Multiple testing corrections for p-values and confidence intervals from generalised linear mixed models

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Abstract. In this article, we describe and propose methods to derive p-values and sets of confidence intervals with strong control of the family-wise error rates and coverage for tests of parameters from multiple generalised linear mixed models. We examine in particular analysis of a cluster randomised trial with multiple outcomes. While the need for corrections for multiple testing is debated, the justification for doing so is that, without correction, the probability of rejecting at least one of a set of null hypotheses is greater than the nominal rate of any single test, and hence the coverage of a confidence set is lower than the nominal rate of any single interval. There are few methods p-value corrections for GLMMs and no efficient methods for deriving confidence intervals, limiting their application in this setting. We adapt the Bonferroni and Holm methods, and the randomisation-test approach of Romano & Wolf (2005) to a generalised linear model framework. A search procedure for confidence interval limits using randomisation tests is developed to produce a set of confidence intervals under each method of correction. We show that the Romano-Wolf type procedure has nominal error rates and coverage under non-independent correlation structures in a simulation-based study, but the other methods only have nominal rates when outcomes are independent. We also compare results from the analysis of a real-world trial.

Key words and phrases: GLMM, Cluster trial, Multiple testing.

1. INTRODUCTION

We describe in this article methods to efficiently derive p-values and sets of confidence intervals with strong control of the family-wise error rates (FWER) and family-wise coverage for tests of parameters from multiple generalised linear mixed models (GLMM). We frame our discussion around randomised trials where the issue is a point of frequent debate, and in particular examine analyses of cluster trials with multiple outcomes, which typically use GLMMs. However, the issue pertains to any analysis where these models are routinely used, for example, in genomics.[33, 19] For a randomised controlled trials, the requirement to state a single primary outcome has become accepted, even required, practice. For example, the influential CONSORT statement on clinical trials requires the pre-specification of a single primary outcome, which they describe as the “outcome considered to be of greatest importance to relevant stakeholders”, and recommends against multiple primary outcomes.[32] The reason for this is to ensure appropriate control of the ‘false discovery rate’ when using null hypothesis significance testing.[34] If there are multiple outcomes each with their own associated treatment effect being tested separately, then we are implicitly testing a family of null hypotheses against an alternative that at least one of them is false. Without correction, the type I error rate for this family of null hypotheses will be much greater than the nominal rate of any single test.[27] Indeed, the CONSORT statement notes that that multiple primary outcomes are not recommended as it “incurs the problem of multiplicity of analyses”.[21] Cluster randomised trials are a widely used method to evaluate interventions applied to groups of people, such as clinics, schools, or villages. Often these interventions...
target ‘higher level’ processes and can be complex in nature.[25, 16, 6] Recent examples from our own work include an incentive scheme to improve implementation of a broad package of education and activities designed to improve employee health in the workplace,[1] or a community health worker programme targeting multiple health conditions.[5] The effects of such complex interventions cannot be adequately summarised by a single outcome. Creating a composite outcome is undesirable since it requires applications of arbitrary weights across outcomes and discards information by collapsing a multivariate outcome to a univariate one. The requirement for a single primary outcome therefore clashes with the needs of many cluster randomised trials. The solution is to ensure appropriate methods are used where there are multiple outcomes of interest rather than restricting the outcomes from which we can make inferences. However, the question of appropriate analysis for randomised trials, and particularly cluster randomised trials, with multiple outcomes can be contentious and complex.

The Food and Drug Administration (FDA), the main regulatory body for medicines in the United States, declares that “If the purpose of the trial is to demonstrate effectiveness on all of the designated primary variables, then there is no need for adjustment of the type I error”. They also identify a “gatekeeping” approach where “statistical significance” on a primary outcome is required before a second one can be analysed and state this does not need correction for multiple testing. However, in both cases, the type I error across the two (or more) outcomes jointly may not be nominal with this procedure and their validity is debatable. Other authors differentiate aiming to declare “statistical significance” on at least one of a group of null hypotheses to requiring statistical significance for all tests in order to reject any individual test, and propose different solutions for both.[20, 30]

Where a correction for multiple testing is deemed necessary, we can divide solutions into: (i) multivariate methods that model the joint distribution of the outcomes, which is particularly favoured by Bayesian practitioners;[13] and (ii) univariate solutions that aim to ensure inferential statistics for a set of estimands collectively have the appropriate Frequentist properties.[7] Despite the different approaches and guidance, Wason et al.[34] estimated that only around half of all randomised trials with multiple outcomes or arms corrected for multiple testing. No evidence is available on the use of corrections for multiple testing in cluster randomised trials specifically, but there are few, if any, comprehensive discussions of methods in this area currently available. Furthermore, almost all discussion of multiple testing adjustment relates to corrections for p-values, with few, if any, solutions for confidence intervals. The FDA note that correcting confidence intervals is complex and beyond the scope of their advice. However, the duality between hypothesis testing and confidence intervals means that we should be able to identify the bounds of a ‘confidence set’ adjusted for multiple testing.[27, 28] The primary limiting factor to using corrected confidence intervals is that there are no proposed methods for determining these bounds efficiently.

This article adapts and evaluates univariate methods for the use of multiple primary outcomes in cluster randomised trials. We do not aim to resolve the debate about the necessity of these methods, rather to propose how these methods can be used in cluster trials with multiple outcomes. We then extend these methods to present a novel method for efficiently determining confidence sets with nominal coverage for multiple outcomes.

