

## **Review of recent Methodological Developments in group-randomized trials: Part 2 - Analysis**

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1 **REVIEW OF RECENT METHODOLOGICAL DEVELOPMENTS IN**

2 **GROUP-RANDOMIZED TRIALS: PART 2 - ANALYSIS**

3

4

5 **ABSTRACT**

6 In 2004, Murray et al. published a review of methodological developments in both the design  
7 and analysis of group-randomized trials (GRTs). Over the last 13 years, there have been many  
8 developments in both areas. The goal of the current paper is to review developments in analysis,  
9 with a companion paper to focus on developments in design. As a pair, these papers update the  
10 2004 review. This analysis paper includes developments in topics included in the earlier review,  
11 such as methods for parallel-arm GRTs, inference for conditional and marginal effects, and new  
12 topics including methods to account for multiple levels of clustering and alternative estimation  
13 methods such as augmented GEE, targeted maximum likelihood and quadratic inference  
14 functions. We also examine developments in dealing with missing outcome data, including  
15 doubly robust approaches, software available for analysis, and analysis of alternative group  
16 designs (including stepped wedge GRTs, network-randomized trials, pseudo-cluster randomized  
17 trials and individually-randomized group treatment trials). These alternative designs, like the  
18 parallel-arm GRT, require clustering to be accounted for in both their design and analysis.

19

20 **INTRODUCTION**

21 In a group-randomized trial (GRT), the unit of randomization is a group and outcome  
22 measurements are obtained on members of those groups.<sup>1</sup> Also called a cluster-randomized trial  
23 or community trial,<sup>2-5</sup> a GRT is the best comparative design available if the intervention operates  
24 at a group level, manipulates the physical or social environment, cannot be delivered to  
25 individual members of the group without substantial risk of contamination, or under other  
26 circumstances (e.g., a desire for herd immunity in studies of infectious disease).<sup>1-5</sup>

27 In GRTs, outcomes on members of the same group are likely to be more similar to each other  
28 than to outcomes on members from other groups.<sup>1</sup> Such clustering must be accounted for in the  
29 design to avoid an under-powered study and in the analysis to avoid under-estimated standard  
30 errors and inflated type I error for the intervention effect.<sup>1-5</sup> For analysis, regression modeling  
31 approaches are generally preferred and most commonly used because of their ease of  
32 implementation.<sup>6</sup> Several textbooks now address these and other issues.<sup>1-5</sup>  
33 In 2004, Murray et al.<sup>7</sup> published a review of methodological developments in both the design  
34 and analysis of GRTs. In the 13 years since, there have been many developments in both areas.  
35 The goal of the current paper is to focus on developments in analytic methods, including those  
36 relevant to designs described in a companion paper that focuses on developments in GRT  
37 design.<sup>8</sup> As a pair, these papers update the 2004 review. With both papers, we seek to provide a  
38 broad and comprehensive review to guide the reader to seek out appropriate materials for their  
39 own circumstances.

40

## 41 **DEVELOPMENTS IN THE ANALYSIS OF PARALLEL GROUP-**

## 42 **RANDOMIZED TRIALS**

### 43 **Methods for Superiority, Equivalence, and Non-Inferiority**

44 In GRTs, superiority trials are more common than equivalence or non-inferiority trials: a  
45 PubMed search by one of the authors (DMM) of studies published in 2015 identified 562  
46 superiority GRTs but only 1 equivalence GRT and 2 non-inferiority GRTs. Similarly,  
47 developments in the methods literature have focused on superiority GRTs, with developments  
48 for equivalence and non-inferiority GRTs limited to small sections in two of the more recent

49 textbooks<sup>2,5</sup> and a review paper on sample size methods.<sup>9</sup> As a consequence, the current review  
50 paper focuses on superiority GRTs.

### 51 **Methods for Intention-To-Treat and Alternative Intervention Effects**

52 In GRTs, protocol violations can lead to non-compliance at either the group- or member-level.<sup>5</sup>  
53 In order to minimize bias, intention-to-treat (ITT) principles are recommended at both levels  
54 rather than “on-treatment” and “per-protocol” analyses.<sup>2,4,5</sup> While group-level protocol violations  
55 are usually easy to identify, member-level compliance may be more difficult to ascertain in  
56 practice.<sup>2</sup> Jo et al. demonstrate that analyses which ignore compliance information could be  
57 underpowered to detect an ITT effect and propose a multilevel model combined with a mixture  
58 model.<sup>10</sup> Implications of group-level non-compliance can be considerable in GRTs, given the  
59 small number of groups that are randomized in many GRTs.

