services: improving measurement and accuracy. Medical Care Research and Review. 2006 Apr;63(2):217-35.

Results: Adjusted Cost Estimates

	n	Adjusted cost ($)	*p* Value
CABG hospitalization			
On-pump	1,092	36,046	0.158
Off-pump	1,094	36,536	
Adjusted cost at 1-year			
On-pump	1,092	56,023	
Off-pump	1,094	59,623	0.046
Adjusted cost at 1-year, excluding conversions			
On-pump	1,052	56,127	
Off-pump	960	57,951	0.394
Adjusted cost at 1-year, by timing of conversion			
On-pump (with all conversions)	1,092	56,018	<0.0(1
Off-pump to on-pump (early conversions only)	1,041	58,877	
Off-pump to on-pump (late conversions only)	53	74,514	

Note: Based on semi-log regression with heteroskedastic smearing estimator for retransformation

Modeling

- Local variation
  - Wage adjustment or site fixed effect?
- Model choice
  - OLS (easily interpretable in dollars)
  - Semi-log OLS with smearing estimator (easily interpretable as an elasticity)
  - Square root OLS with smearing estimator
  - GLM (family and link function)

Hosmer Lemeshow Deciles

```
reg totcost1yr `covariate'
predict xb, xb
predict res_ols, resid
xtile xbtile = xb, nq(10)
qui tab xbtile, gen(xbtt)
reg res_ols xbtt*, nocons robust
testparm xbtt*
```

```
      Source |       SS           df       MS      Number of obs   =     2,186
-------------+----------------------------------   F(48, 2137)     =      6.08
       Model |  6.6850e+11         48  1.3927e+10   Prob > F        =    0.0000
    Residual |  4.8956e+12     2,137  2.2909e+09   R-squared       =    0.1201
-------------+----------------------------------   Adj R-squared   =    0.1004
       Total |  5.5641e+12     2,185  2.5465e+09   Root MSE        =     47863

------------------------------------------------------------------------------
  totcost1yr |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     onpump |   -4244.38   2694.476    -1.58   0.115    -9528.449    1039.688
     female |   9908.376   13577.46     0.73   0.466    -16718.04    36534.79
    age_u55 |  -8633.957   3855.124    -2.24   0.025    -16194.14   -1073.77
   age_5564 |  -9644.708   3064.203    -3.15   0.002    -15653.84   -3635.577
```

Hosmer Lemeshow Deciles

```
reg totcost1yr `covariate'
predict xb, xb
predict res_ols, resid
xtile xbtile = xb, nq(10)
qui tab xbtile, gen(xbtt)
reg res_ols xbtt*, nocons robust
testparm xbtt*
```

Predicts the fitted values from the regression model

Predicts the residuals from the regression model

Hosmer Lemeshow Deciles

```
reg totcost1yr `covariate'
predict xb, xb
predict res_ols, resid
xtile xbtile = xb, nq(10)
qui tab xbtile, gen(xbtt)
reg res_ols xbtt*, nocons robust
testparm xbtt*
```

Creates one variable that has the percentiles, deciles in this case, based on the fitted values xb

Creates 10 variable, one for each deciles

Hosmer Lemeshow Deciles

```
reg totcost1yr `covariate'
predict xb, xb
predict res_ols, resid
xtile xbtile = xb, nq(10)
qui tab xbtile, gen(xbtt)
reg res_ols xbtt*, nocons robust
testparm xbtt*
```

Regresses residuals on the fitted value deciles. This tells us how good our model fits for each decile. Ideal would be mean values of 0

Fitted Deciles

```
Linear regression
------------------------------------------------------------------------------
             |               Robust
     res_ols |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       xbtt1 |   8100.454   1804.887     4.49   0.000     4560.973    11639.94
       xbtt2 |    2989.31   1627.003     1.84   0.066    -201.3324    6179.952
       xbtt3 |    1002.09   2077.254     0.48   0.630    -3071.519    5075.699
       xbtt4 |  -1546.241   1727.312    -0.90   0.371    -4933.595    1841.112
       xbtt5 |   1733.935   2477.459     0.70   0.484    -3124.498    6592.367
       xbtt6 |  -2202.326   2643.344    -0.83   0.405    -7386.068    2981.417
       xbtt7 |  -3983.346   2032.583    -1.96   0.050    -7969.352    2.660363
       xbtt8 |  -4787.225   2593.367    -1.85   0.065    -9872.959     298.509
       xbtt9 |   -4573.43    3408.57    -1.34   0.180    -11257.82    2110.962
      xbtt10 |   3272.355   7325.975     0.45   0.655    -11094.28    17638.99
------------------------------------------------------------------------------
```

```
 testparm xbtt*

 ( 1)  xbtt1 = 0
 ( 2)  xbtt2 = 0
 ( 3)  xbtt3 = 0
 ( 4)  xbtt4 = 0
 ( 5)  xbtt5 = 0
 ( 6)  xbtt6 = 0
 ( 7)  xbtt7 = 0
 ( 8)  xbtt8 = 0
 ( 9)  xbtt9 = 0
 (10)  xbtt10 = 0

       F( 10,  2176) =    3.50
            Prob > F =    0.0001
```

