Decisions, decisions, decisions: Selecting methods for data analysis

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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+

Heidi: Poll Question

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

Arbogast, PG & VanderWeele, TJ. *Consideration for Statistical Analysis, In: Velentgas P and Dreyer NA, eds. Developing a Protocol for Observational Comparative Effectiveness Research*: A User's Guide. Rockville, MD: AHRQ; Jan 2013. AHRQ Pub No. 12-EHC099.

Montori, VM, Kim, SP, Guyatt, GH & Shah, ND. *Which design for which question? An exploration toward a translational table for comparative effectiveness research.* J Comparative Effectiveness Research. 2012; 1(3), 271–279.

Maciejewski, ML, Curtis, LH, & Dowd, B. *Study design elements for rigorous quasi-experimental comparative effectiveness research.* J Comparative Effectiveness Research. 2013; 2(2), 159–173.

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

Pros

- Patient-important outcomes (symptomatic venous thrombosis, embolism, death associated with VTE, bleeding and death associated with bleeding) are rare
- Showing differences in event rates between regimens requires very large sample sizes.
- Events are likely to be recorded accurately in administrative databases

Cons

- Not enough known about differences in prognosis attributable to the alternative agents
- No large cohort studies addressed risk prediction, and no validated prediction models exist
- Surgeons' assessments of VTE and bleeding risk will likely affect choice of agents
- Prognostic stratification unlikely to balance prognostic factors

Experimental Design Considerations:
Use Case #1 Anticoagulation Study

Pros

- Likely to balance prognostic factors
- Powered for patient-important outcomes
- Needs to be sufficiently large
- Likelihood that even relatively small prognostic imbalances and other biases can easily mislead

Cons

- Powering only for substitute or surrogate end points (i.e., asymptomatic thrombosis, typically detected by venography) may introduce bias
- May be expensive to engage patients

Experimental Versus Non-Experimental Designs: Weighing Study Features

Design	Feasibility	Protection from Bias	Applicability	Costs
Experimental Design				
Patient-level randomization	+++	+++	++	+++
Non-experimental Design				
Retrospective Observational	+++	+	++	+
Prospective observational	+++	+	++	++

+ 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

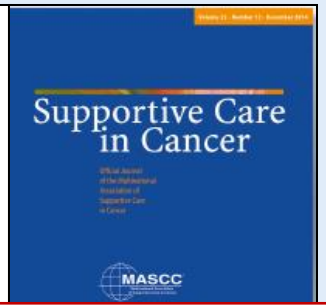
Which Design Approach Summary

- 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



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

CrossMark

Anna C. Porter [a,*], Marian L. Fitzgibbon [b,c], Michael J. Fischer [a,d], Rani Gallardo [b], Michael L. Berbaum [c], James P. Lash [a], Sheila Castillo [e], Linda Schiffer [b], Lisa K. Sharp [f], John Tulley [g], Jose A. Arruda [a], Denise M. Hynes [b,c,h]

Cancer Epidemiology, Biomarkers & Prevention

Research Article

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

Elizabeth Tarlov[1,2], Todd A. Lee[4], Thomas W. Weichle[1,2], Ramon Durazo-Arvizu[1,3], Qiuying Zhang[1,2], Ruth Perrin[1,2], David Bentrem[5,6], and Denise M. Hynes[1,2,7]

