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Manuel Gomes
Richard Grieve
Richard Nixon
Edmond S.-W. Ng,
James Carpenter
Simon G. Thompson

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Manuel Gomes MSc[1], Richard Grieve PhD[1], Richard Nixon PhD[2], Edmond S.-W. Ng MSc[1], James Carpenter PhD[3], Simon G. Thompson DSc[4]

[1]Department of Health Services Research and Policy, London School of Hygiene & Tropical Medicine, London.
[2]Modeling and Simulation Group, Novartis Pharma AG, Basel, Switzerland.
[3]Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London.
[4]Department of Public Health and Primary Care, University of Cambridge, Cambridge.

Correspondence to:
Manuel Gomes, PhD student
Department of Health Services Research and Policy
London School of Hygiene and Tropical Medicine
15 - 17 Tavistock Place.
WC1H 9SH London.
Tel: 0207 299 4734.
Email: manuel.gomes@lshtm.ac.uk

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Abstract

Statistical methods have been developed for cost-effectiveness analyses (CEA) of cluster randomised trials (CRTs) where baseline covariates are balanced. However, CRTs may have systematic differences in individual and cluster-level covariates between the treatment groups. This paper presents three methods to adjust for imbalances in observed covariates: seemingly unrelated regression (SUR) with a robust standard error, a 'two-stage' bootstrap (TSB) approach combined with SUR, and multilevel models (MLMs). We consider the methods in a CEA of a CRT with covariate imbalance, unequal cluster sizes and a prognostic relationship that varied by treatment group. The cost-effectiveness results differed according to the approach for covariate adjustment.

Our simulation study assessed the relative performance of methods for addressing systematic imbalance in baseline covariates. The simulation extended the case study and considered scenarios with: different levels of confounding, cluster size variation and few clusters. Performance was reported as bias, root mean squared error and confidence interval (CI) coverage of the incremental net benefit. Even with low levels of confounding, unadjusted methods were biased, but all adjusted methods were unbiased. MLMs performed well across all settings, and unlike the other methods, reported CI coverage close to nominal levels even when with few clusters of unequal sizes.

1. Introduction

Econometric evaluation often uses observational data to estimate 'average treatment effects' (ATE). In non-randomised studies, baseline characteristics may be correlated with both treatment choice and the endpoints of interest, i.e. the distribution of potential confounders (both observed and unobserved) can be different across treatment groups. Several approaches such as regression, instrumental variables, matching and inverse probability weighting have been advocated for reducing selection bias in observational studies (Basu and Rathouz, 2005, Sekhon and Grieve, 2011, Jones and Rice, 2011). In cost-effectiveness analyses (CEA), many studies use data from clinical trials where individual patients are randomised. Here, if the randomisation is properly conducted, systematic differences in baseline characteristics between the treatment groups can be avoided, and the resultant estimates will be unbiased (Imai et al., 2008, Senn, 1989). For CEA of clinical trials, regression approaches have been proposed for the purposes of improving precision or conducting pre-specified subgroup analyses, (Barber and Thompson, 2004, Briggs, 2006, Hoch et al., 2002, Manca et al., 2005, Nixon and Thompson, 2005, Willan and Briggs, 2006, Willan et al., 2004).

For CEA of interventions that operate at a group rather than an individual-level (e.g. changing incentives for providers), or where there is a high risk of contamination amongst individuals within a geographical setting (e.g. alternative strategies for containing an infectious disease), a cluster randomised trial (CRT) may be preferred. Here the unit of randomisation is the cluster, for example the primary care physician, not the patient. The CRT can be designed to try and avoid selection bias, for example by concealing treatment allocation, and also recruiting individuals at the same time as cluster randomisation.

A general concern with CRTs (Carter, 2010, Donner, 1998, Donner and Klar, 2000, Puffer et al., 2005) is that studies tend to be unblinded, with individuals recruited after treatment allocation is known. CRTs with these flawed designs are prone to differences between the treatment groups in patient and cluster-level baseline characteristics that are systematic, rather than due simply to chance (Eldridge et al., 2008, Hahn et al., 2005, Puffer et al., 2003). For example, potential

participants with particular characteristics (e.g. older patients) may be less likely to enter one of the randomized groups once assignment is known. Hence, the CRT's design can encourage systematic imbalances in baseline characteristics, which if associated with endpoints, can lead to bias. In a CRT with the flawed design described, a baseline cluster-level covariate such as provider volume, may be imbalanced at baseline and this may be correlated with cost due to economies (or diseconomies) of scale. Furthermore, a baseline covariate may have a prognostic relationship that differs by treatment group (Gelman and Pardoe, 2007, Liu and Gustafson, 2008); this may occur if for example, the study protocol is less rigid for the control than the treatment group.

Hence, for CEA of CRTs to provide unbiased estimates, analytical methods are required to adjust appropriately for systematic differences in observed baseline covariates. This raises the issue of which covariates to include and how best to undertake the adjustment (Austin et al., 2010). Methodological guidance emphasises that covariate adjustment should be limited to those variables anticipated to be strongly associated with the endpoints of interest (Altman, 2005, Imai et al., 2008). Consideration should also be given to non-linear terms and covariate by treatment interactions if these are anticipated to be important (Assmann et al., 2000, Gelman and Pardoe, 2007). However, the choice of covariates for adjustment should not simply be according to whether or not there are statistically significant baseline differences between the treatment groups (Imai et al., 2008).

In CEA of CRTs, little attention has been given to analytical methods (Gomes et al., 2011a). Recent work presented methods that allow for clustering and the correlation between costs and outcomes: seemingly unrelated regressions (SUR) and generalised estimating equations (GEEs) both with a robust variance estimator, multilevel models (MLMs) and a two-stage non-parametric bootstrap (TSB) (Gomes et al., 2011b). The study assumed that baseline covariates were balanced between the treatment groups. Indeed, the potential for selection bias seems to be generally ignored in CEA of CRTs. Our review (Gomes et al., 2011a) found that of 62 published CEA of CRTs, about 60% did not report an assessment of covariate balance, and of the 27

studies reporting baseline information, only 16 adjusted for any baseline imbalances. The remaining 11 studies justified reporting unadjusted results by the lack of any statistically significant baseline differences.

The aim of this paper is to assess the relative performance of alternative methods for CEA of CRTs when there are systematic imbalances in individual and cluster-level baseline covariates. This paper considers alternative approaches for CEA of CRT in an extensive simulation study and an empirical application. We consider regression-based methods such as MLMs and SUR, and extend a non-parametric TSB to handle covariate adjustment. We do not consider GEEs as these performed poorly in studies with few clusters (Gomes et al., 2011b). We estimate ATE, as these are of prime interest for policy makers (Claxton, 1999, Imbens and Wooldridge, 2009, Jones and Rice, 2011). In the next section, we outline the methods under comparison. Section 3 presents the motivating example. Sections 4 and 5 report the design and results of the simulation study. The last section discusses the findings and suggests areas for further research.

