

# Pragmatic and Group-Randomized Trials in Public Health and Medicine

## **Part 6: Review of Recent Practices**

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# 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

# A Review of Recent Practices in GRTs

- Murray DM, Pals SP, George SM, Kuzmichev A, Lai GY, Lee J, Myles RL, Nelson SM. Design and analysis of group-randomized trials in cancer: a review of current practices. Preventive Medicine. 2018;111:241-7. doi: 10.1016/j.ypmed.2018.03.010. PMC5930119.

# A Review of Recent Practices in GRTs

## Previous Reviews of the GRT Literature

- The first review was published by Donner et al. in 1990.
  - Only 19% took the ICC into account in the sample size calculations.
  - Only 50% took the ICC into account in the analysis.
- A review by Simpson et al. in 1995 reported little progress.
  - Only 19% took the ICC into account in the sample size calculations.
  - Only 57% took the ICC into account in the analysis.
- Donner A, Brown KS, Brasher P. A methodologic review of non-therapeutic intervention trials employing cluster randomization, 1979-1989. International Journal of Epidemiology. 1990;19(4):795-800.
- Simpson JM, Klar N, Donner A. Accounting for cluster randomization: a review of Primary Prevention Trials, 1990 through 1993. American Journal of Public Health. 1995;85(10):1378-83.

# A Review of Recent Practices in GRTs

## Previous Reviews of the GRT Literature

- A review by Varnell et al. in 2004 reported no progress, though the standards were higher than in previous reviews.
  - Only 15% took the ICC into account in the sample size calculations.
  - Only 54% always took the ICC into account in the analysis.
- A review by Murray et al. in 2008 reported some progress and some regression.
  - Only 24% took the ICC into account in the sample size calculations.
  - Only 45% always took the ICC into account in the analysis.
- We were interested in whether the situation had improved.
- Varnell SP, Murray DM, Janega JB, Blitstein JL. Design and analysis of group-randomized trials: a review of recent practices. American Journal of Public Health. 2004;94(3):393-9. PMC1448264.
- Murray DM, Pals SP, Blitstein JL, Alfano CM, Lehman J. Design and analysis of group-randomized trials in cancer: a review of current practices. Journal of the National Cancer Institute. 2008;100(7):483-91.

# A Review of Recent Practices in GRTs

## Procedures

- Systematic review of cancer-related studies published 2011-2015.
  - Medline and PubMed search.
  - Studies had as their primary outcome cancer risk factors, cancer morbidity, or cancer mortality.
  - Studies used randomization to assign identifiable social groups to study conditions, with observations taken on members of those groups to assess the impact of an intervention.
  - Where the paper referred to an earlier "design paper", we also reviewed that paper.
  - Each reviewer independently assessed the article on items related to design, sample size estimation, and analysis.
  - The reviewers discussed each paper as a group and any disagreements were resolved in discussion.



# A Review of Recent Practices in GRTs

## Findings

- 123 articles from 76 journals met the inclusion criteria.
- 39 background "design" papers.
- 7% in the *Preventive Medicine*
- 4% in *American Journal of Preventive Medicine*
- A steady increase in the rate of publication of GRTs
  - 25.0 per year (2011-15)
  - 15.0 per year (2002-06)
  - 11.6 per year (1998-02)
  - 5.3 per year (1990-93)

Table 1. Analytic methods frequently used in group-randomized trials and the conditions under which their use is appropriate.

Method	Appropriate Application
Mixed-model methods	
ANOVA/ANCOVA <sup>a</sup>	One time point in the analysis
Repeated measures ANOVA/ANCOVA	Two time points in the analysis
Random coefficients approach	Three or more time points in the analysis
Generalized Estimating Equations	
With correction for limited df <sup>b</sup>	< 38 df for the analysis
With no correction for limited df	≥ 38 df for the analysis
Cox regression	
With shared frailty	Time-to-event outcome
Without shared frailty	Not appropriate

<sup>a</sup> ANOVA: analysis of variance; ANCOVA: analysis of covariance

<sup>b</sup> df: degrees of freedom

Table 1. Analytic methods frequently used in group-randomized trials and the conditions under which their use is appropriate.

Method	Appropriate Application
Two-stage Methods (analysis on group means or other summary statistic)	At the level of the unit of assignment
Post-hoc correction based on external estimates of intraclass correlation	Validity depends on validity of external estimates of intraclass correlation
Analysis at subgroup level <sup>c</sup> , ignoring group-level intraclass correlation	Not appropriate
Analysis at individual level, ignoring group-level intraclass correlation	Not appropriate
Analysis at individual level, modeling group as a fixed effect	Not appropriate

<sup>c</sup> Subgroup level: a lower level in the group hierarchy, e.g., classrooms in a trial that randomized schools

Table 2. Characteristics of 123 articles reporting results of group-randomized trials in cancer research in peer-reviewed journals during the period 2011-2015, inclusive.

