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REVIEW OF RECENT METHODOLOGICAL DEVELOPMENTS IN GROUP-RANDOMIZED TRIALS: PART 1 - DESIGN

ABSTRACT

In 2004, Murray et al. published a review of methodological developments in both the design and analysis of GRTs. In the thirteen years since, there have been many developments in both areas. The goal of the current paper is to focus on developments in design with a companion paper to focus on developments in analysis. As a pair, these papers update the 2004 review. This design paper includes developments in topics included in the earlier review (e.g. clustering, matching, and individually randomized group treatment trials) and new topics including constrained randomization and a range of randomized designs that are alternatives to the standard parallel-arm GRT. These include the stepped wedge GRT, the pseudo-cluster randomized trial and the network-randomized GRT, which, like the parallel-arm GRT, require clustering to be accounted for in both their design and analysis.

INTRODUCTION

A group-randomized trial (GRT) is a randomized controlled trial in which the unit of randomization is a group and outcome measurements are obtained on members of those groups.[1] Also called a cluster randomized trial or community trial,[2-5] a GRT is the best comparative design available if the intervention operates at a group level, manipulates the physical or social environment, cannot be delivered to individual members of the group without substantial risk of contamination across study arms, or if there are other circumstances which warrant the design such as a desire for herd immunity or a need to estimate both the direct and indirect intervention effects in studies of infectious diseases.[1-5]

In GRTs, outcomes on members of the same group are likely to be more similar to each other than to outcomes on members from other groups.[1] Such clustering must be accounted for in the

design of GRTs to avoid under-powering the study and accounted for in the analysis to avoid under-estimated standard errors and inflated type I error for the intervention effect.[1-5]

In 2004, Murray et al.[6] published a review of methodological developments in both the design and analysis of GRTs. In the 13 years since, there have been many developments in both areas. The goal of the current paper is to focus on developments in design with a companion paper to focus on developments in analysis.[7] As a pair, these papers update the 2004 review. With both papers, we seek to provide a broad and comprehensive review to guide the reader to seek out appropriate materials for their own circumstances.

DEVELOPMENTS IN FUNDAMENTALS OF DESIGN

Clustering

In its most basic form, a GRT has a hierarchical structure with groups nested within study arm and members nested within groups. Additional levels of nesting may arise through repeated measures over time or from more complex group structures (e.g., children nested in classrooms nested in schools). When designing and analyzing a GRT, it is necessary to account for the clustering associated with the nested design.[1-5]

The intraclass correlation coefficient (ICC) is the clustering measure most commonly used in power calculations and reported in published studies.[8] Eldridge et al.[9] provide a comprehensive review of ICC definitions and measures in general clustered data for both continuous and binary outcomes, the most commonly reported outcomes in GRTs.[10,11] Whereas the ICC for continuous outcome measures is well-defined and generally well understood,[1-4] Eldridge et al.[9] highlight some of the challenges for binary outcomes and provide several definitions (see **Table 1** for the form most commonly presented in GRT texts).[2,4,5,9] Others compare methods to estimate the ICC

of a binary outcome.[12-17] The ICC is not easily defined for rates based on person-time data.[2,4] Recent publications have defined ICC for time-to-event data.[18,19]

The coefficient of variation (CV) is a measure of clustering that is defined for general clustered data when the distributional parameter of interest is a mean, proportion, or rate.[3,17] The CV and ICC for continuous and binary outcomes are related by a mathematical relationship as a function of the distributional parameter of interest (i.e. mean or proportion) and, for continuous outcomes, of the within-group variance, σ_w^2 (**Table 1**).[2,4] Hayes and Moulton[2] advocate for the CV generally in power calculations; Donner and Klar agree for event data analyzed as rates.[3]

[TABLE 1 ABOUT HERE]

Given the central role of clustering in planning GRTs, imprecision in the estimated level of clustering can lead to an under-powered trial. Multiple authors address imprecision, and all focus on the ICC.[20-26] Simultaneously, there has been an increasing number of publications that report ICCs (for example, Moerbeek and Teerenstra[27] provide a comprehensive list of such papers) to aid the planning of future studies, consistent with the CONSORT statement on GRTs.[28]