2. Statistical methods for covariate adjustment in CEA of CRTs

In CEA of CRTs, statistical methods are required that adjust for covariate imbalances while accounting for the clustering and the correlation between costs and health outcomes. We consider three methods: SUR with robust standard errors (SE), MLMs, and an approach that combines the TSB with SUR (TSB+SUR).

We use the following notation: let c_{ij} and e_{ij} represent the costs and outcomes for the ith individual in the jth cluster. For simplicity the models and the simulation study are described for CEA with two alternative treatments but the models extend to evaluations with more than two randomised groups. Each method is illustrated assuming linear additive effects for covariates and

treatment (Nixon and Thompson, 2005, Willan and Briggs, 2006). For simplicity, we illustrate adjustment for one individual-level (x_{ij}) and one cluster-level (z_j) covariate.

Seemingly unrelated regressions (SUR)

SUR consists of a system of regression equations with residuals that are allowed to be correlated (Greene, 2003, Wooldridge, 2010). The set of covariates can differ for each endpoint, and as in model (1), SUR can include individual (x_{ij}) and cluster-level covariates (z_j)

$$\begin{aligned} c_{ij} &= \beta_0^c + \beta_1^c t_j + \beta_2^c x_{ij} + \beta_3^c z_j + \varepsilon_{ij}^c \\ e_{ij} &= \beta_0^e + \beta_1^e t_j + \beta_2^e x_{ij} + \beta_3^e z_j + \varepsilon_{ij}^e \end{aligned} \qquad \begin{pmatrix} \varepsilon_{ij}^c \\ \varepsilon_{ij}^e \end{pmatrix} \sim BVN\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_c^2 & \rho\sigma_c\sigma_e \\ & \sigma_e^2 \end{pmatrix} \right) \tag{1}$$

where t_j is the treatment indicator (t_j =0 for control and 1 for treatment group). The incremental costs (β_1^c) and outcomes (β_1^e), can be estimated by ordinary least squares (OLS). SUR can also assume that the individual error terms (ε) follow a bivariate Normal distribution (BVN), with variances σ_c^2 and σ_e^2. The correlation between costs and outcomes, conditional on covariates, is recognised through the parameter ρ. Model (1) can incorporate interaction terms, for example, of treatment with a continuous individual-level covariate (x_{ij}). The covariate x_{ij} can be centred on the mean so that β_1^c and β_1^e are the incremental costs and outcomes, at that covariate mean. The uncertainty estimates can account for clustering with robust standard errors (SE) (Greene, 2003). However, a potential concern is that the asymptotic assumptions required for the robust variance estimation may not be satisfied in CRTs with few clusters, particularly when there are unequal numbers per cluster (Gomes et al., 2011b).

Multilevel models (MLMs)

MLMs can explicitly recognise clustering by incorporating the cluster-level random effects (u_j^c, u_j^e) while adjusting for cluster and individual-level covariates (Nixon and Thompson, 2005). For

example, an MLM that includes one individual-level covariate (x_{ij}) and one cluster-level (z_j) and can be described as:

$$\begin{aligned} c_{ij} &= \beta_0^c + \beta_1^c t_j + \beta_2^c x_{ij} + \beta_3^c z_j + u_j^c + \varepsilon_{ij}^c \\ e_{ij} &= \beta_0^e + \beta_1^e t_j + \beta_2^e x_{ij} + \beta_3^e z_j + u_j^e + \varepsilon_{ij}^e \end{aligned} \qquad \begin{aligned} \begin{pmatrix} \varepsilon_{ij}^c \\ \varepsilon_{ij}^e \end{pmatrix} &\sim BVN\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_c^2 & \rho\sigma_c\sigma_e \\ & \sigma_e^2 \end{pmatrix}\right) \\ \begin{pmatrix} u_j^c \\ u_j^e \end{pmatrix} &\sim BVN\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \tau_c^2 & \psi\tau_c\tau_e \\ & \tau_e^2 \end{pmatrix}\right) \end{aligned} \tag{2}$$

which as above can be extended to include treatment by covariate interactions. Model (2) acknowledges individual and cluster-level correlation between costs and outcomes, conditional on the covariates, through the parameters ρ and ψ. This particular MLM (2) assumes the error terms are normally distributed but alternative distributions such as a gamma distribution for costs could be chosen. A general concern with MLMs or SUR is whether estimates are unbiased and precise if the model is misspecified, by for example, assuming that the individual-level residuals are normally distributed when cost data are highly skewed.

Two-stage bootstrap (TSB)

We also considered a non-parametric TSB, which can accommodate clustering and the correlation between costs and outcomes, but avoids making distributional assumptions. We provide an overview below, and define the steps taken in the algorithm (Appendix 1) but for full details of the TSB approach readers are referred to (Davison and Hinkley, 1997).

A simple TSB resamples clusters and then individuals within each resampled cluster (Davison and Hinkley, 1997). However, to provide an accurate estimation of the variance, Davison and Hinkley advocate a 'shrinkage correction'. This procedure requires that shrunken cluster means and standardised individual residuals are calculated before any resampling. Bootstrap datasets are then constructed by combining resampled shrunken means with resampled individual-level residuals. The ATE of interest (for example the INB) can be taken as the mean of the INBs across the bootstrap replicates. Uncertainty can be reported by calculating bias-corrected and

accelerated 95% CIs (Nixon et al., 2010). This approach can provide unbiased estimates of the INB and good CI coverage, even with few clusters of unequal size, if baseline covariates are balanced (Gomes et al., 2011b). We used this approach for the TSB without covariate adjustment.

When systematic imbalances are anticipated and covariate adjustment is required, the TSB described above may be insufficient. The previous resampling approach of combining each shrunken cluster mean with individual residuals drawn across all clusters, does not preserve a relationship between the cluster mean and the covariate information within the cluster. To avoid this problem we modify Davison and Hinkley's original resampling routine so that the bootstrap datasets respect the cluster membership. In the modified algorithm, shrunken cluster means and standardised residuals are calculated as before, but each cluster mean is now combined with individual residuals drawn from that same cluster (see Appendix 1 for further details).

We then adjust for covariate imbalances by applying SUR (model 1) to each bootstrap resample, to report adjusted incremental costs and outcomes and INBs, which are then averaged across the bootstrap replicates. The SUR reports SEs for each incremental measure, without applying the robust estimator, because any clustering is recognised by the bootstrap routine. The SEs are then also averaged across the bootstrap replicates, to report 95% CIs. A potential concern is that while the TSB avoids distributional assumptions, the SUR adjustment assumes that cost and outcome data in the bootstrap replicates are from bivariate Normal distributions.