Characteristic	N	%
<b>Number of Study Conditions</b>		
Two	109	88.6
Three	9	7.3
Four or more	5	4.1
<b>Design</b>		
Cohort	94	76.4
Cross-sectional	26	21.1
Combination of Cohort and Cross-sectional	3	2.4
<b>Type of Randomization</b>		
Restricted Randomization	67	54.5%
Matching only	16	13.0
Stratification only	46	37.4
Constrained Randomization only	2	1.6
Matching and Stratification	3	2.4
Simple or Unrestricted Randomization	56	45.5

Table 2. Characteristics of 123 articles reporting results of group-randomized trials in cancer research in peer-reviewed journals during the period 2011-2015, inclusive.

Characteristic	N	%
Type of Group		
Churches	6	4.9
Communities, Neighborhoods or Community Groups	15	12.2
Families	4	3.3
Housing Projects or Apartment Buildings	1	0.8
Clinicians, Provider Groups, Hospitals	65	52.8
Schools, Classes, Day Care Centers	24	19.5
Time period <sup>a</sup>	4	3.3
Worksites	4	3.3

<sup>a</sup> Some studies randomized time periods. For example, some clinic-based studies randomized blocks of six weeks to study conditions, so that patients who saw their provider were given the treatment randomly assigned to their time block.

Table 2. Characteristics of 123 articles reporting results of group-randomized trials in cancer research in peer-reviewed journals during the period 2011-2015, inclusive.

Characteristic	N	%
Average Number of Groups per Condition in the Analysis		
1 Group	0	0.0
2-5 Groups	3	2.4
6-8 Groups	9	7.3
9-12 Groups	16	13.0
13-24 Groups	31	25.2
≥ 25 Groups	58	47.2
Variable	1	0.8
not reported	5	4.1
Average Number of Members per Group in the Analysis		
<10 Members	30	24.4
10-49 Members	44	35.8
50-99 Members	19	15.4
≥100 Members	25	20.3
not reported	5	4.1

Table 2. Characteristics of 123 articles reporting results of group-randomized trials in cancer research in peer-reviewed journals during the period 2011-2015, inclusive.

Characteristic	N	%
<b>Number of Time Points in the Analysis</b>		
1 Time point	94	76.4
2 Time points	21	17.1
3-9 Time points	8	6.5
<b>Focus of Study</b>		
Primary Prevention	45	36.6
Secondary Prevention	54	43.9
Tertiary Prevention	24	19.5
<b>Target Population</b>		
Individuals with no personal history of the target cancer	33	26.8
Cancer survivors during primary treatment	11	8.9
Cancer survivors after primary treatment	5	4.1
Unknown or mixed cancer survivorship	74	60.2

Table 2. Characteristics of 123 articles reporting results of group-randomized trials in cancer research in peer-reviewed journals during the period 2011-2015, inclusive.

Characteristic	N	%
Primary Outcome Variables		
Alcohol Use	3	2.4
Delivery of Health Services	22	17.9
Dietary Variables	9	7.3
Fatigue	0	0.0
Incidence of Cancer	4	3.3
Knowledge of Cancer or Attitudes Regarding Cancer	10	8.1
Lymphedema	0	0.0
Mortality from Cancer	1	0.8
Neuropathy	0	0.0
Pain	3	2.4
Physical Activity	5	4.1
Quality of Life	6	4.9
Screening	33	26.8
Sun Protection	3	2.4
Tobacco Use	10	8.1
Weight	1	0.8
Other	13	10.6



Table 3. Distribution of analytic methods in 123 articles reporting on group-randomized trials in cancer research published in peer-reviewed journals during the period 2011-2015, inclusive.

Criteria	N	%	N	%
Articles reporting only appropriate methods	63	51.2		
Mixed-model ANOVA or ANCOVA with 1 time point			39	56.5
Mixed-model repeated measures with 2 time points			7	10.1
Random coefficients model with >2 time points			2	2.9
Generalized estimating equations with $\geq 38$ degrees of freedom			9	13.0
Cox regression with adjustment for the unit of assignment			4	5.8
Two-stage analysis			6	8.7
Other			2	2.9

Table 3. Distribution of analytic methods in 123 articles reporting on group-randomized trials in cancer research published in peer-reviewed journals during the period 2011-2015, inclusive.

Criteria	N	%	N	%
Articles reporting both appropriate and inappropriate methods	17	13.8		
Appropriate Methods				
Mixed-model ANOVA or ANCOVA with 1 time point			11	64.7
Mixed-model repeated measures with 2 time points			1	5.9
Random coefficients model with >2 time points			0	0.0
Generalized estimating equations with $\geq 38$ degrees of freedom			2	11.8
Cox regression with shared frailty for the unit of assignment			3	17.6
Two-stage analysis			0	0.0
Other			0	0.0

Table 3. Distribution of analytic methods in 123 articles reporting on group-randomized trials in cancer research published in peer-reviewed journals during the period 2011-2015, inclusive.

Criteria	N	%	N	%
Articles reporting both appropriate and inappropriate methods	17	13.8		
Inappropriate Methods				
Analysis at an individual level, ignoring groups			16	94.1
Analysis at a subgroup level, ignoring groups			0	0.0
Analysis with group as a fixed effect			0	0.0
Mixed-model repeated measures, > 2 time points			0	0.0
GEE with $\leq 38$ df and no small sample correction			1	5.9
Individual-level analysis with post-hoc correction			0	0.0
Other			0	0.0

Table 3. Distribution of analytic methods in 123 articles reporting on group-randomized trials in cancer research published in peer-reviewed journals during the period 2011-2015, inclusive.