### 60 **Methods Based on the Randomization Scheme**

61 Matching or stratification in the design has been recommended for some time as a way to ensure  
62 baseline balance on important potential confounders,<sup>1</sup> with constrained randomization more  
63 recently developed.<sup>11</sup> Recent reports suggest that most GRTs follow this advice.<sup>12-15</sup> Matching  
64 and stratification in the design can be ignored in the analysis of intervention effects, without  
65 harm to the type I error rate, and often the saved degrees of freedom will improve power.<sup>16,17</sup>  
66 Recently, Donner et al. reported that ignoring matching can adversely affect other analyses, such  
67 as analyses that examine the relationship between a risk factor and an outcome,<sup>18</sup> for this reason,  
68 investigators considering pair-matching should consider small strata instead (e.g., strata of 4). Li  
69 et al.<sup>19</sup> compared model-based and permutation methods in the context of constrained  
70 randomization adjusting for group-level covariates. They found that both the adjusted F-test and

71 permutation test maintained the nominal size and had improved power under constrained  
72 randomization compared to simple randomization.

### 73 **Model-Based Methods**

74 Model-based methods can be broadly classified according to the interpretation of the model  
75 parameters. Conditional model parameters are typically estimated using mixed-effects regression  
76 via maximum likelihood estimation (MLE) and are referred to as cluster-specific effects (or as  
77 subject-specific effects in the longitudinal analysis literature). Effects are conditional on the  
78 random effects used to account for clustering and on other covariates included in the analysis.  
79 Conditional models are often recommended for studies focused on change within members or on  
80 mediation analyses.<sup>7</sup> Parameters of marginal models are usually estimated using generalized  
81 estimating equations (GEE).<sup>20,21</sup> They define the marginal expectation of the dependent variable  
82 as a function of the independent variables and assume that the variance is a function of the mean;  
83 they separately specify a working correlation structure for observations made on members of the  
84 same group. Marginal models are often preferred for analyses of population-level effects because  
85 the intervention effect coefficient is interpreted as a population-averaged effect. In practice,  
86 marginal models are less frequently used than conditional models.<sup>6</sup>  
87 Marginal and conditional intervention effects are equal for identity and log links<sup>22</sup> and the  
88 distinction between them is only important for link functions such as the logit for binary  
89 outcomes. Although some authors have advocated for the log instead of logit link for binary  
90 outcomes,<sup>23</sup> this approach is not widely used, possibly because of model convergence problems  
91 for some data.<sup>24,25</sup> Alternatively, a modified Poisson approach with log-link and robust standard  
92 errors could be used in the GEE framework,<sup>26</sup> since it does not suffer from the same convergence

93 problems as the binomial model with log link,<sup>27</sup> but it may be less common because of the  
94 familiarity of logistic regression among epidemiologists and biostatisticians.  
95 In practice, the question about which of conditional or marginal effects are desired depends on  
96 the research question. It is essential to understand the underlying assumptions of each method:  
97 conditional models rely on correct specification of untestable aspects of the data distribution,  
98 while marginal models rely on a correct definition of the population of interest, which can make  
99 it difficult to generalize results to other populations.<sup>28</sup> We address each of the two approaches in  
100 more detail below.

### 101 *Conditional Approaches*

102 If the mixed effects model used to estimate conditional effects is misspecified, the estimates are  
103 difficult to interpret and, even if regression diagnostics can help,<sup>29</sup> standard errors (SEs) are not  
104 robust. Fortunately, Murray et al.<sup>30</sup> and Fu<sup>31</sup> have shown that mixed models are robust to  
105 substantial violation of the normality assumptions for member- and group-level errors, so long as  
106 balance is maintained at the group level. Parameter estimation by restricted maximum likelihood  
107 estimation (REML) is preferred to MLE when few groups are available.<sup>32-34</sup> For binary  
108 outcomes, alternative methods for specifying the test degrees of freedom have been examined in  
109 small sample GRTs and the between-within method is recommended.<sup>32,35</sup>