3. Motivating example

Design and description

This CEA of a CRT evaluated alternative interventions for preventing postnatal depression (PoNDER) (Morrell et al., 2009). The CRT included 2659 patients attending 101 GP practices (clusters), and as is typical (Gomes et al., 2011a), the number of patients per cluster varied widely (from 1 to 77). Intra-cluster correlation coefficients (ICCs) were moderate for QALYs

(*ICCe*=0.04), but high for costs (*ICCc*=0.17). While QALYs were approximately normally distributed, costs were moderately skewed.

In PoNDER, prior to patient recruitment, clusters were randomly allocated to usual care (control) or a psychological intervention delivered by a health visitor (treatment). The intervention consisted of health visitor training to identify and manage patients with postnatal depression. Baseline measurements were recorded for variables anticipated *a priori* to be potential confounders (Morrell et al., 2009). Previous studies suggest that cluster size, the number of patients randomised in each cluster, may be a confounder (Campbell et al., 2000, Omar and Thompson, 2000). In PoNDER, because clinical protocols were less restrictive in the control than treatment group, it was anticipated that any relationship between the cluster size and the endpoints would be stronger in the control group. Hence, *a priori* it was judged important to consider models that included an interaction of treatment with cluster size. This analysis used baseline and 6 month endpoints for 1732 patients (70 clusters) with complete information.

Table I describes covariate balance between treatment arms, reported as percent standardised mean differences (Austin, 2009), which allows comparison across different types of variables (e.g. continuous, binary) and is invariant to sample size (Austin, 2009) For example, for a continuous covariate (*x*), the standardised mean difference is calculated as $d_x = (\bar{x}_1 - \bar{x}_0)/\sqrt{(\mathrm{var}_x^1 + \mathrm{var}_x^0)/2} * 100$, with $\bar{x}_1, \bar{x}_0$ and $\mathrm{var}_x^1, \mathrm{var}_x^0$ the means and variances for each group. There is no consensus on the level of imbalance that is of concern, but a standardised difference of 10% has been judged meaningful (Austin, 2009, Rosenbaum and Rubin, 1985).

In PoNDER, a cluster-level covariate, cluster size, and some individual-level covariates were relatively imbalanced (Table I). Cluster size was strongly correlated with costs and QALYs but only for the control group. When the full data set was considered rather than the subset with complete information, covariate imbalance was similar.

<< Table I here >>

We compare the analytical approaches described above, in pre-specified analyses: i) without covariate adjustment ii) with adjustment for main covariate effects and iii) with adjustment that includes main effects and a treatment by cluster size interaction. SUR was estimated in STATA by iterative feasible generalized least squares with a robust SE. The bivariate normal MLM was implemented by maximum likelihood (in R). An MLM that allowed costs to take a Gamma distribution was fitted using Markov Chain Monte Carlo Methods (MCMC) by calling WinBUGS from R (Spiegehalter et al., 2003). The MCMC estimation was with 5000 iterations, three parallel chains with different starting values and assuming diffuse, vague priors (Lambert et al., 2005). The unadjusted TSB was implemented with Davison and Hinkley's shrinkage correction (Davison and Hinkley, 1997). For covariate adjustment after the TSB, we combined our new TSB routine with SUR but without a robust SE. Bootstrap methods were implemented in R, with 1000 replicates. We reported mean (SE) incremental costs, QALYs and INBs (ceiling ratio of £20 000 per QALY), and accompanying Akaike Information Criteria (AIC)[1].

Case study results

The treatment group had lower mean costs, higher mean QALYs, a positive INB and a high probability of being cost-effective (above 0.9) (Table II). Without covariate adjustment, the MLM reported a less negative incremental cost than the other methods; the MLM gave relatively high weight to smaller clusters which in the control group had relatively low costs; hence the mean cost for the control group was lower for the MLM versus SUR (£272 *vs* £303). After each model adjusted for main covariate effects, the estimated INBs were about 50% lower and the AICs were much reduced. Once the models included the treatment by cluster size interaction, SUR and the MLM gave similar estimates, and lower AICs. When the MLM was specified with Gamma rather than Normal costs, the estimated INB was similar, but model fit improved further.

<< Table II here >>

[1] For SUR the AIC is computed from the least squares statistics and does not take into account the robust estimation. For TSB+SUR, the AIC is also taken from the same least squares statistics and averaged over the bootstrap samples.

4. Monte Carlo simulations

Data generating process (DGP)

The simulation study was designed to test the methods across a range of settings where systematic imbalances in baseline covariates may be anticipated in CEA of CRTs. The choice of scenarios was based on the PoNDER case-study, a systematic review of published CEA of CRTs (Gomes et al., 2011a) and previous methodological studies (Campbell et al., 2005, Eldridge et al., 2006, Flynn and Peters, 2005, Pocock et al., 2002, Senn, 1994, Turner et al., 2007). It was judged important to allow the following to differ: the level of covariate imbalance, the correlation of each covariate (individual and cluster-level) with cost and QALY endpoints, the ICCs, the variation in cluster size and the number of clusters per treatment arm.

We designed a flexible DGP that incorporated baseline imbalances and correlations between covariates and endpoints, while recognising clustering, and correlation between costs and health outcomes. Briefly, costs and outcomes were simulated from a bivariate distribution in two stages, at the cluster then the individual level, to reflect the clustering inherent in CRTs. The DGP allowed for a wide range of parameters to be varied, and for each endpoint to have different parametric distributions. All covariates were included additively.

We illustrate below a simple DGP with one continuous cluster-level covariate[2] and one continuous individual-level covariate (equations 3.1 and 3.2). We simulated cost (c) and outcome (e) data from a potential CRT with *M* clusters per arm and n_m ($m = 1,\ldots M$) individuals per cluster. We firstly generated cluster-level mean costs and outcomes (ϕ_j^c, ϕ_j^e) that followed distributions with means (μ_c, μ_e) and cluster-level standard deviations (τ_c, τ_e). Then, individual-level data (c_{ij}, e_{ij}) were simulated from distributions centred at the cluster-level means, and with

[2] In PoNDER, the imbalanced cluster level covariate was cluster size. To afford more flexibility in the simulation study, a different cluster-level characteristic was assumed imbalanced between the treatment groups.

individual-level standard deviations (σ_c, σ_e). Costs and outcomes were allowed to be correlated at both the cluster (ψ) and individual-level (ρ). The level of clustering was defined by the ICCs; for example for costs $ICC_c = \tau_c^2 / (\sigma_c^2 + \tau_c^2)$. The number of individuals per cluster was drawn from a Gamma distribution defined by a mean and coefficient of variation, which ensured cluster size remained positive (Eldridge et al., 2006).