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

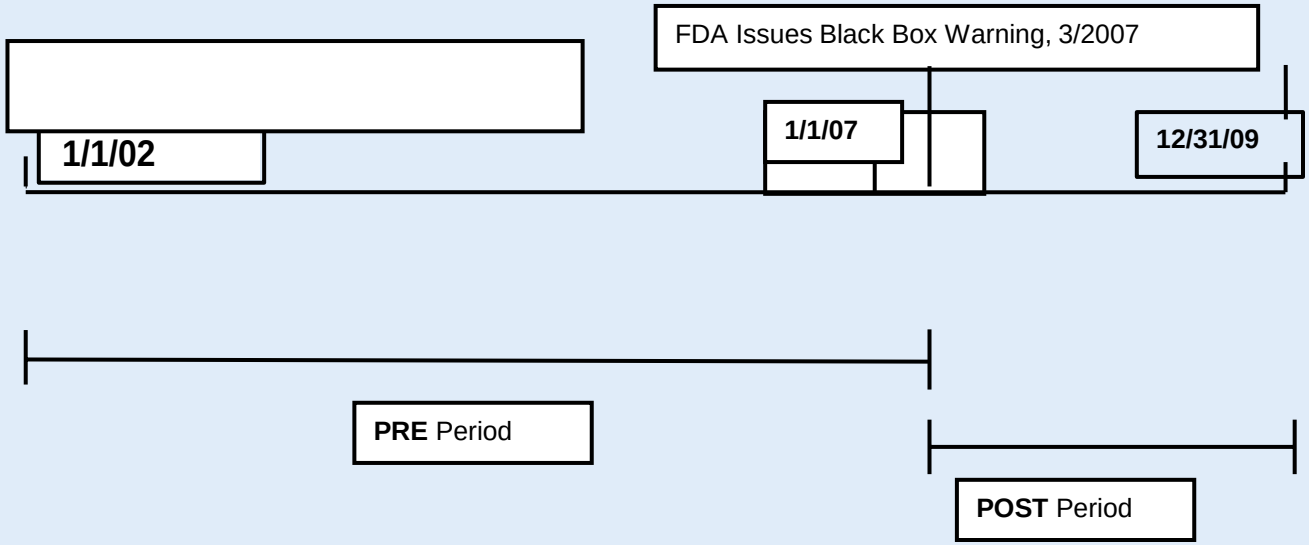
Analysis Approaches
Use Case #2: Impact of ESA Guideline Changes on Costs of Cancer Care

- 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

Index Period
Use Case #2: ESA & Cancer Costs

<u>Key Variable Definition</u>

- *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



Retrospective Observational Cohort Study: Show Exposure/Groups

Table 1 Sample characteristics

	Lung cancer (N=13,630)					Colon cancer (N=3,198)				
	PRE[a] (n=9,570)		POST[b] (n=4,060)			PRE[a] (n=2,182)		POST[b] (n=1,016)		
Sample characteristics	No.	Percent	No.	Percent	P value	No.	Percent	No.	Percent	P value
Age at diagnosis										
Mean (SD)	65.3 (9.1)		65.0 (8.7)		<0.01	66.1 (10.1)		64.9 (9.8)		<0.01
55 and younger	1,456	15.2	464	11.4	<0.01	346	15.9	138	13.6	<0.01
56–65	3,463	36.2	1,903	46.9		693	31.8	447	44.0	
66–75	3,165	33.1	1,131	27.9		689	31.6	257	25.3	
76–85	1,443	15.1	529	13.0		434	19.9	159	15.6	
86–90	43	0.4	33	0.8		20	0.9	15	1.5	
Male	9,369	97.9	3,953	97.4	0.05	2,140	98.1	979	96.4	<0.01
African American	1,513	15.8	665	16.4	0.41	384	17.6	217	21.4	0.01
Hispanic ethnicity	233	2.4	108	2.7	0.44	159	7.3	75	7.4	0.92
Stage at diagnosis					<0.01					0.04
I	1,153	12.0	435	10.7		85	3.9	52	5.1	
II	638	6.7	370	9.1		388	17.8	148	14.6	
III	3,676	38.4	1,525	37.6		1,071	49.1	493	48.5	
IV	4,103	42.9	1,730	42.6		638	29.2	323	31.8	

