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On The Violation Of Bounds For The Correlation In Generalized Estimating Equation Analyses Of Binary Data From Longitudinal Trials

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Abstract

It is well-known that the correlation among binary outcomes is constrained by the marginal means, yet approaches such as generalized estimating equations (GEE) do not check that the constraints for the correlations are satisfied. We explore this issue for Markovian dependence in the context of a GEE analysis of a clinical trial that compares Venlafaxine with Lithium in the prevention of major depressive episode. We obtain simplified expressions for the constraints for the logistic model and the equicorrelated and first-order autoregressive correlation structures. We then obtain the limiting values of the GEE and quasi-least squares (QLS) estimates of the correlation parameter when the working structure has been misspecified and prove that misidentification can lead to a severe violation of bounds. As a result, we suggest that violation of bounds can provide additional evidence in ruling out application of a particular working correlation structure. For a structure that is otherwise plausible and results in only a minor violation, we propose an iterative algorithm that yields an estimate that satifies the constraints. We compare our algorithm with two other approaches for estimation of the correlation that have been proposed to avoid a violation of bounds and demonstrate that it estimates the correlation parameter and bivariate probabilities with smaller mean square error and bias, especially when the correlation is large.

On the violation of bounds for the correlation in generalized estimating equation analyses of binary data from longitudinal trials

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Summary. It is well-known that the correlation among binary outcomes is constrained by the marginal means, yet approaches such as generalized estimating equations (GEE) do not check that the constraints for the correlations are satisfied. We explore this issue for Markovian dependence in the context of a GEE analysis of a clinical trial that compares Venlafaxine with Lithium in the prevention of major depressive episode. We obtain simplified expressions for the constraints for the logistic model and the equicorrelated and first-order autoregressive correlation structures. We then obtain the

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limiting values of the GEE and quasi-least squares (QLS) estimates of the correlation parameter when the working structure has been misspecified and prove that misidentification can lead to a severe violation of bounds. As a result, we suggest that violation of bounds can provide additional evidence in ruling out application of a particular working correlation structure. For a structure that is otherwise plausible and results in only a minor violation, we propose an iterative algorithm that yields an estimate that satisfies the constraints. We compare our algorithm with two other approaches for estimation of the correlation that have been proposed to avoid a violation of bounds and demonstrate that it estimates the correlation parameter and bivariate probabilities with smaller mean square error and bias, especially when the correlation is large.

1. Introduction

1.1 *Venlafaxine Study*

We consider a generalized estimating equation (GEE) analysis of a clinical trial of a new treatment for Bipolar Type II major depressive episode (BP II MDE), Venlafaxine. In this study subjects with moderate to severe depression were randomized in equal numbers to receive either Venlafaxine or Lithium as treatment for their condition. The primary goal for the analysis was to compare trends in the occurrence of MDE between treatment conditions. MDE was defined on the basis of having a 17-item Hamilton Rating Scale for Depression (HAMD17) total score of ≥ 18 and a Clinical Global Impression of Severity (CGI-S) score ≥ 4. In addition to comparing time trends between groups, we had a secondary interest in assessing the occurrence of MDE on each of two visits. For example, an effective treatment

for depression might be expected to have an initial meaningful therapeutic benefit after one month of treatment, which was approximately the time of the fourth visit on each subject. It was therefore of interest to assess the expected likelihood of having MDE both at visit four and at the last visit for each treatment group. If this likelihood was high for one of the conditions, then this might suggest that this treatment is not effective therapy for BP II MDE because subjects in this group are tending to fail at two important measurement occasions: when initial benefit of an effective treatment should be conferred and at the end of the treatment period.

GEE requires specification of a generalized linear model for the binary outcome variable and a structured correlation matrix to describe the pattern of association amongst the repeated measurements Y_{ij} on each subject. As a byproduct, it also provides estimates of the joint probabilities $P(Y_{ij} = y_{ij}, Y_{ik} = y_{ik}) = P(y_{ij}, y_{ik})$: They can be expressed as the following function of the expected values $E(Y_{ij}) = P(Y_{ij} = 1) = P_{ij}$, $Q_{ij} = 1 - P_{ij}$, and the correlation $Corr(Y_{ij}, Y_{ik}) = C_{ijk}$ between measurements Y_{ij} and Y_{ik}, all of which are estimated in a GEE analysis (Prentice, 1988):

$$P(y_{ij}, y_{ik}) = P_{ij}^{y_{ij}}\, Q_{ij}^{1-y_{ij}}\, P_{ik}^{y_{ik}}\, Q_{ik}^{1-y_{ik}} \left[1 + C_{ijk} \frac{(y_{ij} - P_{ij})\,(y_{ik} - P_{ik})}{\sqrt{P_{ij}\, P_{ik}\, Q_{ij}\, Q_{ik}}}\right]. \quad (1)$$

Prentice (1988) noted that the estimated correlations must satisfy certain constraints in order for the probabilities in (1) to be non-negative. In our analysis of the Venlafaxine trial some constraints were violated. As a result, some estimated probabilities were negative. For example, if $C_{ijk} = \alpha$ in a GEE analysis, the expected proportion of subjects treated with Lithium who

will have MDE at visit 8 but not at visit 4 is -0.0031, which is not a valid estimate.

1.2 *Prior Discussion of Violation of Bounds*

Violation of bounds for the correlation in analyses of binary data has been mentioned by many authors, including Prentice (1988), McDonald (1993), Shults (1996), Joe (Section 7.1, 1997), Diggle et al. (2002, p. 144-145), and Jung and Ahn (2005). However, there has been some controversy regarding the likelihood and impact of this potential violation. For example, Rochon (1998) noted that GEE "ignores these constraints" (for the correlation) and cautioned that "the practitioner must be aware of these restrictions, particularly at the design stage." However, he also said this "appears to cause no difficulty in practice". In a recent important publication, Chaganty and Joe (2004) disagree, making the strong claim that "A routine use of the currently available GEE software could lead to incorrect analysis, because there is no check on the dependence of the correlation range as a function of covariates." However, we note that these authors did not define incorrect analysis and its rippling effect on other estimates such as the joint probabilities in (1). To our knowledge no one has explored this issue for the Markovian dependance model that we consider in this manuscript.

However, some approaches have been suggested that could be used to overcome a violation of bounds. The simplest is a working independence approach that implements an identity matrix to describe the pattern of association among observations within a cluster. This has the additional advantage of avoiding bias in estimation of the regression parameter. As pointed out by Pepe and Anderson (1994), a diagonal correlation structure should be

applied in order to avoid potentially serious bias in the regression parameter, unless the following sufficient condition can be satisfied for each subject i:

$$E(Y_{ij} \mid x_{ij}) = E(Y_{ij} \mid x_{i1}, x_{i2}, \ldots, x_{in_i}), \tag{2}$$

where x_{ij} is the $p \times 1$ vector of covariates measured on subject i at measurement occasion j. This condition is satisfied for the Venlafaxine study under the assumption that missing data are missing completely at random (MCAR) because our covariates of interest are external with a defined path, using the terminology of Kabfleish and Prentice (1980). As a result, the events $\{x_{ij}\}$ and $\{x_{i1}, x_{i2}, \ldots, x_{in_i}\}$ are identical and (2) is satisfied, e.g. given that a subject is treated with Venlafaxine at measurement occasion one we know the values of time and treatment status at all other measurement occasions on this subject. However, if the analysis was modified to include a time-varying covariate without a fixed path, such as Young Mania Rating (YMR) score (a score that indicates severity of mania) then (2) could be violated, e.g. the likelihood that a subject has MDE given that they are not currently manic could depend on their history of mania as reflected in their YMR score. Based on an assessment of the reasons for missing values, the MCAR assumption seemed reasonable for the Venlafaxine study.

Limitations of the working independence model include the potential for a serious loss in efficiency in estimation of the regression parameter, especially for time-varying covariates and when the data are highly correlated (Zhao et al, 1992; Fitzmaurice, 1995; Mancl and Leroux, 1996; Sutradhar and Das, 2000; and Wang and Carey, 2003). Schildcrout and Heagerty (2005) explore the bias-efficiency tradeoff associated with choice of different working

correlation structures that include working independence for GEE analysis of binary data.

Chaganty and Joe (Section 7.0,pages 857-858, 2004) also describe an approach for overcoming the violation of bounds in their study of data with a multivariate probit distribution. They suggest that an exchangeable structure should be implemented for a "cluster type samples", while a first-order autoregressive AR(1) structure should be applied for longitudinal data. The correlation parameter α could then be estimated with a value $\hat{\alpha}_r$ that is close to zero (for weak dependence), in the range 0.2- 0.3 (for moderate dependence), or in the range 0.4 - 0.7 (for strong dependence), where "small", "medium", and "large" are defined on the basis of descriptive analyses that include assessment of odds ratios. Alternatively, they suggested that α could be estimated with the midpoint $\hat{\alpha}_m$ of the boundary values for an equicorrelated (exchangeable) structure. The regression parameter is then estimated by solving the GEE estimating equation evaluated at $\hat{\alpha}_r$ or $\hat{\alpha}_m$.

Limitations of this approach include the following. Their suggested ranges for α were chosen according to values of the latent variable in a multivariate probit distribution. For other situations, e.g. in order to allow α to exceed 0.70, the ranges must be modified. This process is also somewhat arbitrary, e.g. which value (midpoint or number within the selected range) should we select as the final estimate? It is also not as easy to implement as direct application of GEE and does not consider application of more complex correlation structures, which they refer to as weight matrices.

Shults (1996) suggested replacing $\hat{\alpha}$ with the estimated upper (lower) boundary value if $\hat{\alpha}$ exceeds (is smaller than) this bound. However, this ap-

proach does not check if the updated bounds, which are a function of the updated estimate of the regression parameter, are satisfied. In this manuscript we therefore propose an iterative algorithm that yields estimates of β and α that do satisfy the constraints for the correlations. We do this using GEE and for comparison, also implement the method of quasi-least squares (QLS), an approach in the framework of GEE.

1.3 *Other Approaches for analysis*

As described in Molenberghs and Verbeke (p. 47, 2005), three useful classes of models for non-Gaussian data include marginal, conditionally specified, and subject-specific models. See Young et al (2006) for a comparison of the population average and conditional likelihood approach. Conditional models have the drawback that interpretations of their parameters are conditional on the value and number of other responses measured within a subject or on a different subject (Diggle et al, 2002). Their application might therefore be difficult for analysis of the Venlafaxine study, which has a variable number of measurements per subject. If subject-specific parameters are treated as random effects, it is also important to note that the resultant model will induce a correlation structure on the outcome variable. For example, see Diggle et al (2002, p.56). As a result, implementation of mixed-effects models could also potentially result in a violation of bounds for the induced correlations. Our primary analysis involves a comparison of average trends over time between treatment groups, for which a marginal model is appropriate (p, 141, Diggle et al, 2002). In this manuscript we focus on application of marginal models with QLS and GEE.

1.4 *Outline for Manuscript*

In § 2 we give some definitions regarding a violation of bounds and present simplified expressions for the constraints for a logistic model and two widely used correlation structures. In § 3 we describe methods, including the Markovian model for dependence; the GEE and QLS approaches; two informal methods for assessment of goodness of fit; and several approaches for adjustment for violation of bounds. In particular, we provide the stage one QLS estimates when $C_{ij} = \alpha$ in (1) and $n_i \neq n$; these have not been published elsewhere. In addition, we prove several results regarding the limiting values of $\hat{\alpha}$ under misidentification of the working correlation structure. We then apply these results in § 4, where we describe when a violation of bounds is more likely to occur. In § 5 we compare several methods for adjustment with respect to bias and efficiency. In § 6, we describe analysis of the Venlafaxine study. Finally, in § 7 we discuss our results and provide recommendations based on our findings.