Cluster-level means:

$$\phi_j^c \sim dist(\mu_c,\ \tau_c), \quad \phi_j^e \sim dist(\mu_e,\ \tau_e)$$
$$\mu_c = \beta_0^c + \beta_1^c t_j + \beta_3^c z_j, \quad \mu_e = \beta_0^e + \beta_1^e t_j + \beta_3^e z_j + \psi(\phi_j^c - \mu_c) \tag{3.1}$$

Individual-level data:

$$c_{ij} \sim dist(\phi_j^c + \beta_2^c x_{ij},\ \sigma_c)$$
$$e_{ij} \sim dist(\phi_j^e + \beta_2^e x_{ij} + \rho(c_{ij} - (\phi_j^c + \beta_2^c x_{ij}))\ ,\ \sigma_e) \tag{3.2}$$

We incorporated the cluster-level covariate (z_j) when simulating the cluster-level mean costs and outcomes, and the individual-level covariate (x_{ij}) when simulating individual-level data[3]. Both cluster and individual-level covariates were assumed to be continuous and drawn from normal distributions, $z_j \sim N\ (\mu_z,\ \sigma_z)$ and $x_{ij} \sim N\ (\mu_x,\ \sigma_x)$.

The DGP introduced systematic baseline imbalances by allowing the covariate means to differ across treatment arms set according to standardised mean differences (Austin, 2009)[4]. For the individual (β_2^c, β_2^e) and cluster-level (β_3^c, β_3^e) covariates, coefficients were simulated as a function of the correlation coefficient (r) between each covariate and the corresponding endpoint (Turner et al., 2007). For instance, the coefficient of the individual-level covariate (Normal) on health outcomes (Normal) was determined as $\beta_2^e = \frac{\sigma_e}{\sigma_x}\sqrt{r_e^2\ /\ (1-r_e^2)}$, and the

[3]As individuals within a cluster tend to be relatively similar, the covariate was allowed to be clustered.
[4] The standardised mean differences assumed constant variance across treatment arms.

corresponding coefficient on costs (Gamma) as $\beta_2^c = \frac{\mu_c}{\sigma_x}\sqrt{(1/shape_c)r_c^2 / (1-r_c^2)}$. The DGP easily extends to allow the prognostic strength of a covariate to differ by treatment group, by including treatment by covariate interaction terms.

Definition of scenarios

Table III lists parameters allowed to vary across the scenarios. Other parameters, such as the level of correlation between costs and health outcomes (0.2), mean cluster size (50) and true INB (£1 000; ceiling ratio £20 000 per QALY), were held constant across scenarios. Covariates x_{ij} and z_j were assumed to follow Normal distributions (mean 50 and SD 20) throughout.

The first group of scenarios (Table III, S1-S5), considered different levels of imbalance for an individual-level covariate, and confounding just for health outcomes. In the initial scenario, baseline imbalance and the correlation between the covariate and health outcome were both set to zero (S1). We then simulated scenarios with increasing levels of baseline imbalance and correlation with health outcomes (S2-S5). For these scenarios, we reported the performance for each method before and after adjustment. The scenario, S5, characterised by high levels of imbalance and confounding, was taken as the base case for subsequent scenarios.

The second group of scenarios, considered the choice of adjustment method across a broader set of circumstances (Table III, S6-S11). These scenarios allowed for confounding in the cost endpoint, assumed to follow a Gamma distribution (S6). Subsequent scenarios allowed: for imbalance in a cluster-level covariate, assumed correlated with both endpoints (S7); high ICCs (S8); unequal cluster sizes (S9); and few clusters (S10). In addition to the change described each scenario incorporated the characteristics of the preceding setting. The final scenario (S11), motivated by PoNDER, and anticipated in CRTs more generally (Campbell et al., 2000), allowed the prognostic relationship of a cluster-level covariate to differ by treatment arm.

<< Table III here >>

Implementation

For each scenario, each method estimated INBs before and after covariate adjustment. MLMs and TSB were implemented in R (R, 2011) and SUR in STATA (STATA, 2009). SUR was estimated by iterative feasible generalized least squares with a robust SE, and the bivariate normal MLMs by maximum likelihood. The TSB was implemented before, and after adjustment with SUR (no robust SE) as in the case study. We conducted 2000 simulations for each scenario[5]. The relative performance of the alternative methods was assessed according to mean (SE) bias, root mean squared error (rMSE), variance, confidence interval (CI) coverage, and CI width of the INB (ceiling ratio of £20 000 per QALY). We reported performance before and after adjustment (S1-6, S11), and across the adjusted methods (S6-10).

5. Simulation results

Table IV reports the results for the first set of scenarios where an individual-level baseline covariate had different levels of imbalance and correlation with health outcome. Even with low levels of baseline imbalance and correlation (S3), methods without adjustment produced slightly biased results. At increased levels of imbalance and correlation (S5), the unadjusted approaches reported high bias (>10%) and low CI coverage (below 0.9 for a nominal level of 0.95). All adjusted approaches reported unbiased estimates of the INB, including the new TSB routine combined with SUR[6]. However, the CI coverage for the TSB combined with SUR was lower than for the other methods (0.91 *vs* 0.94) across all scenarios.

In the scenario without imbalance and confounding (S1) covariate adjustment increased the variance of the INB (after covariate adjustment with the MLM, the average variance was 12 125 vs 12 027 before adjustment). By contrast, if the covariate was balanced but correlated with

[5]2000 simulations provide coverage rates of 0.94 to 0.96 (for true coverage of 0.95) with 95% confidence.
[6]Using Davison and Hinkley's original TSB routine, combined with SUR provided biased results; for example for S5 the mean (SE) bias was 23.6 (2.56).

outcome (S2), the corresponding variance was slightly smaller after adjustment (12 122 *vs* 12 227).

<< Table IV here >>

For the scenarios with confounding on costs (S6), an imbalanced cluster-level covariate correlated with both endpoints (S7), high ICCs (S8), variation in the cluster size (S9) and few clusters (S10) all unadjusted methods reported biased estimates and low CI coverage (below 0.9). Following covariate adjustment, each method provided unbiased estimates of the INB (Appendix 2). However, as Figure 1 shows, CI coverage differed across methods. The combination of TSB and SUR gives poor CI coverage (0.91 or less) under each scenario. The CI coverage with SUR is lower than for the MLM, when the numbers per cluster vary[7] (S9) and there are few clusters (S10). For these scenarios, MLM also reports lower variance and rMSE than SUR (see Appendix 2 for further details). For scenario S10, characterised by imbalanced individual and cluster-level covariates correlated with endpoints, high ICCs, few clusters (8 per arm) and cluster size variation, the adjusted MLM still gives reasonable coverage (0.93).