Cohort vs. Cross-Sectional GRT Designs

The choice between a cohort and cross-sectional GRT design (or a combination) is driven by the nature of the research question.[1] The cross-sectional design is preferred when the question is about change in a population[1] or when the time to the outcome is so short as to make a cohort study impractical (e.g., studies involving acute conditions).[2] For example, in order to observe enough participants with malaria at 6-monthly follow-up time points and to be able to draw conclusions about population-level behavior related to malaria treatment choices, Laktabai et al.[29] chose a cross-sectional design in which different population samples were obtained at each

follow-up time point. In contrast, when interested in change in specific individuals, or in mediation, the most natural choice is the cohort design in which a cohort of individuals is enrolled and followed up over time.[1] For example, Turner et al.[30] chose such a design to study child outcomes in mothers with prenatal depression. Similarly, the cohort design is usually required to generate event data in individuals.[2] A combination design could be used whereby the cross-sectional design is augmented by subsampling a cohort of individuals who are followed over time, such as in the COMMIT study.[31] A recent review[32] indicated that the cohort design is the most common GRT design (67% of 75 GRTs).

DEVELOPMENTS IN THE DESIGN OF PARALLEL-ARM GROUP-RANDOMIZED TRIALS

Baseline Imbalance of Group Sample Size

Imbalance of group sample size means that group sizes are different across the groups randomized in the study, with implications for statistical efficiency. Donner discussed variation in group size for GRTs for a design stratified by group size.[33] Guittet et al.[34] and Carter[35] studied the impact on power using simulations, which showed the greatest reduction in power with few groups and/or high ICC. Several authors have offered adjustments to the standard sample size formula for a GRT to correct for variability in group size based on the mean and variance of the group size, or the actual size of each group.[36-39] Others have offered adjustments based on relative efficiency.[40-43] Candel et al.[40,41] reported that relative efficiency ranged from 1.0-0.8 across a variety of distributions for group size with lower values for higher ICCs and greater variability in group size; the minimum relative efficiency was usually no worse than 0.9 for continuous outcomes. They recommended dividing the result from standard formulae for

93 balanced designs by the relative efficiency for the expected group-size distribution, which was a
94 function of the ICC and the mean and variance of the group size.[40] For binary outcomes, they
95 suggested an additional correction factor based on the estimation method planned for the
96 analysis.[41] You et al.[42] defined relative efficiency in terms of non-centrality parameters; their
97 measure of relative efficiency was a function of the ICC, the mean and variance of the group
98 size, and the number of groups per study arm. Candel and Van Breukelen[43] considered variability
99 not only in group size but also between arms in error variance and the number of groups per arm.
100 They recommended increasing the number of groups in each arm by the inverse of the relative
101 efficiency minus one. Their estimate of the relative efficiency was a function of the number of
102 groups per study arm, the ICC in each study arm, the ratio of the variances in the two study arms,
103 and the mean and variance of the group size.

104 Consistent across these papers was the recommendation that expectations for variation in group
105 sample size be considered during both the planning stages and the analysis stage. Failure in
106 planning can result in an underpowered study[40-43] while failure in analysis can result in type I
107 error rate inflation.[44]

108 **Baseline Imbalance of Covariates**

109 Imbalance of covariates at baseline threatens the internal validity of the trial. Yet GRTs often
110 randomize a limited number of groups that are heterogeneous in baseline covariates and in
111 baseline outcome measurements. As a result, there is a good chance of baseline covariate
112 imbalance.[6,45] Restricted randomization strategies such as stratification, matching or constrained
113 randomization can be implemented in the design phase to address this issue. However,
114 stratification may have limited use in GRTs if there are more than a handful of covariates to

balance, due to the small number of groups in most trials.[46] Pair-matching also comes with several disadvantages[46] as it affects the proper calculation of ICC[47] and complicates the significance testing of individual-level risk factors.[48] More recently, Imai et al. presented a design-based estimator,[49] which led them to advocate for the use of pair-matching based on the unbiasedness and efficiency of their estimator. Several others highlighted features of this work,[50-52] including the authors' power calculation that does not depend on the ICC, thus avoiding the known ICC problem.[53] Despite efficiency gains of pair-matching over stratification, a simulation study conducted by Imbens led him to conclude that stratified randomization would generally be preferred to pair-matching.[54] We note that strata of size four provide virtually all the advantages of pair-matching while avoiding the disadvantages, and may be preferred over pair-matching for that reason.

