Decisions, decisions, decisions: Selecting methods for data analysis

Denise M Hynes, PhD, RN

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Hines VA
VA Information Resource Center
& The University of Illinois at Chicago
Study Design & Analysis Considerations
Focus on Comparative Effectiveness Research

Which Design/Analysis for Which Question?
Slightly Deeper Dive in Design Elements
Poll #1: About you – research role

What is your role in research?

1. Research investigator
2. Data manager/analyst
3. Project coordinator
4. Other – please describe via the Q&A function

Heidi: Poll Question
Poll #2: About you – data experience

How many years of experience do you have working with VA data?

- Less than 1
- 1-2
- 3-6
- 7+
Session Outline

• Overview of study design and analysis relationship
• Overview of analysis decisions
  – Making choices about analysis techniques
• Internal and external validity issues
Three Key References


Which design for which question?
Key Issues to Consider

• Is the study question most appropriately answered with an experimental or non experimental design?

• Within that broad design approach, what is the best study method to address this question?

• Design & analytic feature(s) to ensure the validity, relevance & timeliness of the study results

• Do you have the right team to weigh the options and carry out the study?
Study Design Choices
Use Case #1: Anticoagulation & Joint Replacement

• Research question: What is the relative effectiveness and safety of the available anti-thrombotic alternatives in patients undergoing arthroplasty?

• Study design: observational versus experimental?
  – Large parallel-group randomized trial
### Observational Design Considerations: Use Case #1 Anticoagulation Study

<table>
<thead>
<tr>
<th><strong>Pros</strong></th>
<th><strong>Cons</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patient-important outcomes (symptomatic venous thrombosis, embolism, death associated with VTE, bleeding and death associated with bleeding) are rare</td>
<td>• Not enough known about differences in prognosis attributable to the alternative agents</td>
</tr>
<tr>
<td>• Showing differences in event rates between regimens requires very large sample sizes.</td>
<td>• No large cohort studies addressed risk prediction, and no validated prediction models exist</td>
</tr>
<tr>
<td>• Events are likely to be recorded accurately in administrative databases</td>
<td>• Surgeons’ assessments of VTE and bleeding risk will likely affect choice of agents</td>
</tr>
<tr>
<td></td>
<td>• Prognostic stratification unlikely to balance prognostic factors</td>
</tr>
</tbody>
</table>
### Experimental Design Considerations: Use Case #1 Anticoagulation Study

<table>
<thead>
<tr>
<th><strong>Pros</strong></th>
<th><strong>Cons</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Likely to balance prognostic factors</td>
<td>• Powering only for substitute or surrogate end points (i.e., asymptomatic thrombosis, typically detected by venography) may introduce bias</td>
</tr>
<tr>
<td>• Powered for patient-important outcomes</td>
<td>• May be expensive to engage patients</td>
</tr>
<tr>
<td>• Needs to be sufficiently large</td>
<td>•</td>
</tr>
<tr>
<td>• Likelihood that even relatively small prognostic imbalances and other biases can easily mislead</td>
<td>•</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Design</th>
<th>Feasibility</th>
<th>Protection from Bias</th>
<th>Applicability</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Experimental Design</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient-level randomization</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Non-experimental Design</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrospective Observational</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Prospective observational</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

+ indicates the extent to which the consideration is present

Montori, et al., 2012
Design and Analytic Features

- Concealed randomization
  - Blinding of patients, caregivers, data collectors, adjudicators of outcome, and data analysts
  - Complete follow-up
  - Analysis-as-randomized

- Measurement of outcomes
  - Trade-offs
    - Anticoagulation Study: between the absolute reduction in patient-important VTE and the absolute increase in patient-important bleeding
Which Design Approach Summary

• Experimental or non-experimental?
• Either choice: study design considerations
  – Validity: Protect the results from bias
  – Relevance: Ensure their applicability
  – Timeliness: Provide them in a timely fashion
  – Analysis: Carefully consider outcomes and covariates
Three Non-experimental Use Cases

Costs of care for lung and colon cancer patients receiving chemotherapy following FDA policy changes

Kevin T. Stroupe • Elizabeth Tarlov • Thomas W. Weichle • Qiuying L. Zhang • Laura C. Michaelis • Howard Ozer • Ramon Durazo-Arvizu • Denise M. Hynes