<< Figure 1 here >>

Table V reports the results for the last scenario (S11), where the prognostic relationship for a cluster-level covariate differed by treatment arm, there were unequal numbers per cluster, high ICC (0.2), but moderate numbers of clusters (20 per arm)[8]. The results show that unless the treatment by covariate interaction is incorporated, each method reports biased estimates of the INB and low CI coverage. After including the interaction term, each method reported unbiased estimates, lower rMSE and improved CI coverage. The MLM with the interaction term reported the lowest rMSE and was the only approach to report CI coverage close to the nominal level.

[7] Here, for cluster size we assume a coefficient of variation of 1. Even with a coefficient of variation of 0.5, SUR reports variance and rMSE that are 20% higher than for the MLM.
[8] We also considered a scenario where the interaction of treatment is with an individual-level rather than a cluster-level covariate, but the results are similar to those presented for S11.

<< Table V here >>

6. Discussion

This study presents alternative methods for CEA of CRT where baseline covariates differ between treatment groups. These adjusted methods address systematic imbalances in both individual and cluster-level covariates. The case study illustrates that in CEA of CRT, cost-effectiveness estimates can differ according to method. The simulation extends the case study, and shows that without adjustment, CEA can report biased estimates even with low levels of confounding. By contrast, each adjustment method provides unbiased estimates. Of the alternative methods, the MLMs report CI coverage close to nominal levels across all the circumstances considered (CI coverage of 0.93 to 0.95). In settings with unequal numbers per cluster and few clusters, SUR with a robust variance estimator, reports low CI coverage and high rMSE compared to the MLM. The TSB and SUR approach proposed gives low CI coverage in each setting considered.

This is the first paper to consider analytical methods for addressing systematic covariate imbalance in CEA of CRT. A previous simulation study (Gomes et al., 2011b) suggested that MLMs or a TSB approach were appropriate for CEA of CRTs, but only considered circumstances with balanced covariates. Our paper shows that where the CRT has systematic baseline differences between the treatment groups, methods that assume covariate balance are insufficient. We consider a simple approach to adjusting for systematic imbalances in patient or cluster-level covariates, which is to apply SUR with a robust SE. Previous work reported that SUR performed well for CEA of CRTs unless the number of clusters was small (Gomes et al., 2011b). By contrast, our paper shows that when there are unequal numbers per cluster, adjusted SUR can report poor coverage even with a moderate number of clusters (20 per treatment arm). This is an important concern, as a previous review reported that 75% of studies have uneven

numbers per cluster, and of these about 50% have fewer than 20 clusters per arm (Gomes et al., 2011a).

Rather than relying on the asymptotics required for robust variance estimation, or the distributional assumptions made by MLM, we extend a previous TSB algorithm and combine it with SUR. While this new, combined approach performs well in terms of bias and rMSE, it leads to lower CI coverage than MLMs or SUR alone. Hence, this TSB is less appealing for CEA when covariate adjustment is required. While one alternative would be to combine the TSB with a SUR or GEE that has a robust variance estimator, as our results show the asymptotic assumptions required are unlikely to be satisfied by the numbers of clusters commonly in CRTs. An alternative approach to avoiding distributional assumptions about the endpoints, would be to bootstrap individual-level residuals from adjusted MLMs (Carpenter et al., 2003).

The MLMs proposed have more general appeal for CEA of CRTs. The MLMs that assume bivariate normality, perform relatively well even with highly skewed costs; this corroborates previous findings suggesting that methods that assume normality may be reasonably robust to skewed cost data (Nixon et al., 2010, Willan et al., 2004). In the case study, the MLM was extended to assume a Gamma distribution for costs, and as in previous studies, this slightly reduced the width of the uncertainty intervals (Grieve et al., 2010). The MLMs presented here can be easily extended to report multiplicative treatment effects (Thompson et al., 2006) or ATEs for each subgroup of policy-interest (Vaness and Mullahy, 2006).

In addressing systematic imbalances, issues beyond the choice of estimation method warrant careful consideration. In particular, pre-specified analysis plans for CEA should consider *a priori* what form the potential confounding may take, informed by theory, previous literature and expert opinion. In our case-study, as may be present more generally in CEA, adjusting for main effects was judged insufficient. Here, it was important that each method recognised that a prognostic relationship can differ by treatment group. Indeed, the simulation highlighted that ignoring a more complex prognostic relationship can bias the overall cost-effectiveness estimates.

This research does have some limitations. The methods proposed allow for systematic differences in potential confounders that were observed. The design of CRT may also lead to systematic imbalances in unobserved characteristics. Hence methods such as instrumental variable estimation that can address unobserved differences also warrant careful consideration (Basu et al., 2007, Polsky and Basu, 2006). In some circumstances the CRT may be designed such that the only baseline imbalances are by chance; our study does not apply to these circumstances. The MLMs proposed performed well across a range of settings including skewed cost data, but in the simulation study the DGP did not consider some complexities that can arise including variances that differ across clusters, and non-normal distributions for cluster-level residuals, In principle, the MLMs presented could be extended to allow for such complexities, but previous research suggest the improvements in inference may be relatively small (Grieve et al., 2010).

This paper opens up several areas for further research. In particular, it would be useful to extend the methods to handle nonlinear relationships between covariates and endpoints, missing and censored data. A complementary approach, which can offer protection against misspecification of the covariate adjustment model would be to extend the MLM to doubly robust estimation (Bang and Robins, 2005). Here, a model for treatment choice, a propensity score, could be estimated including covariates anticipated to be potential confounders, with the MLM weighted according to the inverse probability of treatment (Imbens, 2004). Such doubly robust estimators are consistent as long as either the treatment or the endpoint model is correctly specified (Bang and Robins, 2005).

This paper extends the literature examining the relative merits of hierarchical models (Cameron and Trivedi, 2005, Jones, 2009), robust variance estimation (Greene, 2003, Wooldridge, 2010), and non-parametric bootstrap approaches for covariate adjustment. In a context where adjustment methods are required to address systematic differences between treatment groups as well as accommodate clustering and the correlation of costs with health outcomes, we find that MLMs perform relatively well. While any of the adjustment methods proposed reports unbiased

estimates, the MLMs can provide more precise estimates with better CI coverage, than the other approaches.

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References

Altman, D. G. 2005. Adjustment for covariate imbalance. *In:* ARMITAGE, P. & COLTON, T. (eds.) *Encyclopedia of Biostatistics.* Chichester, UK: John Wiley.

Assmann, S. F., Pocock, S. J., Enos, L. E. & Kasten, L. E. 2000. Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet,* 355**,** 1064-9.

Austin, P. C. 2009. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med,* 28**,** 3083-107.

