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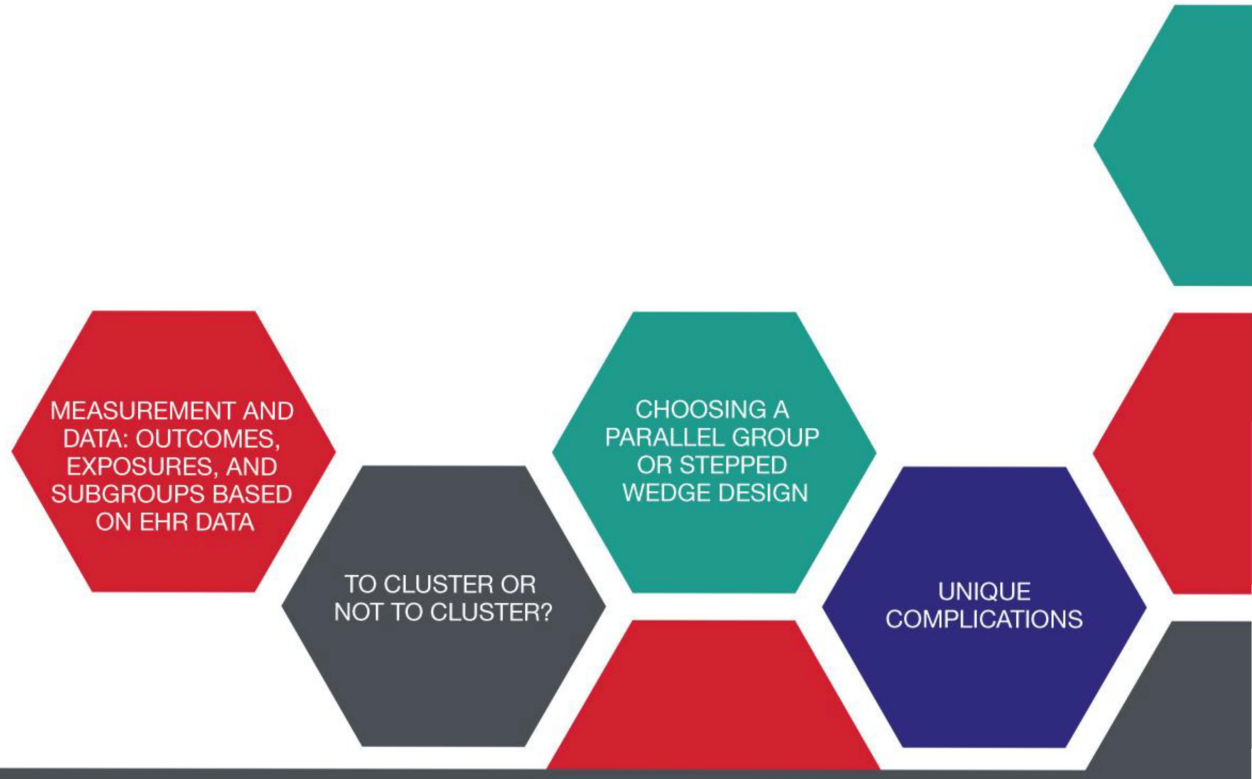
Design & Analysis of Embedded

Pragmatic Clinical Trials



Panel 4:
Unique Complications

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Health Care Systems Research Collaboratory

HiLo Trial

PI: Myles Wolf, MS, MMSc

Statistical Investigator: Hrishikesh Chakraborty, DrPH

HiLo

A Pragmatic Trial Sponsored by the National Institutes of Health

Intervention and primary outcome measures

HiLo will test which of two phosphate management strategies will confer lower rates of all-cause mortality and hospitalization in patients with end-stage renal disease undergoing hemodialysis:

- Lo: Usual target phosphate of <5.5 mg/dl; or
- Hi: Less strict target phosphate of >6.5 mg/dl

Specific binder choices, diet recommendations? Local care teams will treat based on their preferences & practice.