2. Model for Analysis and Definitions

2.1 *Model for Analysis of Venlafaxine Study*

We considered the following logistic model for the mean and variance of the binary MDE scores Y_{ij} measured on subject i at measurement occasion j: $E(Y_{ij}) = g^{-1}(\delta_{ij}) = P_{ij}$ and $Var(Y_{ij}) = \phi\, P_{ij}\,(1 - P_{ij})$, where $\delta_{ij} = x_{ij}^{'}\beta$; x_{ij} is a $p \times 1$ vector of covariates; β is a $p \times 1$ regression parameter; $g^{-1}(\gamma) = exp(\gamma)/(1+exp(\gamma))$; and scalar parameter $\phi = 1$. For the Venlafaxine study,

$$\delta_{ij} = \beta_0 + \beta_1 I(Venlafaxine) + \beta_2 visit + \beta_3 I(Venlafaxine) \times visit, \quad (3)$$

so $x_{ij}^{'} = (x_{ij1}, x_{ij2}, x_{ij3}, x_{ij4})$, where $x_{ij1} = 1$; $x_{ij2} = I(Venlafaxine)$, which equals 1 for subjects treated with Venlafaxine and 0 for subjects

treated with Lithium; $x_{ij3} = visit$, which takes value $1, 2, \ldots, n_i$ for subject i; and $x_{ij4} = I(Venlafaxine) \times visit$, a treatment by visit interaction term. There were 26 subjects per treatment group, so that $i = 1, 2, \ldots 52$. The number of measurements per subject n_i ranged from 2 to 8, with a mean of 6.43.

We suspected that the values of MDE on a subject would tend to be more similar if they were collected more closely together in time. Because the measurements were approximately equally spaced, we therefore identified the AR(1) structure, for which $Corr(Y_{ij}, Y_{ik}) = \alpha^{|j-k|}$, as the most biologically plausible correlation structure for this study. However, we also planned to apply other structures to assess the sensitivity of results to choice of working structure. These included the equicorrelated (EQC), for which $Corr(Y_{ij}, Y_{ik}) = \alpha$ for $j \neq k$, and the identity, for which $Corr(Y_{ij}, Y_{ik}) = 0$ for $j \neq k$.

2.2 *Definitions Regarding Bounds for α*

Prentice (1988) noted that the probabilities in (1) will be non-negative if the correlations $Corr(Y_{ij}, Y_{ik})$ satisfy the following constraints:

$$Lower_i(j,k) \leq Corr(Y_{ij}, Y_{ik}) \leq Upper_i(j,k) \ \forall \ i, \ j \ and \ k, \qquad (4)$$

where $Lower_i(j,k) = \max\left\{-(w_{ij}w_{ik})^{1/2}, -(w_{ij}w_{ik})^{-1/2}\right\}$, $Upper_i(j,k) = \min\left\{(w_{ij}/w_{ik})^{1/2}, (w_{ij}/w_{ik})^{-1/2}\right\}$, and $w_{ij} = P_{ij}(1-P_{ij})^{-1}$. Note that the lower bound for the correlation is always negative, while the upper bound will take value between 0 and 1.

Suppose we specify a working correlation structure to describe the pattern of association so that $Corr(Y_{ij}, Y_{ik})$ is a function of parameter α. We then define the feasible region for α with respect to the true binary bounds

(*feasible region (TBB)*) *for this particular structure* to be the interval on which α satisfies all constraints in (4) when the boundary values $Lower_i(j,k)$ and $Upper_i(j,k)$ are evaluated at the true value of β. The feasible region with respect to the estimated binary bounds (*feasible region (EBB)*) for this structure is the interval on which α satisfies all constraints in (4) when the boundary values are evaluated at the estimated value $\hat{\beta}$ of β.

For the EQC structure $Corr(Y_{ij}, Y_{ik}) = \alpha$, so that all constraints in (4) will be satisfied if

$$\max_{i,j,k} \{\ Lower_i(j,k)\} \ \leq \alpha \leq \ \min_{i,j,k} \{Upper_i(j,k)\ \}. \tag{5}$$

For the AR(1) structure, all constraints for the correlations in (4) will be satisfied if the following is true for all i, j, and k:

$$Lower_i(j,k) \ \leq \ \alpha^{|j-k|} \ \leq \ Upper_i(j,k)$$

which will be true if and only if:

$$-Upper_i(j,k)^{1/|j-k|} \ \leq \ \alpha \ \leq \ Upper_i(j,k)^{1/|j-k|} \ \ for\ all\ |j-k|\ even$$

and

$$Lower_i(j,k)^{1/|j-k|} \ \leq \ \alpha \ \leq \ Upper_i(j,k)^{1/|j-k|} \ \ for\ all\ |j-k|\ \ odd.$$

All constraints for the correlations will therefore be satisfied for the AR(1) structure if

$$\max\{\ \zeta_{even},\ \zeta_{odd}\ \} \leq \ \alpha \leq \ \min_{i,j,k} \left\{\ Upper_i(j,k)^{1/|j-k|}\ \right\}, \tag{6}$$

where

$$\zeta_{even} = \max_{i,j,k} \left\{ -Upper_i(j,k)^{1/|j-k|} \ \ for\ \ |j-k|\ \ even \right\}$$

and

$$\zeta_{odd} = \max_{i,j,k} \left\{ Lower_i(j,k)^{1/|j-k|} \;\; for \;\; |j-k| \;\; odd \right\}.$$

We next simplify the bounds for the logistic link function: First, let $\delta_{ij} = x'_{ij}\,\beta$. Then $w_{ij} = P_{ij}/(1-P_{ij}) = exp(\delta_{ij}) \Rightarrow w_{ij} \times w_{ik} = exp(\delta_{ij} + \delta_{ik}) = exp((x_{ij} + x_{ik})'\beta)$ and $w_{ij}/w_{ik} = exp(\delta_{ij} - \delta_{ik}) = exp((x_{ij} - x_{ik})'\beta)$. Substitution into (5) and (6) and simple arithmetic can then be used to show that the *feasible region (TBB) for the EQC structure* for the logistic model is given by

$$(L_{EQC}, U_{EQC}), \tag{7}$$

where $L_{EQC} = \max_{i,j,k} \left\{ -exp(-|(x_{ij} + x_{ik})'\beta)|/2 \right\}$ and $U_{EQC} = \min_{i,j,k} \left\{ exp(-|(x_{ij} - x_{ik})'\beta)|/2 \right\}$. In addition, the *feasible region (TBB) for the AR(1) structure* for the logistic model is given by

$$(L_{AR1}, U_{AR1}), \tag{8}$$

where $L_{AR1} = \max\left\{\zeta_{even}, \zeta_{odd}\right\}$;

$$\zeta_{even} = \max_{i,j,k} \left\{ -exp(-|(x_{ij} - x_{ik})'\beta)|/(2|j-k|)) \;\; for \;\; |j-k| \;\; even \right\};$$

$$\zeta_{odd} = \max_{i,j,k} \left\{ -exp(-|(x_{ij} + x_{ik})'\beta)|/(2|j-k|)) \;\; for \;\; |j-k| \;\; odd \right\};$$

and

$$U_{AR1} = \min_{i,j,k} \left\{ exp(-|(x_{ij} - x_{ik})'\beta)|/(2|j-k|) \right\}.$$

The feasible regions (EBB) for the EQC and AR(1) structures and the logistic model are then given by $(\hat{L}_{EQC}, \hat{U}_{EQC})$ and $(\hat{L}_{AR1}, \hat{U}_{AR1})$, respectively, where these intervals are obtained by evaluating (7) and (8) at $\hat{\beta}$.

The upper bound for α depends on both the regression parameter β and the *within subject* deviation in covariates; the within subject deviations will

typically be bounded in longitudinal studies. For example, in a one year study with height on adults as a covariate, within subject change in height will be less than 12 inches. If all covariates are all cluster specific, then $P_{ij} = P_{ik} \Rightarrow w_{ij}/w_{ik} = 1$ and $Upper_i(j,k) = 1$ in (4) for all i, j, and k. In addition, if $\beta = 0$ then $w_{ij} = exp(x'_{ij}\,\beta) = 1 \; \forall \; i$ and j, so that the feasible region (TBB) will be $(-1, 1)$ for the AR(1) and EQC structures.

An important characteristic of GEE (and QLS) is that $\hat{\beta}$ is consistent, even when the working correlation structure is misspecified. Let $\xrightarrow{p}$ denote convergence in probability. Because the boundary values in (L_{EQC}, U_{EQC}) and (L_{AR1}, U_{AR1}) are functions of β, $(\hat{L}_{EQC}, \hat{U}_{EQC}) \xrightarrow{p} (L_{EQC}, U_{EQC})$ and $(\hat{L}_{AR1}, \hat{U}_{AR1}) \xrightarrow{p} (L_{AR1}, U_{AR1})$ as $m \to \infty$, *even when the working correlation structure is misspecified*. In other words, the boundary values in the feasible region (TBB) for α for a particular working structure are still estimated consistently when the working structure is misspecified.

It is also important to define the feasible region with respect to being positive-definite (*feasible region (PD))* as the interval on which α yields a positive definite matrix. For example, for an $n \times n$ EQC structure, the feasible region (PD) is $(-1/(n-1), 1)$; for an AR(1) structure the feasible region (PD) is $(-1, 1)$. We will refer to a value of α as feasible if it falls within the particular feasible region of interest; otherwise, we say that it is infeasible. For example $\hat{\alpha} = 1.3$ is infeasible (PD). In addition, we will also refer to an infeasible or feasible estimate (EBB or TBB) as an estimate that violates or satisfies the binary bounds (EBB or TBB), respectively. We also note that one type of violation of bounds can occur alone. For example, in § 6 $\hat{\alpha}_{GEE}$ for the EQC structure is feasible(PD) but infeasible(EBB); i.e. it

yields a positive-definite estimated correlation matrix, but fails to satisfy the estimated binary bounds.

3. Methods

3.1 *Approach for Simulating Binary Data*

To simulate correlated binary data, we assumed the following Markovian dependence model for the likelihood of a particular response on subject i that was discussed by Liu and Liang (1997) and Jung and Ahn (2005):

$$P(Y_{i1} = y_{i1}, \cdots, Y_{in} = y_{in}) = P(Y_{i1} = y_{i1}) \prod_{j=2}^{n} P(Y_{ij} = y_{ij} | Y_{ij-1} = y_{ij-1}). \tag{9}$$

In Appendix A we prove that Markovian dependence coupled with the assumption that $Corr(Y_{ij}, Y_{ij+1}) = \alpha \ \forall i, j$ does indeed yield a first-order autoregressive AR(1) structure for the responses within each subject, so that $Corr(Y_{ij}, Y_{ik}) = \alpha^{|j-k|}$. The Markovian model also allows for straightforward simulation of correlated binary data, that we accomplished according to the approach based on permutation probabilities of Kang & Jung (2001). All programs were written in Stata.