Austin, P. C., Manca, A., Zwarenstein, M., Juurlink, D. N. & Stanbrook, M. B. 2010. A substantial and confusing variation exists in handling of baseline covariates in randomized controlled trials: a review of trials published in leading medical journals. *Journal of Clinical Epidemiology,* 63**,** 142-153.

Bang, H. & Robins, J. M. 2005. Doubly robust estimation in missing data and causal inference models. *Biometrics,* 61**,** 962-73.

Barber, J. & Thompson, S. 2004. Multiple regression of cost data: use of generalised linear models. *Journal of Health Services & Research Policy,* 9**,** 197-204.

Basu, A., Heckman, J. J., Navarro-Lozano, S. & Urzua, S. 2007. Use of instrumental variables in the presence of heterogeneity and self-selection: An application to treatments of breast cancer patients. *Health Economics,* 16**,** 1133-1157.

Basu, A. & Rathouz, P. J. 2005. Estimating marginal and incremental effects on health outcomes using flexible link and variance function models. *Biostatistics,* 6**,** 93-109.

Briggs, A. 2006. Statistical Methods for cost-effectiveness analysis alongside clinical trials. *In:* JONES, A. (ed.) *The Elgar Companion to Health Economics.* Cheltenham, UK: Edward Elgar Publishing.

Cameron, A. C. & Trivedi, P. K. 2005. *Microeconometrics : methods and applications,* Cambridge ; New York, Cambridge University Press.

Campbell, M. K., Fayers, P. M. & Grimshaw, J. M. 2005. Determinants of the intracluster correlation coefficient in cluster randomized trials: the case of implementation research. *Clinical Trials,* 2**,** 99-107.

Campbell, M. K., Mollison, J., Steen, N., Grimshaw, J. M. & Eccles, M. 2000. Analysis of cluster randomized trials in primary care: a practical approach. *Family Practice,* 17**,** 192-196.

Carpenter, J. R., Goldstein, H. & Rasbash, J. 2003. A novel bootstrap procedure for assessing the relationship between class size and achievement. *Journal of the Royal Statistical Society Series C-Applied Statistics,* 52**,** 431-443.

Carter, B. 2010. Cluster size variability and imbalance in cluster randomized controlled trials. *Stat Med,* 29**,** 2984-93.

Claxton, K. 1999. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. *J Health Econ,* 18**,** 341-64.

Davison, A. C. & Hinkley, D. V. 1997. *Bootstrap methods and their application,* Cambridge, UK, Cambridge University Press.

Donner, A. 1998. Some aspects of the design and analysis of cluster randomization trials. *Applied Statistics,* 47**,** 95-113.

Donner, A. & Klar, N. 2000. *Design and analysis of cluster randomization trials in health research,* London, UK, Hodder Arnold Publishers.

Eldridge, S., Ashby, D., Bennett, C., Wakelin, M. & Feder, G. 2008. Internal and external validity of cluster randomised trials: systematic review of recent trials. *British Medical Journal,* 336**,** 876-880.

Eldridge, S. M., Ashby, D. & Kerry, S. 2006. Sample size for cluster randomized trials: effect of coefficient of variation of cluster size and analysis method. *Int J Epidemiol,* 35**,** 1292-300.

Flynn, T. N. & Peters, T. J. 2005. Cluster randomized trials: Another problem for cost-effectiveness ratios. *International Journal of Technology Assessment in Health Care,* 21**,** 403-409.

Gelman, A. & Pardoe, I. 2007. Average Predictive Comparisons for Models with Nonlinearity, Interactions, and Variance Components. *Sociological Methodology 2007, Vol 37,* 37**,** 23-51.

Gomes, M., Grieve, R., Edmunds, J. & Nixon, R. 2011a. Statistical methods for cost-effectiveness analyses that use data from cluster randomised trials: a systematic review and checklist for critical appraisal. *Medical Decision Making,* (in press). DOI:10.1177/0272989X11407341.

Gomes, M., Ng, E. S., Grieve, R., Nixon, R., Carpenter, J. & Thompson, S. 2011b. Developing appropriate analytical methods for cost-effectiveness analyses that use cluster randomized trials. *Medical Decision Making,* Submitted (March 2011).

Greene, W. H. 2003. *Econometric analysis,* Upper Saddle River, N.J., Great Britain, Prentice Hall.

Grieve, R., Nixon, R. & Thompson, S. G. 2010. Bayesian hierarchical models for cost-effectiveness analyses that use data from cluster randomized trials. *Med Decis Making,* 30**,** 163-75.

Hahn, S., Puffer, S., Torgerson, D. J. & Watson, J. 2005. Methodological bias in cluster randomised trials. *BMC Med Res Methodol,* 5**,** 10.

Hoch, J. S., Briggs, A. H. & Willan, A. R. 2002. Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis. *Health Econ,* 11**,** 415-30.

Imai, K., King, G. & Stuart, E. A. 2008. Misunderstandings between experimentalists and observationalists about causal inference. *Journal of the Royal Statistical Society Series a-Statistics in Society,* 171**,** 481-502.

Imbens, G. W. 2004. Nonparametric estimation of average treatment effects under exogeneity: A review. *Review of Economics and Statistics,* 86**,** 4-29.

Imbens, G. W. & Wooldridge, J. M. 2009. Recent Developments in the Econometrics of Program Evaluation. *Journal of Economic Literature,* 47**,** 5-86.

Jones, A. 2009. Panel data methods and applications to health economics. *In:* MILLS, T. & PATTERSON, K. (eds.) *Palgrave Handbook of Econometrics, Volume II: Applied Econometrics.* Hampshire, UK: Palgrave MacMillan.

Jones, A. & Rice, N. 2011. Econometric Evaluation of Health Policies. *In:* GLIED, S. & SMITH, P. (eds.) *The Oxford handbook of health economics.* Oxford, UK: Oxfors University Press.

Lambert, P. C., Sutton, A. J., Burton, P. R., Abrams, K. R. & Jones, D. R. 2005. How vague is vague? A simulation study of the impact of the use of vague prior distributions in MCMC using WinBUGS. *Stat Med,* 24**,** 2401-28.

Liu, J. X. & Gustafson, P. 2008. On Average Predictive Comparisons and Interactions. *International Statistical Review,* 76**,** 419-432.

Manca, A., Hawkins, N. & Sculpher, M. J. 2005. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ,* 14**,** 487-96.

Morrell, C. J., Slade, P., Warner, R., Paley, G., Dixon, S., Walters, S. J., Brugha, T., Barkham, M., Parry, G. J. & Nicholl, J. 2009. Clinical effectiveness of health visitor training in psychologically informed approaches for depression in postnatal women: pragmatic cluster randomised trial in primary care. *BMJ,* 338**,** a3045.