To overcome challenges when trying to balance on multiple, possibly continuous, covariates, Raab and Butcher[55] proposed constrained randomization. It is based on a balancing criterion calculated by a weighted sum of squared differences between the study arm means on any group-level or individual-level covariate and seeks to offer better internal validity than both pair-matching and stratification. The approach randomly selects one allocation scheme from a subset of schemes that achieve acceptable balance, identified based on having the smallest values of the balancing criterion. Carter and Hood[56] extended this work to randomize multiple blocks of groups and provided an efficient computer program for public use. The "best balance" score was proposed to measure imbalance of group-level factors under constrained randomization.[57] In simulations with 4 to 20 groups, constrained randomization with the "best balance" score was shown to optimally reduce quadratic imbalances compared with simple randomization, matching and minimization.

Li et al.[58] systematically studied the design parameters of constrained randomization for continuous outcomes, including choice of balancing criterion, candidate set size, and number of covariates to balance. With extensive simulations, they demonstrated that constrained randomization with a balanced candidate subset could improve study power while maintaining the nominal type I error rate, both for a model-based analysis and for a permutation test, as long as the analysis adjusted for potential confounding. Moulton[59] proposed to check for overly constrained designs by counting the number of times each pair of groups received the same study arm allocation. He revealed the risk of inflated type I error in overly constrained designs using a simulation example with 10 groups per study arm. Li et al. further noticed the limitation of overly constrained designs in that they may fail to support a permutation test with a fixed size.[58] In practice, if covariate imbalance is present even after using one of the design strategies described, such imbalance can be accounted for using adjusted analysis that is either pre-planned in the protocol or through post-hoc sensitivity analysis.[7] In summary, constrained randomization seeks to provide both internal validity and efficiency.

Methods and Software for Power and Sample Size

If the ICC is positive, not accounting for it in the analysis will inflate the type I error rate, and the power of the trial will be unknown. If the ICC is estimated as negative, as it can be when the true value is close to zero and sampling error leads to a negative estimate or when there is competition within groups,[1-4,9,60] not accounting for it will reduce the type I error rate so that the test is more conservative, and the power of the trial will be lower than planned.[61] Thus, a good estimate of the ICC is essential for sample size calculation for all GRTs.

One of the simplest power analysis methods often offered for a standard parallel-arm GRT with a single follow-up measurement is to compute the power for an individually randomized trial using the standard formula, and to then inflate this by the design effect,[62] given by $1 + (m - 1)\rho$. In this formula, m is the number of subjects per group and ρ is the ICC. Unfortunately, this approach only addresses the first of the two penalties associated with group-randomization that were identified by Cornfield almost 40 years ago:[63] extra variation and limited degrees of freedom for the test of the intervention effect. In order to accurately estimate sample size and power for a GRT, it is necessary to also account for the limited degrees of freedom that can arise due to having few groups to randomize. This can be achieved by using appropriate methods detailed in one the GRT texts rather than using the naïve approach of simply inflating the individually randomized trial sample size by the design effect .[1-5,61] In general, appropriate methods calculate sample size using a variance estimate inflated based on the expected ICC and use a t-test rather than a z-test to reflect the desired power and type I error rate, with degrees of freedom based on the number of groups to be randomized.

In practice, both cross-sectional and cohort GRTs are commonly powered based on a comparison between study arms at a single point in time. Then, for GRTs with cohort designs, the analysis section of the study protocol may state that power will be gained by accounting for the repeated measures design in the analysis. However, methods exist for directly computing power in the case of repeated measures in the context of both cross-sectional and cohort designs.[1,27] Authors have noted that regression adjustment for covariates often reduces both the ICC and the residual variance, thereby improving power.[1,64] Heo et al.[65] and Murray et al.[66] provide methods that utilize data from across the entire course of the study, rather than just comparing two means at the end of the study. In practice, the user would require estimates of the variance reduction

expected from repeated measures or from regression adjustment for covariates, which could be obtained from prior studies or pilot data.