3.2 *GEE and Quasi-Least Squares*

Here we describe GEE and QLS. For implementation of GEE (Liang and Zeger, 1986) for the EQC and AR(1) structures, we applied the following moment estimates that were given in Wang and Carey (2003):

$$\hat{\alpha}_{GEE-EQC} = \frac{\sum_{i=1}^{m} \sum_{k \neq j} z_{ik} z_{ij}}{\sum_{i=1}^{m} (n_i - 1) \sum_{j=1}^{n_i} z_{ij}^2} \tag{10}$$

and

$$\hat{\alpha}_{GEE-AR1} = \frac{\sum_{i=1}^{m} \sum_{j=2}^{n_i} z_{ij} z_{ij-1}}{\sum_{i=1}^{m} \left\{ \sum_{j=2}^{n_i - 1} z_{ij}^2 + 1/2(z_{i1}^2 + z_{in_i}^2 \right\}}. \tag{11}$$

For comparison, we also implemented QLS, a two stage procedure in the framework of GEE that was developed in Chaganty (1997), Shults and Chaganty (1998), and Chaganty and Shults (1999). In stage one QLS alternates between updating the estimate of β via the GEE estimating equation for β and updating the estimate of α by solving the *stage one estimating equation* for α:

$$\frac{\partial}{\partial \alpha}\left\{\sum_{i=1}^{m} Z_i'(\beta)\left\{W_i^{-1}(\alpha)\right\} Z_i(\beta)\right\} = 0, \tag{12}$$

where $Z_i(\beta) = \left\{\frac{Y_{ij}-P_{ij}}{P_{ij}\,(1-P_{ij})}\right\}_{n_i \times 1}$ is the vector of Pearson residuals and $W_i(\alpha)$ is the working correlation structure for outcomes on subject i. Because the solution $\hat{\alpha}$ to (12) is not consistent, stage two of QLS obtains a final estimate $\hat{\alpha}_{QLS}$ as the solution to the *stage two estimating equation* for α:

$$\sum_{i=1}^{m} trace\left\{\frac{\partial W_i^{-1}(\delta)}{\partial \delta} W_i(\alpha)\right\}\Bigg|_{\delta=\hat{\alpha}} = 0. \tag{13}$$

QLS then obtains the final estimate $\hat{\beta}_{QLS}$ of β by again solving the GEE estimating equation for β evaluated at $\hat{\alpha}_{QLS}$. This process yields an estimate of β that has the same asymptotic distribution as the GEE estimate $\hat{\beta}_{GEE}$.

For the AR(1) structure Shults and Chaganty (1998) showed that the stage one estimate $\hat{\alpha}$ can be expressed as:

$$\hat{\alpha} = \frac{\sum_{i=1}^{m}\sum_{j=2}^{n_i}(z_{ij}^2 + z_{ij-1}^2) - \sqrt{\sum_{i=1}^{m}\sum_{j=2}^{n_i}(z_{ij}^2 + z_{ij-1}^2)\sum_{i=1}^{m}\sum_{j=2}^{n_i}(z_{ij}^2 - z_{ij-1}^2)}}{2\sum_{i=1}^{m}\sum_{j=2}^{n_i} z_{ij}z_{ij-1}}, \tag{14}$$

while the stage two estimate $\hat{\alpha}_{QLS}$ (Chaganty and Shults, 1999) is given by

$$\hat{\alpha}_{QLS-AR1} = \frac{2\hat{\alpha}}{1+\hat{\alpha}^2}. \tag{15}$$

For the EQC structure, the stage one estimating equation (Shults, 1996) can be expressed as follows:

$$\sum_{i:n_i>1} Z_i' Z_i - \sum_{i:n_i>1} \frac{1+\alpha^2(n_i-1)}{(1+\alpha(n_i-1))^2} \, (Z_i'(\beta)\, e_i)^2 = 0, \tag{16}$$

where I_{n_i} is the identity matrix and e_i is a $n_i \times 1$ column vector of ones. Shults (1996) proved that this equation will have a unique solution in the feasible region (PD) $(-1/(n_{\max}-1), 1)$ for the EQC structure, where $n_{\max}$ is the maximum value of $\{n_i,\, 1 \le i \le m\}$. In general, bisection could be used to obtain a solution; for balanced data, i.e. when $n_i = n$, Chaganty (1997) obtained an explicit solution. Shults and Morrow (C.3,2002) obtained the stage two estimate $\hat{\alpha}_{QLS-EQC}$:

$$\sum_{i:n_i>1} \frac{n_i\,(n_i-1)\,\widehat{\alpha}\,(\widehat{\alpha}\,(n_i-2)+2)}{(1+\widehat{\alpha}(n_i-1))^2} \Big/ \sum_{i:n_i>1} \frac{n_i\,(n_i-1)\,(1+\widehat{\alpha}^2(n_i-1))}{(1+\widehat{\alpha}(n_i-1))^2}. \tag{17}$$

3.3 *Informal Assessment of Goodness of Fit*

In our analysis of the Venlafaxine study in § 6 we used the Rotnizky-Jewell (1990) adequacy criterion as described in Wang and Carey (2004) to informally compare the fit of several working correlation structures: This approach is based on the observation that if the working correlation structure is close to the true structure, the model-based estimate $\hat{\Sigma}_m$ (that assumes correct specification) and the "sandwich" estimate $\hat{\Sigma}_s$ (that is typically robust to misspecification) of the covariance matrix of $\hat{\beta}$ should be similar, so that $Q = \hat{\Sigma}_m^{-1}\hat{\Sigma}_s$ should be close to an identity matrix. In this case the quantities $c_1 = trace(Q)/p$ and $c_2 = trace(Q^2)/p$, where p is the dimension of Q, should

be close to one in value. In addition, $d = \sum_j (e_j - 1)^2 = c_2 - 2c_1 + 1$, where e_j are the eigenvalues of Q, should be close to zero.

In addition, we proposed the following informal goodness of fit statistic to compare the working structures in the Venlafoxine study:

$$gof = \sum_{g=o}^{1} \sum_{j=1}^{7} \sum_{k=j+1}^{8} \sum_{a=0}^{1} \sum_{b=0}^{1} \frac{(O_{gjk}(a,b) - E_{gjk}(a,b))^2}{E_{gjk}(a,b)}, \tag{18}$$

where $O_{gjk}(a,b)$ is the observed number of measurements of MDE for subjects in group g ($g = 1$ for Venlafoxine; $g = 0$ for Lithium treatment group) that take value a and b at visits j and k, respectively. The corresponding expected number of measurements $E_{gjk}(a,b) = P_{gjk}(a,b)\, N_{gjk}$, where $P_{gjk}(a,b)$ is the probability of $(Y_{ij} = a,\, Y_{ik} = b) = (a,b)$ obtained using (1) with P_{ij} and P_{ik}; P_{ik} is the probability of an occurrence of MDE at visit k for a subject in group g (see §2.1); and $N_{gjk} = 0_{gjk}(0,0) + 0_{gjk}(1,0) + 0_{gjk}(0,1) + 0_{gjk}(1,1)$. The statistic gof is the sum of the 56 Chi-Square goodness of fit statistics for the bivariate distributions of MDE at visits j and k for subjects in both treatment groups. Because assumption of a model for the marginal means and working correlation structure of binary outcomes in a GEE (or QLS) analysis induces these joint distributions, it is reasonable to compare the working structures with regard to their ability to yield a model with reasonable fit. Our additional informal assessment therefore identifies the best structure as the one amongst the candidate structures that minimizes the gof statistic.

3.4 *Asymptotic Violation of Bounds*

When the correlation structure is misidentified the bounds (TBB) will be estimated consistently (see §2.2); however, $\hat{\alpha}$ may fail to be consistent (Crow-

der, 1995). In these situations, the bounds (TBB) for a particular working correlation structure can be violated asymptotically. For convenience, we use α and ρ to denote the working and true correlation parameter when the correlation structure is misspecified.

For example, suppose the true structure is AR(1) with parameters ρ_A and ρ_B for subjects in groups A and B, respectively; we correctly specified the AR(1) working structure, but incorrectly assumed that the correlation is constant between groups. In this situation, we prove in part (i) of Appendix B that for both QLS and GEE, $\hat{\alpha} \xrightarrow{p} w_A\,\rho_A + w_B\,\rho_B = lim(\rho_A, \rho_B)$, where w_A is the proportion of subjects in group A. Suppose the feasible region (TBB) is $(L_{AR1}(A), U_{AR1}(A))$ for ρ_A and is $(L_{AR1}(B), U_{AR1}(B))$ for ρ_B. The feasible region (TBB) for the AR(1) structure under the assumption that $\rho_A = \rho_B = \rho$ is then given by (L_{AR1}, U_{AR1}), where $L_{AR1} = \max\{L_{AR1}(A), L_{AR1}(B)\}$ and $U_{AR1} = \min\{U_{AR1}(A), U_{AR1}(B)\}$. The bounds (TBB) for the AR(1) structure will not be misspecified asymptotically for this misspecification scenario, if $L_{AR1} \leq lim(\rho_A, \rho_B) \leq U_{AR1}$; otherwise, the bounds will be violated asymptotically.

Next, suppose that the working AR(1) structure was misspecified as EQC. In part (ii) of Appendix B we prove that $\hat{\alpha}_{QLS-EQC} \xrightarrow{p} lim(\rho)$ in this situation, where $lim(\rho)$ can be obtained using the algorithm given in Appendix B when $n_i \neq n$, or (B.7) when $n_i = n\,\forall\, i$. When $n_i = n \forall\, i$ we also prove that the limiting values for $\hat{\alpha}$ are identical for QLS and GEE; however, they will not agree for unbalanced data. The bounds (TBB) for the EQC structure in (7) will not be violated asymptotically for this misspecification scenario, if $L_{EQC} \leq lim(\rho) \leq U_{EQC}$; otherwise, the bounds will be violated asymp-

totically. (Note that if the EQC structure is misspecified as AR(1) then $\hat{\alpha}_{QLS-EQC}$ (Chaganty and Shults, 1999) and $\hat{\alpha}_{GEE-EQC}$ (Wang and Carey, 2003) will be consistent.)

In an analysis, we will say that the degree of violation of bounds is severe if the distance between $\hat{\alpha}$ and the relevant estimated bound is large, e.g. if $\hat{\alpha} - \hat{U}_{EQC}$ is large. Because $\hat{\beta} \xrightarrow{p} \beta$, even when the correlation structure is misspecified, (see § 2.2) $\hat{U}_{EQC} \xrightarrow{p} U_{EQC}$, so that $\hat{\alpha} - \hat{U}_{EQC} \xrightarrow{p} lim(\rho) - U_{EQC}$. In § 6, we obtained jackknife confidence intervals for $\hat{\alpha} - \hat{U}_{EQC}$. If the confidence interval did not include zero this suggested that the violation of bounds was severe, so that the EQC structure may have been misspecified.

3.5 *Methods for Estimation of* α

In simulations we implemented the following methods for estimation of α that were discussed in § 1.2: (i) *Working Independence Approach:* Let $\hat{\alpha} = 0$; (ii) *Midpoint Approach:* Let $\hat{\alpha} = \hat{\alpha}_m$ where $\hat{\alpha}_m$ is the midpoint of the feasible region (EBB), $(\hat{L}_{EQC}, \hat{U}_{EQC})$, when $\hat{L}_{EQC}$ and $\hat{U}_{EQC}$ in (7) are estimated using GEE (or QLS) with an independence working structure; and (iii) *Iterative Algorithm:* In Appendix C we propose a simple iterative algorithm that can be implemented when the QLS or GEE estimate of α is infeasible (EBB) for a particular working correlation structure. It is also easily modified to allow the correlation parameter to vary between groups. This algorithm will iterate between obtaining an adjusted estimate for α and updating the estimate for β (by solving the GEE estimating equation for β) until the bounds for α are satisfied and the current estimate for α is within a pre-specified distance (tolerance level) from the previous estimate. As noted in § 1.2, iteration is needed because replacing an infeasible $\hat{\alpha}$ with $\hat{U}_{EQC}$,

for example, may yield an updated $\hat{\beta}$ and corresponding updated boundary values that are not satisfied. Please see §7 for our general recommendations regarding when adjustment for violation of bounds (EBB) should be done.