2. FAMILY WISE ERROR RATES

2.1 The multiple testing problem

We first suppose that data X are generated from some probability distribution P, which belongs to some family of probability distributions Ω. The family Ω could be a parametric, semi-parametric, or non-parametric model. The multiple testing problem arises when we have a set of hypotheses Hj versus Hy for j = 1, ..., J, following the notation of Romano and Wolf.[27] Each of these hypotheses is a subset ωj ⊂ Ω and is equivalent to testing P ∈ ωj against P /∈ ωj. So for any subset K ⊂ 1, ..., J, H_K = ∩_{j ∈ K} H_j is the hypothesis that P ∈ ∩_{j ∈ K} ω_j. We assume each null hypothesis H_j is based on a test statistic T_j; we denote the α-quantile of the distribution of T_j as c_j(α, P). In a traditional null hypothesis testing framework we “reject” H_j in favour of H_y at the α level, if T_j ≥ c_j(1 − α, P), which clearly has probability α. Conversely, the p-value p_j of the test is where T_j = c_j(1 − p_j, P), so that the probability of observing Pr(T_j > c_j(1 − p_j, P)|H_j) = p_j. The family-wise error rate (FWER) of this set of hypotheses is the probability of “rejecting” at least one true null hypothesis. That is, if I(I(P) ⊂ 1, ..., J) are the indices of the true null hypotheses, so j ∈ I if and only if P ∈ ω_j, then the FWER is the probability under P of rejecting any H_j∈I, i.e. Pr(∪_{j∈I} T_j > c_j(1 − α, P)), which should be α.

2.2 Corrections for multiple testing

Solutions to the multiple testing problem aim to ensure that FWER ≤ α. Control over the FWER is said to be strong if it holds for any combination of true and false null hypotheses, and weak if it only holds when all null hypotheses are true.[4] Several approaches exist to control the FWER. The Bonferroni method is probably most well known, which sets the critical value for the test of the null hypothesis to be c_j(1 − α/J, P). Equivalently, p-values that maintain the FWER for the family of null hypotheses ensure that Pr(∪_{j∈I} T_j > c_j(1 − P)) = p, so a
crude ‘corrected’ p-value for the null hypothesis \( H_j \) using
the Bonferroni method would be \( \min(J_p, 1) \). However,
while this method exerts strong control over the FWER. It
is very conservative and assumes no correlation between
the test statistics.

Holm[17] proposed a less conservative ‘stepdown’ approach
to multiple testing. One orders the test statistics
from largest to smallest and then compares the largest
statistic to the critical value \( c_j(1 - \alpha / J, P) \). If the test
statistic is larger than this value, then the null hypothesis
is rejected, otherwise we do not reject any null hypothesis
and stop. If we rejected, then the next largest test statistic
is compared to \( c_j(1 - \alpha / (J - 1), P) \), and again it is
either rejected, or we do not reject any remaining null
hypotheses and stop, and so forth. A crude corrected p-value
could therefore be obtained by multiplying the smallest
to the largest p-values by \( J, J - 1 \), etc, respectively. The
stepdown method is less conservative than the Bonferroni
method,[17] but it can still be conservative as it does not
take into account the dependence structure in the data.

2.3 Randomisation test based corrections for
multiple testing

An issue that complicates analyses of cluster ran-
domised trials is that test statistics can fail to have the
expected sampling distribution in a range of circum-
stances, but particularly when the number of clusters is
small.[24, 35, 23, 22] This issue means determining the
critical value of a hypothesis test, even in the absence of
small.[24, 35, 23, 22] This issue means determining the
expected sampling distribution in a range of circum-
stances, but particularly when the number of clusters is
small.

An alternative approach is to use a randomisation test-
ing method. In particular, the null hypothesis implies that
the distribution of the data \( X \) is invariant under a set of
transformations in \( A \), which has \( L \) elements. So, \( aX \) and
\( X \) have the same distribution for all \( a \in A \) whenever \( X 
has distribution \( P \in \omega \). Our observed test statistics with
our sample data are \( T_j(X) \). The test statistic generated by
the \( l \)th permutation is \( T_j(a_l X) \) for \( a_l \in A \) and \( l = 1, ..., L \).
We can use this approach to estimate the critical values
for the Bonferroni or Holm corrections. For example, for
Bonferroni:

\[
\hat{c}_j(1 - \alpha / J, P) = T_{\hat{c}_j|L(1-\alpha/J)}
\]

where \( T_{\hat{c}_j|L(1-\alpha)} \) is the \( L(1-\alpha) \)th (or nearest integer)
largest value from the permutations. And a crude, cor-
corrected two-sided p-value is:

\[
p_j = \min \left( \frac{J}{L} \sum_{l=1}^{L} \mathbb{1}[|T_j(a_l X)| \geq |T_j(X)|], 1 \right)
\]

where \( \mathbb{1} \) is the indicator function. The same approach
can be used for the Holm Stepdown correction, however, these
methods remain conservative.

Romano and Wolf[27, 28] developed an efficient re-
sampling based version of the stepdown method. Their
process is optimal in a maximin sense. We describe the
general stepdown procedure of Romano and Wolf firstly
in terms of accepting or rejecting each null hypothesis at
an \( \alpha \)-level. We let \( \hat{c}_K(\alpha, P) \) denote an \( \alpha \)-quantile of
the distribution of the statistic:

\[
T_K = \max_{j \in K} T_j
\]
for any subset of null hypotheses \( K \). We also denote \( T_r \)
as the \( r \)th largest test statistic so that

\[
T_{\lfloor r \rfloor} \geq T_{\lceil r \rceil} \geq \ldots \geq T_{\lfloor J \rfloor}
\]
corresponding to hypotheses \( H_{\lfloor r \rfloor}, H_{\lceil r \rceil}, \ldots, H_{\lfloor J \rfloor} \). Then the
idealised algorithm is:

1. Let \( K_1 = 1, \ldots, J \). If \( T_{\lfloor r \rfloor} \leq c_{K_1}(1 - \alpha, P) \) then ac-
ccept all hypotheses and stop; otherwise, reject \( H_{\lfloor r \rfloor} \) and
continue;
2. Let \( K_2 \) be the indices of all the hypotheses not pre-
niously rejected. If \( T_{\lceil r \rceil} \leq c_{K_2}(1 - \alpha, P) \), then ac-
ccept all remaining hypotheses and stop; otherwise, reject
\( H_{\lfloor r \rfloor} \) and continue;
3. 
   \( J \). If \( T_{\lfloor r \rfloor} \leq c_{K_J}(1 - \alpha, P) \) then do not reject \( H_{\lfloor r \rfloor} \), oth-
erwise reject.