Regression Models: Weighing Different Approaches

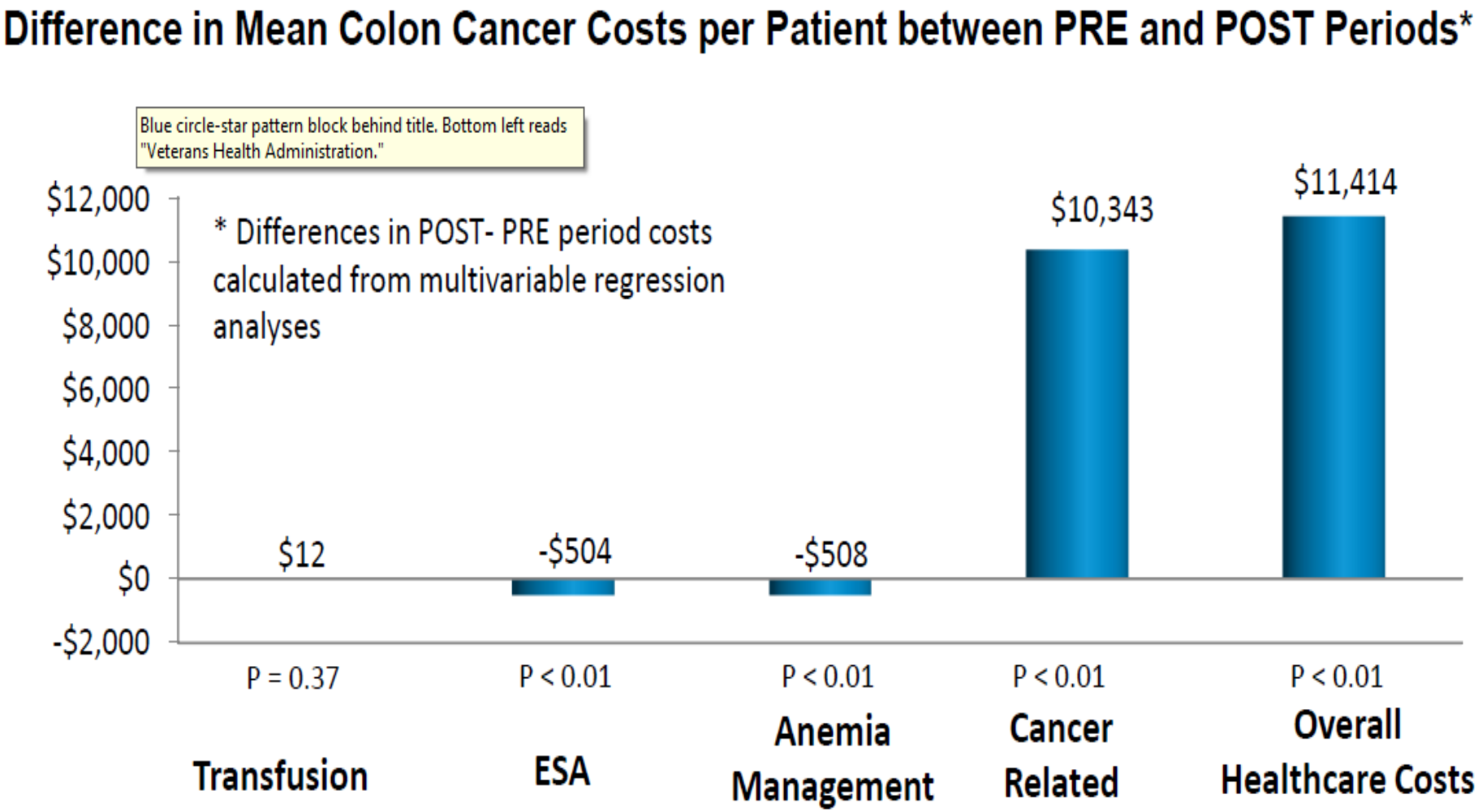
- Time Varying Exposures
- Propensity Scores
- Disease Risk Scores
- Latent Class Analysis
- Instrumental Variables

