Design and Analysis of Group-Randomized Trials

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

2017 OBSSR Summer Institute
July 17, 2017

National Institutes of Health
Office of Disease Prevention

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.)

Methodological Considerations

- Pragmatic trials do not necessarily require a different set of research designs, measures, analytic methods, etc.
- As always, the choice of methods depends on the research question.
- The research question dictates
  - the intervention, target population, and variables of interest,
  - which dictate the setting, research design, measures, and analytic methods.
- Randomized trials will provide the strongest evidence.
  - Which kind of randomized trial will depend on the research question.
- Alternatives to randomized trials are also available.

Three Kinds of Randomized Trials

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

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

- 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

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.
  - In any single realization, there is limited opportunity for randomization to distribute all potential confounders evenly.
  - Confounding is more of a concern in GRTs if G<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.

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

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

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

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 is the fraction of the total variation in the data that is 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,

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

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:

$$\mathrm{DEFF} = 1 + (m-1)\,\mathrm{ICC}_y \mathrm{ICC}_x$$

  - 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.

The Need for GRTs and IRGTs

- 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 without contamination
- An IRGT is the best comparative design whenever...
  - Individual randomization is possible without contamination
  - There are good reasons to deliver the intervention in small groups
- The challenge is to create trials that are:
  - Rigorous enough to avoid threats to validity of the design,
  - Analyzed so as to avoid threats to statistical validity,
  - Powerful enough to provide an answer to the question,
  - And inexpensive enough to be practical.

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 or stratification
  - 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.

Factors That Can Reduce Precision

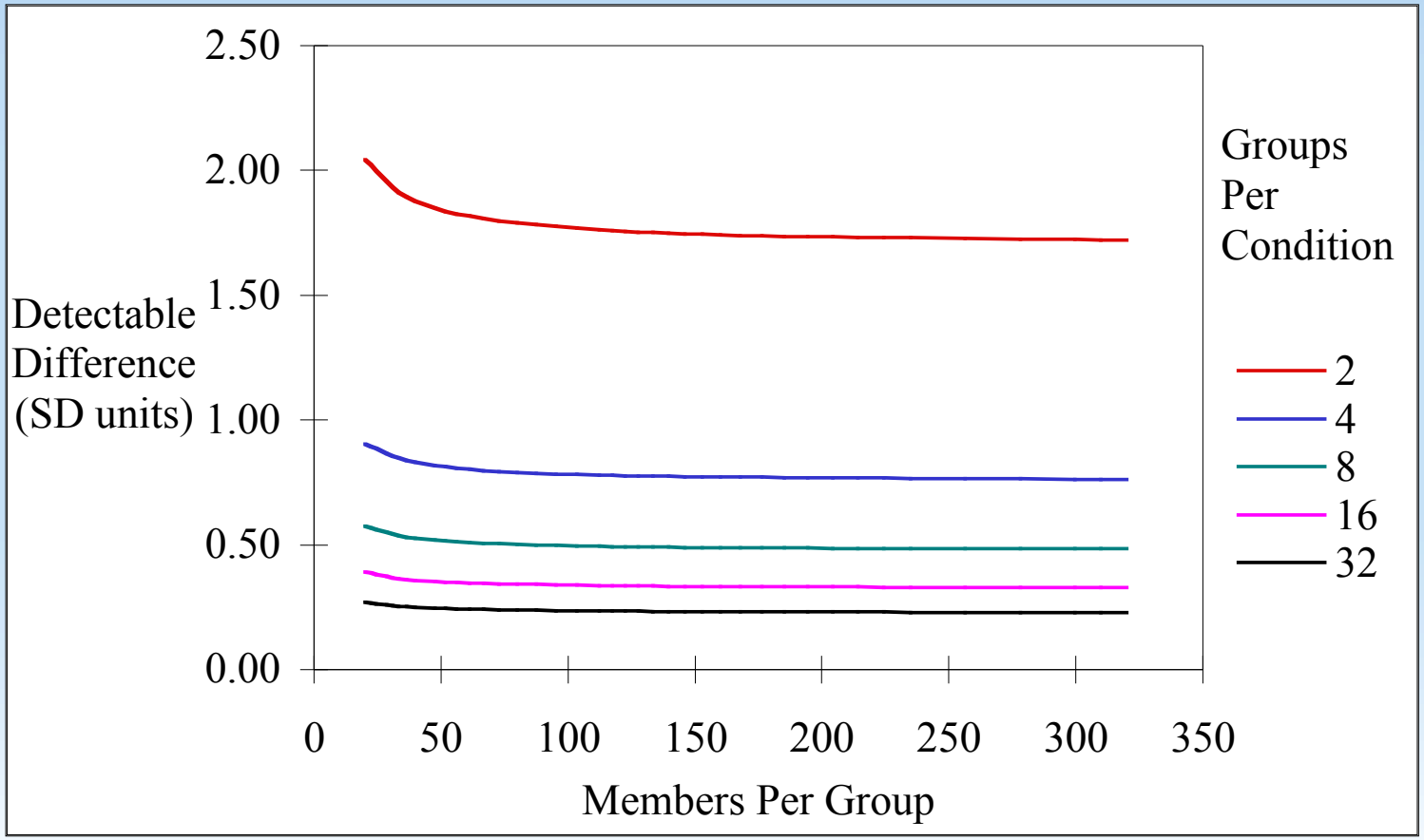
- The variance of the condition mean in a GRT is:

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

- 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

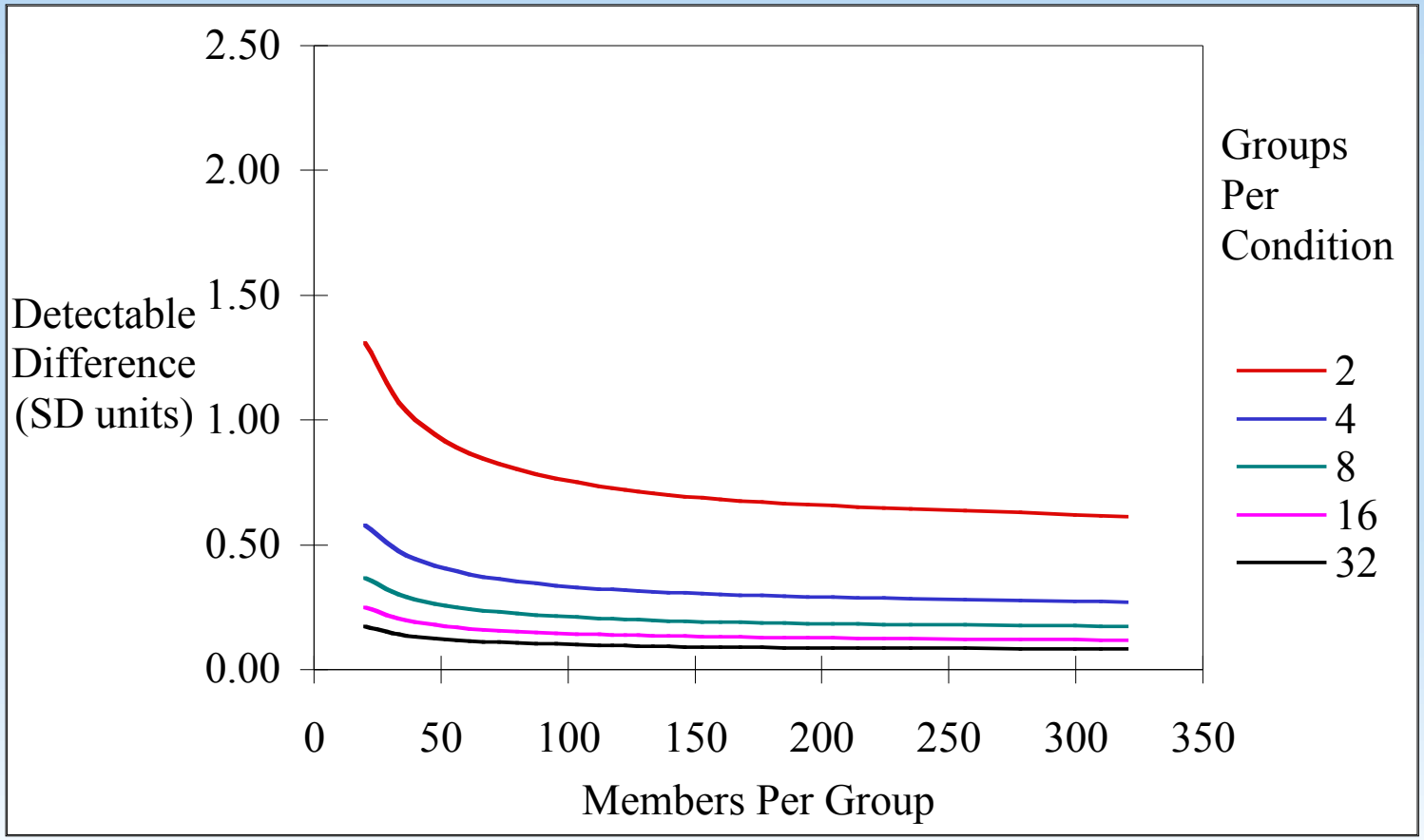
Strategies to Improve Precision

- Increased replication (ICC=0.100)