Rationale and design of a patient-centered medical home intervention for patients with end-stage renal disease on hemodialysis

Anna C. Porter • Marian L. Fitzgibbon • Michael J. Fischer • Rani Gallardo • Michael L. Berbaum • James P. Lash • Sheila Castillo • Linda Schiffer • Lisa K. Sharp • John Tulley • Jose A. Arruda • Denise M. Hynes

Reduced Overall and Event-Free Survival among Colon Cancer Patients Using Dual System Care

Elizabeth Tarlov • Todd A. Lee • Thomas W. Weichle • Ramon Durazo-Arvizu • Qiuying Zhang • Ruth Perrin • David Bentrem • Denise M. Hynes
Which Analysis for Which Outcome?
Analysis Strategies

• Descriptive statistics (unadjusted)
• Adjusted
• Regression Modeling
Descriptive Analysis

Continuous Measures
- Range
- Dispersion
- Central tendency

Categorical Measures:
- Number and percent for categorical variables
- Plots for evaluating data distributions
  - Binary or multinomial
    - Characterizing a population
    - Describing survey responses
    - Summarizing comparison groups/study arms
Analysis Approaches
Use Case #2: Impact of ESA Guideline Changes on Costs of Cancer Care

• Stroupe et al., 2014
• Research Question: Would anemia management costs and overall cancer treatment costs decline with mandated changes in ESA use?
• Design: Retrospective cohort study, 2002-2008
• Outcome measure: Costs of specific and overall treatment for lung and colon cancer care
• Exposure: FDA mandate – pre and post
Use Case #2: ESA & Cancer Costs

Key Variable Definition

- *Chemotherapy episode of care* - period from 30 days before to 90 days after the chemotherapy start and end dates, respectively
- *Treatment Period* - PRE vs. POST black box warning

![Diagram showing PRE and POST periods with dates]

<table>
<thead>
<tr>
<th>1/1/02</th>
<th>1/1/07</th>
<th>12/31/09</th>
</tr>
</thead>
</table>

FDA Issues Black Box Warning, 3/2007
### Table 1: Sample characteristics

<table>
<thead>
<tr>
<th>Sample characteristics</th>
<th>Lung cancer (N=13,630)</th>
<th>Colorectal cancer (N=3,198)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRE&lt;sup&gt;a&lt;/sup&gt; (n=9,570)</td>
<td>POST&lt;sup&gt;b&lt;/sup&gt; (n=4,060)</td>
</tr>
<tr>
<td><strong>Age at diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>65.3 (9.1)</td>
<td>65.0 (8.7)</td>
</tr>
<tr>
<td>55 and younger</td>
<td>1,456 (15.2)</td>
<td>464 (11.4)</td>
</tr>
<tr>
<td>56–65</td>
<td>3,463 (36.2)</td>
<td>1,903 (46.9)</td>
</tr>
<tr>
<td>66–75</td>
<td>3,165 (33.1)</td>
<td>1,131 (27.9)</td>
</tr>
<tr>
<td>76–85</td>
<td>1,443 (15.1)</td>
<td>529 (13.0)</td>
</tr>
<tr>
<td>86–90</td>
<td>43 (0.4)</td>
<td>33 (0.8)</td>
</tr>
<tr>
<td>Male</td>
<td>9,369 (97.9)</td>
<td>3,953 (97.4)</td>
</tr>
<tr>
<td>African American</td>
<td>1,513 (15.8)</td>
<td>665 (16.4)</td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>233 (2.4)</td>
<td>108 (2.7)</td>
</tr>
<tr>
<td>Stage at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1,153 (12.0)</td>
<td>435 (10.7)</td>
</tr>
<tr>
<td>II</td>
<td>638 (6.7)</td>
<td>370 (9.1)</td>
</tr>
<tr>
<td>III</td>
<td>3,676 (38.4)</td>
<td>1,525 (37.6)</td>
</tr>
<tr>
<td>IV</td>
<td>4,103 (42.9)</td>
<td>1,730 (42.6)</td>
</tr>
</tbody>
</table>

*P* values are indicated for the comparison between PRE<sup>a</sup> and POST<sup>b</sup>.
Regression Models: Weighing Different Approaches

• Time Varying Exposures
• Propensity Scores
• Disease Risk Scores
• Latent Class Analysis
• Instrumental Variables
Analysis Approach
Use Case #2: ESA & Cancer Costs