Methods exist to power GRTs with additional layers of clustering, whether from additional structural hierarchies[1,67-69] or from the repeated measures in the cohort design.[1,27,64,66,70-73] Konstantopoulos describes how to incorporate cost into the power calculation for three-level GRTs.[74] Hemming et al. discuss approaches to take when the number of groups is fixed ahead of time.[75] Two recent papers focus specifically on binary outcome variables.[13,76] Candel et al. examine the effects of varying group sizes in the context of a two-arm GRT.[77] Durán Pacheco et al. focus on power methods for overdispersed counts.[78]

Rutterford et al. and Gao et al. summarize a wide array of methods for sample size calculations in GRTs,[79,80] including for GRT designs involving 1-2 measurements per member or per group and for designs involving 3 or more measurements per member or per group. A new textbook on power analysis for studies with multilevel data also provides a thorough treatment.[27] Previous textbooks on the design and analysis of GRTs devoted at least a chapter to methods for power and sample size.[1-5]

[TABLE 2 ABOUT HERE]

DEVELOPMENTS IN THE DESIGN OF ALTERNATIVES TO THE PARALLEL-ARM GRT

We discuss four alternatives that can be used in place of a traditional parallel-arm GRT (**Figure 1A, Table 3**). All of these four designs involve randomization and some form of clustering that must be appropriately accounted for in both the design and analysis. As such, they share key

features of the standard parallel-arm GRT yet all have distinct and different features that are important to understand. In practice, some of these designs are still poorly understood.

[TABLE 3 ABOUT HERE]

[FIGURE 1 ABOUT HERE]

Stepped Wedge GRT

The stepped wedge GRT (SW-GRT) is a one-directional crossover GRT in which time is divided into intervals and in which all groups eventually receive the intervention (**Figure 1B**).[81] Systematic reviews indicate increasing popularity.[82-84] Both Trials (2015) and the Journal of Clinical Epidemiology (2013) recently published special issues focused on the design and analysis of SW-GRTs.

The rationale for this alternative is primarily logistical, i.e., it may not be possible to roll out the intervention in all groups simultaneously,[85-88] although a staggered parallel-arm GRT design could alternatively be used in which blocks of groups were randomized to intervention or control instead of all groups eventually receiving the intervention as in the SW-GRT.[89-91] Others propose a SW-GRT for ethical and acceptability reasons because all groups eventually receive the intervention.[82] This second argument has been discounted as the intervention could be delivered to all control groups at the end of a parallel-arm GRT design,[88,92] often earlier than would be the case in a SW-GRT.[93] When SW-GRTs are conducted in low incidence settings, Hayes et al. emphasized that the order and period of intervention allocation is crucial.[94]

As for the parallel-arm GRT, design choices include cross-sectional[82] vs. cohort[95] with most SW-GRT methodological literature focused on cross-sectional designs whereas most published SW-

GRTs are cohort designs.[96] An additional variation is that of complete vs. incomplete SW-GRTs defined according to whether each group is measured at every time point.[90] Regardless of the specifics of the SW-GRT design, it is important to consider the possible confounding and moderating effects of time in the analysis.[85,90,97-99] Failure to account for both, if they exist, will threaten the internal validity of the study.

Cross-sectional SW-GRT sample size formulae are available for complete and incomplete designs.[90,100-103] Hemming et al. provide a unified approach for the design of both parallel-arm and SW-GRTs and allow for multiple layers of clustering.[90] Cohort SW-GRT sample size calculation relies on simulation.[97,104] Recent work on optimal designs shows that, for large studies, the optimal design is a mixture of a stepped wedge trial embedded in a parallel-arm trial.[105,106] Moerbeek & Teerenstra devote a chapter to sample size methods for SW-GRTs.[27]

Network-Randomized GRT

GRTs have historically been used to minimize the contamination between study arms; such contamination is also called interference.[107] This contamination may give rise to a network of connections between individuals both within- and between-study arms. The latter is of particular relevance to GRT design because it leads to reduced power, although sample size methods exist to preserve power and efficiency.[108]