3.6 *Asymptotic Bias in Estimation of Joint Probabilities*

Suppose that $\hat{\alpha} \xrightarrow{p} f(\rho)$, where ρ is the true correlation parameter, and that $\hat{\beta} \xrightarrow{p} \beta$. Then if the true correlation structure is AR(1) the asymptotic bias in estimation of the bivariate probabilities in (1) is given by:

$$\left(C_{ijk}\left(f(\rho)\right) - \rho^{|j-k|}\right)\, P_{ij}^{y_{ij}}\, Q_{ij}^{1-y_{ij}}\, P_{ik}^{y_{ik}}\, Q_{ik}^{1-y_{ik}} \left[\frac{\left(y_{ij} - P_{ij}\right)\left(y_{ik} - P_{ik}\right)}{\sqrt{P_{ij}\, P_{ik}\, Q_{ij}\, Q_{ik}}}\right], \quad (19)$$

where $C_{ijk}(\gamma) = \gamma$ or $C_{ijk}(\gamma) = \gamma^{|j-k|}$ if the working correlation structures are EQC or AR(1), respectively. Note that $f(\rho) = 0$ for the independence approach and $f(\rho) = (L_{EQC} + U_{EQC})/2$ for the midpoint approach, where (L_{EQC}, U_{EQC}) are given in (7).

4. Conditions Under Which Violation is Likely to Occur

In this section, we assume that β is equal to its estimated value for QLS and the AR(1) working structure in analysis of Venlafaxine (Table 2).

4.1 *When the Working Structure is Correctly Specified*

If the correlation structure is correctly specified as AR(1), then violation of bounds is more likely to occur when α is close to one of the boundary values in the feasible region (TBB) (L_{AR1}, U_{AR1}) given in (8). Figure 1 displays the proportion of 200 simulation runs that yielded infeasible (EBB) GEE estimates of α for $n_i = 3\ \forall\, i$ (left) and $n_i = 8\ \forall\, i$ (right), several group sizes m, and true values of α in its feasible region (TBB). The graphs for QLS were very similar (not shown). Figure 1 shows that the likelihood of obtaining an infeasible estimate (EBB) is high when α is very close to a boundary of the

feasible region and when the sample size is smaller. However, when α was close to the midpoint of the bounds and for larger sample sizes, infeasibility (EBB) was less likely to occur.

We also note that although the likelihood of violation (EBB) was high when α was close to the boundary, the *severity of violation* (see § 3.4) decreased rapidly with increasing sample size. For example, for $\alpha = 0.75$ and $n_i = 8 \ \forall \, i$ the $(5^{th}, 95^{th})$ percentiles of $\hat{\alpha}_{QLS-AR1} - \hat{U}_{AR1}$ (calculated over runs that resulted in a violation of bounds) for $m = 10$ versus $m = 80$ were $(0.003, 0.312)$ and $(0.001, 0.039)$, respectively. Asymptotically, $\hat{\alpha}$ will be feasible (TBB) because as discussed in §2.2, if the working correlation structure is correctly specified, both α and the boundary values in (L_{AR1}, U_{AR1}) will be estimated consistently. The results were very similar for other values of m and β, e.g. see Shults et. al (2005).

[Figure 1 about here.]

4.2 *When the Working Correlation Structure is Misspecified*

As discussed in § 3.4, if the correlation structure is misspecified, the feasible region (TBB) (for α) will be estimated consistently, but $\hat{\alpha}$ may fail to be consistent. As in § 3.4, α represents the working correlation parameter and ρ represents the true parameter when the structure is misspecified.

4.2.1 When α is Incorrectly Assumed to be Constant Here we assume that the correlation structure is AR(1), but we have incorrectly assumed that the working correlation parameter α is constant when it actually takes values ρ_V and ρ_L for subjects in the equally sized Venlafoxine and Lithium groups, respectively. Using (8) the feasible region (TBB) is (-0.3555,0.8926)

for ρ_L and is (-0.0674,0.7740) for ρ_V when $n_i = 8 \; \forall \, i$. The feasible region (TBB) for the AR(1) structure under the assumption that $\rho_L = \rho_V = \rho$ is then given by $(-0.3555, 0.8926) \bigcap (-0.0674, 0.7740) = (-0.0674, 0.7740)$. If $\rho_L = 0.85$ and $\rho_V = 0.72$ then using Appendix B ((i)), the limiting value of $\hat{\alpha}_{QLS}$ for QLS under an incorrect assumption of constant α is equal to $w_L \, 0.85 + w_V \, 0.72 = 0.5 \times 0.85 + 0.5 \times 0.72 = 0.785$, where $w_L = w_V = 0.5$ are the proportion of subjects in the Lithium and Venlafoxine groups, respectively. If $\rho_V > 0.698$, then the limiting value of $\hat{\alpha}_{QLS}$ will exceed 0.774. As a result, the feasible region (TBB) will be violated asymptotically when $\rho_L = 0.85$ and $\rho_V > 0.698$. Figure 2 displays the proportion of infeasible (EBB) estimates for this example, when $\rho_L = 0.85$ and for several values of ρ_V over its feasible region (TBB), when QLS is applied under the incorrect assumption that the correlation is constant between groups. This graph displays a vertical line at $\rho_V = 0.698$. As expected, when the limiting value of $\hat{\alpha}_{QLS}$ exceeds 0.774 (when $\rho_V > 0.698$) we see higher rates of infeasibility as the sample size increases, in contrast to the lower rates we observe when the limiting value is within bounds. (The graphs for GEE are similar and are not shown.) Results for other values of β (Shults et al., 2005) were similar.

[Figure 2 about here.]

4.2.2 When the AR(1) Structure is Misspecified as EQC Here we assume that the true correlation structure is AR(1) but has been misspecified as EQC. As in § 4.2.1 we assume the true value of β equals its estimated value for the AR(1) structure for QLS in the Venlafoxine study (Table 2). Using (7) and (8) the bounds (TBB) for the EQC and AR(1) structures are

$(L_{EQC}, U_{EQC}) = (-.0674, .1665)$ and $(L_{AR1}, U_{AR1}) = (-.0674, .7740)$.

As discussed in § 2.2, even if the true AR(1) structure is misspecified as EQC, $(\hat{L}_{EQC}, \hat{U}_{EQC}) \xrightarrow{p} (L_{EQC}, U_{EQC})$. However, $\hat{\alpha}_{QLS-EQC}$ and $\hat{\alpha}_{GEE-EQC}$ will not be consistent. Figure 3 displays a graph of the limiting value of $\hat{\alpha}_{QLS-EQC}$ versus the true value of ρ when the true structure is AR(1); ρ takes values in the feasible region (TBB) $(L_{AR1}, U_{AR1}) = (-.0674, .7740)$ for the AR(1) structure. The limiting values for QLS were obtained using the algorithm in (ii) of Appendix B; they depend on n_i, which took these values in the Venlafoxine study: n_i (number of subjects): 2 (2),3(7),4(2),5(5),6(5),7(4),and 8(27). Figure 3 also displays a horizontal line at the upper value for the bounds (TBB) for the EQC structure, $U_{EQC} = 0.1665$.

Figure 3 shows that when the AR(1) structure is misspecified as EQC, the limiting value for $\hat{\alpha}_{QLS-EQC}$ can be considerably larger than $U_{EQC} = 0.1665$. For example, if $\rho = 0.7$, the asymptotic violation of bounds (see § 3.4) might be considered severe because

$$\hat{\alpha}_{QLS-EQC} - \hat{U}_{EQC} \xrightarrow{p} 0.4376 - 0.1665 = 0.2711.$$

[Figure 3 about here.]

5. Comparison of Different Methods of Adjustment

To assess estimation in small samples, we simulated data with Markovian dependence and β equal to its estimated value for the AR(1) structure and QLS (Table 2). Table 1 displays the mean square error (MSE $= 1/1000 \sum_{r=1}^{1000} (\hat{\alpha}_r - \alpha_r)^2$) and bias (BIAS $= 1/1000 \sum_{r=1}^{1000} (\hat{\alpha}_r - \alpha_r)$) based on 1000 simulation runs for GEE, QLS, the working independence approach (IND), and midpoint approach (MID)(see § 3.5). For GEE and QLS, we

implemented the algorithm in Appendix C for estimation of α if the initial unadjusted estimates were infeasible (EBB). Because the methods only differ with regard to estimation of α, we displayed simulation results for $\hat{\alpha}$ with a working AR(1) structure. (This was primarily for comparison of GEE, QLS, and the midpoint approach because $\hat{\alpha} = 0$ for the independence approach, so that its bias and mean square error for estimation of α are known.) In addition, because they were of interest in the Venlafaxine study, we also obtained the MSE and bias for the joint probabilities $P(Y_{i4} = 1, Y_{i8} = 1)_L$ for subjects treated with Lithium.

Table 1 shows that application of MID or IND can result in biased and inefficient estimation of α and of $P(Y_{i4} = 1, Y_{i8} = 1)_L$ for small samples. For example, when $\alpha = 0.75$ and $m = 20$, (i) the bias and MSE of $\hat{\alpha}$ were -0.7070 and 0.5003 for the midpoint approach, versus -0.0192 and 0.0030 for GEE; and (ii) the bias and MSE of $\hat{P}(Y_{i4} = 1, Y_{i8} = 1)_L$ were -0.0615 and 0.0072 for the midpoint approach, versus -0.0021 and 0.0047 for GEE. Results were very similar for the midpoint and working independence approach because $\hat{\alpha}_{mid} \approx 0$. In addition, results were very similar for QLS and GEE. Asymptotically, (see § 3.6), $\hat{\alpha}_{mid} \xrightarrow{p} (L_{EQC} + U_{EQC})/2 = (-0.0674 + 0.1665)/2 = 0.0496$. The asymptotic bias for estimation of α with the midpoint approach is therefore -0.5504 when $\alpha = 0.60$ and is -0.7004 when $\alpha = 0.75$. The asymptotic bias for estimation of the joint probabilities with the working independence and midpoint approaches (see § 3.6) were -0.0275 and -0.0672 when $\alpha = 0.60$ and $\alpha = 0.75$, respectively. These asymptotic values are similar to the estimates in Table 1 for the largest sample size $m = 80$.

[Table 1 about here.]

6. Analysis of Venlafaxine Study

Table 2 displays the results of the analysis of the Venlafaxine study, for the model given in §2.1. The feasible regions (EBB) for the EQC and AR(1) structures were obtained using (7) and (8) evaluated at $\hat{\beta}$, respectively. The informally measured goodness of fit statistics gof and (c_1, c_2, c_3) were obtained using (18) and expressions given in § 3.3, respectively.

The GEE and QLS estimates $\hat{\alpha}_{GEE}$ and $\hat{\alpha}_{QLS}$ were infeasible (EBB) (see § 2.2) but were feasible (PD) for the EQC structure. The degree of violation of bounds (see § 3.4) might be considered severe because the 95 percent jackknife confidence interval (CI) for $\alpha - U_{EQC}$ did not include zero for either approach: $\hat{\alpha}_{GEE} - U_{EQC} = 0.2327$ (CI $= (0.227, 0.233)$) and $\hat{\alpha}_{QLS} - U_{EQC} = 0.2503$ (CI $= (0.244, 0.251)$). (The limiting value of $\hat{\alpha}$ is not the same for QLS and GEE when the working structure is misspecified as EQC and $n_i \neq n \forall i$. As a result it is not surprising that the confidence intervals did not overlap for QLS and GEE.)