GLM Model Choice

```
*boxcox
boxcox DV `covariates'
```

```
1.00: no transformation needed
0.50: square root transformation
0.00: natural log transformation
```

```
*modified park test
glm DV `covariates', fam(gaussian) link(log)
predict mu, mu
gen lnmu = ln(mu)
gen r2 = (cost - mu)^2
glm r2 lnmu, link(log) family(gamma) robust
test lnmu=0
test lnmu=1
test lnmu=2
test lnmu=3
```

```
if the coefficient = 0, Gaussian distribution. Variance is constant.
if the coefficient = 1, Poisson distribution. Variance is proportional to mean.
if the coefficient = 2, Gamma distribution. Variance is proportional to square
     of mean.
if the coefficient = 3, Inverse Gaussian or Wald distribution. Variance is
     proportional to cube of mean
```

Examine Fits for Each Model

- A bit tedious, but helpful for understanding fit across different models
- You can program this into Stata

- Often no one model is best. You can present one and use another in a sensitivity analysis
  - It is possible to have different optimal models for intervention costs and follow-up costs.
  - Tradeoff between best model and additional complexity / less interpretability

Follow-up

- With multiple follow-up periods per person, you need to deal with the non-independence in error terms.

- Common options are a person level random effect (RE) or a person level fixed effect (FE).
  - If randomization happened at the person level, usually the RE model and FE model yield similar results and the RE is more efficient than a FE model.
  - If randomization happened at the facility, then not clear cut and you should consider clustering at the facility level (similar to a hierarchical model)

Mortality

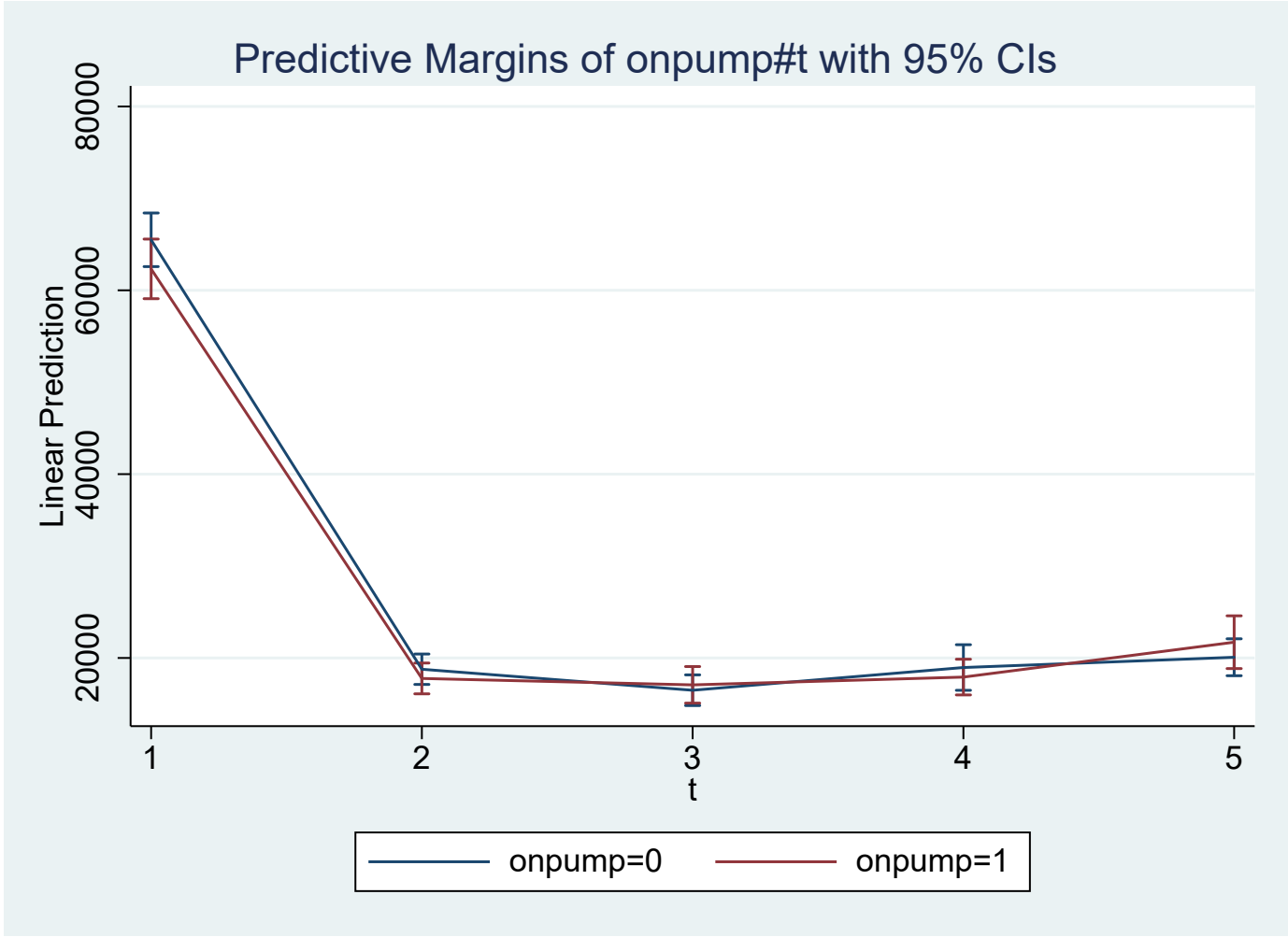
- Complete VA data while the person lives
- In our five year analysis, the ROOBY trial had complete costs on people who died in the year and then censored those who were alive. This censoring biases OLS estimates.
- Two methods:
  - Weight the cases by the inverse probability of being censored.[1]
  - Two-part model to deal with random right censoring and for continuous death and censoring times.[2]