110 *Multiple Levels of Clustering in Conditional Models.* GRTs may involve multiple levels of  
111 clustering due to repeated measures on individuals or groups or additional hierarchical levels in  
112 the design. Murray<sup>1</sup> distinguished between mixed-effects models based on the number of  
113 measurements included in the analysis and recommended mixed-effects analysis of variance  
114 (ANOVA) or covariance (ANCOVA), or mixed-effects repeated measures ANOVA/ANCOVA,  
115 for analyses involving 1 or 2 measurements per person or per group; those models can account

116 for all sources of random variation in such data if they are properly specified.<sup>36</sup> However, that is  
117 not the case in analyses involving 3 or more measurements per person or per group, where the  
118 sources of random variation may be different; instead, such analyses require a random  
119 coefficients model in which random trends and intercepts are calculated for each member (in  
120 cohort GRT designs) and group (in cohort and cross-sectional GRT designs), average trends and  
121 intercepts are calculated for each study arm, and the intervention effect is the net difference in  
122 the average study-arm trends.<sup>36</sup> Trends are often estimated as linear slopes, but can take another  
123 form.

124 *Variable Group Size in Conditional Models* Johnson et al. focused on the analysis of Gaussian  
125 outcomes from GRTs with variable group size.<sup>37</sup> They compared ten model-based approaches  
126 and found that a one-stage mixed model with Kenward-Roger<sup>32</sup> degrees of freedom and  
127 unconstrained variance components performed well for GRTs with 14 or more groups per study  
128 arm. A two-stage model weighted by the inverse of the estimated theoretical variance of the  
129 group means and with unconstrained variance components performed well for GRTs with 6 or  
130 more groups per study arm. A number of other models resulted in an inflated type I error rate  
131 when there was substantial variability in group size.

### 132 *Marginal Approaches*

133 When the GEE approach is used to estimate marginal effects, unbiased intervention effects can  
134 be estimated even if the working correlation structure is incorrect (e.g. using robust SEs via the  
135 sandwich estimator), although precision is increased if the working matrix is correct. Where  
136 degrees of freedom are limited for the test of interest, as often happens in GRTs, SE estimation is  
137 often biased downward and no method corrects for it in all cases, although several have been  
138 proposed.<sup>38-44</sup>



139 *Multiple Levels of Clustering in Marginal Models.* While multilevel clustering is easy to account  
140 for in mixed-effects regression, there is less literature for the GEE approach. The alternating  
141 logistic regression approach<sup>45</sup> for binary and ordinal outcomes can be used to account for  
142 correlation due to repeated measures on individuals within groups and can be implemented  
143 within a GEE framework in both R (the `a1r` package) and SAS (PROC GEE).<sup>46</sup> The second-  
144 order GEE approach which, in contrast to regular GEE, models the working correlation structure  
145 as a function of covariates, can be implemented in R (`geepack` in R<sup>47</sup>).<sup>48</sup> For more general  
146 working correlation matrices, the user typically needs to perform additional programming in  
147 order to provide the appropriate covariance matrix and convergence may not be achieved. In  
148 addition, although the intervention effect is unbiased when the marginal model is not correctly  
149 specified, the SEs estimated using GEE may be too small. To correct this, a robust sandwich  
150 estimator of the variance can be used but such an approach leads to loss of power.<sup>49</sup> Because of  
151 this accuracy-power trade-off, mixed-effects models may be a better option to deal with GRTs  
152 involving more than two levels, although the effects estimated in such models are conditional  
153 rather than marginal effects.

154 *Variable Group Size in Marginal Models.* Although GEE analysis can accommodate variable  
155 group size, informative group size can negatively impact efficiency. In this case, Williamson et  
156 al.<sup>50</sup> showed that GEE weighted by group size can correct bias in the estimated intervention  
157 effect. This approach is equivalent and less computationally demanding than within-cluster  
158 resampling.<sup>51</sup>

159 *Advanced GEE Approaches to Improve Efficiency.* For binary outcomes, GEE is more  
160 conservative (i.e. the intervention effect will be estimated closer to the null) than mixed-effects  
161 models.<sup>28,52</sup> Moreover, the SE of the estimated intervention effect is also typically larger when