In this procedure it is assumed the critical values are
known. However, as before, they can be replaced by esti-
mates from randomisation tests.

For each permutation we can determine the test statistic
as in Equation (3) as \( T_{K,l} = \max_{j \in K} T_j(a_l X) \). As before
we denote \( T_{K,\lfloor r \rfloor} \) as the \( r \)th largest of all the permutational
test statistics \( \{T_{K,l}: l = 1, \ldots, L\} \). Then our estimator for
the critical value is:

\[
\hat{c}_K(1 - \alpha, P) = T_{K,\lfloor L(1-\alpha) \rfloor}
\]

We can see how this procedure produces p-values for a
two-sided hypothesis that also maintains the FWER for a
given \( \alpha \) [29]

\[
p_K = \frac{1}{L} \sum_{l=1}^{L} \mathbb{1}[|T_{K,\lfloor l \rfloor}(a_l X)| \geq |T_K(X)|]
\]
For a one-sided test we would not use the absolute values
of the test statistics.

Often the size of \( A \) can be very large, and increases ex-
ponentially with the number of clusters. A Monte Carlo
approach can be used that instead generates a random sub-
set of \( A \) of fixed sized in order to generate realisations
of the test statistics. If we conduct \( M \) such permutations
then the estimator of the p-value for a given null hypo-
thesis versus some alternative is

\[
\hat{p}_K = \frac{1}{M + 1} \sum_{m=1}^{M} (1 + 1[T(a_m X) \leq T(X)])
\]
Obtaining p-values in this way is described in detail by Romano.[29]

The preceding section is not an exhaustive review of all univariate multiple testing corrections, however the application of other methods in the context we describe below should be clear from the discussion of these four key approaches. Other methods for controlling the FWER have been proposed, which are surveyed elsewhere.[7]

3. RANDOMISATION TESTS FOR CLUSTER TRIALS

We next introduce a generalised linear mixed model commonly used in the analysis of cluster randomised trials (e.g.[18]). We denote $Y_{ict}$ as the outcome of the $i$th individual, $i = 1,...,N$, in cluster $c = 1,...,C$ at time $t = 1,...,T$. We do not restrict the outcome, it could be continuous or discrete. We specify the linear predictor:

$$\eta_{ict} = \mu_0 + \delta D_{ct} + X_{ict}'\beta + \theta_{ct}$$

where $D_{ct}$ is an indicator for whether cluster $c$ has received the intervention at time $t$ and so $\delta$ is the parameter of interest, our “treatment effect”. We also have a vector of individual and/or cluster-level covariates, $X_{ict}$, which may also contain temporal fixed effects. The parameter $\theta_{ct}$ represents a general ‘random-effect’ term that captures the within cluster and cluster-time correlation, although we do not provide a specific structure here. The overall model is then

$$Y_{ict} \sim P(h(\eta_{ict}))$$

where $h(.)$ is a link function. For example, $P$ could be a Binomial distribution and $h(.)$ the logistic link function.

Gail et al.[9] provided the first extensive examination of permutation tests for cluster-based study designs. Their work principally used unweighted differences of cluster means as the basis of permutation tests. In particular, if $\bar{Y}_{ct} = \sum_i Y_{ict}$ then one can base inference on the mean difference:

$$U = \frac{1}{C} \sum_c \left( \bar{Y}_{ct} D_{ct} - \bar{Y}_{ct} (1 - D_{ct}) \right)$$

Under the null hypothesis that $H_0 : U = 0$ the clusters are exchangeable, so we can re-assign them to a new allocation $a \in A$. In this way critical values of the distribution of $U$ under this null, or associated p-values, can be generated. This statistic is the basis of a statistical package for inference from stepped-wedge cluster randomised trials using randomisation tests (cptest[10]). The authors of that package also implement a “within-period” version of the analysis which takes estimates “within period” treatment effects as:

$$U_t = \frac{1}{C} \sum_c (\bar{Y}_{ct} D_{ct} - \bar{Y}_{ct} (1 - D_{ct}))$$

and then takes a weighted average of them based on the number of clusters in treatment and control conditions in each time period. One can extend these ideas to allow for covariate adjustment.[9]

Braun and Feng[3] examine optimal permutation tests for cluster randomised trials. The test statistics they consider are weighted sums of residuals. In particular, they consider a score-based statistic derived from the marginal means of the observations modelled separately from the correlation structure of the data. The mean of each observation is

$$h^{-1}(\mu_{ict}) = \mu_0 + \delta D_{ct} + X_{ict}'\beta$$

which is devoid of the of the cluster effect $\theta_{ct}$. The “quasi-score” statistic is then:

$$\sum_c \{D_{ct}'G_c V_c^{-1}[Y_{ict} - \mu_{ict}]\}_| = \delta^*$$

where $D_{ct}'[D_{c1t}, D_{c2t}, ..., D_{cNt}, D_{cTt}']$ is a $(1 \times n_c)$ vector of modified intervention indicators equal to 1 if the intervention was present in cluster $c$ at time $t$ and -1 otherwise, and where $n_c = \sum_i n_{ct}$ and $n_{ct}$ is the number of individuals in cluster $c$ at time $t$. $G_c$ is a $(1 \times n_c)$ vector with elements $(\partial h^{-1}_c/\partial \eta_{ict})^{-1}$, and $V_c$ is an $(n_c \times n_c)$ covariance matrix for cluster $c$ with non-zero elements off its diagonal. As an example, if we assume the data are normally distributed with mean given by Equation (8), identity link function, variance $\sigma^2$, and $\theta_{ct} \sim N(0, \tau^2)$, then the diagonal elements of $V_c$ are $\sigma^2 + \tau^2$ and the off-diagonal elements are $\tau^2$. More complex structures might include temporal decay in correlation, for example. We use $\Theta$ to represent the parameters of the variance-covariance matrix. Finally $[Y_c - \mu_c]$ represents generalised residuals: $Y_c = [Y_{1ct}, Y_{2ct}, ..., Y_{nct}, Y_{1ct}, Y_{2ct}, ..., Y_{nct}]$ is a $(1 \times n_c)$ vector of outcomes and $\mu_c$ is a $(1 \times n_c)$ vector of means.

For the permutation test to be valid the ‘nuisance’ parameters ($\mu, \beta, \Theta$), i.e. those other than $\delta$, must be invariant to permutation.[3] This means we cannot re-estimate them for each new permutation. In practice the maximum likelihood estimates of these parameters are used to construct the test statistic, so that we use the estimates:

$$\hat{\mu}_{ict} = h(\hat{\mu}_0 + \delta^* D_{ct} + X_{ict}'\hat{\beta})$$

for the linear predictor under the null $H_0 : \delta = \delta^*$. Estimating $\Theta$ is more difficult, however, particularly when the number of clusters is small.[24, 35] As an alternative to (13) we can replace $G_c V_c^{-1}$ with a $(1 \times n_c)$ vector of ones $1_c$:

$$\sum_c \sum_t \{D_{ct}'1_c[Y_{ict} - \mu_{ict}]\}_| = \delta^*$$

so that the sum of residuals is weighted only by the size of each cluster or cluster-time period. Braun and Feng[3]
provide proof of the optimality of the quasi-score in Equation (13) in the context of a single hypothesis test; the second test in Equation (15) is likely to be suboptimal if there is a (strong) dependence structure in the data. Nevertheless, in simulation-based experiments, they show both have nominal or near-nominal type I error rates for various levels of intra-cluster correlation.

For the purposes of correcting for multiple testing we use a studentized version of Equation (15):

\[
T(X)_{\delta=\delta_0} = \frac{\sum_{\alpha} \sum_{\delta} \sum_{\delta_i} \{ D_{\alpha i} \delta_{\alpha i} [ Y_{\alpha i} - \mu_{\alpha i} ] \}}{\sum_{\alpha} \sum_{\delta} \sum_{\delta_i} \{ D_{\alpha i} \delta_{\alpha i} [ Y_{\alpha i} - \mu_{\alpha i} ] \}}^2
\]

where the terms on the right-hand side have been evaluated at \( \delta = \delta^* \). In the absence of studentization, the variances of the test statistics are not scale-free and depend on, among other things, the null hypothesis being tested so that different tests will have different power under stepdown testing.[27] The lack of balance is particularly consequential for the construction of confidence sets discussed in the next section. While confidence sets constructed on the basis of stepdown methods will have joint coverage of \( 1 - \alpha \), without balance the individual coverage probabilities of each interval will differ, perhaps substantially.[28]

The test statistic described in this section can be used with the stepdown procedure to provide a basis for generating \( p \)-values for multiple hypothesis tests across multiple outcomes with a nominal FWER. However, a point estimate and \( p \)-value is often not considered sufficient for providing inferences from trials. The \( p \)-value can provide relatively little indication of the magnitude of sampling variation associated with a particular parameter, and often confidence intervals are expected or required.

### 4. CONFIDENCE SETS AND MULTIPLE TESTING

The multiple testing problem extends to the construction of simultaneous confidence intervals or a “confidence set”. Let the parameters of interest be \( \delta_j \) with associated confidence intervals \([L_j, U_j]\), so that \([L_1, U_1] \times [L_2, U_2] \times \ldots \times [L_J, U_J]\) forms a confidence set. Similar to the FWER, we want appropriate control of the coverage of the 100(1 - \( \alpha \))% confidence set such that the process produces confidence sets with the property:

\[
Pr(\cup_j \delta_j \in [L_j, U_j]) = 1 - \alpha
\]

we refer to this as ‘family-wise coverage’. If we construct 100(1 - \( \alpha \))% confidence intervals independently then the probability that at least one interval in the set excludes the true value can significantly exceed \( \alpha \). There have been some attempts to construct exact confidence sets for parameters based on the stepdown procedure.[28] For example, Guiltbald,[14] extending the proposal of Hayter and Hsu,[15] uses the acceptance/rejection of null hypotheses by the stepdown procedure as a basis of determining upper or lower limits of confidence intervals if we conclude they are strictly negative or positive, respectively. However, these procedures can only provide information on the upper or lower bound respectively - the other end of the interval is infinity - so they provide little extra information on the extent of sampling variation beyond the \( p \)-value.

