Pragmatic and Group-Randomized Trials in Public Health and Medicine
Part 2: Designing the Trial

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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

Planning the Trial

- The driving force must be the research question.
  - The question will identify the target population, the setting, the endpoints, and the intervention.
  - Those factors will shape the design and analytic plan.
- The primary criteria for choosing that question should be:
  - Is it important enough to do?
    - Will the trial address an important public health question?
    - Will the results advance the field?
  - Is this the right time to do it?
    - Is there preliminary evidence of feasibility and efficacy for the intervention?
    - Are there good estimates for the parameters needed to size the study?
- The investigators should keep the question in mind.

Fundamentals of Research Design

- The goal in any comparative trial is to allow valid inference that the intervention as implemented caused the result as observed.
- Three elements are required:
  - Control observations
  - A minimum of bias in the estimate of the intervention effect
  - Sufficient precision for that estimate
- The three most important tools to limit bias and improve precision in any comparative trial, including a GRT, are:
  - Randomization
  - Replication
  - Variance reduction

Potential Threats to Internal Validity

- Four primary threats in a GRT are:
  - Selection refers to pre-existing differences between the study conditions associated with the groups or members that are nested within conditions.
  - Differential history is any external influence other than the intervention that can affect the outcome and that affects one condition more than the other.
  - Differential maturation reflects growth or development at the group or member level that can affect the outcome and that affects one condition more than the other.
  - Contamination exists when important components of the intervention find their way into the control condition, either directly, or indirectly.

Strategies to Limit Threats to Internal Validity

- Randomization
- A priori matching, stratification, or constrained randomization
  - Of groups in GRTs, of members in IRGTs
- Objective measures
- Independent evaluation personnel who are blind to conditions
- Analytic strategies
  - Regression adjustment for covariates
- Avoid the pitfalls that invite threats to internal validity
  - Testing and differential testing
  - Instrumentation and differential instrumentation
  - Regression to the mean and differential regression to the mean
  - Attrition and differential attrition

Threats to the Validity of the Analysis

- Misspecification of the analysis model
  - Ignore a measurable source of random variation
  - Misrepresent a measurable source of random variation
  - Misrepresent the pattern of over-time correlation in the data
- Low power
  - Weak interventions
  - Insufficient replication of groups and time intervals
  - High variance or intraclass correlation in endpoints
  - Poor reliability of intervention implementation

Strategies to Protect the Validity of the Analysis

- Avoid model misspecification
  - Plan the analysis concurrent with the design.
  - Plan the analysis around the primary endpoints.
  - Anticipate all sources of random variation.
  - Anticipate patterns of over-time correlation.
  - Consider alternate models for time.
  - Assess potential confounding and effect modification.

Strategies to Protect the Validity of the Analysis

- Avoid low power
  - Employ strong interventions with good reach.
  - Maintain reliability of intervention implementation.
  - Employ more and smaller groups instead of a few large groups.
  - Employ more and smaller surveys or continuous surveillance instead of a few large surveys.
  - Employ regression adjustment for covariates to reduce variance and intraclass correlation.

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.