As discussed in §1, it was of secondary interest to compare the likelihood of MDE at visits 4 and 8 for the Venlafaxine versus Lithium treatment groups. The violation of bounds (EBB) for the EQC structure would complicate this assessment because it results in an invalid bivariate distribution for MDE at these visits, i.e. some of the estimates of $P(Y_{i4} = 1, Y_{i8} = 1)$, $P(Y_{i4} = 1, Y_{i8} = 0)$, $P(Y_{i4} = 0, Y_{i8} = 1)$, $P(Y_{i4} = 1, Y_{i8} = 1)$ (calculated using (3) to calculate the P_{ij} and (1) to calculate the bivariate probabilities) were negative. For example, the GEE estimate for Venlafaxine

$\hat{P}(Y_{i4} = 0, Y_{i8} = 1)_{Ven} = -0.0044$. (For brevity, Table 2 only displays one of the four estimated probabilities for each treatment group.)

To assess the sensitivity of results to choice of working correlation structure, we implemented the algorithm in Appendix C to obtain a feasible estimate $\hat{\alpha}$ (EBB) for the EQC structure. This required 17 iterations. The adjusted estimates for the *(i) regression coefficients* were $\hat{\beta}_0 = 0.6885$ ($p = 0.109$); $\hat{\beta}_1 = 0.2262$ ($p = 0.707$), $\hat{\beta}_2 = -0.2575$ ($p = 0.005$); $\hat{\beta}_3 = -0.2329$ ($p = 0.170$); *(ii) bounds (EBB)* were $(\hat{L}_{EQC}, \hat{U}_{EQC}) = (-0.0631, 0.1797)$; and *(iii) correlation parameter* was $\hat{\alpha} = 0.1797$. The gof statistic was not available for the unadjusted EQC structure; for the adjusted analysis the value of the statistic was 186.3245. The Rotnizky-Jewell informal goodness of fit statistics (c_1, c_2, d) were $(1.7241, 3.3636, 0.9153)$.

The analysis results differed according to choice of working structure. For example, results based on application of the AR(1) structure might be more suggestive of a difference between treatment groups with regard to time trends in the likelihood of occurrence of MDE. Although the interaction between time and treatment group was not significant at the 0.05 level for any structure, the estimated regression coefficient $\hat{\beta}_3$ for the interaction term was significant for the AR(1) structure at a 0.10 significance level. In addition, $\hat{\beta}_3$ was greatest in absolute value for the AR(1) structure ($\hat{\beta}_3 = -0.2850$ for QLS and GEE versus -0.2329 for the adjusted EQC structure and -0.2469 for an identity structure).

In the secondary analysis of occurrence of MDE at visits four and eight, the differences between structures was striking. (For illustration, we based estimates of these probabilities on their estimated regression coefficients in

Table 2, irrespective of the corresponding p-values.) For example, the joint probabilities of MDE at visits four and eight for the Venlafaxine versus Lithium treatment groups, respectively, were 0.0289 and 0.1197 for the EQC structure (adjusted estimate); 0.0246 and 0.1283 for the AR(1) structure and GEE; 0.0245 and 0.1282 for the AR(1) structure and QLS; and 0.0145 and 0.0954 for the identity structure. This resulted in an estimated odds-ratio for having MDE at visits one of four for Lithium versus Venlafaxine of 5.8403 and 5.8475 for the AR(1) structure with GEE and QLS, respectively; 4.5658 for the EQC structure; and of 7.1735 for the identity structure. As discussed in §3.6 the joint probabilities will be estimated with asymptotic bias if the working structure is misspecified, so that it is not surprising that these estimates varied according to choice of working structure.

For our final choice of working correlation structure, we ruled out the EQC structure for the following reasons: (i) The fit for this structure, as assessed using the Rotnizky-Jewel informal assessment (see §3.3) was relatively poor; e.g. (c_1, c_2, d) should be close to $(1, 1, 0)$ for good fit, but was $(1.7241, 3.3635, 0.9153)$ for the EQC structure (with adjusted approach) versus $(1.1712, 1.5886, 0.2461)$ for the AR(1) structure (with GEE). In addition, the informally measured gof statistics was larger for this structure; e.g. gof = 186.32 for the EQC structure versus gof = 159.12 for the AR(1) structure with GEE; (ii) This structure was not identified a priori as the most biologically plausible structure, as discussed in §2.1; and (iii) There was a severe violation of bounds (EBB) for this structure, as noted earlier in this section. We also ruled out application of the identity structure because, although there can be no violation of bounds for this structure, it was not biologically

plausible and had poor fit, e.g. with $(c_1, c_2, d) = (2.5723, 8.2379, 4.0933)$ and gof $= 313.88$. We therefore based our results for analysis on the AR(1) working structure which had the best fit, was most biologically plausible, and had no violation of bounds for $\hat{\alpha}$.

[Table 2 about here.]

7. Conclusions and Recommendations

We discussed the potential for violation of bounds for the correlation in GEE and QLS analysis of correlated binary data in the context of a longitudinal clinical trial that compared Venlafaxine with Lithium. We demonstrated that violation is more likely to occur for smaller samples, when α is close to the boundary value for the feasible region (TBB), and when the correlation structure is misspecified. For example, we proved that the limiting value of $\hat{\alpha}$ can exceed the upper bound U_{AR1} in (8) if the parameter α in the AR(1) structure is incorrectly assumed to be equal across groups. In addition, if the true AR(1) structure is misspecified as EQC and α is large, then we proved that the limiting value of $\hat{\alpha}$ can be substantially greater than the upper bound U_{EQC} for α in (7) for the EQC working structure.

That a severe violation of bounds can result from an incorrect choice of working structure suggests that following descriptive analyses, the initial implementation of GEE should *not* automatically force the bounds on α to be satisfied. We suggest that the initial analyses should involve application of traditional (unadjusted) GEE or QLS, with a working structure that was chosen on the basis of biological plausibility; other simple structures could also be applied in order to assess the sensitivity of the analysis results to the choice of working structure. If we anticipate that the degree of association

depends on group membership in a longitudinal trial, we might allow $\hat{\alpha}$ to depend on group membership, e.g. as in Shults and Morrow (2002) who anticipated that the correlation would vary between control and treatment groups in an educational intervention to promote exclusive breast-feeding among lactating women in Mexico. Next, the feasible region (EBB) for α should be evaluated at $\hat{\beta}$ and $\hat{\alpha}$. If $\hat{\alpha}$ if infeasible (EBB) and the degree of violation is severe for a particular structure then this should be taken into consideration *along with other criteria* regarding suitability of this structure. For example, in our analysis of Venlafaxine, there was a severe violation of bounds for the EQC structure, which was less biologically plausible than the AR(1) structure and had worse fit according to the informally measured Rotnizky-Jewell criterion and the informal statistics based on the bivariate distributions. In addition, the 95 percent jackknife confidence interval for $\alpha - U_{EQC}$ did not contain zero (see § 6.0). This severe violation of bounds provided additional evidence in support of ruling out the EQC structure as the final working structure in this analysis.

If there is a minor violation of bounds for a structure that is biologically appropriate and has reasonable fit, we suggest that an adjusted estimate of α could be obtained that is feasible (EBB). This will be necessary if estimation of the joint probabilities is of interest; otherwise, some estimated probabilities will be negative. If $\hat{\alpha}$ is infeasible (EBB), we suggest that an adjusted estimate of α could be obtained using the iterative algorithm in Appendix C. After several iterations this will yield an estimate that is close the boundary value (EBB) for the specified working structure. We believe that this is a reasonable approach because (see § 4.1) violation of bounds is likely when α

is close to the boundary, and is unlikely otherwise. If we apply the working independence or midpoint approach (see § 5) we demonstrated that this can result in biased and inefficient estimation of α and of the bivariate probabilities. We also note that our algorithm could be applied after implementation of other approaches that alternate between estimation of the regression and correlation parameters, e.g. the GEE1 approach of Prentice (1988).

Although estimation of bivariate probabilities is typically not a primary goal of GEE analyses, estimates of these probabilities can always be obtained as a by-product of GEE analysis, because specification of the marginal means and first order correlations completely determines the bivariate distributions of the binary outcomes (Prentice, 1988). Their estimation was helpful in the Venlafaxine trial because the estimated odds-ratio based on the estimated joint probabilities for having MDE at two important treatment occasions (visits 4 and 8) was 5.8453 (with the AR(1) structure) which was suggestive of a strong treatment benefit with Venlafaxine. An analysis that includes assessment of joint probabilities with the primary comparison of trends over time might therefore be more encouraging with regard to conducting future research into the potential benefits of treatment with Venlafaxine.

Additional future research might include describing the correlation structures that are implicitly assumed under assumption of some complex mixed models and then studying the potential for violation of bounds for these models. In addition, obtaining the limiting values of $\hat{\alpha}$ under other misspecification scenarios would be of interest, as would continuation of development of methods for choosing between several plausible correlation structures.

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References

CHAGANTY, N.R. (1997). An alternative approach to the analysis of longitudinal data via generalized estimating equations. *Journal of Statistical Planning and Inference* **63**, 39-54.

CHAGANTY, N.R. AND JOE, H. (2004). Efficiency of generalized estimating equations for binary responses. *Journal of the Royal Statistical Society, Series B* **66**, 851-860.

CHAGANTY, N.R. AND SHULTS, J. (1999). On eliminating the asymptotic bias in the quasi-least squares estimate of the correlation parameter. *Journal of Statistical Planning and Inference* **76**, 127-144.

CROWDER, M. (1995). On the use of a working correlation matrix in using generalised linear models in repeated measures. *Biometrika* **82**, 407-410.

DIGGLE, P.J., HEAGERTY, P., LIANG, K.L.AND ZEGER, S.L. (2002). *Analysis of Longitudinal Data*. Oxford University Press Inc., New York.

FITZMAURICE, G.M. (1995). A caveat concerning independence estimating equations with multivariate binary data. *Biometrics* **51**, 309-317.

JOE, H. (1997). *Multivariate Models and Dependence Concepts.* Chapman & Hall. New York.

JUNG, S.H. AND AHN, W.W. (2005). Sample size for a two-group comparison of repeated binary measurements using GEE. *Statistics in Medicine* **24**, 2583-2596.

KABFLEISH, J.D. AND PRENTICE, R.L. (1990). *The Statistical Analysis of Failure Time Data.* New York: John Wiley.

KANG, S.H. AND JUNG, S.H. (2001). Generating correlated binary variables with complete specification of the joint distribution. *Biometrical Journal* **43**, 263-269.

LIANG, K.L. AND ZEGER, S.L. (1986). Longitudinal data analysis using generalized linear models. *Biometrika* **73**, 13-22.

LIU, G. AND LIANG, K.Y. (1997). Sample size calculation for studies with correlated observations. *Biometrics* **53**, 937- 947.

MANCL, L.A. AND LEROUX, B.G. (1996). Efficiency of regression estimates for clustered data. *Biometrics* **52**, 500-511.

MCDONALD, B.W. (1993). Estimating logistic regression parameters for bivariate binary data. *Journal of the Royal Statistical Society, Series B***54**, 309-317.