162 using GEE so that much recent effort has focused on efficient estimation. GEE is most efficient  
163 when the true correlation structure of the data is chosen as the working correlation structure. Hin  
164 et al. compared multiple selection criteria for the working correlation matrix.<sup>53</sup> An alternative  
165 approach is augmented GEE (AU-GEE), a method developed for independent data using a causal  
166 inference framework,<sup>54</sup> which has been extended to clustered data.<sup>55</sup> AU-GEE uses covariate  
167 information to improve efficiency in a two-stage approach that specifies a model for the potential  
168 outcomes under the treatment not received. AU-GEE is unbiased and robust to misspecification  
169 of the potential outcome model, though correct specification improves efficiency. As for the  
170 analysis of all trials, only baseline covariates should be included in AU-GEE for the analysis of  
171 GRT data because adjustment for post-baseline covariates may lead to bias.<sup>56</sup> Alternative  
172 methods are available to account for post-baseline, time-varying confounding.<sup>57-59</sup>

173 *Alternatives to GEE.* The quadratic inference function (QIF) method is an alternative to GEE for  
174 the estimation of marginal effects. Song et al.<sup>60</sup> demonstrate that QIF has advantages over GEE:  
175 it is more efficient and more robust to outliers; it has a goodness-of-fit test of the marginal mean  
176 model and permits straightforward extensions to model selection. In large samples, QIF is more  
177 efficient than GEE when the working correlation structure for the data is misspecified.<sup>61</sup>  
178 However, the SEs may be under-estimated for small and medium sample size or for variable  
179 group size.<sup>62</sup> More recent work by Westgate<sup>63,64</sup> provides improvements by using a bias-  
180 corrected sandwich covariance estimate and by simultaneously selecting the QIF or GEE while  
181 selecting the best working correlation structure.<sup>65</sup> Despite the many attractive properties of QIF,  
182 at this time there are few applications in public health.<sup>66-68</sup>

183 A second alternative estimation method is targeted maximum likelihood estimation (tMLE).<sup>69</sup>  
184 tMLE is a maximum likelihood-based G-computation estimator that targets the fit of the data-

185 generating distribution to reduce bias in the parameter of interest. It is based on a machine  
186 learning approach that fluctuates an initial estimate of the conditional mean outcome and  
187 minimizes a loss function to provide an estimate of the parameter of interest.<sup>70</sup> The approach has  
188 been used in public health<sup>71,72</sup> and shows much promise for GRTs<sup>73,74</sup> because it can improve  
189 efficiency by simultaneously accounting for missing data and chance baseline covariate  
190 imbalance without committing to a specific functional form.<sup>75</sup>

### 191 **Permutation Methods**

192 Permutation analysis was introduced for GRTs by Gail et al. for the COMMIT trial.<sup>76</sup> They  
193 found that the permutation test had nominal type I and II error rates across a variety of settings  
194 common to GRTs, when the member-level errors were Gaussian or binomial, even when very  
195 few heterogeneous groups were randomized to each study arm, and even when the ICC was  
196 large, so long as there was balance at the level of the group. Murray et al.<sup>30</sup> extended this work,  
197 showing that unadjusted permutation tests offer no more protection against confounding than  
198 unadjusted model-based tests, while the adjusted versions of both tests perform similarly. The  
199 permutation test was more powerful than the model-based test when the data were binomial and  
200 the  $ICC \geq 0.01$ . Fu<sup>31</sup> extended the work to heavy tailed and very skewed distributions and  
201 reported similar results.

202 Li et al. compared model-based and permutation methods in the context of constrained  
203 randomization adjusting for group-level covariates. They found that both the adjusted F-test and  
204 permutation test maintained the nominal size and had similar power, but cautioned that the  
205 randomization distribution must be calculated within the constrained randomization space to  
206 prevent inflating the type I error rate.<sup>19</sup>

207 **DEVELOPMENTS IN THE ANALYSIS OF ALTERNATIVES TO THE**  
208 **PARALLEL GRT**

209 **Stepped Wedge GRT**

210 Both between- and within-group information is available to estimate the intervention effect from  
211 a stepped wedge group randomized trial (SW-GRT).<sup>77,78</sup> However, because the control condition  
212 is typically observed earlier than the intervention condition, time is a potential confounder and  
213 should be accommodated in the analysis of SW-GRTs, typically by accounting for time as a  
214 predictor.<sup>79</sup> As for parallel GRTs, clustering by group must be accounted for, and longitudinal  
215 measures on individuals can be accommodated within either the mixed-effects or GEE  
216 framework, though more easily using mixed-effects models (see both *Multiple Levels of*  
217 *Clustering* sections). Conditional approaches are more commonly used in practice and reported  
218 on in the methods literature.<sup>79,80</sup> Several authors have highlighted other characteristics specific to  
219 SW-GRT including lagged intervention effects<sup>81</sup> and fidelity loss over time.<sup>79</sup>

