Pragmatic and Group-Randomized Trials in Public Health and Medicine
Part 5: Examples

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A free, 7-part, self-paced, online course from NIH
with instructional slide sets, readings, and guided activities

Target Audience

- Faculty, post-doctoral fellows, and graduate students interested in learning more about the design and analysis of group-randomized trials.
- Program directors, program officers, and scientific review officers at the NIH interested in learning more about the design and analysis of group-randomized trials.
- Participants should be familiar with the design and analysis of individually randomized trials (RCTs).
  - Participants should be familiar with the concepts of internal and statistical validity, their threats, and their defenses.
  - Participants should be familiar with linear regression, analysis of variance and covariance, and logistic regression.

Learning Objectives

- And the end of the course, participants will be able to…
  - Discuss the distinguishing features of group-randomized trials (GRTs), individually randomized group-treatment trials (IRGTs), and individually randomized trials (RCTs).
  - Discuss their appropriate uses in public health and medicine.
  - For GRTs and IRGTs…
    - Discuss the major threats to internal validity and their defenses.
    - Discuss the major threats to statistical validity and their defenses.
    - Discuss the strengths and weaknesses of design alternatives.
    - Discuss the strengths and weaknesses of analytic alternatives.
    - Perform sample size calculations for a simple GRT.
  - Discuss the advantages and disadvantages of alternatives to GRTs for the evaluation of multi-level interventions.

Organization of the Course

- Part 1: Introduction and Overview
- Part 2: Designing the Trial
- Part 3: Analysis Approaches
- Part 4: Power and Sample Size
- **Part 5: Examples**
- Part 6: Review of Recent Practices
- Part 7: Alternative Designs and References

Examples of GRTs

- Group-randomized trials: Health Care Systems Collaboratory
  - 9 pragmatic trials conducted in collaboration with health care systems, funded as UH2/UH3 trials by a variety of NIH ICs.
  - 8 are group-randomized trials (GRT)
    - Hospital acquired infections
    - **CRC screening (STOP CRC)**
    - Healthcare utilization in spinal injuries
    - Chronic pain management
    - Mortality in dialysis patients
    - Management of PTSD in trauma patients
    - Advanced care planning in nursing homes
    - Management of multiple chronic conditions

Strategies and Opportunities to STOP CRC in Priority Populations

- Key personnel
  - PI: Gloria Coronado, PhD
  - Statistician: Bill Vollmer, PhD
  - Institution: Kaiser Permanente Center for Health Research
- Primary objective
  - Test the effectiveness of automated EMR-driven strategies to raise CRC screening rates in safety-net clinics
- Primary outcome
  - Proportion of targeted patients who complete FIT kit during first year of intervention.

STOP CRC Design

- Group-randomized trial
  - 26 federally qualified health clinics
    - Affiliated with 8 larger administrative networks
    - Clinic-level randomization stratified by network
  - EMR used to drive system-level intervention
  - Control clinics roll out intervention in year 2
  - Consent waived for this minimal risk study

- Illustrates *a priori* stratification in a GRT, with clinic as the unit of assignment and a delayed-treatment control condition.

STOP CRC Analytic Approach

- Weighted logistic regression accounting for clustering at clinic level and adjusting for selected individual and clinic level covariates.
  - Individual level data weighted by inverse clinic size so that resulting clinic means all have equal weight (consistent with primary focus on clinic level outcomes).
- cf. Coronado et al., 2014 for details on the design and analytic plan.
- Illustrates a mixed-model ANCOVA approach adapted to a dichotomous primary outcome.

- Coronado GD, Vollmer WM, Petrik A, Taplin SH, Burdick TE, Meenan RT, Green BB. Strategies and Opportunities to STOP Colon Cancer in Priority Populations: design of a cluster-randomized pragmatic trial. Contemporary Clinical Trials. 2014;38(2):344-9. PMC4226652.

