Pragmatic and Group-Randomized Trials in Public Health and Medicine
Part 7: Alternative Designs

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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**

What About Alternative Designs?

- Many alternatives to GRTs have been proposed.
  - Multiple baseline designs
  - Time series designs
  - Quasi-experimental designs
  - Dynamic wait-list or stepped-wedge designs
  - Regression discontinuity designs
- Murray et al. (2010) compared these alternatives to GRTs for power and cost in terms of sample size and time.

- Murray DM, Pennell M, Rhoda D, Hade EM, Paskett ED. Designing studies that would address the multilayered nature of health care. Journal of the National Cancer Institute Monographs. 2010(40):90-6. PMC3482955.
- See also Shadish WR, Cook TD, Campbell DT. Experimental and Quasi-Experimental Designs for Generalized Causal Inference. Boston, MA: Houghton Mifflin Company; 2002.

Multiple Baseline Designs

- Intervention introduced into groups one by one on a staggered schedule
  - Measurement in all groups with each new entry.
  - Often used with just a few groups, e.g., 3-4 groups.
  - Data examined for changes associated with the intervention.

Multiple Baseline Designs

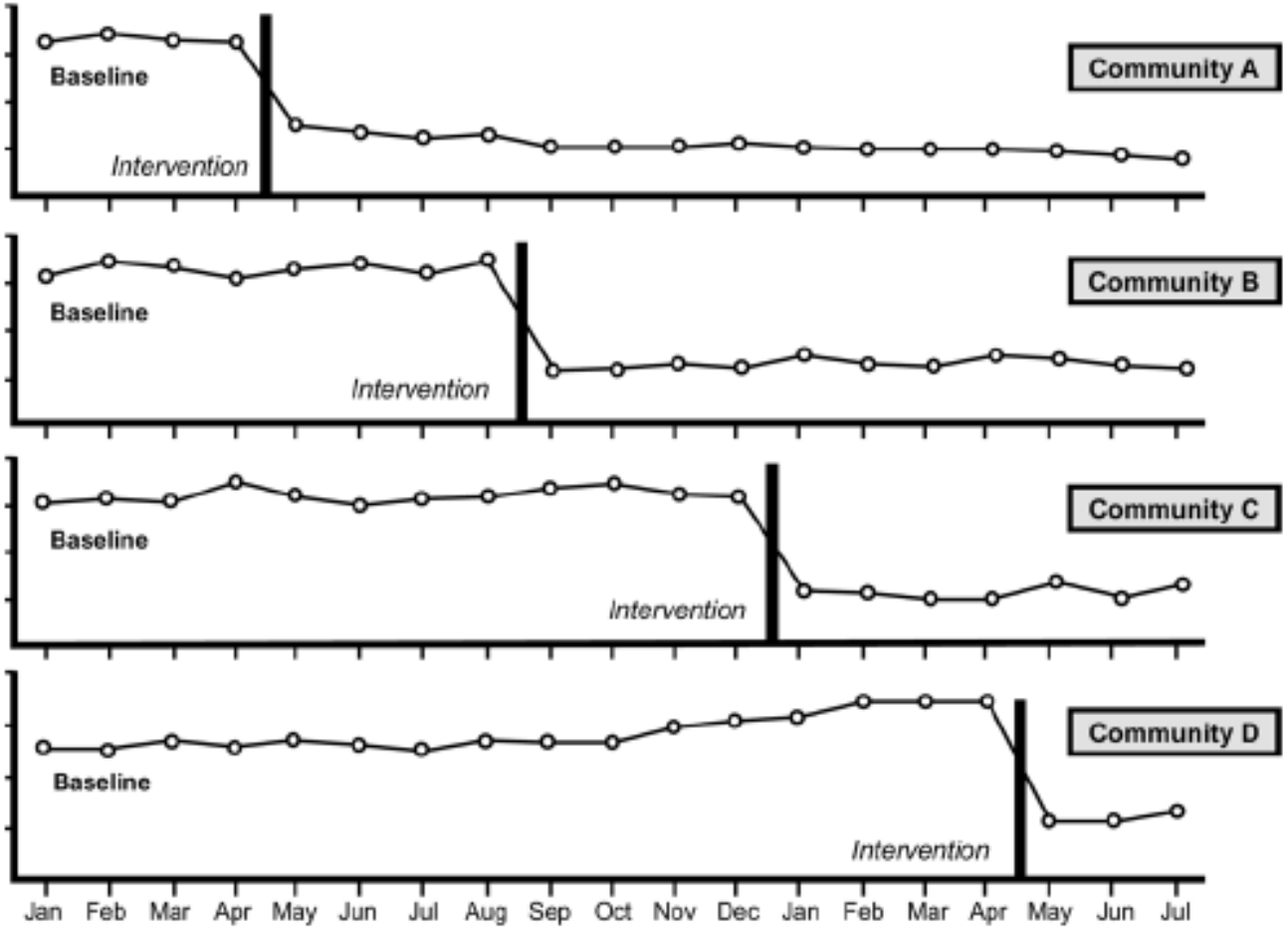


Figure 1. Hypothetical example of a multiple baseline design used to assess behavior change following an intervention in four communities.