MOLENNBERGHS, G. AND VERBEKE, G. (2005). *Models for discrete longitudinal data.* Springer Science+Business Media, New York, NY 10013, USA.

PEPE, M.S. AND ANDERSON, G.L. (1994). A cautionary note on inference for marginal regression models with longitudinal data and general correlated response data. *Communications in Statistics, Part B- Simulation*

and Computation **23**, 939-951,1994.

PRENTICE, R.L. (1988). Correlated binary regression with covariates specific to each binary observation. *Biometrics* **44**, 1033-1048.

ROCHON, J. (1998). Application of GEE procedures for sample size calculations in repeated measures experiments. *Statistics in Medicine* **17**, 1643-1658.

ROTNIZKY, A. AND JEWELL, N.P. (1990). Hypothesis testing of regression parameters in semiparametric generalized linear models for cluster correlated data, *Biometrika* **77**, 485-497.

SCHILDCROUT, J.S. AND HEAGERTY, P.J. (2005). Regression analysis of longitudinal binary data with time-dependent environmental covariates: bias and efficiency. *Biostatistics* **6**, 633 - 652.

SHULTS, J. (1996). The analysis of unbalanced and unequally spaced longitudinal data using quasi-least squares. Ph.D. Thesis, Department of Mathematics and Statistics, Old Dominion University, Norfolk, Virginia.

SHULTS, J. AND CHAGANTY, N.R. (1998). Analysis of serially correlated data using quasi-least squares. *Biometrics* **54**, 1622-1630.

SHULTS, J. AND MORROW, A. (2002). Use of quasi-least squares to adjust for two levels of correlation. *Biometrics* **58**, 521-530.

SHULTS, J., SUN, W., TU, X.AND AMSTERDAM, J. (2005). On the violation of bounds for the correlation in generalized estimating equation analyses of binary data from longitudinal trials, Technical Report 200501. Department of Biostatistics and Epidemiology. University of Pennsylvania School of Medicine.

SUTRADHAR, B.C. AND DAS, KAYLAN. (2000). On the accuracy of

efficiency of estimating equation approach. *Biometrics* **56**, 622-625.

WANG, Y.G. AND CAREY, V. (2003). Working correlation misspecification, estimation and covariate design: implications for generalized estimating equation performance. *Biometrika* **90**, 29-41.

WANG, Y.G. AND CAREY. V. (2004). Unbiased estimating equations from working correlation models for irregularly timed repeated measures. *Journal of the American Statistical Association* **99**, 845-852.

YOUNG, M.L.,PREISSER, J.S., QAQISH, B.F. AND WOLFSON, M. (2006). A comparison of subject-specific and population-averaged models for count data from cluster-unit intervention trials. *Statistical Methods in Medicial Research* (In Press)

ZHAO, L.P., PRENTICE, R.L. AND SELF, S.G. (1992). Multivariate mean parameter estimation by using a partly exponential model. *Journal of the Royal Statistical Society, Series B, Methodological* **54**, 805-811.

Appendix A

Proof that Markov Dependence Coupled with the Assumption that $Corr(y_{ij}, y_{ij+1}) = \rho \; \forall \; i, \; j$ yields Data with an AR(1) Correlation Structure

This is easily shown using induction. First, we can use direct calculation to show that

$$\begin{aligned} P(y_{ij} = 1, y_{ij+2} = 1) &= \sum_{o_{ij+1} \in \{0,1\}} P(y_{ij} = 1, y_{ij+1} = o_{ij+1}, y_{ij+2} = 1) \\ &= \rho^2 \sqrt{p_{ij} q_{ij} p_{ij+2} q_{ij+2}} + p_{ij} p_{ij+2}, \end{aligned}$$

so that $Corr(y_{ij}, y_{ij+2}) = \rho^2$. Next, if we assume that $Corr(y_{ij}, y_{ij+k}) =$

ρ^k, we can again use direct calculations to show that

$$\begin{aligned} P(y_{ij}=1, y_{ij+k+1}=1) &= \sum_{o_{ij+k}\in\{0,1\}} P(y_{ij}=1, y_{ij+k}=o_{ij+k}, y_{ij+k+1}=1) \\ &= \rho^{k+1}\sqrt{p_{ij}q_{ij}p_{ij+k+1}q_{ij+k+1}} + p_{ij}p_{ij+k+1} \end{aligned}$$

so that $Corr(y_{ij}, y_{ij+k+1}) = \rho^{k+1}$.

Appendix B

Limiting value of $\hat{\alpha}$ when the Working Correlation Structure is Misspecified.

We assume the working correlation structure for subject i is $W_i(\alpha)$ and the true structure is $R_i(\rho)$, where $W_i(\alpha) \neq R_i(\rho)$. Let s_g equal the number of subjects with n_g measurements, so that $s_1 + s_2 + \ldots s_G = m$. We also assume that $s_i/m = w_i$ is fixed so that $min\ \{s_i : i = 1, \cdots, G\}$ goes to infinity as m goes to infinity. In addition, we assume that $W_i(\alpha) = W_g(\alpha)$ and $R_i(\rho) = R_g(\rho)$ when subject i is in group g; i.e. when $n_i = s_g$. We first need to prove that $\frac{1}{m}\sum_{i=1}^{m}\frac{\partial}{\partial\alpha}W_i^{-1}(\alpha)Z_i(\beta)Z_i'(\beta) \xrightarrow{p} \phi\frac{1}{m}\sum_{i=1}^{m}\frac{\partial}{\partial\alpha}W_i^{-1}(\alpha)R_i(\rho)$, as $m \to \infty$. To do this note that since $s_g \to \infty$ as $m \to \infty$ and $E(Z_i(\beta)Z_i'(\beta)) = \phi R_g(\rho)$ for subject i in group g, if follows that $\lim_{m\to\infty}\frac{1}{m}\sum_{i=1}^{m}\frac{\partial}{\partial\alpha}\ W_i^{-1}(\alpha)\ Z_i(\beta)\, Z_i'(\beta)$

$$\begin{aligned} &= \lim_{m\to\infty}\sum_{g=1}^{G}\frac{s_g}{m}\ \frac{\partial}{\partial\alpha}\ W_g^{-1}(\alpha)\ \frac{1}{s_g}\sum_{i\ in\ group\ g} Z_i(\beta)Z_i'(\beta) \\ &= \sum_{g=1}^{G} w_g\ \frac{\partial}{\partial\alpha}\, W_g^{-1}(\alpha) \lim_{s_g\to\infty}\frac{1}{s_g}\sum_{i\ in\ group\ g} Z_i(\beta)Z_i'(\beta) \\ &= \sum_{g=1}^{G} w_g\ \frac{\partial}{\partial\alpha}\ W_g^{-1}(\alpha)\ \phi\ R_g(\rho) \end{aligned}$$

$$= \phi \sum_{g=1}^{G} \sum_{\text{i } in \ group \ g} \frac{1}{m} \frac{\partial}{\partial \alpha} W_i^{-1}(\alpha) \ R_i(\rho)$$

$$= \phi \ \frac{1}{m} \sum_{i=1}^{m} \frac{\partial}{\partial \alpha} W_i^{-1}(\alpha) \ R_i(\rho).$$

Next, using arguments similar to those given in Theorem 3.2 of Chaganty and Shults (1999), we note that the stage one estimating equation (12) can be expressed as

$$trace \left(\frac{1}{m} \sum_{i=1}^{m} \frac{\partial}{\partial \alpha} W_i^{-1}(\alpha) Z_i(\hat{\beta}) Z_i'(\hat{\beta}) \right) = 0. \tag{B.1}$$

Because $\hat{\beta} \xrightarrow{p} \beta$, even under misspecification of the true correlation structure, and $\frac{1}{m}\sum_{i=1}^{m} \frac{\partial}{\partial \alpha} W_i^{-1}(\alpha) Z_i(\beta) Z_i'(\beta) \xrightarrow{p} \phi \frac{1}{m}\sum_{i=1}^{m} \frac{\partial}{\partial \alpha} W_i^{-1}(\alpha) R_i(\rho)$, it follows that $\frac{1}{m}\sum_{i=1}^{m} \frac{\partial}{\partial \alpha} W_i^{-1}(\alpha) Z_i(\hat{\beta}) Z_i'(\hat{\beta}) \xrightarrow{p} \phi \frac{1}{m}\sum_{i=1}^{m} \frac{\partial}{\partial \alpha} W_i^{-1}(\alpha) R_i(\rho)$. The solution $\hat{\alpha}$ to (B.1) therefore converges in probability to the solution $g(\rho)$ of the following equation, as $m \to \infty$:

$$trace \left(\sum_{i=1}^{m} \frac{\partial}{\partial \alpha} W_i^{-1}(\alpha) R_i(\rho) \right) = 0. \tag{B.2}$$

Assume that the stage two estimate, which is the solution to (13), can be expressed as $f(\hat{\alpha})$. Since $\hat{\alpha} \xrightarrow{p} g(\rho)$, it follows that $f(\hat{\alpha}) \xrightarrow{p} f(g(\rho))$.

We will now consider two special cases:

(i) *When the True Structure is AR(1) but the Correlation Parameter is Incorrectly Assumed to be Equal Across Groups:* Let w_g be the proportion of subjects in group g and assume that $n_i = n \ \forall \ i$. Without loss of generality assume that we have two groups of subjects, so that $w_A + w_B = 1$. The true

correlation structure for subjects in groups A and B are $R(\rho_A)$ and $R(\rho_B)$ respectively, where $R(\rho_A)$ is an AR(1) structure with parameter ρ_A. The correlation parameters are incorrectly assumed to be equal across groups, so that the working structure is AR(1) structure, $W(\alpha)$. Equation (B.2) can then be simplified as follows:

$$trace\left(\sum_{i\,\in\,grp\,A}\frac{\partial}{\partial\alpha}W^{-1}(\alpha)R(\rho_A)+\sum_{i\,\in\,grp\,B}\frac{\partial}{\partial\alpha}W^{-1}(\alpha)R(\rho_B)\right)=0\implies$$

$$trace\left(\frac{\partial}{\partial\alpha}W^{-1}(\alpha)\left[w_A\,R(\rho_A)+w_B\,R(\rho_B)\right]\right)=0. \tag{B.3}$$

Because $W^{-1}(\alpha)$ is a tri-diagonal matrix for an AR(1) structure, only the diagonal and off-diagonal elements of $w_A\,R(\rho_A)+w_B\,R(\rho_B)$ are involved in the solution of (B.3); the diagonal elements are $w_A+w_B=1$ and the off-diagonal elements are $w_A\rho_A+w_B\rho_B$. The solution to (B.3) can be simplified as follows; also see (3.11) of Chaganty and Shults (1999):

$$\alpha\;=\;\frac{2f(\rho_A,\rho_B)}{1+f(\rho_A,\rho_B)^2}\;, \tag{B.4}$$

where

$$f(\rho_A,\rho_B)=\begin{cases}\frac{1-\sqrt{1-(w_A\rho_A+w_B\rho_B)2}}{w_A\rho_A+w_B\rho_B} & \text{if } w_A\rho_A+w_B\rho_B\neq 0\\ 0 \quad \text{if } \; w_A\rho_A+w_B\rho_B=0\end{cases} \tag{B.5}$$

Because the stage one estimate $\hat{\alpha}\xrightarrow{p}f(\rho_A,\rho_B)$ in probability, the stage two estimate $2\hat{\alpha}/(1+\hat{\alpha}^2)$ for a working AR(1) structure therefore converges to $2f(\rho_A,\rho_B)/(1+f(\rho_A,\rho_B)^2)\;=\;w_A\,\rho_A+w_B\,\rho_B$ in probability, as $m\to\infty$.