1. Lin DY. Linear regression analysis of censored medical costs. Biostatistics. 2000 Mar 1;1(1):35-47.
2. Basu A, Manning WG. Estimating lifetime or episode-of-illness costs under censoring. Health economics. 2010 Sep;19(9):1010-28.

Margins

- Stata has a margins command that you use after your regression

```
margins i.onpump#i.t,  level(95)
marginsplot, x(t) recast (line) level(95)
```



Cumulative Costs vs Annual Costs

- The XT models show the costs per year.

- Clinicians sometimes ask me to create cumulative totals.
  - That is equivalent to summing each person's costs for the 5 years and using that as a dependent variable.
  - That ignores mortality, and the Lin method doesn't work there because the interval is too broad.

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

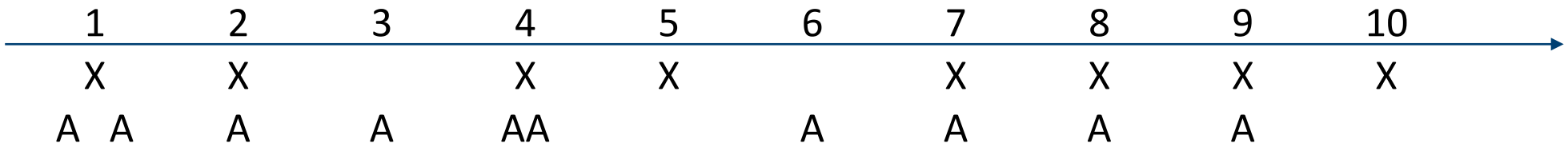
Heterogenous Treatment Effects

- Are the main trial effects consistent across subgroups?
  - If yes, then you have homogenous treatment effects
  - If no, then you have heterogenous treatment effects

- Considerably less power than main effects.
- If not specified in the protocol, these should be described as exploratory
- Consider penalties for multiple comparisons.