Specific problem 1: Informed consent

- Intervention: more than minimal risk
- Cluster randomization: randomize individual facilities
- Key issues:
  - How to handle individual-level informed consent in the setting of facility-specific randomization
  - How to structure informed consent materials
  - Logistically: how to obtain consent in real world practice without on-site study coordinators

Specific problem 2: Primary outcome

Originally, all-cause hospitalization

- Critical to all stakeholders: patients, providers, payers
- For many patients, avoiding hospitalization >>> prolong survival
- Hyperphosphatemia contributes to complications → hospitalization
- Accepted endpoint in other areas (e.g., heart failure)
- Dialysis providers: near 100% complete data about hospitalizations
- Collecting real-time hospitalization data eliminates adjudication
- Continuous variable desirable statistically

Limitations:

- Zero-inflated distribution of hospitalization: effect on sample size calculation and ICC
- Death before hospitalization: worst outcome not “counted”

Resolutions

Problem 1:

- Video consent + paper consent
- Tablets in dialysis units
- Two separate consent forms – one for Hi, one for Lo
- Collect contemporary anonymized data to assess non-participating patient characteristics and outcomes within participating facilities

Problem 2:

- Using hierarchical endpoint - all-cause mortality followed by all-cause hospitalization
- Determined power by simulation and estimated the tolerance level for ICC (more than our current estimate)
  - Incorporated zero-inflated hospitalizations
  - Used Generalization of the Gehan Wilcoxon (GGW) test

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Strategies and Opportunities to Stop Colon Cancer in Priority Populations

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William Volmer, PhD

NIH/NCI: UH3 AT007782 (Coronado, Green)

No Disclosures

The US Preventive Services Task Force recommends routine colorectal cancer screening for individuals aged 50 – 75.

Screening rates are suboptimal particular in disadvantaged populations

Design, Setting, Participants

- Cluster randomized pragmatic trial
- 26 FQHCs within 8 health centers in Oregon and California, were randomized to intervention (n = 13) or usual care (n = 13)
- The EHR was used to identify eligible individuals and facilitate implementation of a 3 step mailed intervention: (1) an introductory letter; (2) a mailed FIT; and a reminder
- Participants were age 50-75, had a clinic visit in the prior year, be overdue for CRC screening, and had an address in the EHR.
- 41,193 adults met these criteria during the accrual interval (February 4, 2014 to February 3, 2015)

Main outcomes and Measures

- Clinic-level proportions of adults who completed FIT, and secondarily any colorectal cancer screening with 12 months of accrual or by August 3, 2015
- Adoption, Reach, Implementation, and Maintenance of the Intervention
- Compared with UC clinics, intervention clinics had significantly higher adjusted clinic-level proportion of participants who completed a FIT (13.9% vs 10.4%; difference, 3.4 percentage points; 95% CI, 0.1%-6.8%)*
- We observed large variation across health centers in effectiveness (FIT completion differences range, −7.4 percentage points to 17.6 percentage points) and implementation (proportion who were mailed a FIT range, 6.5% to 68.2%)

* JAMA Internal Medicine, October 2018

Challenge
Population Definitions were Dynamic

- Clinic membership was defined as the patient having a visit within the prior 12 months.
- Eligible patients were accrued after clinic randomization but they fell off the clinic registry list if 12 months had passed without additional visits
- System and clinic start-up delays were problematic with patients dropped from the clinics list (these patients couldn't get interventions)
  - A system-wide EHR upgrade delayed intervention startup by 4 months
  - Clinic training delays led to even longer delays
- Patients would be removed from the but remained in the STOP denominator

Solutions

- We performed a secondary lagged analysis evaluating patients who were accrued after the EPIC delay (June 4, 2014 – February 3, 2015)
- Lagged analysis net increase in FIT uptake = 4.7% (vs. 3.4% in the intent to treat analysis)
- We also assessed how often patients were dropped from the clinic's EHR embedded list and received no interventions and remained unscreened
- The proportion of patients this effected was smaller than expected (5.4% remained off the list)