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



Key Dimensions That Drive Analysis Approach

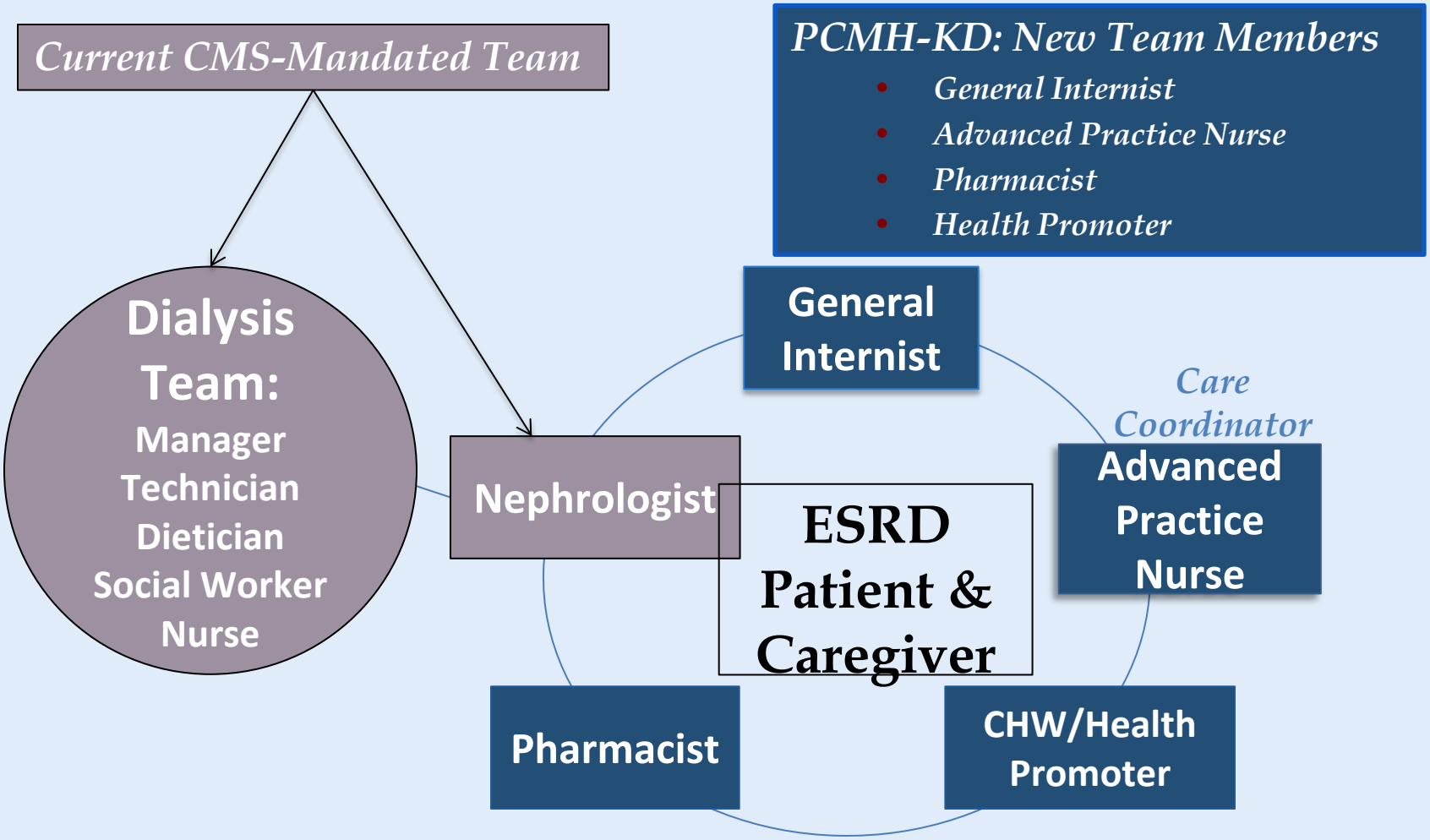
- Study design
- Outcome measure characteristics
- Covariate characteristics
- Single or repeated measurement
- Temporal aspects