Factors That Can Reduce Precision

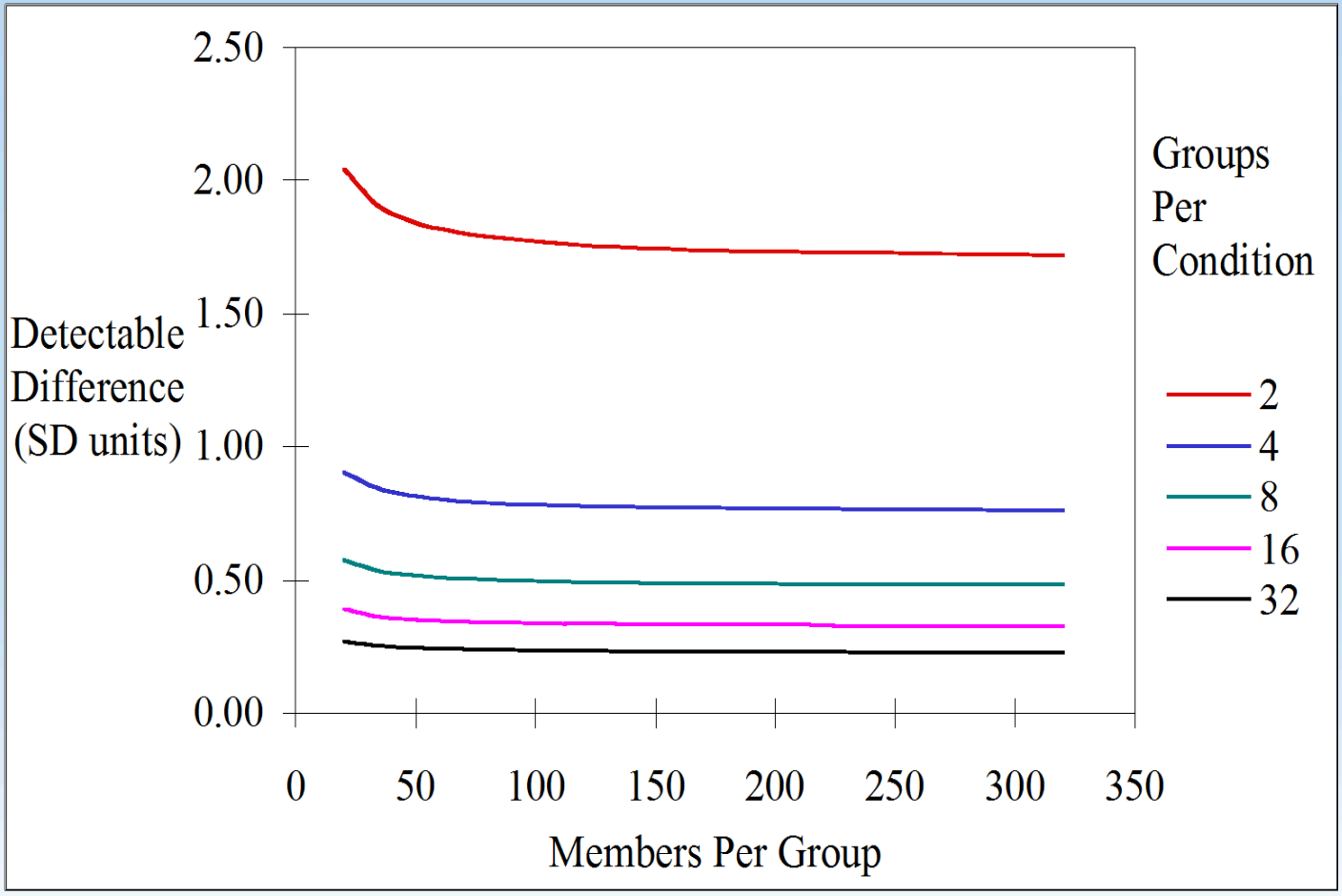
- The variance of the condition mean in a GRT is:

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

- This equation must be adapted for more complex analyses, but the precision of the analysis will always be directly related to the components of this formula operative in the proposed analysis:
  - Replication of members and groups
  - Variation in measures
  - Intraclass correlation