The network-randomized GRT is a novel design that uses network information to address the challenge of potential contamination in GRTs of infectious diseases.[109-111] In such a design, groups are defined as the network contacts of a disease (index) case and those groups are randomized to study arms. Examples include the snowball trial and the ring trial, each with a distinct way in which the intervention is delivered. In the snowball trial, only the index case

directly receives the intervention, which he is encouraged to share with his contacts (e.g. see Latkin et al.[109] for such a trial of HIV prevention in injection drug users). In the ring trial, 'rings' of contacts of the index case are randomized to receive the intervention (**Figure 1C**). This design has been used to study foot-and-mouth,[112] smallpox,[113] and Ebola.[114] For the same sample size, ring trials are more powerful than classical GRTs when the incidence of the infection is low.[115]

Pseudo-Cluster Randomized Trial

In GRTs where all members of the selected groups are recruited to the study, study participants are expected to be representative of the underlying population and, as a result, selection bias is expected to be minimal. In contrast, GRTs with unblinded recruitment after randomization are at risk of selection bias. For example, consider a GRT used to evaluate the effect of a behavioral intervention delivered by providers in the primary care setting. If a provider is first randomized to study arm and then prospectively recruits participants, he may differentially select participants depending on whether he is randomized to the intervention or control arm.[116]

To reduce the risk of such selection bias, Borm et al. introduced the pseudo-cluster randomized trial (PCRT) to allocate intervention to participants in a two-stage process.[117] In the first stage, providers are randomized to a patient allocation-mix (e.g., patients predominantly randomized to intervention vs. patients predominantly randomized to control). In the second stage, patients recruited to the PCRT are individually randomized to intervention or control according to the allocation probability of their provider (e.g., 80% to intervention vs. 20% to intervention) (**Figure 1D**).

An obvious threat to a PCRT design is that the same providers are asked to implement both the intervention and the control arms, depending on which patient they are seeing. Concerns about

contamination are a common reason to randomize providers (i.e. group randomization) so that they deliver either the intervention or the control but not both. The PCRT design would not be appropriate if there are concerns about contamination, and if they exceed concerns about selection bias.

In two published cases, providers were blinded to the two-stage form of randomization and instead assumed that patients were individually randomized to the intervention arm with equal probability.[118,119] Later publications indicate that the PCRT design did well at balancing contamination and selection bias in both studies.[120-122]

Borm et al. provide sample size calculations for continuous outcomes.[117] The clustering by provider (or unit of first stage randomization) must be accounted for in both the design and analysis. No explicit sample size methods are known to be available for non-continuous outcomes. Moerbeek & Teerenstra devote a chapter to sample size methods for PCRTs.[27]

Individually Randomized Group Treatment Trial

Pals et al.[123] identified studies that randomize individuals to study arms but deliver interventions in small groups or through a common change agent as individually randomized group-treatment (IRGT) trials, also called partially clustered or partially nested designs (**Figure 1E**).[72,124] Examples include studies of psychotherapy,[125] weight loss,[126] reduction in sun exposure,[127] and many other outcomes. Clustering associated with these small groups or change agents must be accounted for in the analysis to avoid type I error rate inflation.[72,123,124,128,129] Even so, this accounting appears to be rare in practice.[123,130-133]

Recent papers have reported sample size formulae for IRGT trials with clustering in only one study arm, both for balanced[72,123,128,134] and unbalanced designs.[77,128] Moerbeek & Teerenstra

devote a chapter to sample size methods for IRGT trials focused on methods with clustering in either one or both arms.[27] Roberts addresses sample size methods for IRGT trials in which members belong to more than one small group at the same time or change small groups over the course of the study.[135] Both features have been shown to increase the type I error rate if ignored in the analysis.[135,136]

DISCUSSION

We have summarized many of the most important advances in the design of GRTs during the 13 years since the publication of the earlier review by Murray et al.[6] Many of these developments have focused on alternatives to the standard parallel-arm GRT design, as well as those related to the nature of clustering and its features in all of the designs presented. Space limitations have prevented us from including recent developments involving pilot and feasibility GRTs and group designs such as cutoff designs and regression discontinuity applied to groups. Interested readers are directed to the recently launched *Pilot and Feasibility Studies* peer-reviewed journal and related references [4,137] and to cutoff design references by Pennell et al.[138] and by Schochet.[139]

Through this review, we have sought to ensure that the reader is reminded of the value of good design and gains knowledge in the fundamental principles of a range of recent and potentially beneficial design strategies. Pairing this knowledge with our companion review of developments in the analysis of GRTs,[7] we hope that our work leads to continued improvements in the design and analysis of GRTs.