Challenge
Real-World Clinic Implementation

- Our study was a Type 2 Hybrid study with equal emphasis on effectiveness and implementation outcomes
- Delays in clinic start up-meant some patients could not get the intervention even if they caught up later (because patients no longer met the definition of a clinic patient)
- Once clinics were trained and began mailing letters and FITs, some found it difficult to complete all the mailings
- The proportion of patients mailed FITs ranged from 3% to 68% across health centers (18% - 82% in the lagged data set)

Solutions

- Per protocol analysis – among patients that were mailed FIT completion rate was 21% (25% if they also got a reminder letter)
- Mixed methods assessment of implementation barriers and facilitators: clinic (demographics, turnover of staff), surveys, interviews, observation (attendance at training, IT meetings)
- Thematic analysis and qualitative comparative analyses
- Led to a subsequent grant BeneFITs evaluating health plan/vendor mailing support

TiME to Reduce Mortality in End-Stage Renal Disease Trial (TiME)

Laura M. Dember, MD – Principal Investigator

Jesse Hsu, PhD – Biostatistician

J. Richard Landis, PhD – Biostatistician

Design and Analysis of Embedded Pragmatic Clinical Trials
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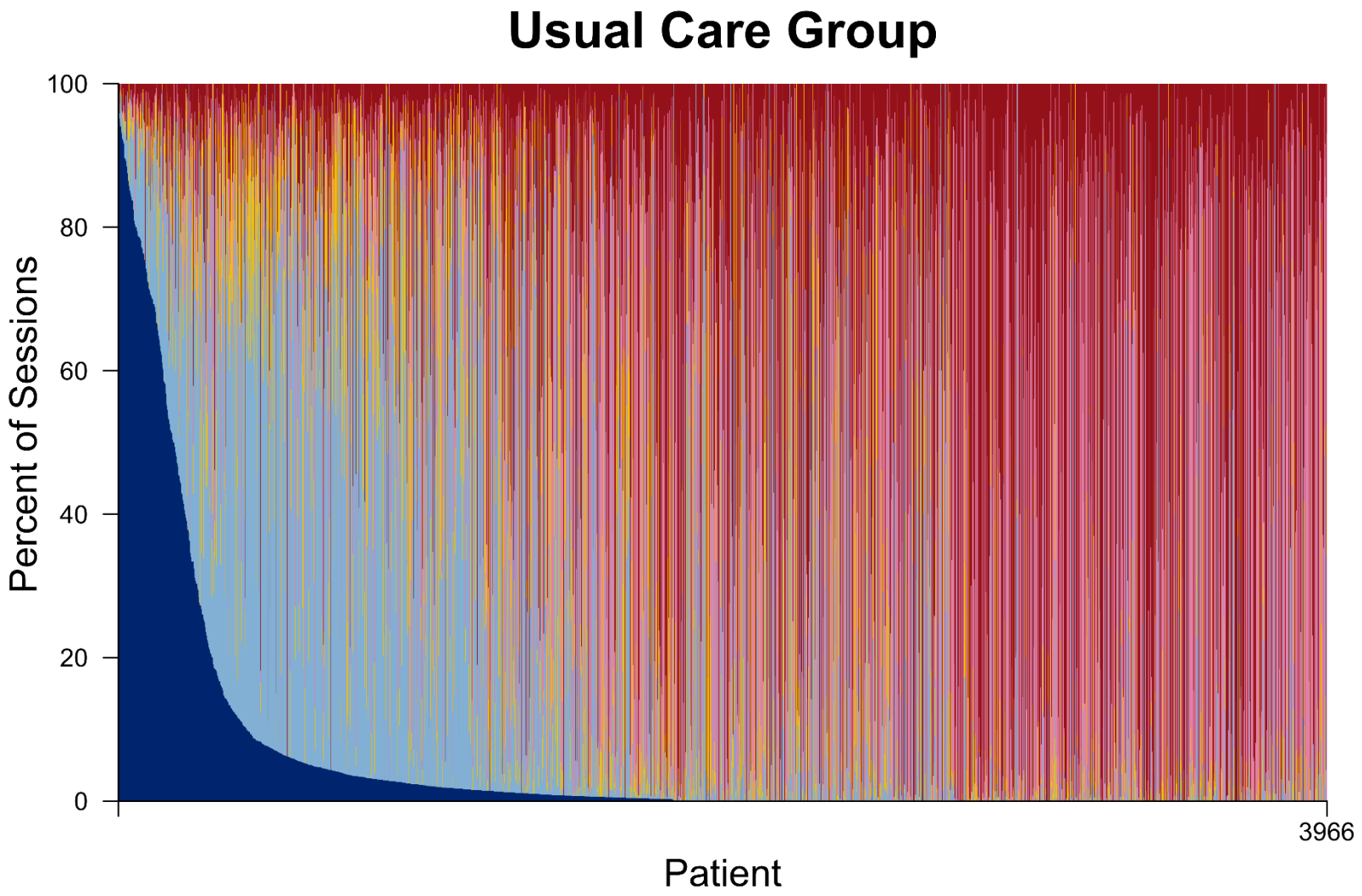
Trial Overview and Problem for Discussion