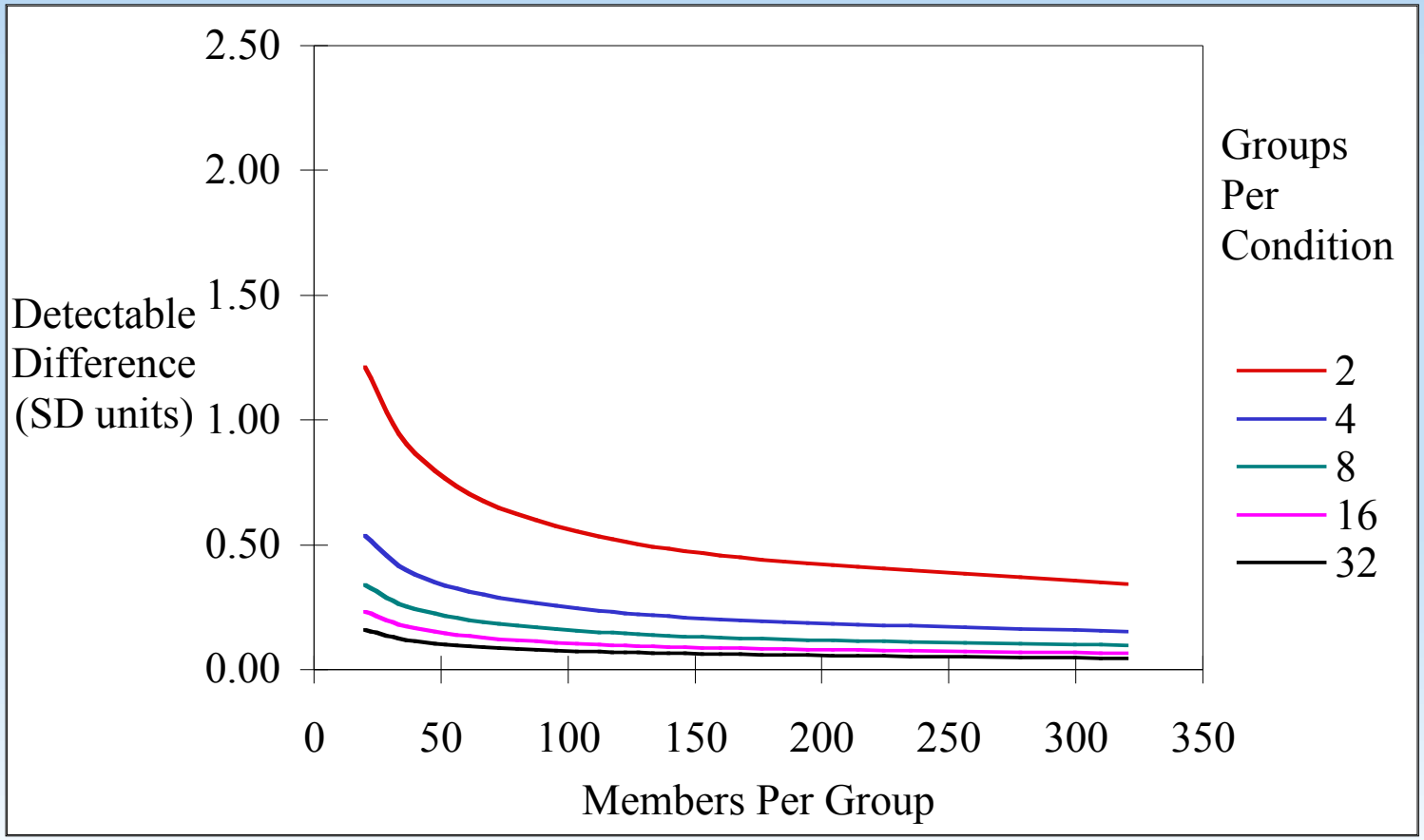
Strategies to Improve Precision

- Reduced ICC (ICC=0.010)



Strategies to Improve Precision

- The law of diminishing returns (ICC=0.001)



Power for Group-Randomized Trials

- The usual methods must be adapted to reflect the nested design
  - The variance is greater in a GRT due to the expected ICC.
  - df should be based on the number of groups, not the number of members.
- A good source on power is Chapter 9 in Murray (1998).
- Many papers now report ICCs and show how to plan a GRT.
  - cf. Murray & Blitstein, 2003 and Murray et al., 2004.
- Power in GRTs is tricky, and investigators are advised to get help from someone familiar with these methods.
- Power for IRGTs is often even trickier, and the literature is more limited.
  - cf. Pals et al. 2008.

Power - RCTs vs GRTs

- A simple RCT

$$n = \frac{2\sigma_y^2\left(t_{\alpha/2} + t_\beta\right)^2}{\Delta^2}, \quad df = 2(n-1)$$

- A simple GRT

$$g = \frac{2\sigma_y^2\left(t_{\alpha/2} + t_\beta\right)^2\left(1 + \left(m-1\right)ICC_{m:g:c}\right)}{m\Delta^2}, \quad df = 2(g-1)$$

A Classification Scheme for Statistical Models

	Gaussian Distribution	Non-Gaussian Distribution
One Random Effect	General Linear Model	Generalized Linear Model
Two Or More Random Effects	General Linear Mixed Model	Generalized Linear Mixed Model

- Fixed effect: the investigators want to draw inferences only about the levels used in the study.
- Random effect: the investigators want to draw inferences about some larger population of levels that are only represented by the levels used in the study.