APPENDIX: GLOSSARY

Balanced candidate subset: In constrained randomization, where a subset of randomization schemes is chosen that has "sufficient balance across potentially confounding covariates" according to "some pre-specified balance metric."[58]

Baseline covariate balance: The group-level and individual-level covariate distributions are similar in all study arms.[55]

Candidate set size: "The number of possible randomization schemes in a specific implementation."[58] "Simple randomization draws from the complete set of candidate schemes, while constrained randomization considers a subset of schemes."[58]

Choice of balancing criterion: Li et al. describe several balancing criteria to assess how well a GRT is balanced across covariates. These include the "best balance" (BB) metric of de Hoop et al.,[57] the balance criterion (B) of Raab and Butcher,[55] and the total balance score introduced by Li et al.[58]

Coefficient of variation: A measure of between-group variation, defined in Table 1.

Cohort GRT design: A cohort of individuals is enrolled at baseline and those same individuals are followed up over time.

Constrained randomization: Refers "to those designs that go beyond the basic design constraints to specify classes of randomization outcomes that satisfy certain balancing criteria, while retaining validity of the design."[59]

Cross-sectional GRT design: A different set of individuals is obtained at each time point.

Designed balance at the group level: When there are equal numbers of groups randomized to each study arm.

Equivalence: Assessing whether the new intervention is equivalent to the comparison intervention.

Individually Randomized Group Treatment Trials: Studies that randomize individuals to study arms but deliver treatments in small groups or through a common change agent.[123]

Intraclass correlation: A measure of between-group variation, defined in Table 1.

Minimization in GRTs: When the researchers allocate groups to intervention arms based on groups-specific characteristics in order to achieve a high degree of balance by minimizing the differences between intervention arms.[57] May be performed sequentially or all at once when group characteristics are known at the beginning of the study.

Network-Randomized GRT: The network-randomized GRT is a novel design that uses network information to address the challenge of potential contamination in GRTs of infectious diseases.[109-111]

Non-inferiority: When a trial is designed to show that the new intervention is not worse than the comparison intervention.

Pair-matching: At randomization, when groups are matched based on factors thought to be related to the outcome. Then within each pair of groups, one is allocated at random to one study arm and the other to the comparison study arm.[140]

Pseudo-cluster randomized trial: Intervention is allocated to individuals in a two-stage process. In the first stage, providers are randomized to a patient allocation-mix. In the second stage, patients recruited to the PCRT are individually randomized to intervention or control according to the allocation probability of their provider.

Selection bias: In some GRTs, groups are randomized before participant recruitment. This can lead to selection bias if researchers (either consciously or unconsciously) recruit specific participants for inclusion in treatment and exclude others based on certain participant characteristics, even when the aforementioned participants are all eligible for participation in the trial (see Farrin et al.[116]).

Stepped Wedge GRT: A one-directional crossover GRT in which time is divided into intervals and in which all groups eventually receive the intervention (**Figure 1B**).[81]

Stratification: At randomization, when groups are placed into strata based on factors thought to be related to the outcome.[141] Then groups are separately randomized within each strata.

Superiority: When a trial is designed to establish whether a new intervention is superior to the comparison intervention (e.g., another drug, a placebo, enhanced usual care). However, the statistical test is still two-sided, allowing for the possibility that the new intervention is actually worse than the comparison.

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No human subjects participated in this research therefore no IRB approval was sought.

Figure 1 The Parallel-Arm GRT and Alternative Group Designs

Abbreviation: GRT – Group-randomized trial.

Each pictorial representation is an example of the specific design in which baseline measurements are taken. Other versions of each design exist. All examples show 5 individuals per group.

*The stepped wedge group-randomized trial is a one-directional crossover GRT in which time is divided into intervals and in which all groups eventually receive the intervention, indicated by the shading of the boxes in the figure. The design shown in this figure is known as a "complete design"—that is, every group is measured at every time point. Like parallel-arm GRTs, SW-GRTs can either be cross-sectional or cohort.