For GEE, if we divide the numerator and denominator of (10) by m it is straightforward to show that the numerator converges in probability

to $w_A\, n\,(n-1)\,\phi\,\rho_A + w_B\, n\,(n-1)\,\phi\,\rho_B$, while the denominator converges in probability to $n\,(n-1)\,\phi$, where $\phi = 1$ for our model. As a result, $\hat{\alpha}_{GEE-EQC} \xrightarrow{p} w_A\,\rho_A + w_B\,\rho_B$.

(ii) *When the true AR(1) structure is misspecified as EQC:* For an EQC structure $W_i^{-1}(\alpha) = \dfrac{1}{(1-\alpha)} I_{n_i} - \dfrac{\alpha}{(1-\alpha)(1+(n_i-1)\alpha)}\, e_i\, e_i'$, where I_{n_i} is the identity matrix and e_i is a $n_i \times 1$ vector of ones. If we note that $trace(e_i\, e_i' R_i(\rho)) = trace(e_i' R_i(\rho) e_i) = \sum_{j=1}^{n_i} \sum_{k=1}^{n_i} \rho^{|j-k|}$ when $R_i(\rho)$ is an $n_i \times n_i$ AR(1) structure, then it is easy to show that (B.2) can be simplified as:

$$\sum_{i=1}^{m} n_i - \sum_{i=1}^{m} \frac{1+\alpha^2(n_i-1)}{(1+\alpha(n_i-1))^2} \sum_{j=1}^{n_i} \sum_{k=1}^{n_i} \rho^{|j-k|} = 0. \tag{B.6}$$

In general, a solution $g(\rho)$ to (B.6) can be obtained using the bisection method. Since $\hat{\alpha} \xrightarrow{p} g(\rho)$, it follows that $f(\hat{\alpha}) \xrightarrow{p} f(g(\rho))$, where $f(g(\rho))$ is obtained by evaluating (17) at $g(\rho)$. This can be accomplished in the following algorithm:

Algorithm to obtain limiting value of $\hat{\alpha}_{QLS-EQC}$ when the true AR(1) structure is misspecified as EQC

(i) Use the method of bisection to obtain the solution $\alpha = g(\rho)$ to equation (B.6).

(ii) Obtain the limit of $\hat{\alpha}_{QLS-EQC}$ by evaluating (17) at $\widehat{\alpha} = g(\rho)$.

When $n_i = n\ \forall\ i$ the limiting values for $\hat{\alpha}_{QLS-EQC}$ and $\hat{\alpha}_{GEE-EQC}$ are identical and are given by:

$$\frac{2\sum_{j=1}^{n-1}\sum_{k=j+1}^{n}\rho^{k-j}}{(n-1)n} = \frac{e_n' R\,(\rho)\, e_n - n}{(n-1)n}. \tag{B.7}$$

To prove this, note that the limiting value of $\hat{\alpha}_{QLS-EQC}$ is the solution to the stage two estimating equation, evaluated at δ that (when substituted for α) satisfies the limiting value of the stage one estimating equation, i.e. we need to show that (B.7) (substituted for α) satisfies (13), when (13) is evaluated at δ that (when substituted for α) satisfies (B.6). To show this, we first note that for balanced data when $n_i = n$, (B.6) can be expressed as

$$n - \frac{1 + \alpha^2(n-1)}{(1 + \alpha(n-1))^2} \; e_n^{'} \, R(\rho) \, e_n = 0. \tag{B.8}$$

For an EQC working structure with $n_i = n \; \forall \; i$, (13) can be expressed as

$$n - \frac{1 + \delta^2(n-1)}{(1 + \delta(n-1))^2} \; [n + n \, (n-1) \, \alpha] = 0. \tag{B.9}$$

If we substitute (B.7) for α in (B.9) and then let $\delta = \alpha$, we easily obtain the left-hand side of (B.6). Therefore it is clear that (B.7) does indeed satisfy (13) when (13) is evaluated at α that satisfies (B.6). The proof is therefore complete. We also note that (B.7) can also be expressed as $\sum_{i=1}^{n} \frac{2\,(n-i)\rho^i}{n(n-1)}$ which was shown in Wang and Carey (2003) to be the limiting value for the moment estimate $\hat{\alpha}_{GEE-EQC}$, so that the limiting values agree for QLS and GEE, when $n_i = n$.

Appendix C

An algorithm to Obtain a Feasible (EBB) Estimate $\hat{\alpha}$

Without loss of generality we assume the working structure for subject i is $W_i(\alpha)$, where $W_i(\alpha)$ is AR(1). First fit unadjusted GEE or QLS to obtain $\hat{\beta}$, $\hat{\alpha}$ and the feasible region (EBB) $(\hat{L}_{AR1}, \hat{U}_{AR1})$ for α given in (8). If $\hat{\alpha}$ is

infeasible (EBB) because $\hat{\alpha} > U_{AR1}$ then do the following. Set a tolerance level, e.g. $tolerance = 0.00001$. Let $count = 1$; $j = 1$; and $upper = \hat{\alpha}$.

Step One: Let $\hat{\alpha} = upper - \frac{1}{10}^{count} \times j$.

Step Two: Update the estimate $\hat{\beta}$ of β by solving the GEE estimating equation evaluated at $W_i(\hat{\alpha})$. Update the estimates of feasible region (EBB) in (8) and check if $\hat{\alpha}$ is feasible (EBB), i.e. if $\hat{L}_{AR1} \leq \hat{\alpha} \leq \hat{U}_{AR1}$). If $\hat{\alpha} > \hat{U}_{AR1}$ then let $j = j + 1$ and repeat steps one and two. If $\hat{L}_{AR1} \leq \hat{\alpha} \leq \hat{U}_{AR1}$ but $tolerance < \frac{1}{10}^{count}$, then let $upper = \hat{\alpha} + \frac{1}{10}^{count}$; then $j = 1$; $count = count + 1$; and repeat steps one and two. If $\hat{L}_{AR1} \leq \hat{\alpha} \leq \hat{U}_{AR1}$ and $tolerance \geq \frac{1}{10}^{count}$, then the process is done and the adjusted estimate $\hat{\alpha}_{ADJ}$ will be given by $\hat{\alpha}$.

If $\hat{\alpha}$ is infeasible (EBB) because $\hat{\alpha} < \hat{L}_{AR1}$ then the above algorithm can be applied, for $lower = \hat{\alpha}$, $\hat{\alpha} = lower + \frac{1}{10}^{count} \times j$ and $lower = \hat{\alpha} - \frac{1}{10}^{count}$ substituted for their corresponding values for *upper* in steps one and two, respectively. For other working structures, the above algorithm can be applied but must be based on the feasible region (EBB) (for α) for that particular structure. For example, for the EQC structure the above approach will be based on the feasible region (EBB) $(\hat{L}_{EQC}, \hat{U}_{EQC})$ given in (7).

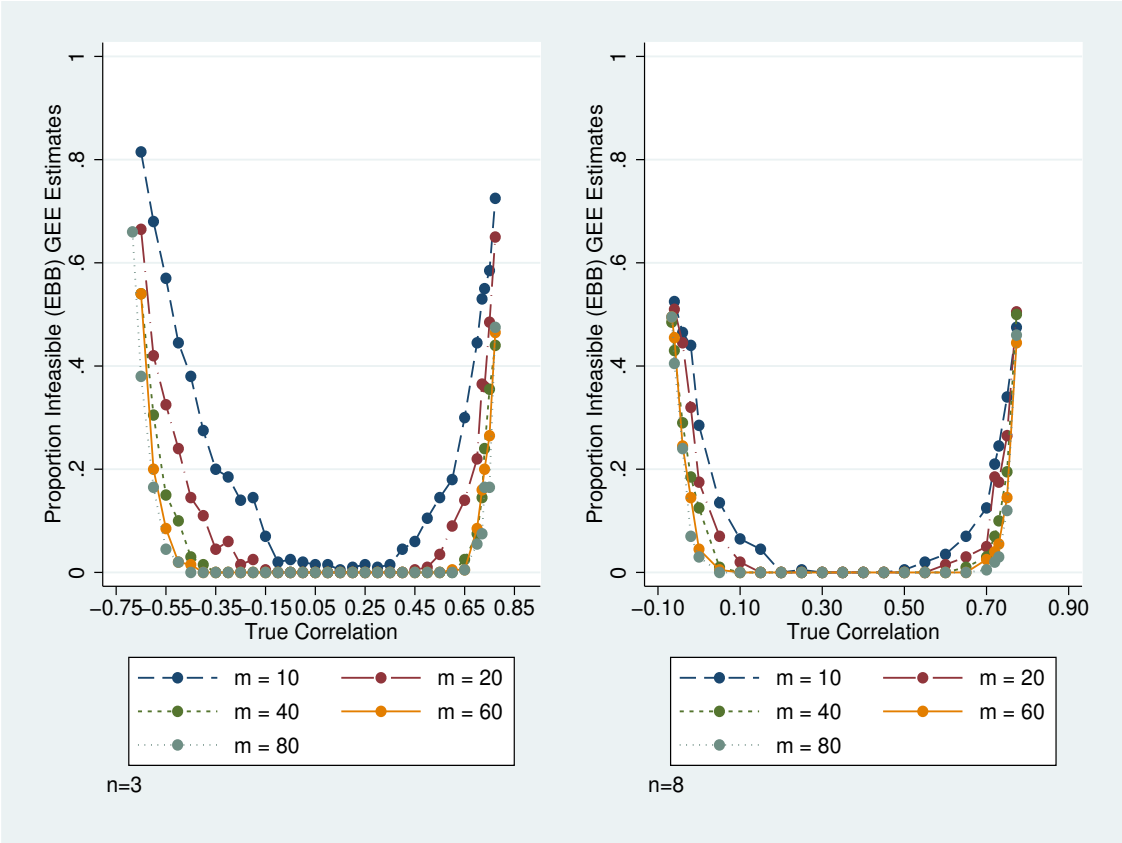

Figure 1. *Proportion of infeasible (EBB) estimates versus the true correlation for GEE;* β *=*$(0.6707,\ 0.4753,\ -0.2273,\ -0.2850)'$*; the true correlation structure is correctly specified as AR(1) with* $n_i = 3\ \forall\ i$ *(left);* $n_i = 8\ \forall\ i$ *(right); and the number of subjects per group is* $m = 10,\ 20,\ 40,\ 60,$ *and* 80.