Multiple Baseline Designs

- Evaluation relies on logic rather than statistical evidence.
  - Replication of the pattern in each group, coupled with the absence of such changes otherwise, is taken as evidence of an intervention effect.
  - With just a few groups, there is little power for a valid analysis.
- Good choice if effects are expected to be large and rapid.
- Poor choice if effects are expected to be small or gradual.
- Very poor choice if the intervention effect is expected to be inconsistent across groups.

- Rhoda DA, Murray DM, Andridge RR, Pennell ML, Hade EM. Studies with staggered starts: multiple baseline designs and group-randomized trials. American Journal of Public Health. 2011;101(11):2164-9. PMC3222403.

Time Series Designs

- Often used to evaluate a policy change in a single group.
- Require repeated and reliable measurements.
  - Standard methods require ~50 observations before and again after the intervention.
- Rely on a combination of logic and statistical evidence.
  - Standard methods provide evidence for change in a single group.
  - One-group designs provide no statistical evidence for between-group comparisons.
- Best used in with an archival data collection system.
  - Could be a strong approach with archival data on many groups.
- May require several cycles of data.

Quasi-Experimental Designs

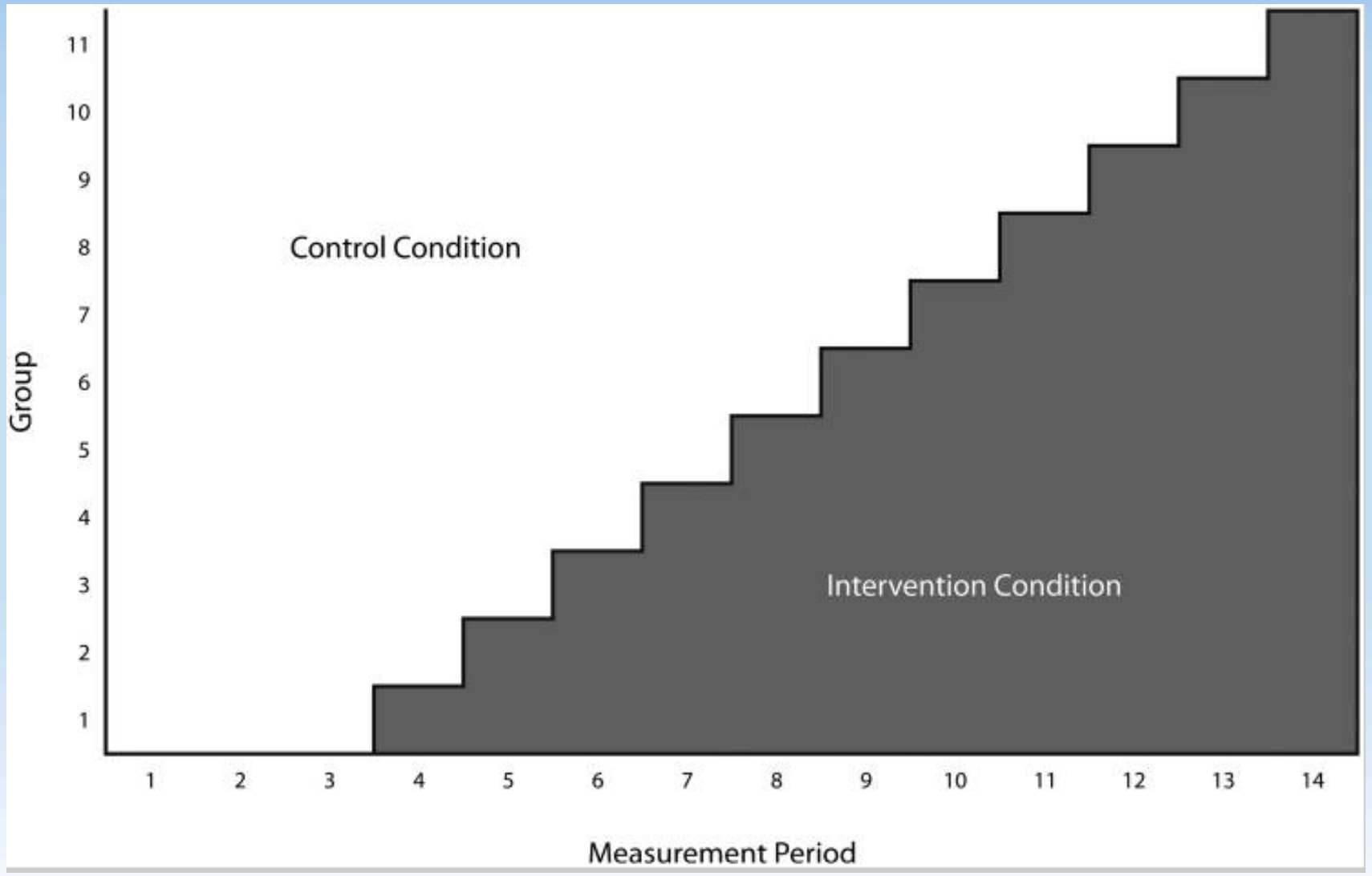
- QEs have all the features of experiments except randomization.
  - Causal inference requires elimination of plausible alternatives.
- If groups are assigned and members are observed, analysis and power issues are the same as in GRTs.
- Useful when randomization is not possible.
  - Can provide experience with recruitment, measurement, intervention.
  - Can provide evidence of treatment effects if executed properly.
- Well-designed and analyzed QEs are usually more difficult and more expensive than well-designed and analyzed GRTs.
- cf. Shadish et al. (2000).