STOP CRC Challenges

- Challenges
  - Overlap of year 1 measurement window and year 2 intervention rollout for control clinics
  - Use of real-time EMR tools that may be discordant with our static randomization tables
  - Implementation delays and ACA rollout

- These challenges threatened the validity of the primary analysis

STOP CRC Solutions

- Solutions
  - Delayed rollout of intervention for control clinics in year 2 to deal with the overlap problem.
  - Formulated a number of sensitivity analyses to try to overcome impact of lags in startup and hence give a more accurate estimate of true intervention impact.
  - Include a stepped wedge framework in which data from both years 1 and 2, as well as year prior to randomization, are used to estimate separate startup effects in year 1 of intervention and steady state effects in year 2 of intervention.

- Adaptations required during planning year to accommodate real world complexities.

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    - **Chronic pain management (PACT)**
    - Mortality in dialysis patients
    - Management of PTSD in trauma patients
    - Advanced care planning in nursing homes
    - Management of multiple chronic conditions

Collaborative Care for Chronic Pain in Primary Care: PACT

- Key personnel
  - PI: Lynn DeBar, PhD, MPH
  - Statistician: Bill Vollmer, PhD
  - Institution: Kaiser Permanente Center for Health Research
- Primary objective
  - Test whether an integrative pain management program embedded within primary care: decreases pain, opioid use, and healthcare utilization; and improves function for patients with complex chronic pain
- Primary outcome
  - Trajectory of change in self-reported pain scores over the first six months of intervention

PACT Design

- Stratified group-randomized trial
  - Strata are three regions of the Kaiser Permanente Health Plan
  - Physicians are unit of randomization
  - EMR screen to identify potentially eligible patients
  - Vet list with PCPs
  - Verbal consent obtained from patients prior to randomization

- Illustrates stratified group-randomized trial with physician as the unit of assignment.

PACT Analytic Approach

- Two-stage analysis
  - Compute slopes for individual pain score trajectories
  - Analyze slopes using mixed model ANCOVA adjusting for selected individual and cluster level variables, including baseline pain score
  - cf. DeBar et al., 2012 for details on the rationale for this approach.
- Illustrates two-stage analysis with regression adjustment for covariates.

- Debar LL, Kindler L, Keefe FJ, Green CA, Smith DH, Deyo RA, Ames K, Feldstein A. A primary care-based interdisciplinary team approach to the treatment of chronic pain utilizing a pragmatic clinical trials framework. Transl Behav Med. 2012;2(4):523-30. PMC3578318.

PACT Challenges

- Challenges
  - Weaving a complex, multi-modal intervention into fabric of usual care
  - Everyone doing things/creating partnerships never done before:
    - Redeploying/hiring clinical staff for intervention roles not well-aligned with existing health plan structure or traditional scope of practice
    - Expanding use of EHR
    - Creating scalable training model with attention to fidelity and cost/resources
    - Sharing costs and building infrastructure processes
    - IRBs uneasy relinquishing tight research constraint.
- Pragmatic trials are not easy, especially working in new systems with new methods for data collection and intervention delivery.

PACT Solutions

- Solutions
  - Had to adapt the intervention structure to accommodate clinical work flow and stakeholder input.
  - Had to redefine some clusters by grouping PCPs due to smaller than expected number of consenting patients for some PCPs.
  - Delayed startup in some regions until systems could be put in place to properly implement the intervention.
  - Shifted projected N between regions to reflect what was possible.
  - Team has been forced to devote a much larger proportion of their effort than anticipated to solve implementation issues.
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Examples of GRTs

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    - Chronic pain management
    - Mortality in dialysis patients
    - **Management of PTSD in trauma patients (TSOS)**
    - Advanced care planning in nursing homes
    - Management of multiple chronic conditions

Trauma Survivors Outcomes & Support TSOS

- Key personnel
  - PI: Douglas Zatzick, MD
  - Statistician: Patrick Heagerty, PhD
    - Joan Russo, Bryan Comstock, Jin Wang
  - Institution: University of Washington
- Primary objective
  - Explore intervention effect in patients with pre-injury chronic medical conditions
- Primary outcome
  - PTSD symptoms

TSOS Design

- Stepped wedge design
  - 24 US Level I trauma centers randomized to 4 waves
  - 960 patients with PTSD (40 patients/trauma center)
    - All co-morbidities included
  - All trauma centers recruit both control and intervention patients
  - All trauma centers begin recruiting controls
  - Data collected at baseline, 3, 6, and 12 months
  - Intervention “turned on” at each trauma center per design
  - Implementation advantage: all trauma centers trained
  - Design adds analytic complexity

- Illustrates stepped wedge design.