†In the PCRT, a group randomized to "intervention" contains a larger proportion of group members receiving the intervention than a group randomized to control.

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Table 1. Two Common Measures of Clustering for General Clustered Data for Two Common Types of Outcome

Outcome measure	Intra-cluster correlation coefficient (ICC, ρ)[a]	Coefficient of Variation (CV, k)	Relationship of ICC to CV[b]
Continuous	$\sigma_B^2/(\sigma_B^2+\sigma_W^2)$	σ_B/μ	$1/\left(1+\frac{\sigma_w^2}{k^2\mu^2}\right)$
Binary	$\sigma_B^2/\pi(1-\pi)$	σ_B/π	$k^2\pi/(1-\pi)$

Note: μ = overall mean for continuous outcome data; π = overall proportion for binary outcome data; σ_B^2 = between-group variance; σ_W^2 = within-group variance (i.e. residual error variance). As is common practice, the two clustering measures are for general clustered data and do not focus on the GRT design in which the intervention effect is of primary interest (e.g. see Chapter 2 of Hayes and Moulton[2] for more details). The intervention parameter of interest in GRT is typically: difference of means for continuous outcomes; difference of proportions, ratio of proportions or odds ratio for binary outcomes; rate difference or rate ratio for event outcomes.

[a] There are multiple definitions of the ICC for binary outcomes (see [12-17]). The specific formulation provided here is one of the simplest and most commonly used (see, for example, equation (2.4) of Hayes and Moulton[2] and equation (8) of Eldridge et al.[9]).

[b] Note that, while the relationship for binary outcomes is only a function of k and the distributional parameter of interest (π), the relationship for continuous outcomes is a function of both the distributional parameter of interest (μ) and σ_W^2.

716 **Table 2. Software for Sample Size Calculations in Parallel-Arm GRTs**

Software	Functionality
PASS	Sample size calculations for GRTs comparing two means (non-inferiority, equivalence, or superiority), two proportions (non-inferiority, equivalence, or superiority), two Poisson rates, and for a logrank test.
nQuery	Comparison of two means, proportions, and rates.
Stata	User-provided command clustersampsi. Can compute sample size for continuous, binary, and rate outcomes for two-sided tests in equal-sized arms.
R	Package CRTSize for comparing two means or two binary proportions.
SAS	No built-in functionality at this time.
Calculator	For some simple designs, parameter values can be plugged in to formulas provided in textbooks and online.

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719 **Table 3. Characteristics of the Parallel-Arm Group Randomized Trial (GRT) and of Alternative Group Designs**

		One-stage randomization		Two-stage randomization	Type of follow-up possible	720
Design	**Acronym**	**By Group**	**By Individual**		**Cross-sectional**	**Cohort**
Parallel-Arm GRT	GRT	✓	-	-	✓	✓
Stepped Wedge GRT	SW-GRT	✓	-	-	✓	✓
Network-Randomized GRT	NR-GRT	✓	-	-	-	✓[1]
Pseudo-Cluster Randomized Trial	PCRT	-	-	✓	-	✓[2]
Individually Randomized Group Treatment Trial	IRGT trial	-	✓	-	-	✓[3]

[1] In the network-randomized GRT, the index case and its network is usually defined at baseline and therefore the design is expected to use a cohort design and not allow a cross-sectional design

[2] In the pseudo-cluster randomized trial, because randomization is undertaken in two stages with individuals randomized to intervention or control in the second stage, the design requires that a cohort of individuals be enrolled at study baseline in order to be followed over time

[3] In the individually randomized group treatment trial, individual randomization is performed and therefore, like the pseudo-cluster randomized trial, a cohort of individuals is enrolled and followed over time.

