Essential Ingredients and Innovations in the Design and Analysis of Group-Randomized Trials

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Three Kinds of Randomized Trials

• Randomized Clinical Trials (RCTs)
  ◦ Individuals randomized to study conditions with no interaction among participants after randomization (no group sessions, virtual interaction, or shared intervention agent)
    • Most drug trials

• Individually Randomized Group Treatment Trials (IRGTs)
  ◦ Individuals randomized to study conditions with interaction among participants after randomization or with a shared intervention agent
    • Many surgical trials
    • 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.
Two Kinds of Group-Randomized Trials

• Parallel GRT
  ◦ Separate but parallel intervention and control conditions throughout the trial, with no crossover.

• Stepped Wedge GRT
  ◦ All groups start in the control condition.
  ◦ All groups crossover to the intervention condition, but in a random order and on a staggered schedule.
  ◦ All groups receive the intervention before the end of the study.
Choosing Among These Designs

Is there a strong rationale for randomizing groups rather than individuals to study conditions?

- No
- Yes

Do participants receive their treatment in a group format or from a shared interventionist?

- No
- Yes

- RCT
- IRGT Trial

Is there a strong rationale for rolling out the intervention to all groups before the end of the trial?

- Yes
- No

- SW-GRT
- GRT

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a If the intervention is delivered through a physical or a virtual group, or through shared interventionists who each work with multiple participants, positive ICC can develop over the course of the trial.

b There may be logistical reasons to randomize groups or it may not be possible to deliver the intervention to individuals without substantial risk of contamination.

c There may be good political or logistical reasons to roll out the intervention to all groups before the end of the trial.

Analysis Issues in a GRT or IRGT

• Nested factors must be modeled as 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 is often limited.
  ◦ This is almost always true in a GRT and 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 (Cornfield, 1978).
  ◦ 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.


Analysis Issues for SW-GRTs

• Crossing of groups with study conditions often reduces the impact of the ICC compared to a parallel GRT, either improving power or allowing a smaller study.

• There are other potential sources of bias in the SW-GRT:
  ◦ The intervention is confounded with time.
  ◦ The intervention effect may vary over time.
  ◦ The intervention effect may vary by group.
  ◦ Patterns of correlation may vary over time.

• Any analysis that assumes that the intervention effect is constant over time and across groups, and that the pattern of correlation is constant, may be biased.

• Compared to a parallel GRT, SW-GRTs are at greater risk to the effects of external events that affect the outcomes of the trial.
Evolution of the Methods

- The co-authors identified 4514 candidate reports through 2018.
- Preliminary screening identified 926 focused on GRTs, IRGTs, or SW-GRTs.
- The Relative Citation Ratio (RCR) and citation counts were used to identify influential reports.
  - The RCR is an article-level and field-independent metric that reflects the degree to which an article is cited relative to the articles that appear alongside it in reference lists of other papers – the co-citation network (Hutchins et al., 2016).
    - RCR values were available for 85.4% of the reports.
    - GRTs – RCR in top 1% or >200 citations
    - IRGTs – RCR in top 5% or >100 citations
    - SW-GRTs – RCR in top 2.5% or >150 citations
- 50 influential reports were identified (Murray et al., 2020).

Hutchins BI, Yuan X, Anderson JM, Santangelo GM. Relative Citation Ratio (RCR): A New Metric That Uses Citation Rates to Measure Influence at the Article Level. PLoS Biol. 2016;14(9):e1002541. PMID27599104.

Group-Randomized Trials

- Cornfield (1978) – the two penalties of extra variation and limited df
- Donner et al. (1981) – methods for sample size and analysis
- Feldman (1988) – random coefficients models
- Murray et al. (1990) – design, analytic, and sample size methods
- Donner & Klar (1992) – methods for meta-analysis
- Hedeker & Gibbons (1994) – methods for ordinal outcomes
- Hedeker & Gibbons (1996) – software for ordinal outcomes
- Bland et al. (1997) – brief summary of the design and analytic issues
- Raudenbush (1997) – analytic methods and optimal design
- Murray (1998) – first textbook on design and analytic methods
- Guiliford et al. (1999) – estimates of intraclass correlation
Group-Randomized Trials

- Donner & Klar (2000) – second textbook on design and analytic methods
- Eccles et al. (2003) – alternative research designs, including GRTs
- Adams et al. (2004) – estimates of intraclass correlation
- Murray et al., (2004) – state of the practice for design and analysis of GRTs
- Campbell et al. (2004, 2012) – the CONSORT statement for GRTs
- Hayes & Moulton (2009) – third textbook on design and analytic methods
- Emsley et al. (2010) – methods for mediation and moderation
- Eldridge & Kerry (2012) – fourth textbook on design and analytic methods
- Zou & Donner (2013) – modified Poisson regression model
- Grant et al. (2013) – methods for process evaluation
Individually Randomized Group-Treatment Trials

- Whiting-O’Keefe et al. (1984) – the correct unit of analysis in medical experiments
- Crits-Cristoph & Mintz (2001) – implications of therapist effects
- Nye et al. (2004) – estimates of variance components in IRGTs
- Baldwin et al. (2005) – the impact of ignoring therapist effects
- Roberts & Roberts (2005) – analytic methods for IRGTs
- Boutron et al. (2008) – CONSORT statement for non-pharmacologic interventions
- Kahan & Morris (2013) – sources of clustering in individually randomized trials
- Heo et al. (2017) – sample size methods for IRGTs
- Sterba (2017) – modeling developments for partially nested designs
Stepped Wedge Group-Randomized Trials

- Hussey & Hughes (2005) – analytic methods for SW-GRTs
- Brown & Lilford (2006) – state of the practice for design and analysis of SW-GRTs
- Mdege et al. (2011) – state of the practice for design and analysis of SW-GRTs
- Woertman et al. (2013) – sample size methods for SW-GRTs
- Baio et al. (2015) – sample size methods for SW-GRTs
- Beard et al. (2015) – state of the practice for design and analysis of SW-GRTs
- Copas et al. (2015) – typology for SW-GRT designs
- Davey et al. (2015) – state of the practice for design and analysis of SW-GRTs
- Hemming et al. (2015) – rationale, design, and analysis for SW-GRTs
- Hemming et al. (2015) – sample size methods for SW-GRTs
- Girling & Hemming (2016) – statistical efficiency and optimal design for SW-GRTs
- Hemming & Taljaard (2016) – sample size methods for SW-GRTs
- Scott et al. (2017) – small sample correction for GEE in SW-GRTs
Limitations

• The review considered papers published through 2018.
• Papers published in 2017 and 2018 will usually have fewer citations and may not yet have had an RCR value in 2019.
• Taken together, these issues may underestimate the influence of papers published in 2017 and 2018.
• Papers published after 2018 were not considered.
NIH Resources

• Pragmatic and Group-Randomized Trials in Public Health and Medicine
  ◦ https://prevention.nih.gov/grt
  ◦ 7-part online course on GRTs and IRGTs

• Mind the Gap Webinars
    • SW-GRTs for Disease Prevention Research (Monica Taljaard, July 11, 2018)
    • Design and Analysis of IRGTs in Public Health (Sherri Pals, April 24, 2017)
    • Research Methods Resources for Clinical Trials Involving Groups or Clusters (David Murray, December 13, 2017)

• Research Methods Resources Website
  ◦ https://researchmethodsresources.nih.gov/
  ◦ Material on GRTs and IRGTs and a sample size calculators for GRTs and IRGTs.