• Anemia Management Costs (ESA, blood transfusion, and total anemia management costs) using two-part models
  – Logistic regression - to predict whether any cost was incurred
  – GLM (gamma family based on modified Park test with log link) to predict costs conditional on having non-zero costs
  – Results from the logistic and GLM analyses - applied to produce predicted anemia management costs per patient

• Cancer-related and overall healthcare costs
  – GLM models to predict cancer-related & total health costs
Show Predicted Outcomes
Use Case #2: ESA & Cancer Costs

Difference in Mean Colon Cancer Costs per Patient between PRE and POST Periods*

* Differences in POST- PRE period costs calculated from multivariable regression analyses

- Transfusion: $12, p = 0.37
- ESA: -$504, p < 0.01
- Anemia Management: -$508, p < 0.01
- Cancer Related: $10,343, p < 0.01
- Overall Healthcare Costs: $11,414, p < 0.01
Key Dimensions That Drive Analysis Approach

- Study design
- Outcome measure characteristics
- Covariate characteristics
- Single or repeated measurement
- Temporal aspects
Use Case #3: Adaptation of PCMH for CKD

- Porter, et al., 2015
- Research Question: Can we improve patient QOL by implementing a new model of care?
- Study Design: Multisite, prospective intervention, pre/post design, 2 yr
- Outcome measure: KDQOL
- Repeated measures: Every six months
- Clustering: Sites
Analysis Approach
Use Case #3: Adaptation of PCMH for CKD

PCMH-KD: Care Team Intervention

Current CMS-Mandated Team

Dialysis Team:
- Manager
- Technician
- Dietician
- Social Worker
- Nurse

Nephrologist

ESRD Patient & Caregiver

PCMH-KD: New Team Members
- General Internist
- Advanced Practice Nurse
- Pharmacist
- Health Promoter

Care Coordinator

Advanced Practice Nurse

CHW/Health Promoter

Pharmacist
Analysis Approach
Use Case #3: Adaptation of PCMH for CKD

Consider Site Differences

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Dialysis patient characteristics.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UIHS-D</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age in years</td>
<td>55</td>
</tr>
<tr>
<td>Race/ethnicity (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>4</td>
</tr>
<tr>
<td>Black</td>
<td>63</td>
</tr>
<tr>
<td>Hispanic</td>
<td>30</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
<tr>
<td>Length of dialysis (%)</td>
<td></td>
</tr>
<tr>
<td>≤180 days since initiation</td>
<td>25</td>
</tr>
<tr>
<td>&gt;180 days since initiation</td>
<td>75</td>
</tr>
<tr>
<td>Comorbidities (%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>72</td>
</tr>
<tr>
<td>Hypertension</td>
<td>59</td>
</tr>
<tr>
<td>Other</td>
<td>54</td>
</tr>
</tbody>
</table>
Analysis Approach
Use Case #3: Adaptation of PCMH for CKD

PCMH-KD: Outcomes

**Improved:**
- Quality of Life
- Care Coordination
- Health Literacy/Education

**Improved:**
- Co-morbidity management
- Adequate Hemodialysis
- Patient/Provider Satisfaction
- Rx and diet compliance
- AVF grafts

**Fewer:**
- Vascular Access Complications
- Hospitalizations
- ER visits
Analysis Approach

Use Case #3: Adaptation of PCMH for CKD

1. “Population-Averaged” marginal generalized estimating equation, (GEE) estimation of generalized linear models (GLMs)
   - SAS PROC GENMOD

2. “Subject-Specific” generalized linear mixed models (GLMMs)
   - SAS PROC GLIMMIX (and PROC MIXED for continuous outcomes with Gaussian errors)
Analysis Approach

Use Case #3: Adaptation of PCMH for CKD

Avoidance of Bias

• Careful assessment of reasons for missing data guides analysis
• Will conduct sensitivity analysis, and may use distribution-free methods for exploring impact of missing data on results
• Will include covariates for subgroup analysis
• Will use GEE and propensity adjustment as warranted for subgroup comparison.
<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Single Measure</th>
<th>Repeated Measure, Fixed Intervals</th>
<th>Repeated Measure, Variable Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dichotomous</td>
<td>Logistic regression</td>
<td>Multilevel (mixed) logistic regression, GLMM, GEE, conditional logistic regression</td>
<td>Repeated measures ANOVA (MANOVA), GLMM, GEE</td>
</tr>
<tr>
<td>Continuous</td>
<td>Linear regression</td>
<td>Multilevel (mixed) linear regression, GLMM, GEE</td>
<td>Repeated measures ANOVA (MANOVA), GLMM, GEE</td>
</tr>
</tbody>
</table>