As an alternative, consider for a moment, a single parameter \( \delta_1 \). Its 100(1 - \( \alpha \))% confidence interval is \([L_1, U_1]\); for any value \( \delta^*_1 \) inside this interval the null hypothesis \( H_1' : \delta_1 = \delta^*_1 \) will not be rejected in favour of the two-sided alternative \( H_1 : \delta_1 \neq \delta^*_1 \) at the \( \alpha \) level. The question is then how to find the values of \( L_1 \) and \( U_1 \) efficiently. As suggested by Braun and Feng,[3] one could iteratively perform a series of permutation tests to identify the limits as \( U_1 = \sup \{ \delta^*_1 : \text{do not reject } H_1' : \delta_1 = \delta^*_1 \} \) and \( L_1 = \inf \{ \delta^*_1 : \text{do not reject } H_1' : \delta_1 = \delta^*_1 \} \). However, this procedure is inefficient, particularly when testing multiple parameters: if there are \( M \) permutations per test and \( J \) outcomes, then for each increment in \( U \) we must calculate \( JM \) permutation test statistics and perform the stepdown procedure. Moreover, since the test statistic and its randomisation distribution depends on the values of the other null hypotheses being tested, a very large number of combinations of values of the parameters must be tested to ensure we have identified with reasonable certainty the limits of the confidence set.

Garthwaite and Buckland[11] developed a method for searching for confidence interval endpoints efficiently, which Garthwaite[12] later adapted for use with randomisation tests. Their method is based on the search process devised by Robbins and Munro,[26] who developed a stochastic approximation procedure to find the \( \alpha \)-quantile of a particular distribution. Multivariate Robbins-Monro processes follow the same procedures as their univariate equivalents.[31] For our multiple testing scenario the upper limits to the confidence set correspond to where all hypotheses \( H_j : \theta_j = U_j \) for \( j = 1, ..., J \) are all rejected in favour of the two-sided alternative with a FWER of \( \alpha \) but for any smaller values of \( U_j \) not all hypotheses are rejected, and equivalently for the lower limits.

We describe the method initially based on the Romano-Wolf stepdown procedure, as it is explicitly a randomisation test based approach. However, we also show how the method proposed here can be used to derive confidence intervals for other multiple testing corrections.

Returning to Equation 2 and following the logic of the stepdown procedure, if the FWER rate for this family of hypotheses is preserved then \( Pr(\{ |T_{K_\alpha}(aX)| \geq |T_{[j]}(X)| \}) = \alpha \) (and equivalently \( Pr(\{ |T_{K_\alpha}(aX)| < |T_{[j]}(X)| \}) = 1 - \alpha \) where \( T_{K_\alpha}(aX) \) is the largest of the permutational test statistic corresponding to the hypotheses \( H_{[j]} \) to \( H_{[j]} \). This provides a probabilistic basis for the search procedure based on single iterations of a randomisation test. 
At the $q$th step of $Q$ steps total, we have estimates of the upper confidence interval limits of our $J$ parameters $u_q = [u_{1q}, u_{2q}, \ldots, u_{Jq}]$. We generate the set of test statistics $T_j(X)|_{\delta = u_q}$, which correspond to the null hypotheses $H_j : \delta_j = u_{jq}$. We then generate a single permutation of a randomisation test for the same hypotheses $|T_j(a_qX)|_{\delta = u_q}$. The probability that $|T_j(a_qX)|_{\delta = u_q}$ is less than $|T_j(X)|_{\delta = u_q}$ is $\alpha$. The estimates of the upper limits are then updated as (we drop the subscript $\delta = u_{jq}$ for ease of notation, but the test statistics are evaluated at this value for each iteration):

\begin{equation}
\begin{aligned}
&u_{j,q+1} = \begin{cases} 
  u_{jq} - s_j\alpha/q & \text{if } |T_{K_j}(a_qX)| < |T_{[j]}(X)| \\
  u_{jq} + s_j(1 - \alpha)/q & \text{if } |T_{K_j}(a_qX)| \geq |T_{[j]}(X)|
\end{cases}
\end{aligned}
\end{equation}

where $s_j$ is the "step length constant". The mean increment of each estimate at each step is $\alpha q s_j(1 - \alpha)/q - (1 - \alpha) s_j \alpha/q = s_j(\alpha - \alpha)/q$ so that it is clear that each step reduces the expected distance from $U_j$. Similarly for the lower limits, the updating rule is:

\begin{equation}
\begin{aligned}
&l_{j,q+1} = \begin{cases} 
  l_{jq} + s_j\alpha/q & \text{if } |T_{K_j}(a_qX)| < |T_{[j]}(X)| \\
  l_{jq} - s_j(1 - \alpha)/i & \text{if } |T_{K_j}(a_qX)| \geq |T_{[j]}(X)|
\end{cases}
\end{aligned}
\end{equation}

The step length constants are $s_j = k(u_{jq} - \hat{\theta}_j)$ and $s_j = k(\theta_j - l_{jq})$ for the upper and lower limits, respectively, where $\hat{\theta}_j$ is a point estimate of the parameter and:

\begin{equation}
\begin{aligned}
k &= \frac{2}{z_1 - \alpha(2\pi)^{-1/2}\exp(-z_1^2/2)}
\end{aligned}
\end{equation}

where $z_\alpha$ is the $\alpha$-quantile of the standard normal distribution. Under relatively weak regularity conditions this process converges in probability to the correct confidence limits as $l \rightarrow \infty$ [11, 31].

The method described here can be used to generate confidence sets for the other methods of correcting for multiple testing. In particular, for the Bonferroni and Holm methods we modify the value of $\alpha$ in the updating of the estimates of the bounds, and use the test statistics for each test respectively. For example, for Bonferroni, the upper limits would be updated as:

\begin{equation}
\begin{aligned}
&u_{j,q+1} = \begin{cases} 
  u_{jq} - s_j\alpha/Jq & \text{if } |T_j(a_qX)| < |T_j(X)| \\
  u_{jq} + s_j(1 - \alpha)/Jq & \text{if } |T_j(a_qX)| \geq |T_j(X)|
\end{cases}
\end{aligned}
\end{equation}

the step length $k$ would similarly modify $\alpha$, and we would equivalently modify the procedure for the lower bound. For the Holm method the value of $\alpha$ would be divided by $J$ for the $j$ with the largest test statistic, by $J - 1$ for the next largest, and so forth.

