Pragmatic and Group-Randomized Trials in Public Health and Medicine
Part 1: Introduction and Overview

David M. Murray, Ph.D.
Associate Director for Prevention
Director, Office of Disease Prevention
National Institutes of Health

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

Three Kinds of Randomized Trials

- Individually Randomized Clinical Trials (RCTs)
  - Individuals randomized to study conditions with no connection among participants after randomization.
    - Most surgical and drug trials, some behavioral trials
- Individually Randomized Group Treatment Trials (IRGTs)
  - Individuals randomized to study conditions with some connection among participants after randomization.
    - Many behavioral trials
- Group-Randomized Trials (GRTs)
  - Groups randomized to study conditions with some connection among participants before and after randomization.
    - Many trials conducted in communities, worksites, schools, etc.

Distinguishing Characteristics

- Group-randomized trials
  - The unit of assignment is an identifiable group.
  - Different groups are allocated to each condition.
  - The units of observation are members of the groups.
  - The number of groups allocated to each condition is usually limited.
- Individually randomized group-treatment trials
  - The unit of assignment is the individual participant.
  - Participants receive some of their treatment in physical or virtual groups or through a common change agent.
  - The number of groups or change agents is usually limited.

Alternative Labels

- Group-randomized trials are also called…
  - Cluster-randomized trials.
  - They are sometimes called community trials.
  - These labels are interchangeable.
- Individually randomized clinical trials are also called….
  - Randomized clinical trials,
  - Randomized controlled trials,
  - Controlled clinical trials.
  - These labels are interchangeable.

Pragmatic Trials

- GRTs are often used for pragmatic trials.
  - Pragmatic and explanatory trials were first described by Schwartz & Lellouch (1967).
    - Explanatory trials test causal research hypotheses.
    - Pragmatic trials help users choose between options for care.
  - Similar to efficacy and effectiveness trials (Cochrane, 1971).
    - Efficacy trials evaluate an intervention under controlled conditions.
    - Effectiveness trials evaluate an intervention under real-world conditions.

- Schwartz, D., & Lellouch, J. Explanatory and pragmatic attitudes in therapeutical trials. Journal of Chronic Diseases, 1967, 20(8), 637-648.
- Cochrane, A.L. Effectiveness and efficacy: random reflections on health services. Nuffield Provincial Hospitals Trust, London, 1971. (cited in Flay, Brian R. Efficacy and effectiveness trials (and other phases of research) in the development of health promotion programs. Preventive Medicine, 1986, 15(5), 451-474.)

Examples

- 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.
    - Hospital acquired infections
    - CRC screening
    - Healthcare utilization in back pain care
    - Chronic pain management
    - Mortality in dialysis patients
    - Management of PTSD in trauma patients
    - Advanced care planning in nursing homes
    - Management of multiple chronic conditions

Examples

- Group-randomized trials: Health Care Systems Collaboratory
  - Overview papers
    - Anderson ML et al., Ethical and regulatory issues of pragmatic cluster randomized trials in contemporary health systems. Clinical Trials. 2015;12(3):276-86. PMC4498459.
    - Johnson KE et al., A guide to research partnerships for pragmatic clinical trials. BMJ. 2014;349:g6826.
    - Richesson RL et al., Electronic health records based phenotyping in next-generation clinical trials: a perspective from the NIH Health Care Systems Collaboratory. Journal of the American Medical Informatics Association. 2013;20(e2):e226-31. PMC3861929.

Examples

- Individually randomized group treatment trials: Childhood Obesity Prevention and Treatment Research (COPTR)
  - 4 trials funded by NHLBI as U01s
  - Two prevention studies targeting young children
  - Two treatment studies targeting youth
  - All involve substantial participant interaction post-randomization
  - Overview paper
    - Pratt CA et al., Childhood Obesity Prevention and Treatment Research (COPTR): interventions addressing multiple influences in childhood and adolescent obesity. Contemporary Clinical Trials. 2013;36(2):406-13.

Notation

- Following Murray (1998)
  - Dependent variable (Y)
  - Condition, C_l (l=1…c), will identify the study conditions
  - Time, T_j (j=1…t), will identify the measurement occasion
  - Group, $\mathbf{G}_k$ (k=1…g), will identify the unit of assignment
  - Member, $\mathbf{M}_i$(i=1…m), will identify the unit of observation
  - Covariate, X_o(o=1…x), will identify covariates
  - Random effects will be **BOLD**, fixed effects will be PLAIN

- Murray, D.M. Design and Analysis of Group-Randomized Trials. New York: Oxford University Press, 1998.

Impact on the Design

- Randomized clinical trials
  - There is usually good opportunity for randomization to distribute potential confounders evenly, as most RCTs have N>100.
  - If well executed, confounding is not usually a concern.
- Individually randomized group treatment trials
  - There may be less opportunity for randomization to distribute potential confounders evenly, as most IRGTs have N<100. Confounding can be more of a concern in IRGTs than in RCTs.
- Group-randomized trials
  - GRTs often involve a limited number of groups, often <50.
  - There may be limited opportunity for randomization to distribute potential confounders evenly.
  - Confounding is usually a concern in GRTs if G is <50.