Stepped-Wedge Designs

- Sometimes called Dynamic Wait-List Designs
- Combine the features of multiple baseline designs and GRTs.
  - Measurement is frequent and on the same schedule in all groups.
  - Time is divided into intervals.
  - Groups selected at random for the intervention in each interval.
  - By the end of the study, all the groups have the intervention.
- Both *Trials* (2015) and the *Journal of Clinical Epidemiology* (2013) recently published issues focused on the design and analysis of stepped wedge designs.

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

Stepped Wedge Design



Stepped Wedge Design

- The analysis estimates a weighted average intervention effect across the intervals.
  - Assumes that the intervention effect is rapid and lasting.
  - Not very sensitive to intervention effects that develop gradually or fade over time.
- These designs can be more efficient but usually take longer to complete and cost more than the standard GRT (Rhoda, 2011).

- Rhoda DA, Murray DM, Andridge RR, Pennell ML, Hade EM. Studies with staggered starts: multiple baseline designs and group-randomized trials. American Journal of Public Health. 2011;101(11):2164-9. PMC3222403.

Regression Discontinuity Designs

- Individuals are assigned to conditions based on a score, often reflecting the need for the intervention (Shadish et al., 2002).
- The analysis models the relationship between the assignment variable and the outcome.
  - The difference in intercepts at the cutoff is the intervention effect.
- Several recent papers have focused on regression discontinuity designs in public health and medicine (Moscoe et al., 2015; Bor et al., 2015).

- Moscoe E, Bor J, Barnighausen T. Regression discontinuity designs are underutilized in medicine, epidemiology, and public health: a review of current and best practice. Journal of Clinical Epidemiology. 2015;68(2):122-33.
- Bor J, Moscoe E, Barnighausen T. Three approaches to causal inference in regression discontinuity designs. Epidemiology. 2015;26(2):e28-30; discussion e.