220 **Network-Randomized GRT**

221 Because the network properties of a network-randomized GRT are primarily used at the design  
222 stage,<sup>82</sup> and because they differ from regular GRTs only in the novel way in which groups are  
223 defined, the theory on the analysis of parallel-arm GRTs can be applied to parallel-arm network-  
224 randomized GRTs.<sup>83</sup> For example, in a ring trial of an Ebola vaccine,<sup>83</sup> in which a network was  
225 defined as all individuals who had regular physical contact with the incident (index) case of  
226 Ebola and in which all contacts received the vaccine (placebo or active), standard GRT methods  
227 were used. For network-randomized GRTs in which the intervention is not directly administered  
228 to all individuals and in which it is expected that the intervention spreads over the network (e.g.  
229 the snowball trials of a HIV prevention intervention for drug users<sup>84</sup> or a microfinance

230 intervention<sup>85</sup>), methods<sup>86,87</sup> are available to estimate both the direct and indirect effects of the  
231 intervention. When network information is available and the outcome of interest is known to be a  
232 disseminated process, adjusting for network features such as information on the location of each  
233 individual within the network (i.e. group) can improve both the efficiency and power of the  
234 analysis.<sup>88</sup>

### 235 **Pseudo-Cluster Randomized Trial**

236 Teerenstra et al.<sup>89</sup> compared analytic methods for continuous outcomes in pseudo-cluster  
237 randomized trials (PCRT) and Campbell and Walters discussed principles in their recent  
238 textbook.<sup>5</sup> Clustering by the unit of randomization at the first stage (e.g. provider) must be  
239 accounted for in both the design and analysis of PCRT. No explicit sample size or analytic  
240 methods are known to be available for non-continuous outcomes.

### 241 **Individually Randomized Group Treatment Trial**

242 Baldwin et al. compared four analytic models for IRGTs and three methods for calculating  
243 degrees of freedom.<sup>90</sup> A multilevel model adapted to reflect clustering in only one study arm,  
244 combined with either Satterthwaite<sup>91</sup> or Kenward-Roger<sup>32</sup> degrees of freedom, provided better  
245 type I error control, better efficiency, and less bias, even with heteroscedasticity at the member  
246 level. This finding is consistent with earlier reports by Pals et al.<sup>92</sup> and Roberts et al.<sup>93</sup> More  
247 recently, Roberts & Walwyn<sup>94</sup> and Andridge et al.<sup>95</sup> considered the circumstance in which  
248 members are associated with more than one small group or change agent. Both found that  
249 ignoring membership in multiple groups further inflates the type I error rate. Roberts & Walwyn  
250 reported that multiple member multilevel models maintained the nominal type I error rate; they  
251 also provide sample size and power formulae.<sup>94</sup>

## 252 **DEVELOPMENTS TO ADDRESS DATA CHALLENGES**

## 253 **Missing Outcome Data**

254 Two recent reviews<sup>6,96</sup> indicate that missing outcome data is common in GRTs, though  
255 investigators frequently analyze only available data without accounting for the missing data  
256 pattern. When the covariate-dependent missingness (CDM) assumption is plausible, both mixed  
257 effects and GEE models provide unbiased estimates of the intervention effect when the CDM  
258 covariates are included in an analysis of all available data.<sup>97,98</sup> AU-GEE also can provide  
259 unbiased effects by including all CDM covariates in the augmentation component<sup>55</sup> and has the  
260 advantage that all estimates can still be interpreted as marginal effects. Other two-stage  
261 approaches such as multiple imputation (MI) or inverse probability weighting (IPW) can provide  
262 unbiased intervention effects under certain conditions for more general missing at random  
263 (MAR) patterns and may provide increased precision compared to covariate-adjusted conditional  
264 or marginal models for CDM.<sup>97,99</sup> Although there is less literature on how to deal with missing  
265 not-at-random (MNAR) data,<sup>100</sup> sensitivity analyses are recommended.<sup>101</sup> A recent review  
266 showed that very few GRTs performed any sensitivity analyses for their missing data  
267 assumptions.<sup>6</sup>