Nixon, R. M. & Thompson, S. G. 2005. Methods for incorporating covariate adjustment, subgroup analysis and between-centre differences into cost-effectiveness evaluations. *Health Econ,* 14**,** 1217-29.

Nixon, R. M., Wonderling, D. & Grieve, R. D. 2010. Non-parametric methods for cost-effectiveness analysis: the central limit theorem and the bootstrap compared. *Health Econ,* 19**,** 316-33.

Omar, R. Z. & Thompson, S. G. 2000. Analysis of a cluster randomized trial with binary outcome data using a multi-level model. *Stat Med,* 19**,** 2675-88.

Pocock, S. J., Assmann, S. E., Enos, L. E. & Kasten, L. E. 2002. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. *Stat Med,* 21**,** 2917-30.

Polsky, D. & Basu, A. 2006. Selection bias in observational data. *In:* JONES, A. (ed.) *The Elgar Companion to Health Economics.* Cheltenham, UK: Edward Elgar.

Puffer, S., Torgerson, D. & Watson, J. 2003. Evidence for risk of bias in cluster randomised trials: review of recent trials published in three general medical journals. *BMJ,* 327**,** 785-9.

Puffer, S., Torgerson, D. J. & Watson, J. 2005. Cluster randomized controlled trials. *J Eval Clin Pract,* 11**,** 479-83.

R 2011. The R project for statistical computing. http://www.r-project.org/.
Rosenbaum, P. R. & Rubin, D. B. 1985. Constructing a Control-Group Using Multivariate Matched Sampling Methods That Incorporate the Propensity Score. *American Statistician,* 39**,** 33-38.
Sekhon, J. S. & Grieve, R. 2011. A matching method for improving covariate balance in cost-effectiveness analyses. *Health Economics,* Accepted (April 2011).
Senn, S. 1994. Testing for baseline balance in clinical trials. *Stat Med,* 13**,** 1715-26.
Senn, S. J. 1989. Covariate Imbalance and Random Allocation in Clinical-Trials. *Statistics in Medicine,* 8**,** 467-475.
Smeeth, L. & Ng, E. S. 2002. Intraclass correlation coefficients for cluster randomized trials in primary care: data from the MRC Trial of the Assessment and Management of Older People in the Community. *Control Clin Trials,* 23**,** 409-21.
Spiegehalter, D., Thomas, A., Best, N. & Lunn, D. 2003. WinBUGS User Manual, version 1.4. MRC Biostatistics Unit. Cambridge, UK. .
Stata 2009. Stata programming reference manual, Version 11. Texas, US: StataCorp.
Thompson, S. G., Nixon, R. M. & Grieve, R. 2006. Addressing the issues that arise in analysing multicentre cost data, with application to a multinational study. *J Health Econ,* 25**,** 1015-28.
Turner, R. M., White, I. R. & Croudace, T. 2007. Analysis of cluster randomized cross-over trial data: a comparison of methods. *Stat Med,* 26**,** 274-89.
Vaness, D. & Mullahy, J. 2006. Perspectives on mean-based evaluation of health care. *In:* JONES, A. (ed.) *The Elgar Companion to Health Economics.* Cheltenham, UK: Edward Elgar.
Willan, A. & Briggs, A. 2006. *Statistical Analysis of cost-effectiveness data,* Chichester, UK, John Wiley & Sons, Ltd. .
Willan, A. R., Briggs, A. H. & Hoch, J. S. 2004. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. *Health Econ,* 13**,** 461-75.
Wooldridge, J. M. 2010. *Econometric analysis of cross section and panel data,* Cambridge, Mass., MIT Press.

Table I. The PoNDER case-study. Covariate balance for baseline covariates, and correlation of those covariates with endpoints.

Covariates	**Control group** (n=495)	**Treatment group** (n=1237)	**Standardised difference** (%)	**Correlation with endpoints**	
Cluster-level					
Cluster size	35.2 (21.08)	39.8 (19.71)	26.3	$r_0^{cost} = 0.46$ $r_0^{qaly} = 0.29$	$r_1^{cost} = -0.03$ $r_1^{qaly} = 0.05$
Individual-level					
Age	32.0 (5.12)	31.3 (5.03)	13.8	$r_0^{cost} = 0.03$ $r_0^{qaly} = -0.04$	$r_1^{cost} = -0.04$ $r_1^{qaly} = -0.02$
Baseline QALY	0.256 (0.035)	0.259 (0.034)	7.4	$r_0^{cost} = -0.12$ $r_0^{qaly} = 0.77$	$r_1^{cost} = -0.19$ $r_1^{qaly} = 0.76$
Depression score	6.85 (4.95)	6.57 (4.81)	5.7	$r_0^{cost} = 0.10$ $r_0^{qaly} = -0.56$	$r_1^{cost} = 0.30$ $r_1^{qaly} = -0.54$
Socio-economic Status	345 (69.8%)	876 (70.8%)	2.3	$r_0^{cost} = 0.03$ $r_0^{qaly} = 0.08$	$r_1^{cost} = 0.02$ $r_1^{qaly} = 0.01$
Major life events	202 (40.8%)	492 (39.8%)	2.1	$r_0^{cost} = -0.02$ $r_0^{qaly} = -0.16$	$r_1^{cost} = 0.05$ $r_1^{qaly} = -0.17$
Previous Depression	40 (8.1%)	107 (8.6%)	2.1	$r_0^{cost} = -0.02$ $r_0^{qaly} = -0.09$	$r_1^{cost} = 0.11$ $r_1^{qaly} = -0.16$
Living alone	22 (4.4%)	44 (3.6%)	4.5	$r_0^{cost} = -0.06$ $r_0^{qaly} = -0.05$	$r_1^{cost} = 0.04$ $r_1^{qaly} = -0.13$

Note: continuous covariates reported as Mean (SD) and binary covariates as N (%).

Table II. PoNDER case-study. Mean (SE) incremental cost (£), incremental QALY, INB (£) for models without and with covariate adjustment.

	SUR			MLM			TSB		
	Base case[1]	**Adjusted for key covariates[2]**	**With interaction[3 †]**	**Base case[1]**	**Adjusted for key covariates[2]**	**With interaction[3 †]**	**Base case[1]**	**Adjusted for key covariates[2]**	**With interaction[3 †]**
Incremental cost	-63.4 (50.2)	-67.5 (45.0)	-86.4 (29.1)	-21.4 (25.3)	-19.9 (25.2)	-78.4 (29.7)	-61.7 (45.7)	-37.2 (10.1)	-43.0 (10.4)
Incremental QALY	0.0043 (0.0020)	0.0019 (0.0012)	0.0021 (0.0013)	0.0044 (0.0021)	0.0019 (0.0013)	0.0021 (0.0013)	0.0042 (0.0024)	0.0027 (0.0011)	0.0028 (0.0012)
INB (λ=£20 000)	149.4 (70.1)	105.5 (57.9)	127.8 (47.8)	109.0 (50.0)	58.1 (36.8)	119.7 (42.4)	146.1 (65.3)	91.7 (25.5)	99.6 (28.8)
AIC	16 886	15 110	14 808	16 630	14 936	14 742	16 894	15 090	14 840

[1]Model without covariates; [2]Model adjusted for cluster size, socio-economic status, age and other key clinical factors (Morrell et al., 2009); [3]Model with previous covariates plus a treatment interaction with cluster size; [†]results reported at the mean cluster size.