Preferred Models for Designs With One or Two Time Intervals

- Mixed-model ANOVA/ANCOVA
  - Extension of the familiar ANOVA/ANCOVA based on the General Linear Model.
  - Fit using the General Linear Mixed Model or the Generalized Linear Mixed Model.
  - Accommodates regression adjustment for covariates.
  - Can not misrepresent over-time correlation.
  - Can take several forms
    - Posttest-only ANOVA/ANCOVA
    - ANCOVA of posttest with regression adjustment for pretest
    - Repeated measures ANOVA/ANCOVA for pretest-posttest design
  - Simulations have shown these methods have the nominal Type I error rate across a wide range of conditions common in GRTs.

Preferred Models for Designs With More Than Two Time Intervals

- Random coefficients models
  - Also called growth curve models.
  - The intervention effect is estimated as the difference in the condition mean trends.
  - Mixed-model ANOVA/ANCOVA assumes homogeneity of group-specific trends.
    - Simulations have shown that mixed-model ANOVA/ANCOVA has an inflated Type I error rate if those trends are heterogeneous.
  - Random coefficients models allow for heterogeneity of those trends.
  - Simulations have shown these methods have the nominal Type I error rate across a wide range of conditions common in GRTs.

Mixed Models

- Mixed models need to be specified correctly.
  - For models that use 1 time point for the outcome (e.g., analysis of posttest data with regression adjustment for baseline), the units of assignment should be modeled as levels of a nested random effect.
    - Failure to include this random effect will result in an inflated type 1 error rate.
  - For models that use 2 or more time points for the outcome (e.g., repeated measures models, random coefficient models), the units of assignment and the interaction between the units of assignment and time should be modeled as random effects.
    - Failure to include both random effects will result in an inflated type 1 error rate.
  - Quite generally, any nested factor should be modeled as a random effect (Zucker, 1990).

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

What About Randomization Tests?

- The intervention effect is a function of unadjusted or adjusted group-specific means, slopes or other group-level statistic.
- Under the null hypothesis of no intervention effect, the actual arrangement of those group-level statistics among the study conditions is but one of many equally likely arrangements.
- The randomization test systematically computes the effect for all possible arrangements.
- The probability of getting a result more extreme than that observed is the proportion of effects that are greater than that observed.
- No distributional or other assumptions are required.

What About Randomization Tests?

- Strengths
  - Gail et al. (1996) found that randomization tests had nominal Type I and II error rates across conditions common to GRTs.
    - Even when the member-level errors were non-normal,
    - Even when very few heterogeneous groups are assigned to each condition,
    - Even when the ICC was large or small,
    - So long as there was balance at the level of the group.
  - Programs for randomization tests are available in print and on the web.

- Gail MH, Mark SD, Carroll RJ, Green SB, Pee D. On design considerations and randomization-based inference for community intervention trials. Statistics in Medicine. 1996;15(11):1069-92.

What About Randomization Tests?

- Weaknesses
  - The unadjusted randomization test does not offer any more protection against confounding than other unadjusted tests (Murray et al., 2006).
  - Randomization tests provide only a point estimate and a p-value.
  - Regression adjustment for covariates requires many of the same assumptions as the model-based tests.

- Murray DM, Hannan PJ, Varnell SP, McCowen RG, Baker WL, Blitstein JL. A comparison of permutation and mixed-model regression methods for the analysis of simulated data in the context of a group-randomized trial. Statistics in Medicine. 2006;25(3):375-88.

What About Randomization Tests?

- Model-based methods provide parameter estimates, standard errors, and the nominal Type I error rate (Murray et al., 2006).
  - Even if the member- or group-level errors were non-normal, unless they were very skewed or heavy tailed (unpublished dissertation).
  - Even when few heterogeneous groups were assigned to each condition.
  - Even when the ICC was large or small.
  - So long as there was balance at the level of the group.
- Randomization tests and model-based tests perform similarly under most conditions.
- Randomization tests are preferred for very skewed or heavy tailed distributions.

What About a Method Like GEE That is Robust Against Misspecification?

- Methods based on GEE use an empirical sandwich estimator for standard errors.
- That estimator is asymptotically robust against misspecification of the random-effects covariance matrix.
- When the degrees of freedom are limited (<40), the empirical sandwich estimator has a downward bias.
- Recent work provides corrections for that problem; several have recently be incorporated into SAS PROC GLIMMIX (9.1.3).
- Methods that employ the corrected empirical sandwich estimator may have broad application in GRTs.

What About Fixed-Effect Methods in Two Stages?

- Introduced as the a solution for nested designs in the 1950s.
  - Commonly known as the means analysis.
  - Simple to do and easy to explain.
  - Gives results identical to the mixed-model ANOVA/ANCOVA if both are properly implemented.
  - Can be adapted to perform random coefficients analyses.
  - Can be adapted to complex designs where one-stage analyses are not possible.
  - Used in several large trials, including CATCH, MHHP, REACT, CYDS, and TAAG.