Criteria	N	%	N	%
Articles reporting only inappropriate methods	37	30.1		
Analysis at an individual level, ignoring groups			18	45.0
Analysis at a subgroup level, ignoring groups			7	17.5
Analysis with group as a fixed effect			2	5.0
Mixed-model repeated measures, > 2 time points			3	7.5
GEE with $\leq 38$ df and no small sample correction			8	20.0
Individual-level analysis with post-hoc correction			1	2.5
Other			1	2.5
Not enough information provided	6	4.9		

# A Review of Recent Practices in IRGTs

- 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

# A Review of Recent Practices in IRGTs

## Procedures

- There were no prior systematic reviews of IRGT trials.
- We manually searched six journals for the period 2002-06.
  - American Journal of Public Health
  - Preventive Medicine
  - Health Psychology
  - Obesity Research
  - Addictive Behaviors
  - AIDS and Behavior
- Procedures parallel to those used for the GRT review
- Criteria for sample size and analysis methods parallel to those used for the GRT review
- 34 eligible articles

TABLE 2- Characteristics of the Studies Described in 34 Articles Reviewed 2002-2006

Study characteristics	Number of articles	%
<b>Journal</b>		
American Journal of Public Health	4	11.8
Preventive Medicine	6	17.6
Health Psychology	8	23.5
Obesity	7	20.6
Addictive Behaviors	7	20.6
AIDS and Behavior	2	5.9
<b>Year of publication</b>		
2002	5	14.7
2003	6	17.6
2004	6	17.6
2005	5	14.7
2006	12	35.3

TABLE 2- Characteristics of the Studies Described in 34 Articles Reviewed 2002-2006

Study characteristics	Number of articles	%
Number of study conditions <sup>a</sup>		
Two	23	67.6
Three	8	23.5
Four	3	8.8
Number of group treatment conditions <sup>b</sup>		
One	11	32.3
Two	17	50
Three	4	11.8
Four	2	5.9
Baseline sample size		
<100	15	44.1
100-<200	9	26.5
200-<300	4	11.8
>300	6	17.6



TABLE 2- Characteristics of the Studies Described in 34 Articles Reviewed 2002-2006

Study characteristics	Number of articles	%
Target population		
Adults or adolescents with mental health issues	3	8.8
Overweight or obese children	2	5.9
Overweight or obese adults	9	26.5
Adults with cardiovascular risk factors other than weight	3	8.8
Cancer patients	2	5.9
College or University students	2	5.9
HIV-positive adults	3	8.8
Smokers or substance abusers	7	20.6
Other	3	8.8

TABLE 2- Characteristics of the Studies Described in 34 Articles Reviewed 2002-2006

Study characteristics	Number of articles	%
Primary Outcome Variable <sup>c</sup>		
Weight, BMI, Body Fat percentage or Dietary Variables	13	38.2
Physical activity/ physical fitness variables	5	14.7
Smoking or substance use variables	7	20.6
Mental health variables	6	17.6
Sex behavior variables	6	17.6
Treatment retention	2	5.9
Medication adherence	2	5.9
Other variables	7	20.6

TABLE 3- Results of the Review of Sample Size Calculations and Analytic Methods in 34 Articles Reviewed, 2002-2006

Study characteristics	Number of articles	%
Sample size calculations		
Authors reported sample size calculations at individual level	6	17.6
Authors stated power calculations performed, but no detail	1	2.9
No mention of sample size calculation	25	73.5
Authors claimed sample size accounted for ICC, but no detail	1	2.9
Other	1	2.9
Any significant results reported		
Yes	27	79.4
No	7	20.6

TABLE 3- Results of the Review of Sample Size Calculations and Analytic Methods in 34 Articles Reviewed, 2002-2006

Study characteristics	Number of articles	%
Analytic approaches <sup>a</sup>		
Analysis at an individual level, ignoring group entirely	32	94.1
Mixed-model approach with baseline as covariate	2	5.9
Structural equation modeling	1	2.9
Appropriateness of analytic methods		
All analytic methods appropriate	1	2.9
No analytic methods appropriate	32	94.1
Not enough information	1	2.9

# Summary

- Our results for GRTs suggested improvement from earlier reviews.
  - 54% of the articles reported appropriate sample size estimation.
    - vs 24% in 2008
  - 51% of the articles reported only analyses judged to be appropriate.
    - vs 45% in 2008
  - 30% reported only analyses deemed inappropriate.
    - Unchanged from 2008
- The progress on sample size estimation is encouraging.
- There is still much room for improvement.

# Summary

- Warnings have appeared in the literature for at least 30 years regarding the development of intraclass correlation in IRGTs.
- Even so, the literature on the design and analysis of IRGTs is limited.
- The use of inappropriate design and analytic methods is very common for IRGTs.
- The picture is similar to what GRTs looked like in the mid 1970s.
- Hopefully, the pattern will improve with time.

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