TSOS Analytic Approach

- Intervention vs. Control Comparisons
  - PTSD (Primary)
  - Alcohol
  - Depression
- Subgroup Analyses
  - Pre-injury Medical Conditions (ICD)
  - Traumatic brain injury (ICD)
- cf. Hughes et al. 2015 for a discussion of some of the analysis issues in stepped wedge designs.
- Illustrates mixed effect regression approach with adjustment for covariates.

- Hughes JP, Granston TS, Heagerty PJ. Current issues in the design and analysis of stepped wedge trials. Contemp Clinical Trials. 2015;45(Pt A):55-60. PMC4639463.

TSOS Challenges

- Challenges Raised by 24 site Design
  - Site Variability
    - Sites vary in rates of violent injury (↑PTSD with ↑violence)
    - Sites vary in other characteristics (e.g., admission volumes)
  - Implementation challenge
    - In consideration of American College of Surgeons mandate for PTSD screening and intervention, all sites want intervention training

TSOS Solution

- Solution: Stepped Wedge Design
  - Site Variability: Each site contributes control & intervention patients
  - Implementation challenge: All sites receive intervention training

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    - Advanced care planning in nursing homes
    - **Management of multiple chronic conditions (PIECES)**

Improving Chronic Disease Management with Pieces™

- Key personnel
  - PI: Miguel Vazquez, MD
  - Biostatisticians: Chul Ahn, PhD and Song Zhang, PhD
  - Institution: University of Texas Southwestern Medical Center
- Primary objective
  - To evaluate the management of patients with CKD, diabetes, and hypertension with a clinician support model enhanced by technology support (Pieces™) compared with standard of care.
- Primary outcome
  - 1-year all cause hospitalization

Pieces^{TM} Design

- Stratified group-randomized trial
  - Four healthcare systems with 249 clinics and >35,000 patients available.
  - Within each healthcare system, clinics or practice sites will be randomized to either Pieces^{TM} or standard care group.
  - Every patient assigned to a given clinic or practice site will receive the intervention to which the clinic or practice site was randomized.

- Illustrates stratified group-randomized trial with clinic or practice site as the unit of assignment.

Pieces™ Analytic Approach

- Primary analysis
  - The generalized Mantel-Haenszel testing procedure (Donner 1992) will be applied to detect any difference in hospitalization rate between Pieces™ and standard care.
- Secondary analysis
  - Mixed logistic regression to assess intervention effect on hospitalization rate controlling for clustering and patient, clinician, and clinic factors.
  - Cox models to assess the intervention effect on time to hospitalization with frailty to control for clustering.
- Illustrates non-parametric approach to primary analysis and model-based approach to secondary analysis.

- Donner A. Sample size requirements for stratified cluster randomization designs. Statistics in Medicine. 1992;11(6):743-50.

Pieces™ Challenges

- Challenges
  - Getting informed consent waivers.
  - Resolving heavy work loads among participating centers.
  - Streamlining clinical workflows for each site
  - Competing priorities for IT build
  - Slow approval process at one of the study healthcare systems
  - Training of PCPs and staff at each clinic site

- Such logistical issues are common in pragmatic trials in the health care setting

Pieces™ Solutions

- Solutions
  - The team is currently addressing these logistical issues.

Summary

- GRTs and IRGTs can be applied in a wide variety of settings for a wide variety of primary outcomes.
- GRTs should be avoided if individual randomization is possible with no threat of contamination or interaction among participants post randomization.
- Absent those assurances, GRTs and IRGTs provide the strongest comparative design.
- These studies are often conducted in settings where the investigators have limited control.
- Teams should include experts in the settings and operations, not just in the intervention or outcomes.

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  Part 6: Review of Recent Practices

Send questions to:

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