Adapted from Arbogast & VanderWeele, 2013
### Dimensions That Drive Analysis Approaches

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Single Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No clustering</strong></td>
<td><strong>Clustering (e.g., multi-site study)</strong></td>
</tr>
<tr>
<td><strong>Time to event</strong></td>
<td>Cox proportional hazards regression</td>
</tr>
<tr>
<td><strong>Time to event (aggregate or count data)</strong></td>
<td>Poisson regression</td>
</tr>
</tbody>
</table>

Adapted from Arbogast & VanderWeele, 2013
Analysis Approach
Use Case #4: Event Free Survival in a Cancer Cohort

- Tarlov et al., 2012
- Research Question: Are there differences in 3 year OS ad EFS among patients with nonmetastatic colon cancer
- Design: Retrospective cohort design
- Outcome Measure: Overall & Event-free survival
- Key covariate: Predominance of VA use
- Time varying component: **Time to relapse, time to subsequent treatment**
- Analysis Approach: Cox proportional hazard regression model
### Table 4. Estimated HR comparing healthcare system user groups: revised dual use measure

<table>
<thead>
<tr>
<th>Healthcare system use</th>
<th>Overall survival</th>
<th>EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Stage I (N = 1,028)</td>
<td>Stage II (N = 1,129)</td>
</tr>
<tr>
<td>Predominantly VA</td>
<td>0.50 (0.35–0.71)</td>
<td>0.72 (0.52–0.99)</td>
</tr>
<tr>
<td>Dual User</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Predominantly Non-VA</td>
<td>0.63 (0.43–0.91)</td>
<td>0.79 (0.57–1.11)</td>
</tr>
</tbody>
</table>

Note: HR were obtained from Extended Cox survival models adjusted for age, race, comorbidity score, marital status, area high school graduation rate, tumor grade, number of regional lymph nodes examined, colectomy (stage I), chemotherapy (stages II and III), distance to VA outpatient center, and geographic region. Dual use status was held static at its value 30 days before the event.
Poll #3 Your Grant Experience

• How many grant proposals have you worked on as PI or part of a team?
  – None or not applicable
  – 1
  – 2-3
  – Over 3

Heidi: Poll Question
**Guidance and key considerations for developing a statistical analysis section of an observational CER protocol**

Checklist from Arbogast & VanderWeele, 2013

<table>
<thead>
<tr>
<th>Guidance</th>
<th>Key Considerations</th>
<th>Check</th>
</tr>
</thead>
</table>
| Describe the key variables of interest with regard to factors that determine appropriate statistical analysis. | - Should discuss independent variables (when they are measured, whether they are fixed or time-varying; e.g., exposures, confounders, effect modifiers).  
- Should discuss dependent variables or outcomes (continuous or categorical, single or repeated measure, time to event).  
- Should state if there will be a “multilevel” analysis (e.g., an analysis of effects of both practice-level and patient-level characteristics on outcome). | □     |
| Propose descriptive analysis or graph according to treatment group.      | - Should include the available numbers per group, number missing for all key covariates, distributions or graphs that are needed to decide if transformation of data is needed or to determine an accurate functional form of the final model.  
- Should include all potential confounders and effect modifiers to assess initial covariate balance by study group. | □     |
| Propose the model that will be used for primary and secondary analysis objectives. | - Should take into account the design (independent vs. dependent observations, matched, repeated measurement, clustered), objectives, functional form of model, fixed/time-varying followup period, fixed and time-varying exposure and other covariates, assessment of effect modification/heterogeneity, type of outcome variables (categorical, ordinal, or continuous), censored data, and the degree of rarity of outcome and exposure.  
- Should propose a suitable approach for adjusting for confounding (e.g., multiple regression model, propensity scores, instrumental variable [as secondary or main analysis]). | □     |
<table>
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<tr>
<th>Describe the key variables of interest with regard to factors that determine appropriate statistical analysis.</th>
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</tr>
<tr>
<td>Proposal</td>
</tr>
<tr>
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</table>
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- Should include all potential confounders and effect modifiers to assess initial covariate balance by study group. |
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| Should propose a suitable approach for adjusting for confounding (e.g., multiple regression model, propensity scores, instrumental variable [as secondary or main analysis]). |
Poll # 4 – Your future research studies

What kinds of studies do you anticipate working on in the next 3 years?