268 To avoid possible type I error, MI should account for the clustered data structure.<sup>102,103</sup> Fixed  
269 group effects should not be used due to reduced power.<sup>104</sup> For binary outcomes, Ma et al.<sup>105</sup> and  
270 Caille et al.<sup>106</sup> show that the preferred MI method depends on the number of groups and the  
271 design effect, and note that bias may arise for some approaches even for CDM missingness.  
272 Using group-specific mean imputation may be adequate for continuous outcomes.<sup>98,102</sup> Hossain  
273 et al.<sup>98</sup> show that if the missing data mechanism has an interaction between a covariate predictive  
274 of the outcome and study arm, the imputation strategy must account for this interaction to be  
275 unbiased.

276 Whereas MI requires specifying the distribution of the missing data conditional on covariates,  
277 IPW requires specifying the probability of being missing depending on covariates. Theoretically,  
278 both approaches can be used for any type of outcome and for both CDM and more general forms  
279 of MAR mechanisms.<sup>99</sup> While IPW requires an additional assumption of positivity (all  
280 participants have a non-zero probability of being observed), it may be viewed as easier to define,  
281 particularly in the presence of non-intermittent missingness.<sup>107</sup> Importantly, and as for MI, if the  
282 missing data mechanism has an interaction between a covariate predictive of the outcome and  
283 study arm, the weights must be generated by accounting for this interaction in order to be  
284 unbiased.<sup>108</sup> Prague et al.<sup>109,110</sup> developed a doubly robust estimator in the context of IPW, which  
285 provides an unbiased estimate if either the marginal mean model or the missing data model is  
286 correctly specified. They demonstrated that a doubly-robust augmented GEE approach can  
287 simultaneously account for both CDM and baseline covariate imbalance in GRTs when the  
288 parameter of interest is a marginal effect. Combining MI and IPW is a promising new approach  
289 which may have superior performance to IPW or MI alone when there are missing covariates in  
290 addition to missing outcomes.<sup>111</sup>

### 291 **Baseline Imbalance of Covariates**

292 While design strategies such as restricted randomization<sup>8</sup> can help to achieve baseline covariate  
293 balance, they may not be easy to implement (e.g. if group characteristics are unknown in  
294 advance) and chance imbalance may arise regardless. In this case, some form of model-based  
295 covariate adjustment could be used such as standard multivariate regression for conditional  
296 models or AU-GEE for marginal models.<sup>55</sup> The advantage of AU-GEE in this case is that it is  
297 doubly robust in that the consistency of intervention effect estimate requires correct specification  
298 of either the marginal mean structure or the treatment model, and it separates covariate

299 adjustment from intervention effect estimation thereby reducing the risk of choosing the  
300 adjustment models to obtain the most significant results. The standard multivariate regression  
301 adjustment approach does not enjoy either of these benefits.  
302 Alternatively, Hansen and Bowers<sup>112</sup> proposed a balancing criterion and studied its  
303 randomization distribution in order to simultaneously test for balance of multiple covariates in  
304 both RCTs and GRTs. Leyrat et al.<sup>113</sup> suggested to use the c-statistic of the propensity score  
305 model to measure covariate balance at the individual level. Leon et al.<sup>114</sup> recommended  
306 propensity score matching to correct for baseline imbalance; in a simulation study, they report a  
307 median 90% reduction in bias. Nevertheless, the Consolidated Standards for Reporting of Trials  
308 (CONSORT)<sup>115</sup> recommends that the adjustment covariates be specified a priori for primary  
309 analyses so that secondary analyses could test sensitivity of the primary findings to adjustment  
310 for covariates identified post hoc.

### 311 **Software**

312 Table 1 identifies three software programs that can be used to analyze data from GRTs. The  
313 table is organized around topics considered in the current paper. While none of the three software  
314 programs can readily implement both QIF and tMLE for GRTs, the R program offers the most  
315 ready-to-use functionality given its broad applicability to the methods cited in the current paper.

316 [TABLE 1 ABOUT HERE.]