- Two-staged models can be very useful in GRTs.

What About Analysis by Subgroups?

- Some have suggested analysis by subgroup rather than group, especially when the number of groups is limited.
  - Classrooms instead of schools
  - Physicians instead of clinics
- This approach rests on the strong assumption that the subgroup captures all of the variation due to the group.
- This approach has an inflated Type I error rate even when the subgroup captures 80% of the group variation (Murray et al., 1996).
- Analysis by subgroups is not recommended.

- Murray DM, Hannan PJ, Baker WL. A Monte Carlo study of alternative responses to intraclass correlation in community trials: Is it ever possible to avoid Cornfield's penalties? Evaluation Review. 1996;20(3):313-37.

What About Deleting the Unit of Assignment From the Model if it is not Significant?

- The df for such tests are usually limited; as such, their power is usually limited.
- Standard errors for variance components are not well estimated when the variance components are near zero.
- Even a small ICC, if ignored, can inflate the Type I error rate if the number of members per group is moderate to large.

- The prudent course is to retain all random effects associated with the study design and sampling plan.

What About Unbalanced Designs?

- Group-level imbalance can create analytic problems (Gail et al., 1996; Murray et al., 2006).
- Member-level imbalance can create Type I error inflation and the risk increases with the level of imbalance.
- Johnson et al. (2015) compared 10 model-based approaches to member imbalance.
  - A one-stage mixed model with Kenward-Roger df and unconstrained variance components performed well for $g \geq 14$.
  - A two-stage model weighted by the inverse of the estimated theoretical variance of the group means and with unconstrained variance components performed well for $g \geq 6$.

- Johnson JL, Kreidler SM, Catellier DJ, Murray DM, Muller KE, Glueck DH. Recommendations for choosing an analysis method that controls Type I error for unbalanced cluster sample designs with Gaussian outcomes. Statistics in Medicine. 2015;34(27):3531-45.

What About Constrained Randomization?

- Li et al. (2015) evaluated model-based and randomization tests in the context of constrained randomization in a GRT.
  - The unadjusted randomization test maintained the nominal Type I error rate; the unadjusted model-based test was conservative.
  - Adjusted model-based and randomization tests were similar.
    - Both maintained the nominal Type I error rate.
    - Both had better power under constrained randomization.
  - Correct specification of the permutation distribution is essential under constrained randomization.
- Constrained randomization can improve power if used well.

- Li F, Lokhnygina Y, Murray DM, Heagerty PJ, DeLong ER. An evaluation of constrained randomization for the design and analysis of group-randomized trials. Statistics in Medicine. 2015;35(10):1565-79. PMC4826850.

Is the Non-Negativity Constraint OK?

- Software based on maximum likelihood routinely constrains variance estimates to be non-negative.
  - Combined with traditional methods for calculating df, this constraint introduces a positive bias in the variance component estimates and depresses the Type I error rate, often dramatically (Swallow & Monahan, 1984; Murray et al., 1996).
  - Earlier advice was to avoid the non-negativity constraint.
- Recent evidence suggests that the Kenward-Roger method for df addresses this problem (Andridge et al., 2014).

- Swallow WH, Monahan JF. Monte Carlo comparison of ANOVA, MIVQUE, REML, and ML estimators of variance components. Technometrics. 1984;26(1):47-57.
- Andridge RR, Shoben AB, Muller KE, Murray DM. Analytic methods for individually randomized group treatment trials and group-randomized trials when subjects belong to multiple groups. Statistics in Medicine. 2014;33(13):2178-90. PMC4013262.

What About Individually Randomized Group Treatment Trials (IRGTs)?

- Many studies randomize participants as individuals but deliver treatments in small groups (cf. Pals et al., 2008).
  - Psychotherapy, weight loss, smoking cessation, etc.
  - Participants nested within groups, facilitators nested within conditions
  - Little or no group-level ICC at baseline.
  - Positive ICC later, with the magnitude proportional to the intensity and duration of the interaction among the group members.

- Pals SP, Murray DM, Alfano CM, Shadish WR, Hannan PJ, Baker WL. Individually randomized group treatment trials: a critical appraisal of frequently used design and analytic approaches. American Journal of Public Health. 2008;98(8):1418-24. PMC2446464
- Pals SL, Murray DM, Alfano CM, Shadish WR, Hannan PJ, Baker WL. Erratum. American Journal of Public Health. 2008;98(12):2120.

What About Individually Randomized Group Treatment Trials (IRGTs)?

- Analyses that ignore the ICC risk an inflated Type I error rate (cf. Pals et al., 2008; Baldwin et al., 2011).
  - Not as severe as in a GRT, but can exceed 15% under conditions common to these studies.
  - The solution is the same as in a GRT.
    - Analyze to reflect the variation attributable to the small groups.
    - Base df on the number of small groups, not the number of members.