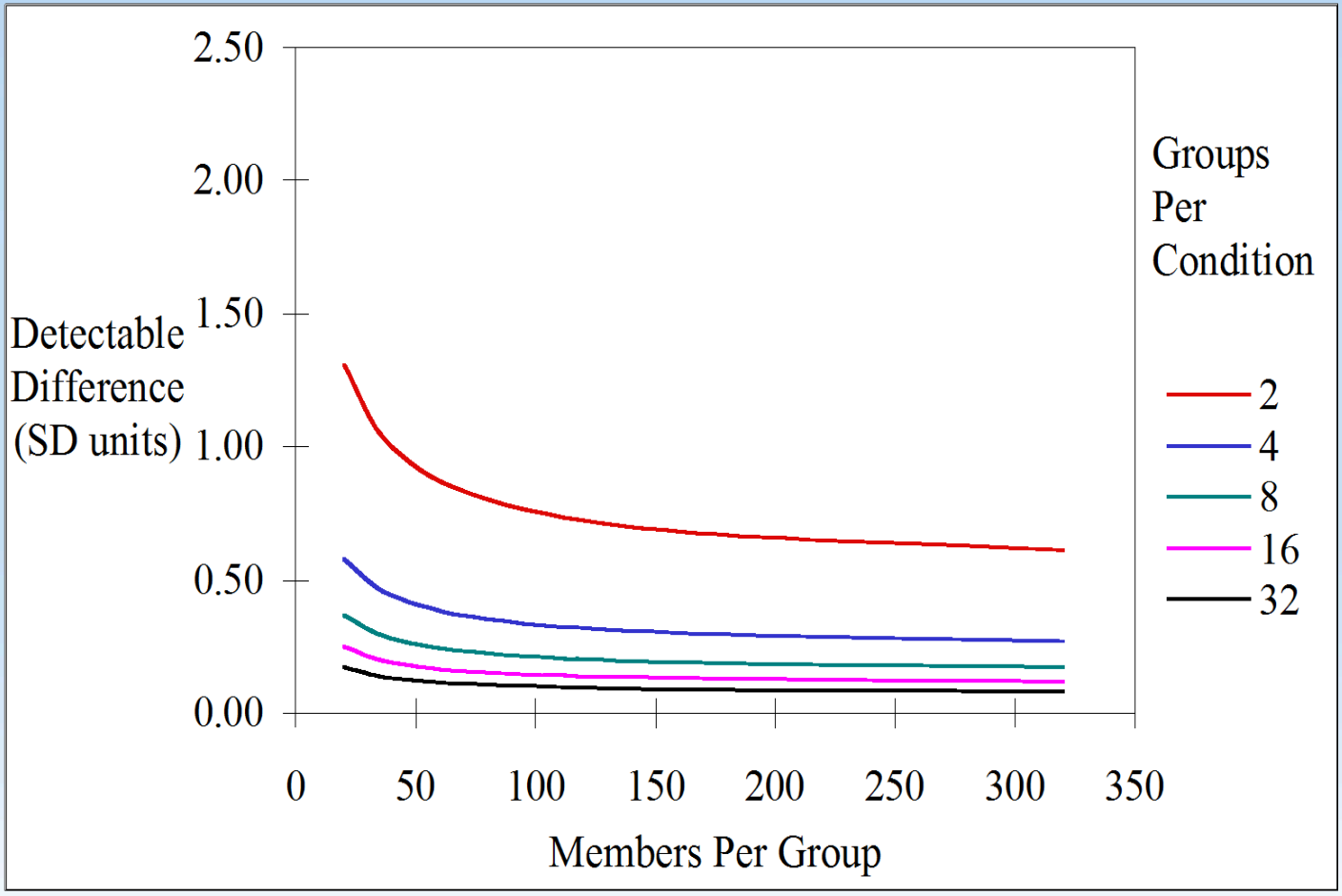
Strategies to Improve Precision

- Increased replication (ICC=0.100)