Analysis Approach
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



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

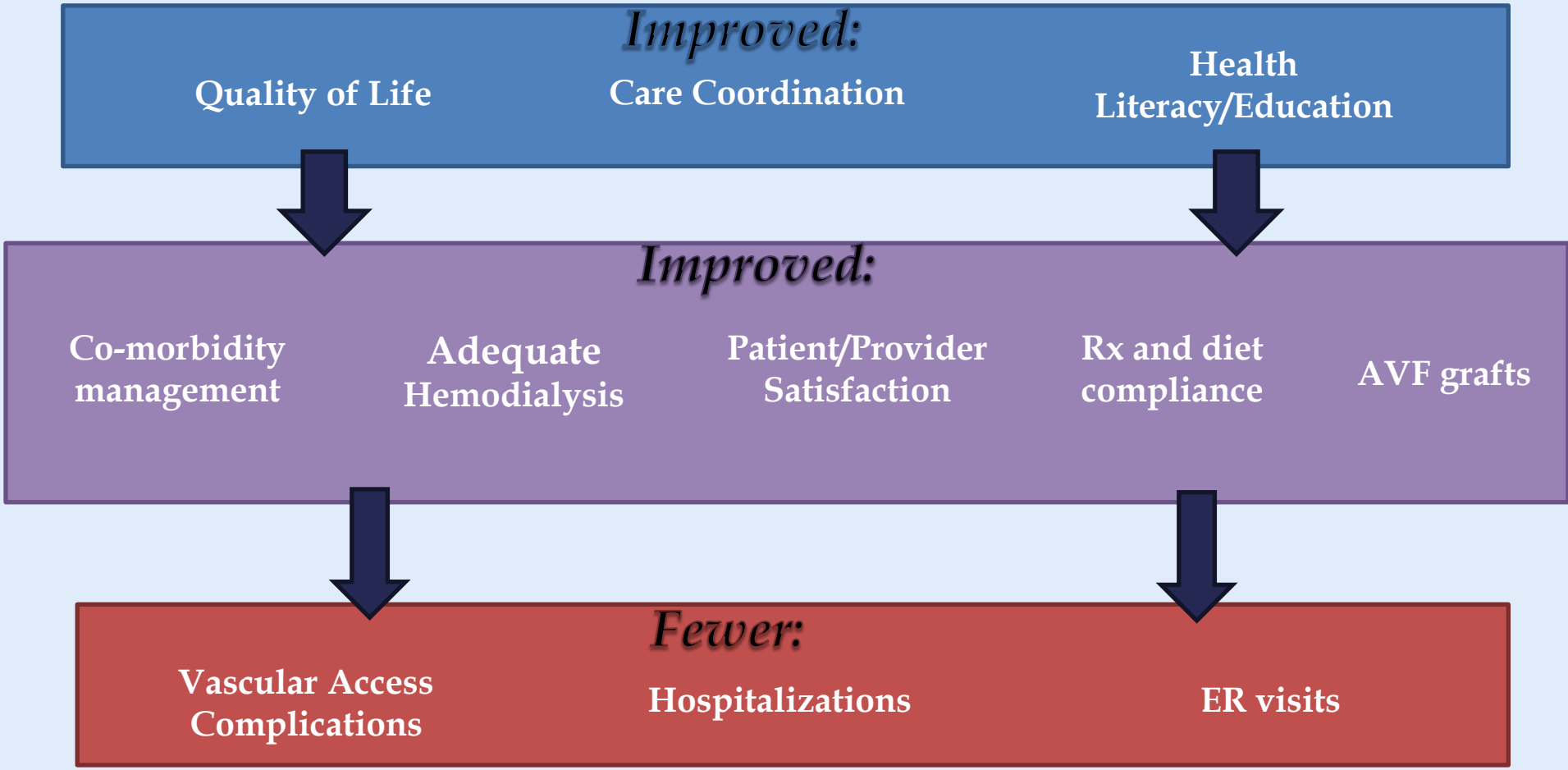
Consider Site Differences

Table 1
Dialysis patient characteristics.

	UIHS-D ($N = 138$)	FMC ($N = 78$)	USRDS dialysis cohort ($N = 103{,}874$)
Mean age in years	55	50	NA
Race/ethnicity (%)			
White	4	3	66
Black	63	40	29
Hispanic	30	56	Hispanic/non-Hispanic 14/86
Other	3	1	6
Length of dialysis (%)			
≤180 days since initiation	25	31	NA
>180 days since initiation	75	69	NA
Comorbidities (%)			
Diabetes	72	28	45
Hypertension	59	48	29
Other	54	24	26

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

PCMH-KD: Outcomes



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.