### 317 **REPORTING OF RESULTS**

318 The CONSORT guidelines for individually randomized trials were extended to GRTs in 2004<sup>115</sup>  
319 and most journals now require authors to conform to these guidelines. Based on a review of 300  
320 GRTs published between 2000-2008, Ivers et al. reported that 60% and 70% accounted for  
321 clustering in the sample size calculation and in the analysis, respectively, 56% used restricted



322 randomization, and most (86%) allocated more than 4 groups per arm.<sup>14</sup> A more recent review  
323 of 86 trials published in 2013-2014 showed that 77% and 78% accounted for clustering in the  
324 sample size calculation and in the analysis, respectively, and that 51% used some form of  
325 restricted randomization.<sup>15</sup>

326 Given concerns about the ethical conduct of GRTs,<sup>116,117</sup> recent reports on conduct and reporting  
327 have focused on the ethics of GRTs. For example, Sim and Dawson discuss the challenges  
328 associated with obtaining informed consent in GRTs.<sup>118</sup> The Ottawa Statement on the ethical  
329 design and conduct of GRTs was published in 2012<sup>119</sup> with a reevaluation in 2015.<sup>120</sup>

## 330 **DISCUSSION**

331 In this review, we have summarized many of the most important advances in the analysis of  
332 GRTs during the 13 years since the publication of the earlier review by Murray et al.<sup>7</sup> Many of  
333 these developments have focused on developments in marginal model parameter estimation (e.g.  
334 augmented GEE, QIF and tMLE) and missing data methods. Some topics that space limitations  
335 have prevented include review of recent developments in survival outcomes,<sup>2,121-125</sup> measurement  
336 bias,<sup>126,127</sup> validity,<sup>128,129</sup> Bayesian methods,<sup>4,130-132</sup> cost-effectiveness analyses<sup>4,133-136</sup> and  
337 mediation analyses to uncover mechanisms of action.<sup>137-140</sup>

338 Through this review, we have sought to ensure that the reader is reminded of the value of well-  
339 thought out analysis of GRTs and of keeping up to date with the many recent developments in  
340 this area. Pairing this knowledge with our companion review of developments in the design of  
341 GRTs,<sup>8</sup> we hope that our review leads to continued improvements in the design and analysis of  
342 GRTs.

## 343 **APPENDIX: GLOSSARY**

344 **Augmented GEE:** “Augmenting the standard GEE with a function of baseline covariates.”<sup>55</sup>

345 These methods adapt semiparametric theory developed by Robins<sup>141</sup> and Robins, Rotnitzky, and  
346 Zhao<sup>142</sup> for observational studies with time-varying exposures and missing data problems,  
347 respectively. They consist of leveraging the estimating equation by a predictor function for  
348 counterfactual outcomes under the intervention not received by the group/cluster considered  
349 missing.<sup>55</sup>

350 **Baseline covariate balance:** The group-level and individual-level covariate distributions are  
351 similar in all study arms.<sup>11</sup>

352 **Choice of balancing criterion:** Li et al. describe several balancing criteria to assess how well a  
353 GRT is balanced across covariates. These include the “best balance” (BB) metric of de Hoop et  
354 al.,<sup>143</sup> the balance criterion (B) of Raab and Butcher,<sup>11</sup> and the total balance score introduced by  
355 Li et al.<sup>19</sup>

356 **Coefficient of variation:** A measure of between-group variation, defined in Table 1 of our  
357 companion paper.<sup>8</sup>

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

360 **Constrained randomization:** Refers “to those designs that go beyond the basic design  
361 constraints to specify classes of randomization outcomes that satisfy certain balancing criteria,  
362 while retaining validity of the design.”<sup>144</sup>

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

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

366 **Intraclass correlation:** A measure of between-group variation, defined in Table 1 of our  
367 companion paper.<sup>8</sup>

368 **Covariate-dependent missingness (CDM) assumption:** The assumption that “missingness in  
369 outcomes depends on covariates measured at baseline, but not on the outcome itself.”<sup>98</sup>

370 **Doubly-robust augmented GEE approach:** Combining augmented GEE and IPW, a doubly-  
371 robust estimator is obtained, which provides an unbiased estimate if either the marginal mean  
372 model or the missing data model is correctly specified.<sup>109,110</sup>

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

375 **G-computation estimator:** A computational method to estimate causal effect in structural  
376 nested models. These models are designed to deal with confounding by variables affected by  
377 intervention.<sup>145</sup>