- Baldwin SA, Bauer DJ, Stice E, Rohde P. Evaluating models for partially clustered designs. Psychological Methods. 2011;16(2):149-65. PMC3987820.

What About IRGTs In Which Members Belong to More than one Group or Change Groups?

- The IRGT literature assumes that each member belongs to a single group and that group membership does not change.
  - That pattern is not likely to hold in practice.
  - Andridge (2014) found that failure to account for multiple group membership can inflate Type I error for the methods described thus far.
  - Roberts (2013) found that multiple membership multilevel models address this problem.
    - They require data on membership time in each group, which is not routinely collected in IRGTs.

- Andridge RR, Shoben AB, Muller KE, Murray DM. Analytic methods for individually randomized group treatment trials and group-randomized trials when subjects belong to multiple groups. Statistics in Medicine. 2014;33(13):2178-90. PMC4013262.
- Roberts C, Walwyn R. Design and analysis of non-pharmacological treatment trials with multiple therapists per patient. Statistics in Medicine. 2013;32(1):81-98.

State of the Science for Analytic Methods in GRTs and IRGTs

- GRTs and IRGTs require analyses that reflect the nested designs inherent in these studies.
- Used alone, the usual methods based on the General or Generalized Linear Model are not valid.
- Methods based on the General Linear Mixed Model and on the Generalized Linear Mixed Model are widely applicable.
  - For designs having one or two time intervals, mixed-model ANOVA/ANCOVA is recommended.
  - For designs having three or more time intervals, random coefficients models are recommended.
- Other methods can be used effectively, with proper care, including randomization tests, GEE, and two-stage methods.

State of the Science for Analytic Methods in GRTs and IRGTs

- Other approaches are not appropriate, including analysis at a subgroup level, deleting the unit of assignment if it or the ICC is not significant, designs with one group per condition, and Kish's effective df.
- Unbalanced designs can create analytic problems and an inflated Type I error rate; special methods are required.
- Constrained randomization can be helpful.
- IRGTs face similar problems to GRTs and the solutions are similar: model the small groups or common change agents as nested random effects, with implications for df and testing.
- In addition, IRGTs often have different hierarchical structures in the study conditions, and that must be reflected in the analytic plan.