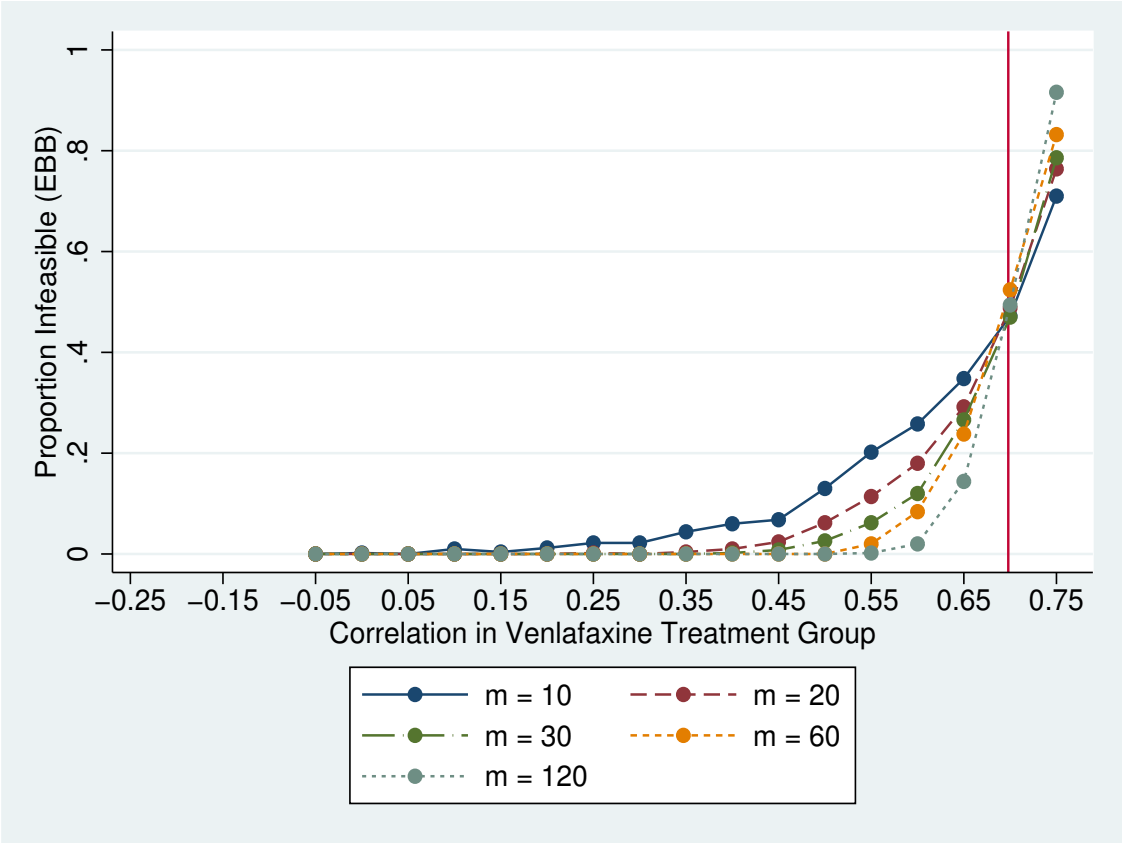

Figure 2. *Proportion of infeasible (EBB) estimates of* $\hat{\alpha}_{QLS}$ *versus* ρ_V *when the correlation is incorrectly assumed to be equal in the treatment groups;* $\rho_L = 0.85$; $\beta = (0.6707, 0.4753, -0.2273, -0.2850)'$; *the true correlation structure is AR(1) with* $n_i = 8$ $\forall$ *i; and the number of subjects per group is* $m = 10$, 20, 30, 60, and 120.

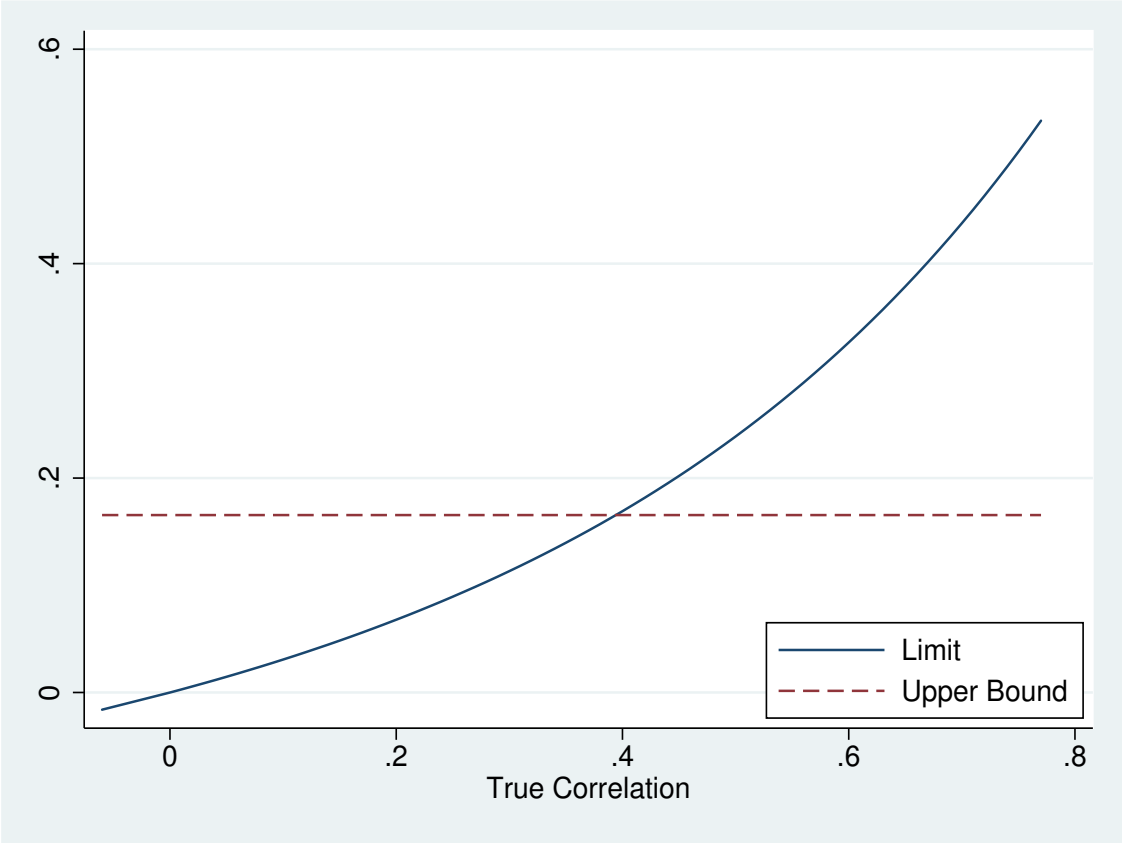

Figure 3. *Limiting value of $\hat{\alpha}_{QLS}$ versus the true correlation when the AR(1) structure is misspecified as EQC in the Venlafoxine Study; the upper bound in (L_{EQC}, U_{EQC}) is displayed as a horizontal line.*

Table 1

Simulation Results

Design			Bias				MSE			
m	n	α	GEE	QLS	IND	MID	GEE	QLS	IND	MID
					Estimation of α					
10	8	.6	-0.0461	-0.0479	-0.6000	-0.5597	0.0114	0.0114	0.3600	0.3141
20	8	.6	-0.0209	-0.0218	-0.6000	-0.5531	0.0050	0.0050	0.3600	0.3065
30	8	.6	-0.0113	-0.0120	-0.6000	-0.5518	0.0027	0.0027	0.3600	0.3049
60	8	.6	-0.0049	-0.0051	-0.6000	-0.5508	0.0013	0.0013	0.3600	0.3035
80	8	.6	-0.0032	-0.0034	-0.6000	-0.5508	0.0009	0.0009	0.3600	0.3035
					Estimation of α					
10	8	.75	-0.0202	-0.0231	-0.7500	-0.7121	0.0110	0.0111	0.5625	0.5080
20	8	.75	-0.0192	-0.0208	-0.7500	-0.7070	0.0030	0.0030	0.5625	0.5003
30	8	.75	-0.0084	-0.0094	-0.7500	-0.7030	0.0016	0.0016	0.5625	0.4946
60	8	.75	-0.0044	-0.0048	-0.7500	-0.7023	0.0007	0.0007	0.5625	0.4934
80	8	.75	-0.0027	-0.0030	-0.7500	-0.7014	0.0005	0.0005	0.5625	0.4922
					Estimation of $P(Y_{i4}=1, Y_{i8}=1)$ *for Lithium group*					
10	8	.6	0.0034	0.0030	-0.0191	-0.0186	0.0060	0.0059	0.0054	0.0055
20	8	.6	0.0033	0.0031	-0.0220	-0.0219	0.0028	0.0028	0.0027	0.0028
30	8	.6	0.0009	0.0008	-0.0251	-0.0248	0.0019	0.0019	0.0022	0.0023
60	8	.6	0.0037	0.0036	-0.0235	-0.0235	0.0011	0.0011	0.0014	0.0014
80	8	.6	0.0018	0.0017	-0.0254	-0.0255	0.0007	0.0007	0.0013	0.0013
					Estimation of $P(Y_{i4}=1, Y_{i8}=1)$ *for Lithium group*					
10	8	.75	-0.0014	-0.0025	-0.0558	-0.0550	0.0090	0.0089	0.0096	0.0099
20	8	.75	-0.0021	-0.0026	-0.0622	-0.0615	0.0047	0.0047	0.0070	0.0072
30	8	.75	-0.0014	-0.0018	-0.0650	-0.0642	0.0033	0.0033	0.0064	0.0064
60	8	.75	0.0008	0.0007	-0.0647	-0.0644	0.0016	0.0016	0.0052	0.0052
80	8	.75	-0.0000	-0.0001	-0.0659	-0.0659	0.0013	0.0013	0.0052	0.0052

Table 2

Analysis of Venlafaxine versus Lithium: $\hat{\alpha}$ and bounds (EBB); Rotnizky-Jewell informal goodness of fit measures (c_1, c_2, and d); and estimated regression parameters with standard errors (Std.Err.) and p-values for the tests of H_o: $\beta_j = 0$; $P(0,1)_{Ven}$ and $P(0,1)_{Lithium} = P(Y_{i4} = 0, Y_{i8} = 1)$ for subjects treated with Venlafaxine and Lithium, respectively; Approaches used include GEE with EQC (GEE/EQC) or AR(1) (GEE/AR(1)) structures; QLS with EQC (QLS/EQC) or AR(1) (QLS/AR(1)) structures; and GEE with working independence (IND).

	QLS/EQC	GEE/EQC	QLS/AR(1)	GEE/AR(1)	GEE/IND
$\hat{\alpha}$	0.4177	0.4013	0.5678	0.5684	0
Bounds (EBB)	(-.0475,.1674)	(-.0489,.1686)	(-.0674,.7740)	(-.0674,.7740)	NA
c_1	1.8074	1.7756	1.1719	1.1712	2.5723
c_2	4.4756	4.2321	1.5907	1.5886	8.2379
d	1.8608	1.6810	0.2468	0.2461	4.0933
gof	NA	NA	159.11	159.12	313.88
$\hat{\beta}_0$	0.6875	0.6884	0.6707	0.6708	0.6589
$Std.Err.(\hat{\beta}_0)$	0.4224	0.4227	0.4205	0.4205	0.4489
$p-value$	0.104	0.103	0.111	0.111	0.142
$\hat{\beta}_1$	0.0962	0.1086	0.4753	0.4755	0.3233
$Std.Err.(\hat{\beta}_1)$	0.6365	0.6320	0.5971	0.5971	0.6042
$p-value$	0.880	0.864	0.426	0.426	0.593
$\hat{\beta}_2$	-0.2686	-0.2680	-0.2273	-0.2273	-0.2381
$Std.Err.(\hat{\beta}_2)$	0.0929	0.0928	0.0892	0.0892	0.1025
$p-value$	0.004	0.004	0.011	0.011	0.020
$\hat{\beta}_3$	-0.2421	-0.2407	-0.2850	-0.2850	-0.2469
$Std.Err.(\hat{\beta}_3)$	0.1879	0.1860	0.1672	0.1672	0.1679
$p-value$	0.198	0.196	0.088	0.088	0.141
$\hat{P}(0,1)_{Ven}$	-0.0044	-0.0031	0.0251	0.0250	0.0378
$\hat{P}(0,1)_{Lithium}$	0.0320	0.0353	0.1127	0.1126	0.1280