### 4.1 Computation

An R package to execute the analyses described in this paper is available from CRAN as crctStepdown including implementations of the Romano-Wolf, Holm, and Bonferroni methods for correcting p-values and confidence sets using randomisation-based tests.
For the three-outcome simulation we increase the variance to 0.05. The FWER also depends on the correlation between outcomes. For a design in which the treatment is assigned at cluster level, it is the correlation between cluster means via the random effect terms, that has this effect. So we also compare estimates from simulations where the cluster-level random effects are not correlated ($\rho = 0$) to those where there is a high degree of correlation ($\rho = 0.5$).

### 5.1 Simulation methods and evaluation

Each set of simulations is run 10,000 times. We note the Monte Carlo error will be moderately higher than expected due to variation arising from the randomisation tests, confidence set search procedure, and simulations. We use 1,000 iterations for the randomisation test $p$-values and 2,000 steps for the search procedure as these produced stable values for these simulations (although we note that for more outcomes longer runs were often required for the confidence interval search procedure for it to reach a stable equilibrium). However increasing the number of iterations was deemed infeasible as the reported set of simulations took one month to run. We estimate the FWER for $p \leq 0.05$, which has a nominal rate of 5%, and also estimate coverage of 95% confidence sets. To conduct the simulations we used the R package `crtStepdown` described above.

### 5.2 Results

Table 1 reports the results from the two outcome trial simulations. Under all tested conditions the FWER (for $p \leq 0.05$) and coverage (95%) were approximately nominal in all scenarios under the Romano-Wolf procedure. Figure 1 shows an example of the confidence interval search procedure. The Bonferroni and Holm methods also provided approximately nominal FWER and coverage when all parameters of interest were zero; they were conservative when at least one of the parameters was not zero. The Bonferroni procedure was more conservative than the Holm method, as expected. Without any correction, and in the absence of between-outcome correlation, the FWER was around $J \alpha$ as expected. Using the naive output from `lme4` resulted in even worse performance due to the small sample bias in the test statistics, also as expected [22, 35], with FWER around 30-50% higher. We note that the cluster level variance was small such that the correlation had little effect in these examples. Table 2 reports the results from the two outcome trial simulations with a larger 20 clusters per arm. The same pattern is observed as the smaller two-arm experiments, but the small sample bias using the naive method is reduced. To illustrate the efficiency of the procedure, a single run of the function to derive $p$-values and confidence sets took between 10-60 seconds depending on the number of outcomes and size and number of the clusters.

| Method                  | $\rho$ | $\delta$ | FWER | Coverage |
|-------------------------|--------|----------|------|----------|
| None (naive)            | 0.0    | (0,0)    | 0.161| 0.841    |
| None (randomisation)    | 0.0    | (0,0)    | 0.103| 0.896    |
| Bonferroni              | 0.0    | (0,0)    | 0.054| 0.958    |
| Holm                    | 0.0    | (0,0)    | 0.053| 0.935    |
| Romano-Wolf             | 0.0    | (0,0)    | 0.055| 0.960    |

| Method                  | $\rho$ | $\delta$ | FWER | Coverage |
|-------------------------|--------|----------|------|----------|
| None (naive)            | 0.5    | (0,0)    | 0.158| 0.844    |
| None (randomisation)    | 0.5    | (0,0)    | 0.106| 0.899    |
| Bonferroni              | 0.5    | (0,0)    | 0.051| 0.980    |
| Holm                    | 0.5    | (0,0)    | 0.052| 0.939    |
| Romano-Wolf             | 0.5    | (0,0)    | 0.052| 0.961    |

Table 1

### Results of simulation experiments with two outcomes, seven clusters per arm, and with 10,000 iterations each. Each iteration used 1,000 permutations for the permutation test and 2,000 iterations in each of the lower and upper confidence interval search processes.

| Method                  | $\rho$ | $\delta$ | FWER | Coverage |
|-------------------------|--------|----------|------|----------|
| None (naive)            | 0.0    | (0,0)    | 0.068| 0.839    |
| None (randomisation)    | 0.0    | (0,0)    | 0.049| 0.914    |
| Bonferroni              | 0.0    | (0,0)    | 0.049| 0.942    |
| Holm                    | 0.0    | (0,0)    | 0.049| 0.942    |
| Romano-Wolf             | 0.0    | (0,0)    | 0.051| 0.964    |

| Method                  | $\rho$ | $\delta$ | FWER | Coverage |
|-------------------------|--------|----------|------|----------|
| None (naive)            | 0.5    | (0,0)    | 0.068| 0.846    |
| None (randomisation)    | 0.5    | (0,0)    | 0.050| 0.908    |
| Bonferroni              | 0.5    | (0,0)    | 0.025| 0.962    |
| Holm                    | 0.5    | (0,0)    | 0.047| 0.941    |
| Romano-Wolf             | 0.5    | (0,0)    | 0.049| 0.965    |

Table 2

### Results of simulation experiments with two outcomes, twenty clusters per arm, and with 10,000 iterations each. Each iteration used 1,000 permutations for the permutation test and 2,000 iterations in each of the lower and upper confidence interval search processes.