Dimensions That Drive Analysis Approaches

Number of Follow-up Measures and Time Intervals				
Outcome Measure	**Single Measure**		**Repeated Measure, Fixed Intervals**	**Repeated Measure, Variable Intervals**
	No clustering	*Clustering (e.g., multi-site study)*		
Dichotomous	Logistic regression	Multilevel (mixed) logistic regression, GLMM, GEE, conditional logistic regression	Repeated measures ANOVA (MANOVA), GLMM, GEE	GLMM, GEE
Continuous	Linear regression	Multilevel (mixed) linear regression, GLMM, GEE	Repeated measures ANOVA (MANOVA), GLMM, GEE	GLMM, GEE

Adapted from Arbogast & VanderWeele, 2013

Dimensions That Drive Analysis Approaches

Number of Follow-up Measures and Time Intervals		
Outcome Measure	**Single Measure**	
	No clustering	*Clustering (e.g., multi-site study)*
Time to event	Cox proportional hazards regression	Variance-adjusted Cox model or shared frailty model
Time to event (aggregate or count data)	Poisson regression	Multilevel (mixed) Poisson regression

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

Cox Proportional Hazards Model

Table 4. Estimated HR comparing healthcare system user groups: revised dual use measure[a]

	HR (95% CI)		
	Overall survival		
Healthcare system use	Stage I (N = 1,028)	Stage II (N = 1,129)	Stage III (N = 857)
Predominantly VA	0.50 (0.35–0.71)	0.72 (0.52–0.99)	0.71 (0.53–0.96)
Dual User	Ref	Ref	Ref
Predominantly Non-VA	0.63 (0.43–0.91)	0.79 (0.57–1.11)	0.80 (0.59–1.09)
	EFS		
Healthcare system use	Stage I (352 events)	Stage II (524 events)	Stage III (575 events)
Predominantly VA	0.55 (0.41–0.74)	0.91 (0.68–1.23)	0.84 (0.64–1.09)
Dual User	Ref	Ref	Ref
Predominantly Non-VA	0.69 (0.50–0.94)	1.12 (0.83–1.51)	0.90 (0.68–1.18)

[a]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

Checklist: Guidance and key considerations for developing a statistical analysis section of an observational CER protocol		
Guidance	**Key Considerations**	**Check**
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]).	☐

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]).

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)

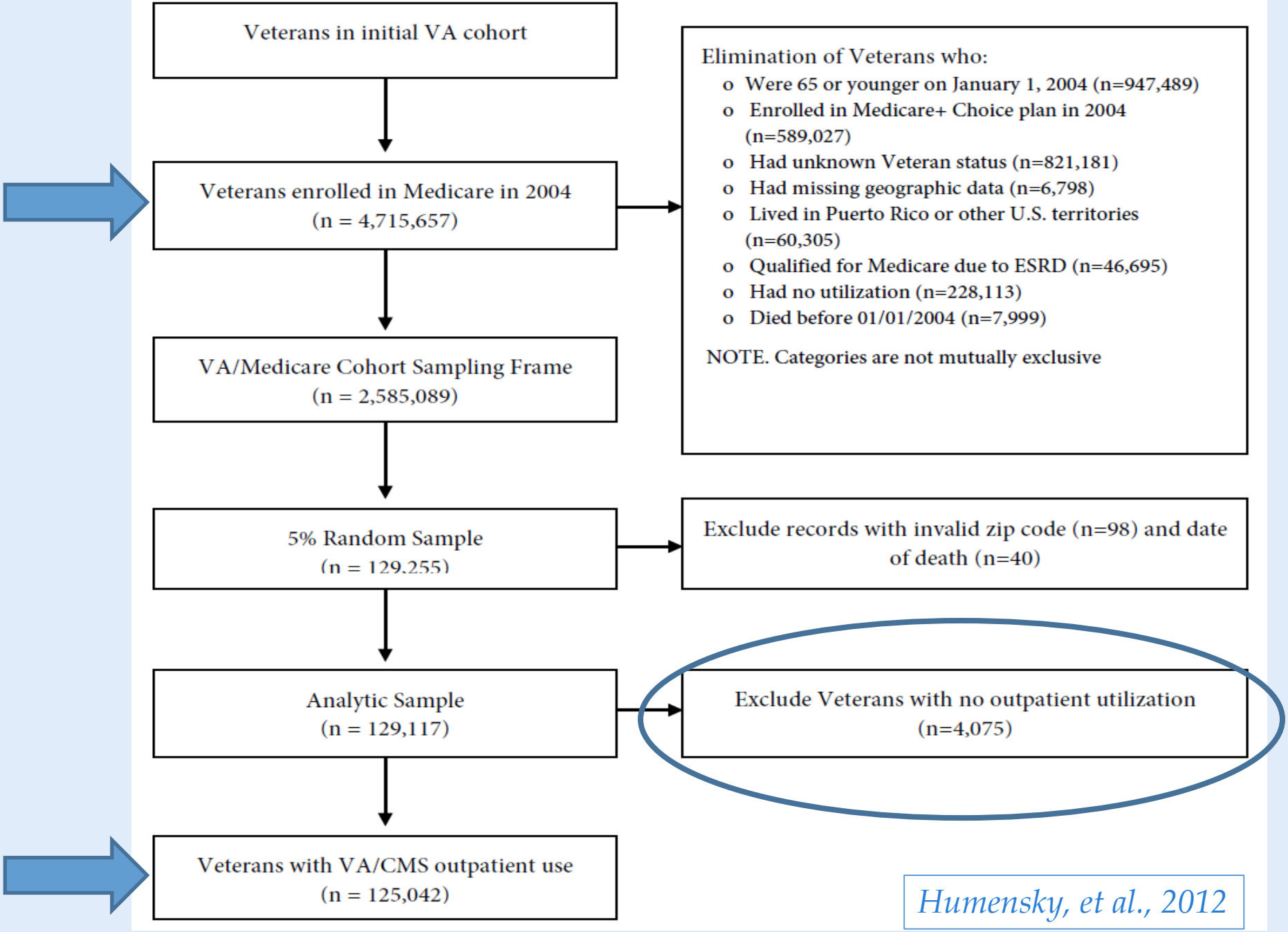
  Definition: Average effect of a treatment (compared with control) for a patient selected randomly from the population of patients eligible for the treatment

