NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

Small-Sample Robust Variance Correction for Generalized Estimating Equations for Use in Cluster Randomized Clinical Trials

This working guidance document is part of a biostatistical research tool set developed by the NIH Health Care Systems Research Collaboratory Biostatistics and Study Design Core. These documents, which focus on detailed aspects of statistical design for conducting pragmatic clinical trials, provide a synthesis of current developments, discuss possible future directions, and, where appropriate, make recommendations for application to pragmatic clinical research. This work was supported by a cooperative agreement (U54 AT007748) from the NIH Common Fund for the NIH Health Care Systems Research Collaboratory. The views presented here are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Background

When analyses are conducted on cluster randomized trial data, the correlation of observations within the same cluster should be incorporated. Randomizing at the cluster level induces correlation among observations within the same cluster, but observations between clusters remain independent. Therefore, the structure of the design must be taken into account in the analysis. There are two common analytical approaches for clustered data: 1) mixed models, comprising Linear Mixed Models (LMM) [1] for continuous outcomes or Generalized Linear Mixed Models (GLMM) for binary or count outcomes; and 2) marginal models as implemented by generalized estimating equations (GEE) [2]. Both methods are valid for cluster-randomized studies, but have different tradeoffs and may estimate different effect estimates (numerous books are available for more information) [3].

This guidance assumes that the correct type of model has been chosen to answer the scientific question of interest, and will discuss available approaches to estimate the variance, especially in the situation of a small number of clusters.

Small number of cluster problem

One common issue across approaches is to correctly estimate the variance of the parameter of interest, which is more nuanced for correlated data than independent data. There has been ample literature suggesting that the use of a robust variance estimate (otherwise known as a *sandwich variance estimate* [4,5]) when conducting such analyses, and is

especially suggested for use in conjunction with GEE [6]. These robust variance estimates allow the correct specification of the mean model while relaxing the assumption of correctly specifying the form of the variance model (the working correlation), such as independent, exchangeable, or autoregressive, among others. That is, the GEE is generally robust to misspecification of the variance model.

A known limitation of the sandwich variance estimate is that it can present issues in underestimating the variance when there are not enough clusters [7]. A rule of thumb states that with fewer than 50 clusters there may be concern about a biased estimate, but with more than 50 clusters, the estimate is likely to be asymptotically unbiased. However, this is a general guidance only and may not be applicable to all situations (e.g., the outcome type, number of variables being adjusted for, and how closely the working correlation approximates the actual correlation structure likely all affect the variance estimation performance).

At the end of this guidance we will discuss potential future work that may be helpful in assessing situations in which small-sample variance corrections are needed. For this guidance we will assume a situation in which a small sample size corrected estimate is needed and provide a brief summary of several available bias-corrected sandwich estimators for use in the small cluster setting implemented in standard statistical software, including SAS and Stata.

Available methods in SAS

For this guidance, we will denote available methods in SAS Version 9.3. Note that although GENMOD is the standard SAS procedure for implementing GEE models, the methods that are currently available from SAS with small-sample variance correction for marginal models are only implemented in the procedure GLIMMIX and were not available in the procedure GENMOD. SAS help documentation for the procedure GLIMMIX details that this procedure generalizes the MIXED and GENMOD procedures by allowing for both mixed model cluster- specific (conditional) and GEE population-average (marginal) inference to be conducted in the same procedure simultaneously. They also note that GLIMMIX uses likelihood based methods for model fitting instead of the more standard methods of moments when fitting GEE-type models. The SAS documentation does not detail how different these types of fitting approaches will be in practice and therefore one should assess for differences in results beyond just variance calculation differences when applying these approaches.

When using the GLIMMIX procedure to initially estimate the standard robust variance estimate and to obtain a small cluster size variance correction, the option “Empirical” must be specified in the initial procedure call (e.g., proc GLIMMIX empirical). Table 1 provides details with references of different small sample size variance correction options implemented in SAS.

Table 1. Small Cluster Size Variance Correction Options for GLIMMIX

Method Call	Brief Summary and References*
Empirical=DF or HC1	Simple degrees of freedom (DF) correction of the form m/(m- k) where is m is the number of clusters and k is the number of parameters estimated in the mean model (covariate parameters) [8]
Empirical-ROOT or HC2	Residual approximation estimator, but requires the inverse square root of a nonsymmetric matrix and is computationally more demanding than others [9]
Empirical=FIRORES or HC3	Residual approximation estimator, but can be motivated as a jack-knife estimator. Has shown for linear regression as being the recommended estimate, but unknown for other situations [10,11].
Empirical=FIROEEQ (r)	Based on approximating unbiased estimating equations and is less computationally demanding as the ROOT method, but equivalent in balanced cluster size situations [12].
Empirical=MBN (mbn-options)	Residual-based estimator that applies an additive adjustment to the residual crossproduct. Suboptions include a DF correction for sample size and a design effect parameter using an R option [13].

**See SAS documentation and references for further details.*

Available methods in Stata

For this guidance, we will refer to available methods in STATA Version 12. The most common function to implement GEE in STATA is xtgee, which has several options to obtain robust standards errors as outlined by STATA help documentation for xtgee. To obtain the standard robust variance estimate without correction for small sample size, the option is vce(robust). Table 2 provides details with references provided by Stata documentation of different small sample size variance correction options implemented in Stata.

Table 2. Small Cluster Size Variance Correction Options for xtgee

Method Call	Brief Summary and References*
nmp	Simple degrees of freedom (DF) correction of the form m/(m- k) where is m is the number of clusters and k is the number of parameters estimated in the mean model (covariate parameters) [8].

rgf	Simple degrees of freedom (DF) correction of the form (m- 1)/(m-k) where is m is the number of clusters and k is the number of parameters estimated in the mean model (covariate parameters).
Vce(bootstrap)	Uses a bootstrap to obtain corrected standard errors.
Vce(jackknife)	Uses the delete-one jackknife to obtain corrected standard errors.

** See STATA documentation and references for further details.*

Next steps

Now that methods are available in standard software to implement small cluster size corrections, choosing which method is most appropriate for a wide variety of situations would be extremely informative. Should we always correct for the potential for small sample size issues as the standard approach? Do we lose power doing these corrections? Which corrections work best in which situations? These are all open questions. Future work, including simulation studies based on actual applications to inform such practical applications when implementing cluster randomized trials, would be extremely informative.

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