Impact on the Analysis

- Observations on randomized individuals who do not interact are independent and are analyzed with standard methods.
- The members of the same group in a GRT will share some physical, geographic, social or other connection.
- The members of groups created for an IRGT will develop similar connections.
- Those connections will create a positive intraclass correlation that reflects extra variation attributable to the group.

$$ICC_{m:g:c} = corr\left(y_{i:k:l}, y_{i':k:l}\right)$$

- The positive ICC reduces the variation among the members of the same group so the within-group variance is:

$$\sigma_e^2 = \sigma_y^2\left(1 - ICC_{m:g:c}\right)$$

Impact on the Analysis

- The between-group component is the one's complement:

$$\sigma^2_{g:c} = \sigma^2_y \left(ICC_{m:g:c} \right)$$

- The total variance is the sum of the two components:

$$\sigma^2_y = \sigma^2_e + \sigma^2_{g:c}$$

- The intraclass correlation (ICC) is the fraction of the total variation in the data attributable to the unit of assignment:

$$ICC_{m:g:c} = \frac{\sigma^2_{g:c}}{\sigma^2_e + \sigma^2_{g:c}}$$

Impact on the Analysis in a GRT

- Given m members in each of g groups...
  - When group membership is established by random assignment,

$$\sigma^2_{\bar{y}_g} = \frac{\sigma^2_y}{m}$$

  - When group membership is not established by random assignment,

$$\sigma^2_{\bar{y}_g} = \frac{\sigma^2_e}{m} + \sigma^2_g$$

  - Or equivalently,

$$\sigma^2_{\bar{y}_g} = \frac{\sigma^2_y}{m}\left(1 + (m-1)\,ICC\right)$$

Impact on the Analysis

- Nested factors must be random effects (Zucker, 1990).
- The variance of any group-level statistic will be larger.
- The df to estimate the group-level component of variance will be based on the number of groups, and so is often limited.
  - This is almost always true in a GRT, can be true in an IRGT.
- Any analysis that ignores the extra variation or the limited df will have a Type I error rate that is inflated, often badly.
  - Type I error rate may be 30-50% in a GRT, even with small ICC
  - Type I error rate may be 15-25% in an IRGT, even with small ICC
- Extra variation and limited df always reduce power.

- Zucker DM. An analysis of variance pitfall: The fixed effects analysis in a nested design. Educational and Psychological Measurement. 1990;50(4):731-8.

Impact on the Analysis

- Scott & Holt (1982) estimate the effect of the ICC as:

$$DEFF = 1 + (m - 1) ICC_y ICC_x$$

  - DEFF is the ratio of the variance as observed to the variance under simple random sampling.
  - ICC_y is the ICC for the dependent variable.
  - ICC_x is the ICC for the independent variable.

- Scott AJ, Holt D. The effect of two-stage sampling on ordinary least squares methods. Journal of the American Statistical Association. 1982;77(380):848-54.

Impact on the Analysis

- For most health related outcomes, ICC values are …
  - 0.00-0.05 for large aggregates (e.g., schools, worksites),
  - 0.05-0.25 for small aggregates (e.g., classrooms, departments),
  - 0.25-0.75 for very small aggregates (e.g., families, spouse pairs).
- ICCs tend to be larger for knowledge and attitudes, smaller for behaviors, and smaller still for physiologic measures.
- If the groups are crossed with the levels of the exposure of interest (most observational studies), $ICC_x \approx ICC_y$.
- If the groups are nested within the levels of the exposure of interest (IRGTs, GRTs), $ICC_x=1$, because all members of a group will have the same value for exposure.

Impact on the Analysis

- Given the ICC and m per group, DEFF is…

Surveys			IRGTs			GRTs		
	$ICC_y=ICC_x$			$ICC_x=1$			$ICC_x=1$	
m	0.05	0.01	m	0.25	0.10	m	0.05	0.01
50	1.12	1.00	10	3.25	1.90	20	1.95	1.19
100	1.25	1.01	20	5.75	2.90	100	5.95	1.99
200	1.50	1.02	40	10.75	4.90	500	25.95	5.99

- The usual F-test, corrected for the ICC, is:

$$F_{corrected} = \frac{F_{uncorrected}}{DEFF}$$

The Warning

Randomization by cluster accompanied by an analysis appropriate to randomization by individual is an exercise in self-deception, however, and should be discouraged.

Cornfield (1978)

- Though Cornfield's remarks were addressed only to GRTs, they also apply to IRGTs.

- Cornfield J. Randomization by group: a formal analysis. American Journal of Epidemiology. 1978;108(2):100-2.

Summary

- A GRT remains the best comparative design available when the investigator wants to evaluate an intervention that…
  - operates at a group level
  - manipulates the social or physical environment
  - cannot be delivered to individuals without contamination
- An IRGT is the best comparative design when...
  - Individual randomization is possible without contamination
  - There are good reasons to deliver the intervention in groups
- The challenge is to create trials that are:
  - Rigorous enough to avoid threats to validity of the design,
  - Analyzed to avoid threats to statistical validity,
  - Powerful enough to provide an answer to the question,
  - And inexpensive enough to be practical.

Pragmatic and Group-Randomized Trials in Public Health and Medicine

Visit **https://prevention.nih.gov/grt** to:

- Provide feedback on this series
- Download the slides, references, and suggested activities
- View this module again
- View the next module in this series:
  Part 2: Designing the Trial

Send questions to:

GRT@mail.nih.gov

National Institutes of Health
Office of Disease Prevention