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

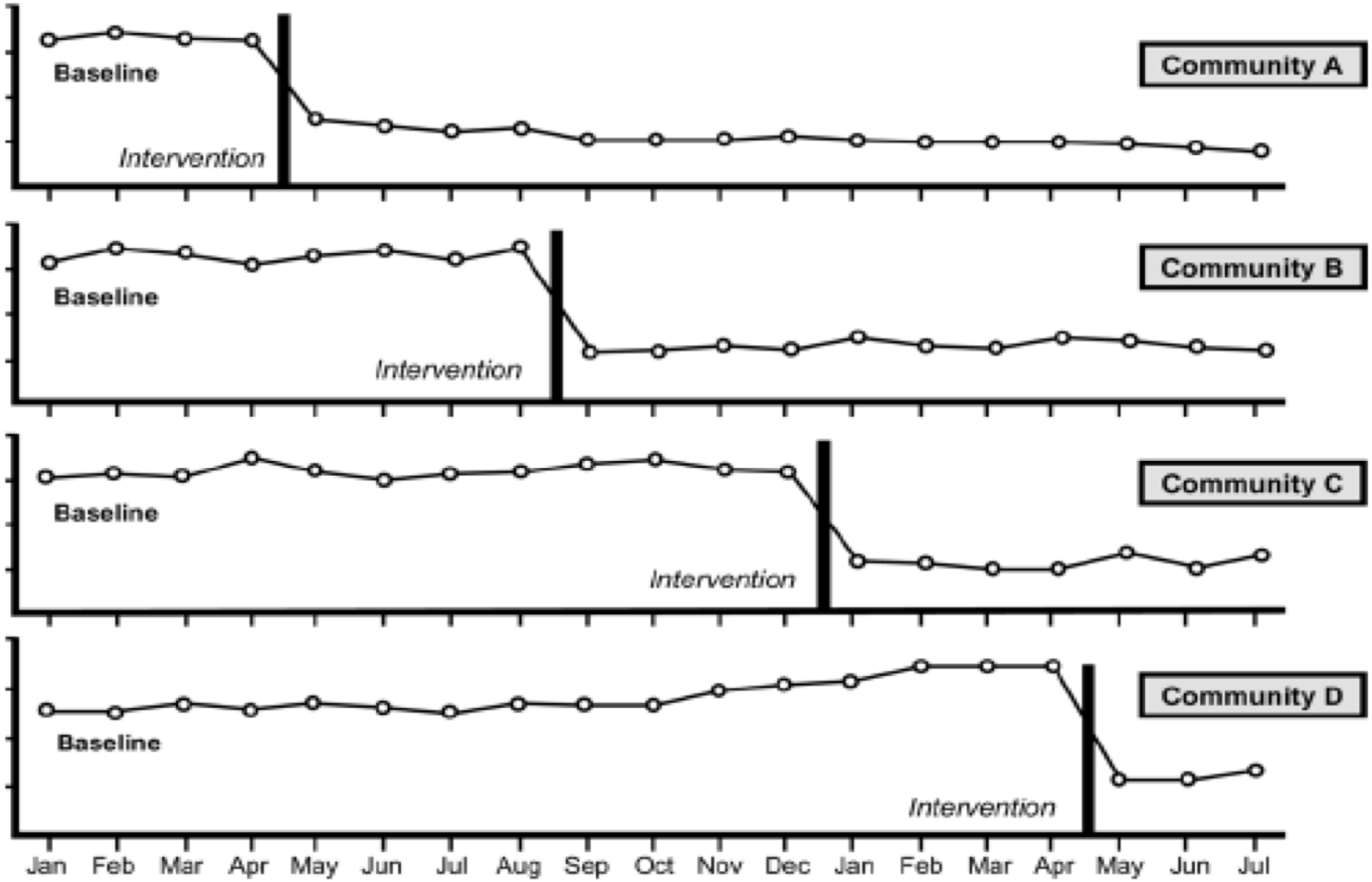


Figure 1. Hypothetical example of a multiple baseline design used to assess behavior change following an intervention in four communities.

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

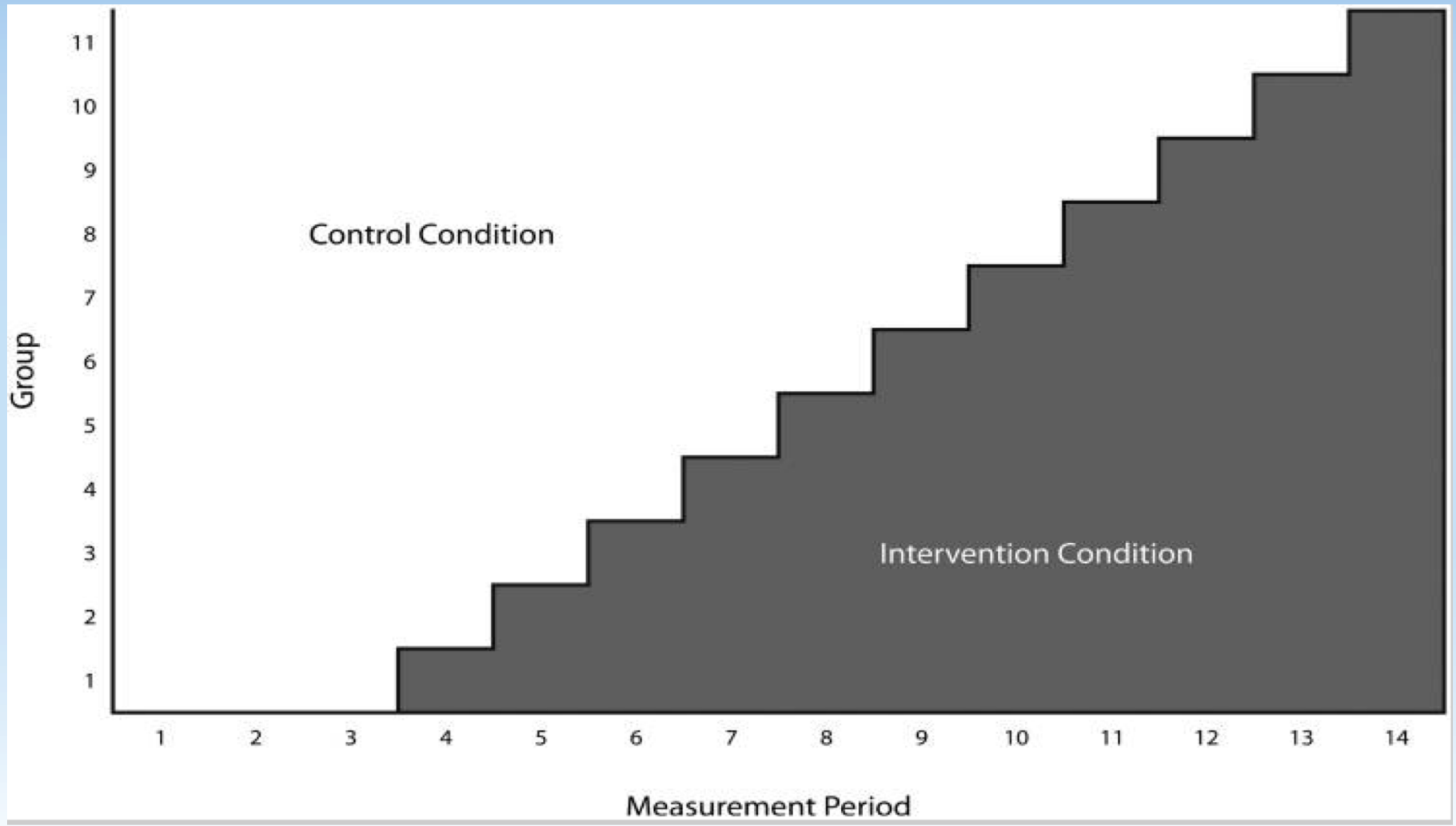
- QEs have all the features of experiments except randomization.
  - Causal inference requires elimination of plausible alternatives.
- If groups are assigned and members are observed, analysis and power issues are the same as in GRTs.
- Useful when randomization is not possible.
  - Can provide experience 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.