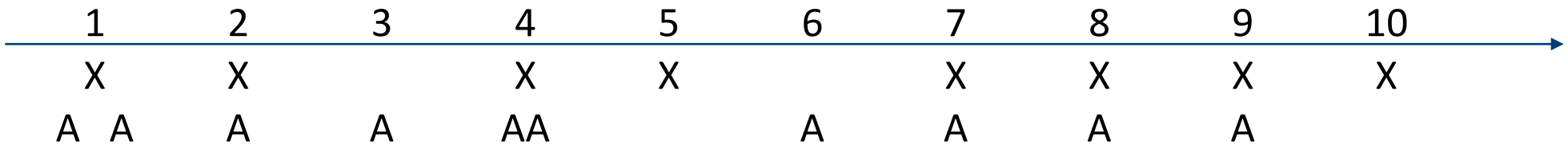
Treatment costs

- The ROOBY surgery example was simple
- Consider a trial testing stroke rehab that continues for 10 weeks
  - Patients will often get other care while getting rehab
  - Administrative data (A) may not match data collected by trial (X)



- Two options
  1. Use trial data with average unit costs
  2. Use admin data, clean and impute missing

A Bit More Complicated

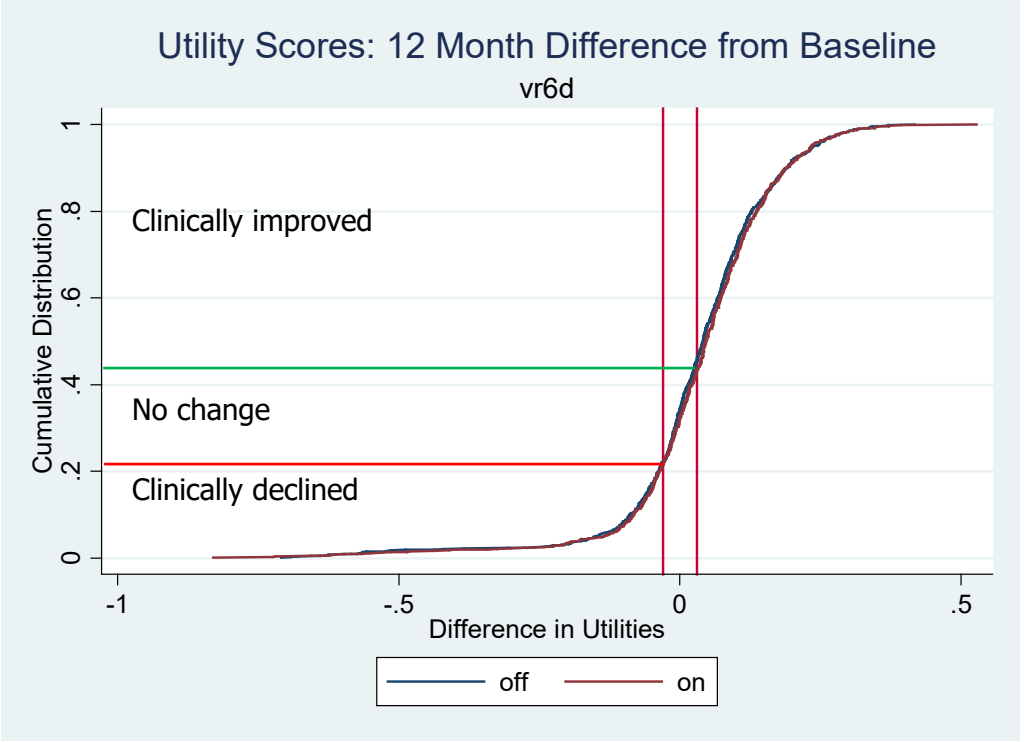


- If you use trial data, what do you do with the administrative data?
- If you use administrative data, what do with the extras

- No easy answer
- But don’t double count

Results: Quality of Life at 1 year

- 56% of patients improved by 12 months.
- No difference between on-pump and off-pump
- Clinic Follow-up ended at 1 year.



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.

Net Benefit

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

- Quality Adjusted Life Years (QALYs) are the preferred metric. If we knew the dollar value per QALY, then we can turn the CEA into a net benefit analysis

  $NB = (\text{Cost}_a - \$ \text{ value per QALY}_a) - (\text{Cost}_b - \$ \text{ value per QALY}_b)$

- This NB calculation can be done for each person, and then you can use regression to examine NB and if there are heterogenous treatment effects

Hoch JS, Briggs AH, Willan AR. Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis. Health economics. 2002 Jul;11(5):415-30.
Hoch JS, Rockx MA, Krahn AD. Using the net benefit regression framework to construct cost-effectiveness acceptability curves: an example using data from a trial of external loop recorders versus Holter monitoring for ambulatory monitoring of" community acquired" syncope. BMC Health Services Research. 2006 Dec;6(1):68.

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 my 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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