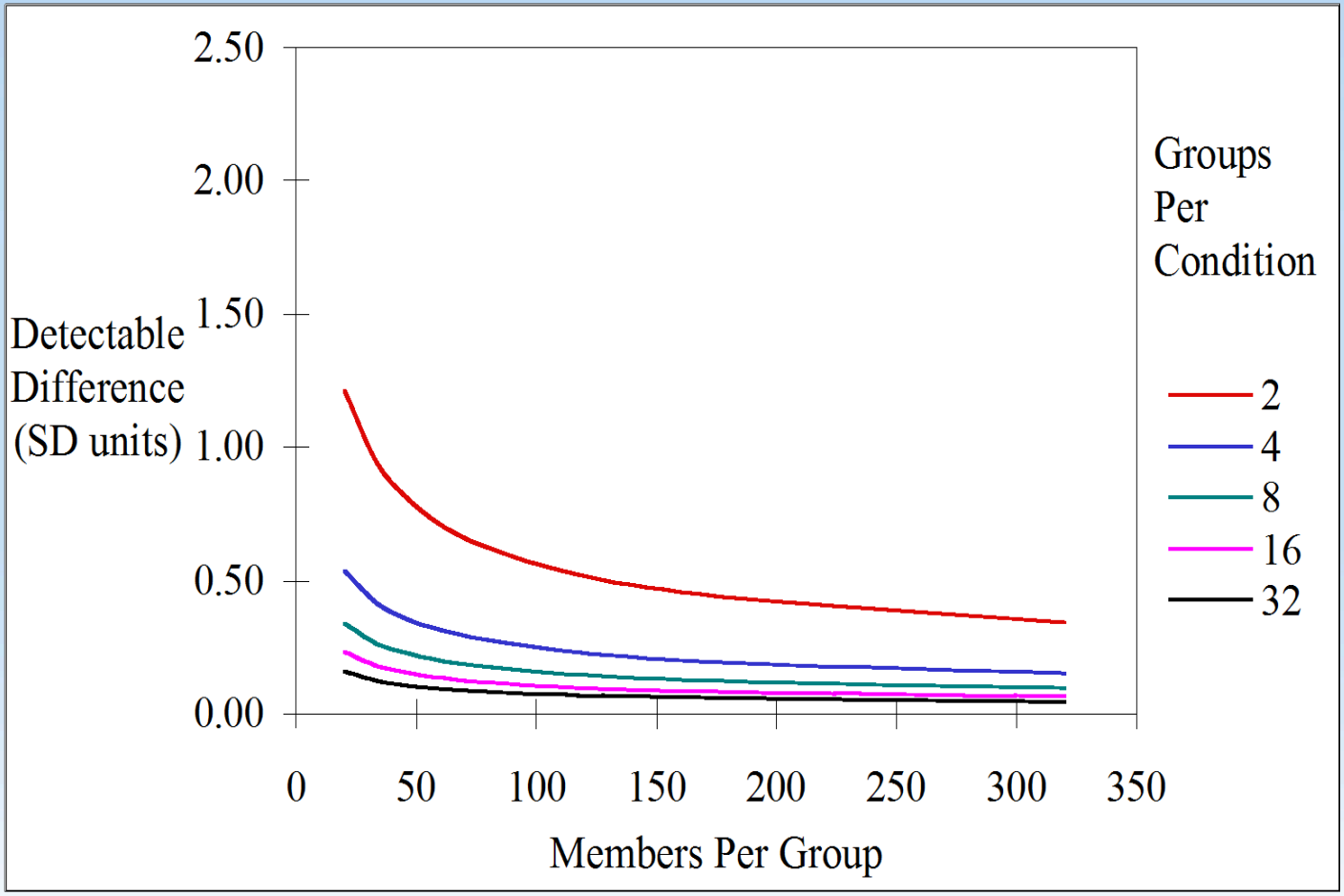
Strategies to Improve Precision

- Reduced ICC (ICC=0.010)



Strategies to Improve Precision

- The law of diminishing returns (ICC=0.001)



Group-Randomized Trial Designs

- Single factor and factorial designs
- Time as a factor
- Cohort vs. cross-sectional designs
- *A priori* matching and stratification
- *Post hoc* stratification
- Constrained randomization

Single Factor and Factorial Designs

- Most GRTs involve only one treatment factor.
  - Condition
- Most GRTs have only two levels of that treatment factor.
  - Intervention vs. control.
- Most GRTs cross Condition with Time.
  - Nested cohort designs
  - Nested cross-sectional designs
- Some GRTs include stratification factors.
  - Multi-center GRTs cross Condition with Field Center.
  - Single-center GRTs often stratify on factors related to the outcome or to the ease of implementation of the intervention.

Time as a Factor

- Posttest-only design
- Pretest-posttest design
- Extended designs
  - Additional discrete time intervals before and/or after intervention
  - Continuous surveillance

Cross-Sectional and Cohort Designs

- Nested cohort design
  - The research question involves change in specific members.
  - Measure the same sample at each time data are collected.
- Nested cross-sectional design
  - The research question involves change in an entire population.
  - Select a new sample each time data are collected.

Cross-Sectional and Cohort Designs

- Strengths and weaknesses

Cross-section	*Cohort*
in migration and out migration	mortality
group change	individual change
recruitment costs	tracking and follow-up costs
less powerful?	more powerful?
full dose?	full dose?

A Priori Matching and Stratification

- Rationale
  - Either can be used if the investigators want to ensure balance on an important potential source of bias.
  - A priori stratification is preferred if the investigators expect the intervention effect to be different across strata.
  - A priori matching is useful if the matching factors are well correlated with the primary endpoint.
  - The choice of matching vs. stratification will often depend on the number of groups available and on the expected correlation.
  - Work by Donner et al. (2007) favors stratification when m<100.

- Donner A, Taljaard M, Klar N. The merits of breaking the matches: a cautionary tale. Statistics in Medicine. 2007;26(9):2036-51.

Constrained Randomization

- Stratification or matching are difficult if there are multiple matching or stratification factors and a limited number of groups to be randomized.
- Constrained randomization has been suggested as a solution (Raab and Butcher, 2001).
  - Generate all possible allocations.
  - Identify those that are sufficiently well balanced across conditions
  - Choose one allocation from the constrained set.
  - Use that allocation for the study.
- Recent work has focused on finding the best balance metric to use in constrained randomization (de Hoop et al., 2012).

- de Hoop E, Teerenstra S, et al. The "best balance" allocation led to optimal balance in cluster-controlled trials. Journal of Clinical Epidemiology. 2012;65(2):132-137.
- Raab GM, Butcher I. Balance in cluster randomized trials. Statistics in medicine. 2001;20(3):351-365.

Post Hoc Stratification

- With *a priori* stratification, strata are defined in advance and the units of assignment are randomized to condition x strata cells.
- With *post hoc* stratification, strata are defined *post hoc* and the stratification factor is added to the analysis.
- Common *post hoc* stratification factors include gender, age group, race or ethnic group, etc.
- In designs in which the individual is the unit of assignment, there is no difference between the analysis for *a priori* stratification and the analysis for *post hoc* stratification.
- There is a large difference in GRTs.

Summary

- All the design features common to RCTs are available to GRTs and IRGTs, with the added complication of an extra level of nesting:
  - Nested cohort and nested cross-sectional designs;
  - Post only, pre-post, and extended designs;
  - Single factor designs and factorial designs;
  - A priori matching or stratification, and post hoc stratification;
  - Constrained randomization
- The primary threats to internal and statistical validity are well known, and defenses are available.
  - Plan the study to reflect the nested design, with sufficient power for a valid analysis, and avoid threats to internal validity.

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  Part 3: Analysis Approaches

Send questions to:

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