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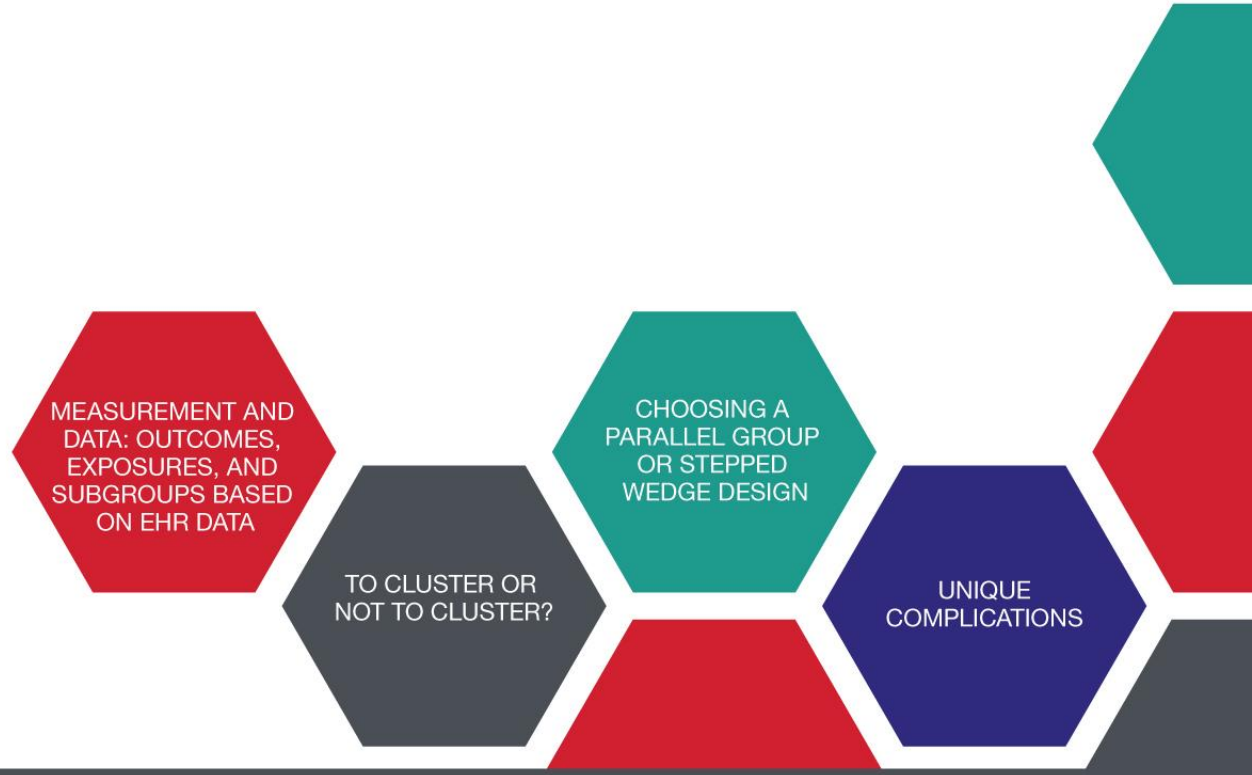
Design & Analysis of Embedded

Pragmatic Clinical Trials



Panel 1: Measurement and Data: Outcomes, Exposures, and Subgroups Based on EHR Data

PROVEN

PRagmatic Trial of Video Education in Nursing Homes

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UH3AG049619

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MGH 1811

PROVEN

- **OBJECTIVE:** To conduct a pragmatic cluster RCT of an Advance Care Planning video intervention in NH patients with advanced comorbid conditions in 360 NH's (120 Ex & 240 Con) from two healthcare systems.
- **INTERVENTION:** Suite of 5 ACP videos; Goals of Care, Advanced Dementia, Hospitalization, Hospice, ACP for Healthy Patients; Offered facility-wide to all new admits and at care-planning meetings for long-stay, readmission
- **OUTCOME:** Number of hospital transfers/person-days alive among Medicare FFS long stay NH residents >=65:
  - advanced dementia, impaired function & multi-morbidity, OR
  - advanced congestive heart failure/chronic obstructive lung disease, impaired function & multi-morbidity
  - N~18,000

Methodological Challenge: Measuring Outcome

- Hospital Transfers Measured via Medicare Claims AND Minimum Data Set BUT
  - Medicare Claims ONLY apply to Fee for Service
  - Minimum Data Set under reports transfers for ED or Observation Stays AND over reports Hospital Admits
  - Added Medicare Outpatient Claims for ED & Obs.
- Minimum Data Set can't substitute for Claims; BUT missing all Medicare Advantage patients
- RESOLUTION
- Created and DSMB Approved Claims outcome for Fee for Service Population

Methodological Challenge: Assessing Exposure

- Built a “VIDEO STATUS REPORT” (VSR) integrated into EMR to document “offers” and “shows”
- Inadequate compliance in intervention facilities, SO added “personal touch” with monthly calls
- 30-40% facilities engaged; 30% intermittently engaged and 20% non-compliant
- RESOLUTION
- Added an “as treated” secondary analysis based upon intervention compliance strata
  - Matching Facilities; patients within facility strata

Summary

- Secular trends affect data availability, outcome prevalence and salience of the intervention
  - Must monitor these factors to respond appropriately

- Critical to Measure Intervention Implementation to still allow for unbiased estimate of effect among the compliers.