1. Experimental
2. Non/Quasi-experimental
3. Not sure/Don't yet know

Heidi: Poll Question
A slightly deeper dive into

Maciejewski, et al., 2013

ADDITIONAL DESIGN ELEMENT CONSIDERATIONS IN NON-EXPERIMENTAL STUDIES
Design Elements to Improve Internal Validity

• Inclusion of control groups
• Pre-intervention measurement
• Inclusion of nonequivalent outcomes.
Considerations for Control Group Design

• Longitudinal pre-post cohort design with a single control group
• Longitudinal post-only cohort design with multiple control groups
• Longitudinal pre-post cohort design with multiple control groups

* each should address a distinct threat to internal validity
Considerations for Defining a Control Group

• Apply inclusion /exclusion criteria
• Consider matching criteria
• Ensure no treatment, i.e. cross contamination
Treatment Effects (TE)

• Population Average Treatment Effect (PATE)
  Definition: Average effect of a treatment (compared with control) for a patient selected randomly from the population of patients eligible for the treatment
  – Has optimal internal and external validity

• Sample Average Treatment Effect (SATE)
  Definition: Average effect of a treatment (compared with control) for a patient in the study sample

• Ideally SATE=PATE
Veterans in initial VA cohort

Veterans enrolled in Medicare in 2004 (n = 4,715,657)

VA/Medicare Cohort Sampling Frame (n = 2,585,089)

5% Random Sample (n = 129,255)

Analytic Sample (n = 129,117)

Veterans with VA/CMS outpatient use (n = 125,042)

Elimination of Veterans who:
- Were 65 or younger on January 1, 2004 (n=947,489)
- Enrolled in Medicare+ Choice plan in 2004 (n=589,027)
- Had unknown Veteran status (n=821,181)
- Had missing geographic data (n=6,798)
- Lived in Puerto Rico or other U.S. territories (n=60,305)
- Qualified for Medicare due to ESRD (n=46,695)
- Had no utilization (n=228,113)
- Died before 01/01/2004 (n=7,999)

NOTE: Categories are not mutually exclusive

Exclude records with invalid zip code (n=98) and date of death (n=40)

Exclude Veterans with no outpatient utilization (n=4,075)
Design Elements to Consider to Improve External Validity

- Treatment settings
- Prognostic risk of patients
- Inclusion of prevalent and/or incident users
Considerations For Use of Incident Cohorts

• Most useful in studies evaluating initial benefits and harms of treatment initiation and/or treatment switching or discontinuation due to harms

• Incident cohorts may be smaller, with less statistical power
  – Example: Incident ESRD may represent only 25%
  – Complication rate is high relative to prevalent

• Use longer index period to minimize risk of misclassification
Considerations for Use of Prevalent Cohort

- Sample size probably larger
- Benefits and harms likely more stable
- Potential to be highly selective of most adherent or those who continued therapy for some extended period
  - Tends to exclude those who are non-adherent, those who could not tolerate, or for whom a treatment was not effective
- Careful consideration of look-back period
Considerations to Minimize Treatment Misclassification

- Limits of observational data and potential ascertainment bias
- Unobserved events
  - Carefully consider limits of administrative data
  - Longer look-back periods
  - Multiple sources
Summary of Strategies for Improving External Validity

• Clinical treatment setting
  – Go beyond academic medical centers
• Prognostic risk of patients
  – Consider Instrumental variable approach
• Prevalent and incident cohorts
  – Include subjects from wide range of risk
• Potential treatment misclassification
  – Carefully consider limits of data sources
Take Aways

Design and Analysis go together
Take Aways

Use critical appraisal principles as you plan & execute
Acknowledgements

• VA HSR&D
  – SDR 02-237 VIREC VA CMS Data Merge
  – IIR 08-354 ESA Cancer Study
  – IIR 03-196 Quality & Costs of Colon Cancer
  – 98-352 VA RCS 98-352

• PCORI
  – IH-12-11-5420: PCMH-KD Study
Study Examples Cited