  – 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



Humensky, et al., 2012

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 mis-classification

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

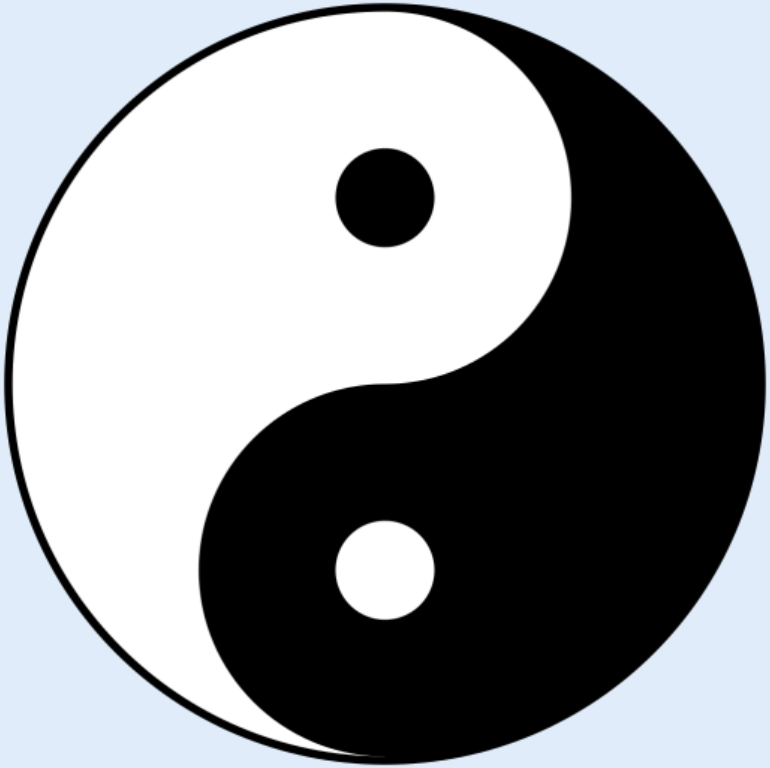
- Limits of observational data and potential ascertainment bias
- Unobserved events
  - Carefully consider limits of administrative data
  - Longer look-back periods
  - Multiple sources

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

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