Figure

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Baseline Follow-up

Legend

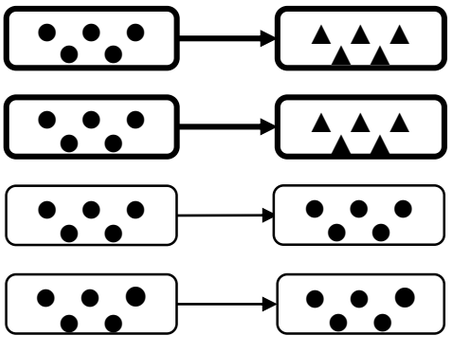
▲ Individual measured under intervention

● Individual measured under no intervention

Group randomized to intervention

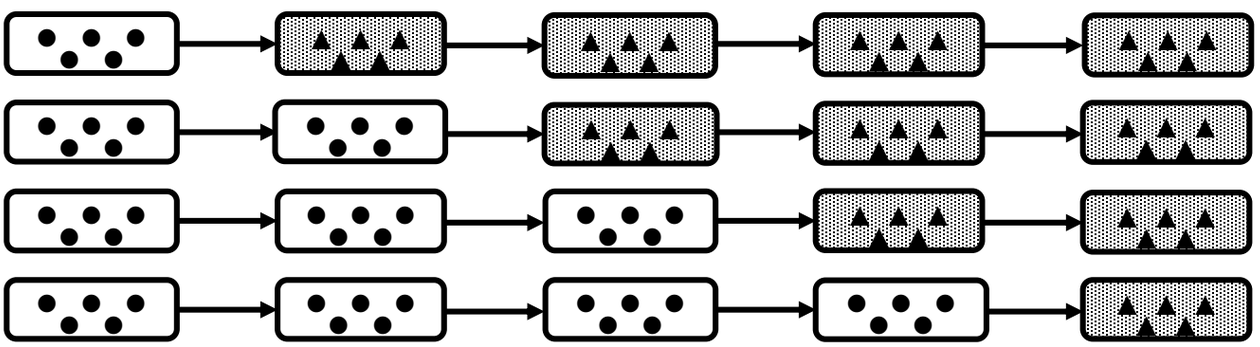
Group randomized to control

A: Parallel GRT

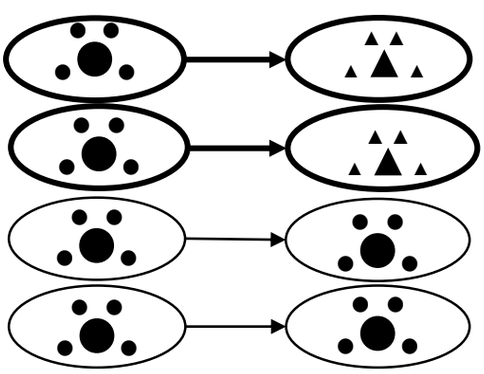


Groups are randomized to intervention or control at baseline, then either the same individuals are followed up over time (cohort GRT) or different individuals in the same group are sampled at different time points (cross-sectional GRT).

B: Stepped Wedge GRT (SW-GRT)*

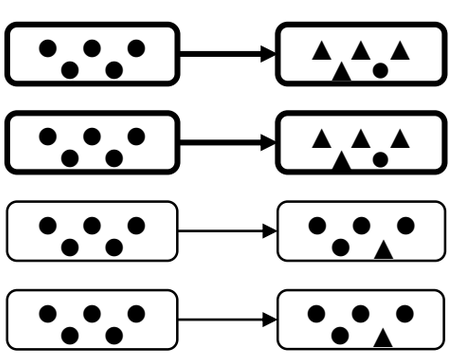


C: Network-Randomized GRT (NR-GRT)



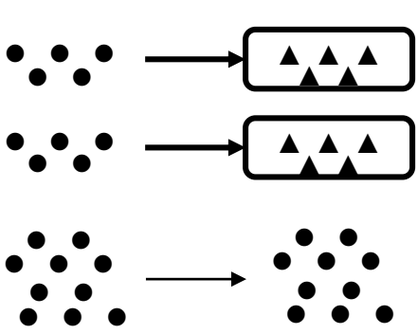
Groups are defined as the network contacts of an index disease case and those groups of contacts are then randomized to intervention or control. The larger symbols represent the index case in each group.

D: Pseudo-Cluster Randomized Trial (PCRT)†



Assignment to intervention is based on a two-stage process. In the first stage, groups (e.g., providers) are randomized to a patient allocation-mix, here shown as predominantly (80%) intervention vs. predominantly (80%) control. In the second stage, patients recruited to the PCRT are individually randomized to intervention or control.

E: Individually Randomized Group Treatment (IGRT) Trial



Individuals are randomized to intervention or control but treatments are delivered in small groups or through a common change agent.