378 **Individually Randomized Group Treatment Trials:** “Studies that randomize individuals to  
379 study arms but deliver treatments in small groups or through a common change agent.”<sup>8,92</sup>

380 **Informative cluster size:** When the outcome measured is related to the size of the cluster.<sup>50</sup>

381 **Missing at Random (MAR) assumption:** Rubin’s (1976) definition is that “data are missing at  
382 random if for each possible value of the parameter  $\phi$  [the parameter of the conditional  
383 distribution of the missing data indicator given the data], the conditional probability of the  
384 observed pattern of missing data, given the missing data and the value of the observed data, is  
385 the same for all possible values of the missing data.”<sup>146</sup>

386 **Network-Randomized GRT:** “The network-randomized GRT is a novel design that uses  
387 network information to address the challenge of potential contamination in GRTs of infectious  
388 diseases.”<sup>8,82,84,147</sup>

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

391 **On treatment analyses:** When groups are analyzed “according to the intervention they actually  
392 received.”<sup>2</sup>

393 **Per protocol analyses:** When groups “not receiving the correct intervention are excluded.”<sup>2</sup>

394 **Pseudo-cluster randomized trial:** Intervention is allocated to individuals in a two-stage  
395 process. “In the first stage, providers are randomized to a patient allocation-mix.... In the  
396 second stage, patients recruited to the PCRT are individually randomized to intervention or  
397 control according to the allocation probability of their provider.”<sup>8</sup>

398 **Stepped Wedge GRT:** “A one-directional crossover GRT in which time is divided into intervals  
399 and in which all groups eventually receive the intervention.”<sup>8,78</sup>

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

404 **Within-cluster resampling:** Randomly sample one observation from each cluster, with  
405 replacement. Then analyze this resampled dataset. Repeat this process a large number of times.  
406 “The within-cluster resampling estimator is constructed as the average” of all of the resample-  
407 based estimates (see Hoffman et al.<sup>51</sup> pp. 1122-3).

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## 410 **CONTRIBUTORS**

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412 **HUMAN PARTICIPANT PROTECTION**

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

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- 742
- 743

744 **Table 1. Summary of known functions and procedures to analyze GRTs using methods**  
 745 **described in the current review.**

Method	SAS	Software Stata	R
<b>Outcomes analysis of all available data</b>			
Mixed-effects models	PROC MIXED PROC NL MIXED PROC GLIMMIX PROC GENMOD <sup>1</sup>	mixed melogit mepoisson xtgee	lme4 nlme geeglm/geeM
Generalized estimating equations (GEE)			
Targeted maximum likelihood (tMLE)	N/A	N/A	N/A <sup>2</sup>
Quadratic inference function (QIF)	%qif	N/A	qif <sup>3</sup>
Permutation tests	%ptest	N/A	N/A
<b>Accounting for missing outcomes</b>			
Multiple imputation for clustered data	%mmi_impute <sup>4</sup> %mmi_analyze	REALCOM Impute mi impute <sup>4</sup>	pan jomo <sup>5</sup>
Inverse probability weighting (IPW)	PROC GENMOD <sup>6</sup>	N/A <sup>7</sup>	CRTgeeDR
<b>Causal-inference based methods<sup>8</sup></b>			
Augmented GEE (AU-GEE)	N/A	N/A	CRTgeeDR
Doubly robust AU-GEE	N/A	N/A	CRTgeeDR

Footnotes: 1. PROC GEE is another option, but is in experimental phase and has limited usefulness for GRTs over and above PROC GENMOD. 2. In R, tmlme is available for tMLE, but at the time of writing, does not allow for clustering. 3. As of the writing, the authors have been unable to load the package and it only allows equal cluster size, but Westgate has modified the code for GRTs with variable cluster size in the appendix of his paper<sup>63</sup> 4. Only useful for continuous outcomes. 5. In R, mice is available for multiple imputation but at the time of writing, does not account for clustering. 6. Cannot account for imprecision in the weights. 7. xtgee cannot accommodate individual-level weights but only group-specific weights. 8. Both of the listed methods are related: AU-GEE accounts for baseline covariate imbalance and doubly robust AU-GEE, an extension of AU-GEE, accounts for both baseline covariate imbalance and missing data. N/A: not available at the time of writing.