Table 3 shows the results from the three outcome simulations, which include a covariate and high cluster variance. Where the correlation was high all three procedures were moderately conservative: The Romano-Wolf procedure was least conservative (FWER between 3 and 5%) overall followed by Holm (3 to 5%) and then Bonferroni (1 to 3%). Where there was no correlation the Romano-Wolf procedure had nominal FWER and coverage, while the Bonferroni and Holm methods were moderately conservative when not all the parameters were zero. In all
Method | $\rho$ | $\delta$ | FWER | Coverage
--- | --- | --- | --- | ---
None (naive) | 0.0 | (0.0,0) | 0.203 | 0.800
None (randomisation) | 0.0 | (0.0,0) | 0.148 | 0.848
Bonferroni | 0.0 | (0.0,0) | 0.047 | 0.962
Holm | 0.0 | (0.0,0) | 0.048 | 0.942
Romano-Wolf | 0.0 | (0.0,0) | 0.049 | 0.954

None (naive) | 0.5 | (0.0,0) | 0.168 | 0.834
None (randomisation) | 0.5 | (0.0,0) | 0.105 | 0.896
Bonferroni | 0.5 | (0.0,0) | 0.037 | 0.972
Holm | 0.5 | (0.0,0) | 0.039 | 0.938
Romano-Wolf | 0.5 | (0.0,0) | 0.050 | 0.961

None (naive) | 0.0 | (0.0,1) | 0.144 | 0.799
None (randomisation) | 0.0 | (0.0,1) | 0.095 | 0.864
Bonferroni | 0.0 | (0.0,1) | 0.035 | 0.956
Holm | 0.0 | (0.0,1) | 0.054 | 0.918
Romano-Wolf | 0.0 | (0.0,1) | 0.049 | 0.943

None (naive) | 0.5 | (0.0,1) | 0.145 | 0.839
None (randomisation) | 0.5 | (0.0,1) | 0.083 | 0.914
Bonferroni | 0.5 | (0.0,1) | 0.030 | 0.972
Holm | 0.5 | (0.0,1) | 0.038 | 0.937
Romano-Wolf | 0.5 | (0.0,1) | 0.043 | 0.953

None (naive) | 0.0 | (0.1,1) | 0.096 | 0.802
None (randomisation) | 0.0 | (0.1,1) | 0.050 | 0.868
Bonferroni | 0.0 | (0.1,1) | 0.014 | 0.964
Holm | 0.0 | (0.1,1) | 0.041 | 0.920
Romano-Wolf | 0.0 | (0.1,1) | 0.047 | 0.948

None (naive) | 0.5 | (0.1,1) | 0.092 | 0.831
None (randomisation) | 0.5 | (0.1,1) | 0.053 | 0.902
Bonferroni | 0.5 | (0.1,1) | 0.017 | 0.978
Holm | 0.5 | (0.1,1) | 0.031 | 0.940
Romano-Wolf | 0.5 | (0.1,1) | 0.033 | 0.953

TABLE 3
Results of simulation experiments with three outcomes, seven clusters per arm, and with 10,000 iterations each. Each iteration used 1,000 permutations for the permutation test and 2,000 iterations in each of the lower and upper confidence interval search processes.

6. APPLIED EXAMPLE

To provide a real-world example of the use of the methods proposed in this article, we re-analyse a cluster randomised trial of a financial incentive to improve workplace health and wellbeing in small and medium sized enterprises (SME) in the United Kingdom. The original trial was relatively complex and included four trial arms with pre- and post-intervention observations comprising a standard control condition (no incentive), two treatment conditions (high and low incentive), and a second control arm with no baseline measures also with no incentive. The trial enrolled 152 clusters (SMEs), which were randomly allocated in an equal ratio to each of the trial arms; 100 SMEs completed the trial. Up to 15 employees were sampled and interviewed from each cluster. The full protocol is published elsewhere[2] (at the time of writing the results from the trial are under review).

6.1 Outcomes

A single primary outcome was specified in the protocol, which was the question “Does your employer take positive action on health and wellbeing?”. However, given the potential lack of insight it might provide into the functioning of the intervention, several secondary outcomes were specified to capture the “causal chain” between intervention and employee health and wellbeing. For each of three separate health categories (mental, musculoskeletal, and lifestyle health) employees were asked:

1. whether the employer provided information in this area;
2. whether the employer had provided activities and services in this area;
3. whether the employee had made a conscious effort to improve in this area;
4. whether the employee had attended any groups or activities in this area at work;
5. whether the employee had attended any groups or activities in this area outside of work.

for a total of 15 outcomes.

6.2 Re-analysis

The original analysis of the trial took a Bayesian approach. The Frequentist re-analysis we conduct here is principally for illustrative purposes, and so we only take a subset of the data and simplify some of the outcomes. In particular, we take only the main control arm and the high incentive intervention arm to estimate the effect of the high incentive. We focus on the set of secondary outcomes listed above, which we collapse into five separate outcomes; whether the employer provided information across all three health areas, and then whether there was a positive response for any of the health areas for the remaining outcomes, for a total of five outcomes. All outcomes are modelled using a Bernoulli-logistic regression model, following the notation above, with $t = 0$ for baseline and $t = 1$ for post-intervention:

$$ Y_{k,ict} \sim \text{Bernoulli}(\logit(\mu_{0,k} + \delta_k D_{ct} + \theta_{k,c} + \theta_{k,ct})) $$
### 6.3 Results

Table 4 shows the results of an analysis using the naive method, alongside ‘corrected’ results using the Bonferroni, Holm, and Romano-Wolf methods. We make several observations. The uncorrected analysis would suggest there is likely good evidence that the intervention improved employer provision of information and activities and services, and increased employee taking part at work. However, this conclusion might contradict our understanding of the causal processes since it would seem contradictory for employees to make more effort but not report making more effort. The results corrected for multiple testing using Romano-Wolf appear to be more consistent in that employers appeared to make more effort but the employees did not take up the new services with small and negative effects now shown to be compatible with the data for the latter three outcomes. The effect of the intervention is also more uncertain than suggested by the uncorrected confidence intervals. In particular, the confidence intervals under the corrected methods, which are based on exact randomisation tests, are not symmetric for several outcomes, unlike under the uncorrected approach. So, smaller effect sizes, particularly for the first two outcomes, are more plausible than the uncorrected method would suggest.