Regression Discontinuity Design

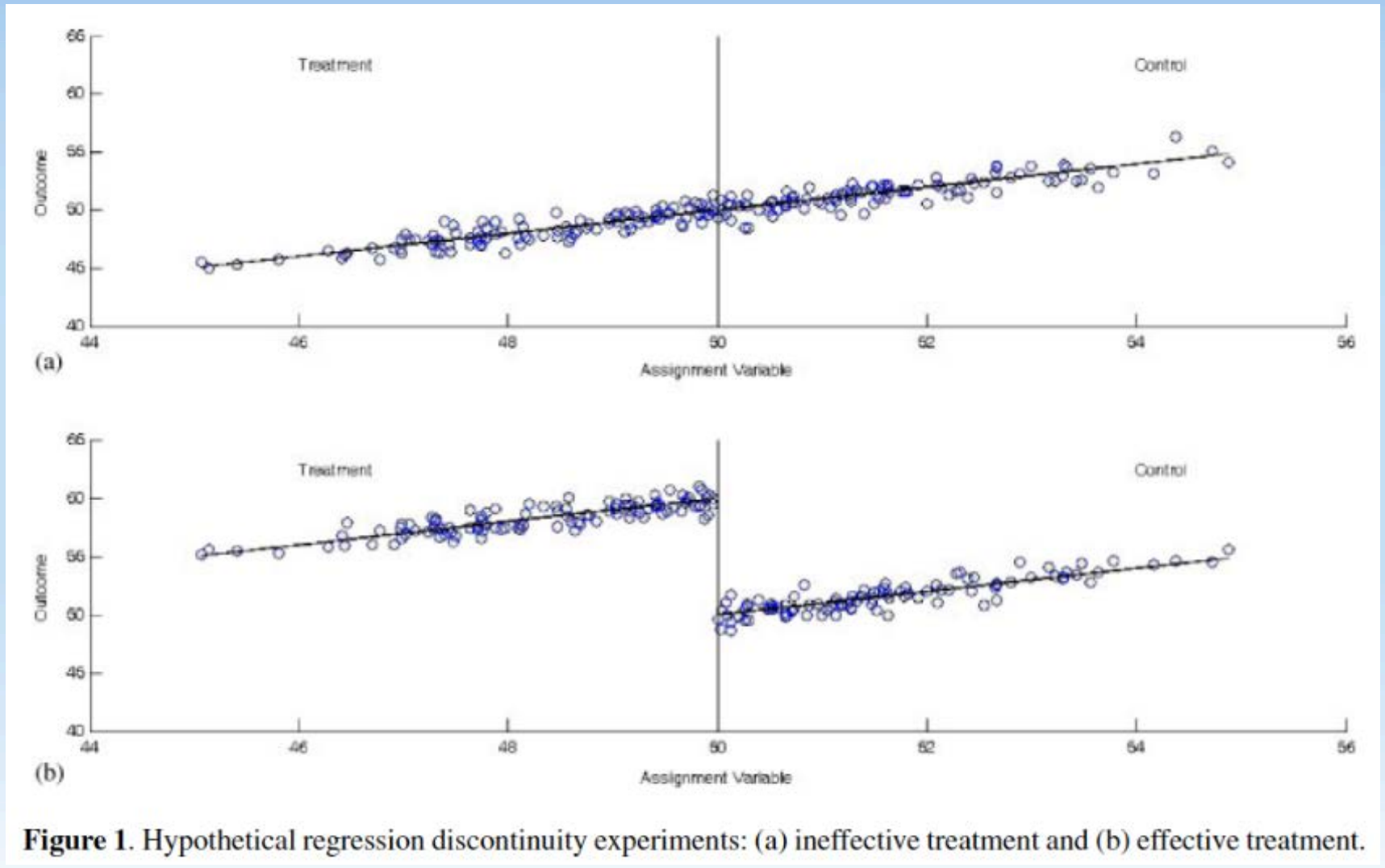


Figure 1. Hypothetical regression discontinuity experiments: (a) ineffective treatment and (b) effective treatment.

Regression Discontinuity Design

- Because assignment is fully explained by the assignment variable, proper modeling supports causal inference (Rubin, 1977).
- RDs avoid randomization, but are as valid as a RCT or GRT.
- RDs are less efficient than the standard RCT or GRT, often requiring twice as many participants.
- RDs can be used in the context of GRTs (Pennell, et al., 2011).

- Pennell ML, Hade EM, Murray DM, Rhoda DA. Cutoff designs for community-based intervention studies. Statistics in Medicine. 2011;30(15):1865-82. PMC3127461.
- Rubin DB. Assignment to treatment group on the basis of a covariate. Journal of Educational and Behavioral Statistics. 1977;2(1):1-26.

Summary

- A GRT remains the best comparative design available whenever the investigator wants to evaluate an intervention that…
  - operates at a group level
  - manipulates the social or physical environment
  - cannot be delivered to individuals
- GRTs provide better or equal quality evidence and are either more efficient or take less time than the alternatives.
- Even so, GRTs are more challenging than the usual RCT.
  - IRGTs present many of the same issues found in GRTs.
  - Investigators new to GRTs and IRGTs should collaborate with more experienced colleagues, especially experienced biostatisticians.

Summary

- Many alternatives to GRTs have been proposed.
  - Multiple baseline designs
  - Time series designs
  - Quasi-experimental designs
  - Dynamic wait-list or stepped-wedge designs
  - Regression discontinuity designs
- Under the right conditions, these alternatives can provide good evidence for causal inference.
  - Some rely on logic more than statistical evidence.
    - Multiple baseline designs, time-series designs
  - Others require studies as large or larger than GRTs and may take longer to complete
    - Quasi-experimental designs, stepped wedge, regression discontinuity

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