STrategies to Reduce Injuries and Develop confidence in Elders

STRIDE

Strategies to Reduce Injuries and Develop Confidence in Elders (STRIDE) Randomized Trial of a Multifactorial Fall Injury Prevention Strategy

David Ganz – adjudication lead

Nancy Latham – study director

Peter Peduzzi – biostatistician and director, Data Coordinating Center

On Behalf of the STRIDE Study Team

PIs: Shalender Bhasin, Thomas Gill, David Reuben

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STrategies to
Reduce
Injuries and
Develop confidence in
Elders

Intervention & primary outcome measure

- **Setting:** 86 primary care practices in 10 US healthcare systems
- **Participants:** people age 70+ at increased risk for falls
- **Intervention:** nurse falls care manager assesses a participant's underlying risks for falls, suggests interventions using motivational interviewing, and then creates, implements and longitudinally follows up on an individualized care plan with the participant, in partnership with the participant's primary care provider
- **Primary outcome (original definition):** fall injury leading to medical attention, including non-vertebral fractures, joint dislocation, head injury, lacerations, and other major sequelae (e.g., rhabdomyolysis, internal injuries, hypothermia)

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STRIDE

Problem

- Intervention considered “good care,” not research
  - Developed iteratively during first year of study
- Discovery: fall care managers might interact with participants after they had a fall, and therefore could be asked by participants whether they should seek medical attention
- Seeking medical attention is part of the primary outcome definition
  - As a measure of injury severity
- This could result in ascertainment bias leading to dilution of the true intervention effect
  - Bias toward the null
  - Reduction in statistical power

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Considerations in addressing the problem

- We proposed a revised definition of the primary outcome
  - Serious fall injury, operationalized as a fall resulting in: (1) (fracture other than thoracic/lumbar vertebral; joint dislocation; or cut requiring closure) AND any medical attention; OR (2) (head injury; sprain or strain; bruising or swelling; or other) requiring hospitalization
- Key change – injuries in which seeking medical attention might be more discretionary now required an overnight stay in the hospital to count as a primary outcome event
- Tradeoff between original and revised definitions
  - Reduced number of events → decreased power
  - Reduced bias → preservation (no dilution) of treatment effect

STRIDE
STrategies to
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Resolution

- We initially adjudicated events using the original definition, but with the ability to tell which of these events fell under revised definition
- Unblinded statistical team ran analyses to address quantitatively the tradeoff between power and bias if we excluded some events under the revised definition
- NIA project officer convened a three-member independent expert panel to review these analyses
- Expert panel recommended the revised definition and NIA/PCORI accepted their recommendation
- Unintended positive consequences included
  - Adjudicators found it easier to reach agreement under the modified definition
  - Fewer events to adjudicate

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Health Care Systems Research Collaboratory

ABATE Infection Project

Active **Bat**hing to **E**liminate Infection Project

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ABATE Infection Project
Active Bathing to Eliminate Infection

Trial Design: CRT of 53 HCA hospitals in adult non-critical care units

Arm 1: Routine bathing and showering with soap and water

Arm 2: Daily CHG shower or CHG cloth bathing for all patients plus mupirocin x 5 days if MRSA+ by history, culture, or screen

Primary Outcomes

- Time to clinical cultures with MRSA or VRE
- Time to clinical cultures with antibiotic-resistant Gram negative rods
- Time to bloodstream infections due to any pathogen

Source of Outcomes

- All outcomes collected from routinely collected EHR data
- Ordering of clinical cultures vary by MD decision, although it is standard to send blood cultures for fever (e.g. >38 C)

ABATE Infection Project
EHR Outcomes Dependent on MD Testing

Trial-Specific Problem

- Sending clinical cultures by physician decision – is this affected by knowledge of intervention?
- Resistant organisms (Gram negative rods) are rising with time

Approach

- Difference in differences design
  - Compares each hospital to own baseline, clusters by hospital
  - MDs likely stable over time (private community hospitals)
- Predominantly a RN intervention. MDs minimally engaged
  - Less likely to differentially affect MD decision to order tests
- Temporal changes in resistant organisms helped by control arm

ABATE Infection Project
How to Address Multiple Admissions

Analytic Problem

- Outcome is rare (1-3 per 1,000 patient days at risk)
- Some patients have multiple admissions
- Sicker patients admitted more, tested more often
- SAS software cannot fit multi-level shared frailty models

Approach

Option 1: Select one admission at random (chosen option)

- Disadvantage of rare outcome
- Trial result may depend on the seed for random selection

Option 2: Use R for multi-level shared frailty models

- Unable to fit rare outcomes (when we had to choose method)

Option 3: Use all admissions and ignore correlation

ABATE Infection Project
Subgroup Selection

Trial result

- No difference between arms

Post-hoc subgroup differences for MRSA/VRE & bacteremia outcomes

- Patients with medical devices
- Patients in dedicated oncology units
- Patients known to have MRSA
- Patients in hospitals with high outcome rates (top quartile)

Selected device types by frequency of use and fidelity of data

- Central venous catheters
- Midlines
- Lumbar drains

Questions and Answers

Please submit questions for the panelists to:

PragClinTrialsWkshp@mail.nih.gov