### 7. DISCUSSION

This article demonstrates how one can estimate Frequentist statistics for cluster randomised trials with multiple outcomes that control for the FWER and coverage of simultaneous confidence intervals, and more generally in any scenario where multiple tests from GLMMs are used. This is also the first description of an efficient method for estimating confidence sets with nominal family-wise coverage in any area, not just for cluster randomised trials. We build on a range of previous work including: randomisation tests for cluster trials,[9, 10] univariate methods for corrections for multiple testing that use randomisation tests,[27, 28, 29] and procedures for estimating confidence interval search procedures used 10,000 steps for Bonferroni, Holm, and Romano-Wolf (RW) methods.

| Outcome                                      | Naive       | Bonferroni  | Holm        | RW          |
|----------------------------------------------|-------------|-------------|-------------|-------------|
| Employer provided information                | 2.91        | [0.11, 3.53]| [0.15, 3.46]| [0.42, 2.96]|
|                                              | <0.01       | 0.03        | 0.01        |             |
| Employer provided activities                 | 2.11        | [-0.22, 2.96]| [-0.01, 2.58]| [0.18, 2.62]|
|                                              | <0.01       | 0.06        | 0.03        |             |
| Employee made a conscious effort             | 0.22        | [-0.48, 1.00]| [-0.43, 0.94]| [-0.40, 0.74]|
|                                              | 0.44        | 1.00        | 0.33        | 0.33        |
| Employee took part at work                   | 1.13        | [-0.38, 1.71]| [-0.39, 1.65]| [-0.20, 1.59]|
|                                              | <0.01       | 1.00        | 0.62        | 0.23        |
| Employee took part outside work              | 0.27        | [-0.11, 1.06]| [-0.01, 0.90]| [-0.01, 0.80]|
|                                              | 0.11        | 0.34        | 0.11        | 0.15        |

**Table 4**

Results from re-analysis of the workplace wellbeing trial. Results are log odds-ratios, 95% confidence intervals, and p-values. Permutation test p-values used 4,000 iterations, and the confidence interval search procedure used 10,000 steps for Bonferroni, Holm, and Romano-Wolf (RW) methods.
may be one or more outcomes, but clusters may receive different 'doses' or variants of the treatment. There are a variety of treatment effects and null hypotheses of interest including pairwise comparisons between arms and a global joint null, which can be estimated from a single univariate model with indicators for each arm.[35] Pairwise null hypotheses in these models do not make statements about the value of the treatment effects in arms outside the pair under comparison as it is left unspecified, so it is not obvious then how a randomisation test could be conducted for the pairwise comparison that is invariant under comparison as it is left unspecified, so statements about the value of the treatment effects in arms outside null hypotheses in these models do not make statements about the value of the treatment effects in arms.

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**SIMULATION DETAILS**

(1) Two-arm, parallel cRCT, two outcomes, and no covariates

For the first simulation we consider a parallel cluster trial with two outcomes measured once in the post-intervention period. The first outcome is specified as Poisson distributed:

\[ Y_{1,ic} \sim \text{Poisson}(\exp(\mu_1 + \delta_1 D_c + \theta_{1,c})) \]

and the second outcome as Gaussian distributed:

\[ Y_{2,ic} \sim N(\mu_2 + \delta_2 D_c + \theta_{2,c}, 1) \]

where

\[ \begin{pmatrix} \theta_{1,c} \\ \theta_{2,c} \end{pmatrix} \sim \left( \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_1^2 & \rho \sigma_1 \sigma_2 \\ \rho \sigma_1 \sigma_2 & \sigma_2^2 \end{pmatrix} \right) \]

We set \( \mu_j = 1 \) and consider both \( \delta = (0, 0) \) and \( \delta = (0, 0.5) \) to compare the FWER under different combinations of true null hypotheses. We also compare \( \rho = 0 \) and \( \rho = 0.5 \).

Analyses of cluster randomised trials usually consider the intraclass correlation coefficient (ICC) \( \text{ICC}_j = \frac{\text{Var}(\theta_{j,c})}{\text{Var}(Y_{j,ic})} \), however the ICC for non-linear models depends on the realised values of the covariates and the parameter values and so will differ between simulations. We choose \( \sigma_j^2 = 0.05^2 \), which gives a range of ICCs between approximately 0.001 and 0.1.

(2) Two-arm, parallel cRCT, three outcomes, and covariates

We next step up the complexity of the design by introducing covariates and including three outcomes of differ-

\[ Y_{1,ic} \sim \text{Poisson}(\exp(\mu_1 + \delta_1 D_c + \beta_1 X_{1c} + \theta_{1,c})) \]

\[ Y_{2,ic} \sim N(\mu_2 + \delta_2 D_c + \beta_2 X_{1c} + \theta_{2,c}, 1) \]

\[ Y_{3,ic} \sim \text{Bernoulli}(\logit(\mu_3 + \delta_3 D_c + \beta_3 X_{1c} + \theta_{3,c})) \]

The random effects have the same multivariate normal specification as the two outcome simulation, however we increase \( \sigma^2_j = 0.05 \) to give ICCs between 0.01 and 0.2. We maintain the same values of \( \rho \) and the numbers of clusters and individuals per cluster as the previous simulation. Similarly \( \mu_j = 1 \) and \( \beta_j = 1 \) for all \( j = 1, 2, 3 \). We vary the choice of \( \delta \) as either \((0, 0, 0), (0, 0, 0.5), \) or \((0, 0.5, 0.5)\); as with the following set of simulations we do not consider a completely exhaustive set of permutations of simulation parameters.

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