- Design and Setting
  - Cluster-randomized trial conducted in 266 outpatient dialysis facilities operated by two national dialysis providers
  - 7035 patients enrolled
  - Centralized implementation with no on-site research staff
- Trial Question: Does longer hemodialysis improve survival and reduce hospitalizations for patients with end-stage renal disease?
- Intervention: Hemodialysis session durations of at least 4.25 hours (255 minutes) for “incident” patients
- Usual Care: No trial-driven approach to hemodialysis session duration
- Problem Encountered: Inadequate implementation of the intervention
- Potential Contributors to Difficulty
  - Patient / Nephrologists factors
  - Facility factors
  - Dialysis provider organization factors

Duration of Hemodialysis (HD) Session (in minutes): As Delivered				
< 210	[210 – 225)	[225 – 240)	[240 – 255)	[255+



–ICCs

No. of Units	Randomized Treatment Arm of Facility		Total
	Intervention	Usual Care	
Facilities	120	132	252
Patients (Facilities)	3,069	3,966	7,035
Sessions (Patients)	495,706	634,161	1,129,867

$$\rho = \frac{\sigma^2_{chh'} + \sigma^2_{shh'}}{\sqrt{\pi_h(1-\pi_h)}\sqrt{\pi_{h'}(1-\pi_{h'})}} \qquad \text{Variance components as Proportion of total variance} \qquad \frac{\sigma^2_{chh'} + \sigma^2_{shh'}}{\sigma^2_{chh'} + \sigma^2_{shh'} + \sigma^2_{rhh'}}.$$

Landis, JR, King, TS, Choi, JW, Chinchilli, VM, & Koch, GG (2011). Measures of agreement and concordance with clinical research applications. *Statistics in Biopharmaceutical Research*, *3*(2), 185-209. DOI:10.1198/sbr.2011.10019

Provider effect

Arm	Variation	< 210	[210 – 225)	[225 – 240)	[240 – 255)	[255+
Intervention	1: Providers	0.003	0.004	0.005	0.010	0.000
	2: Facilities	0.051	0.064	0.009	0.046	**0.181**
	3: Patients	0.443	0.415	0.270	0.398	0.390
	4: Sessions	0.503	0.517	0.716	0.546	0.429
Usual Care	1: Providers	0.024	0.034	0.027	0.033	0.016
	2: Facilities	0.103	0.044	0.015	0.084	**0.033**
	3: Patients	0.440	0.427	0.267	0.407	0.477
	4: Sessions	0.433	0.495	0.691	0.476	0.475

Threshold-Specific Exposure Variable Reliability

1. Agreement measures for ordinal scales can vary considerably by selected category-specific thresholds

2. Heterogeneity of prevalence distribution of exposure variable among clinics in multi-center or cluster-randomized studies inflates subject-level ICCs

3. Category-specific estimators of reliability at clinically relevant thresholds should be adjusted for clinical center ICCs

4. Our findings reinforce the need to understand the patient-level, nephrologist-level, and facility-level factors that would allow a more responsive uptake of the intervention

Questions and Answers

Please submit questions for the panelists to:

PragClinTrialsWkshp@mail.nih.gov