- Shadish WR, Cook TD, Campbell DT. Experimental and Quasi-Experimental Designs for Generalized Causal Inference. Boston, MA: Houghton Mifflin Company; 2002.

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.
- Example
  - Pragmatic Trial of Lumbar Image Reporting with Epidemiology (LIRE), Jeffery Jarvik PI, HCS Collaboratory Project

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

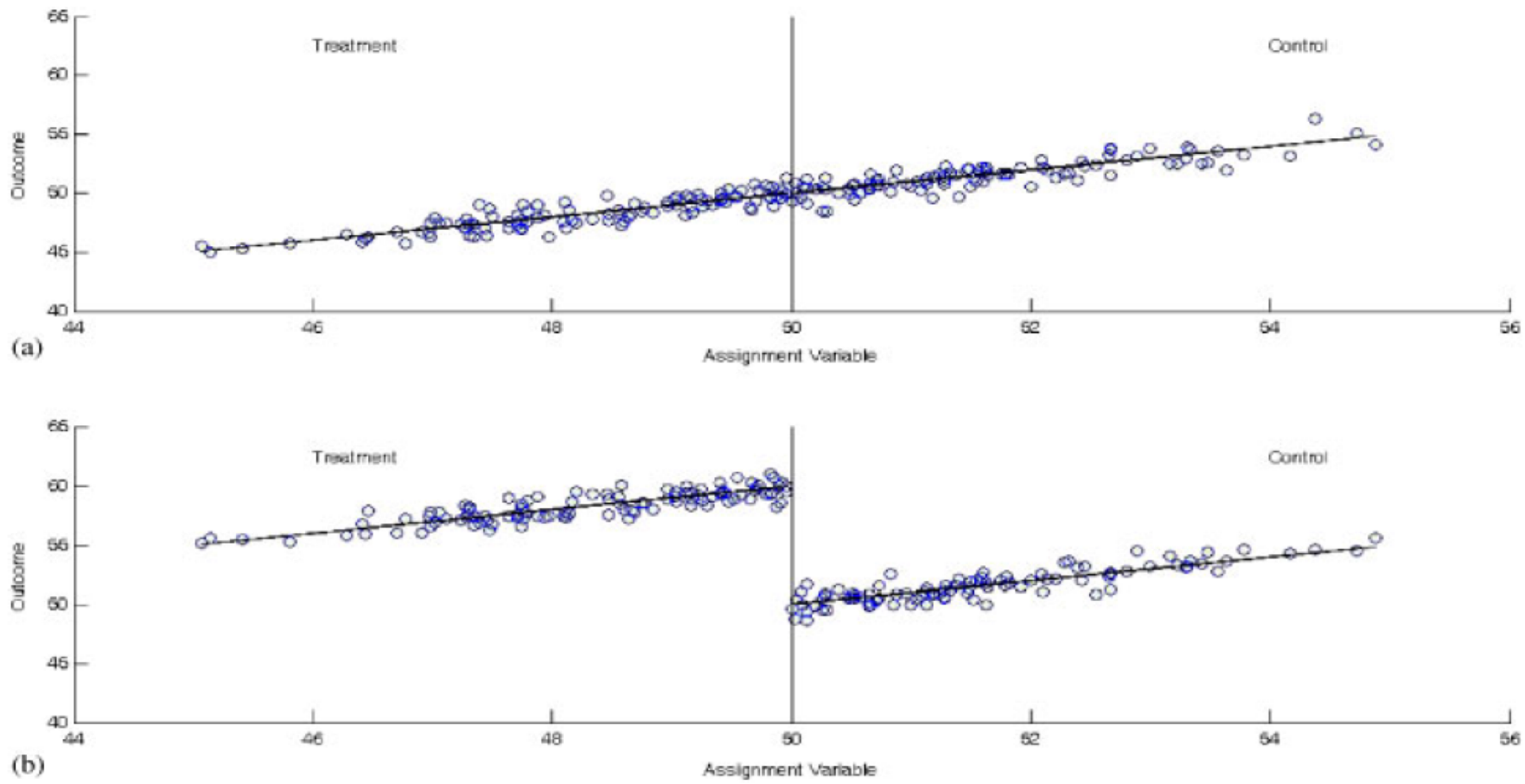


Figure 1. Hypothetical regression discontinuity experiments: (a) ineffective treatment and (b) effective treatment.

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

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 the any of the modules in this series

Send questions to:
GRT@mail.nih.gov

National Institutes of Health
Office of Disease Prevention