Table III. Description of the main parameter values allowed to vary across the different scenarios in the simulation study.

Scenario	Individual-level covariate			Cluster-level covariate			Costs	ICCs	cv_{imb}	M
	d	r_e	r_c	d	r_e	r_c				
S1	0	0	0	0	0	0	Normal	0.01	0	20
S2	0	0.1	0	0	0	0	Normal	0.01	0	20
S3	5	0.1	0	0	0	0	Normal	0.01	0	20
S4	5	0.3	0	0	0	0	Normal	0.01	0	20
S5	20	0.3	0	0	0	0	Normal	0.01	0	20
S6	20	0.3	-0.3	0	0	0	Gamma	0.01	0	20
S7	20	0.3	-0.3	20	0.3	0.3	Gamma	0.01	0	20
S8	20	0.3	-0.3	20	0.3	0.3	Gamma	0.2	0	20
S9	20	0.3	-0.3	20	0.3	0.3	Gamma	0.2	1	20
S10	20	0.3	-0.3	20	0.3	0.3	Gamma	0.2	1	3
S11	20	0.3	-0.3	20	0.3†	0.3†	Gamma	0.2	1	20

Notes: d- standardised difference; r_e – correlation between covariate and outcomes; r_c – correlation between covariate and costs; cv_{imb} - coefficient of variation of the cluster size; M – no. of clusters per arm; †correlation was 50% higher for treatment arm (differential prognostic strength).
The choice of parameter values was informed by previous systematic and conceptual reviews (Gomes et al., 2011a), and from data extracted from eight case studies (Gomes et al., 2011b).

Table IV. Bias (SE) of the INB for a set of scenarios (S1-S5) which allow for increasing levels of baseline imbalance for an individual-level covariate, and increasing levels of correlation of that covariate with health outcome (QALYs, true INB=£1 000).

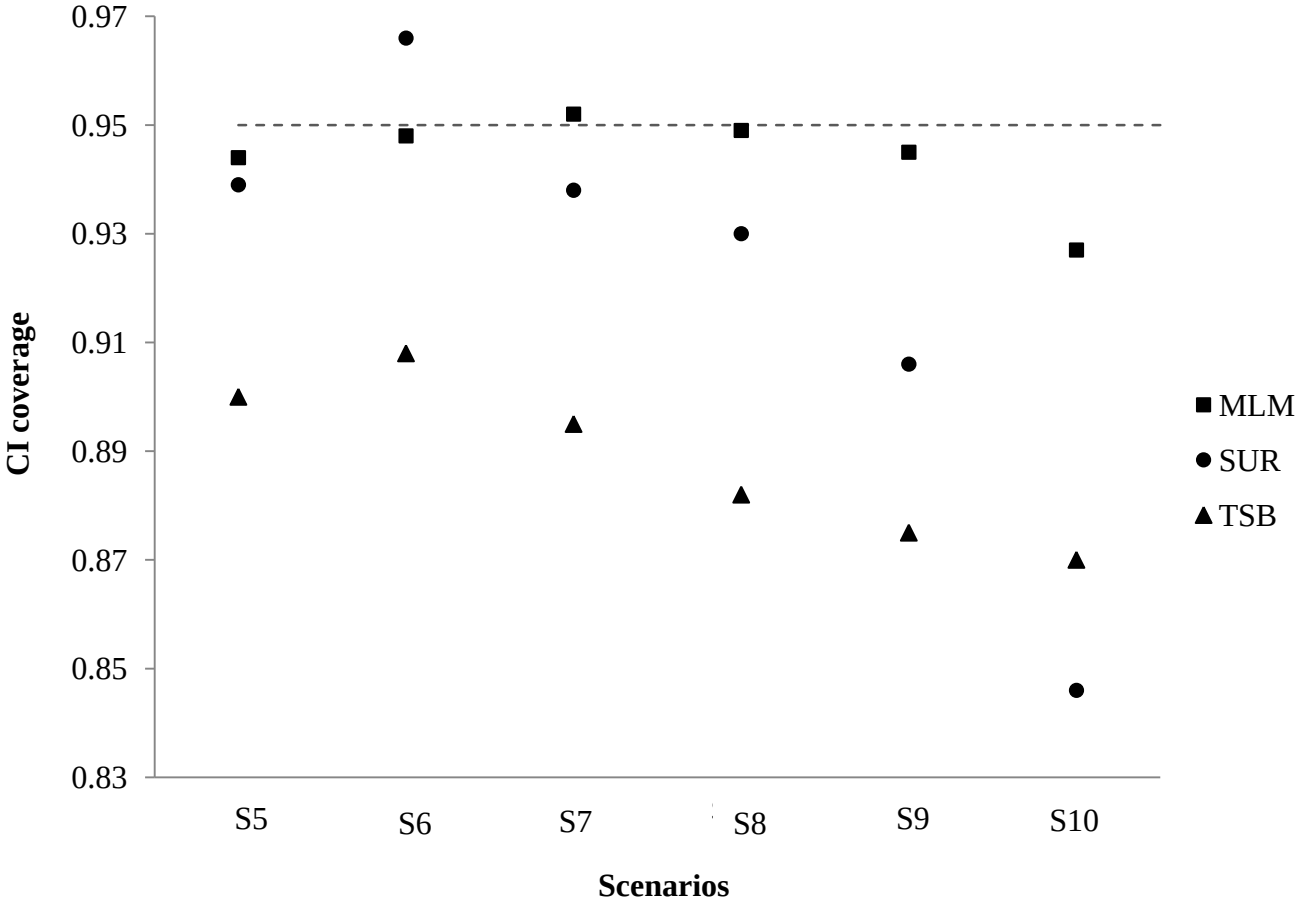
			SUR		MLM		TSB	
Scenario	**Baseline imbalance**	**Correlation between covariate and outcome**	Without covariate adjustment	With covariate adjustment	Without covariate adjustment	With covariate adjustment	Without covariate adjustment	With covariate adjustment
S1	**None**	**None**	0.14 (2.46)	0.56 (2.50)	0.14 (2.46)	0.56 (2.50)	0.13 (2.47)	0.43 (2.47)
S2	**None**	**Low (0.1)**	0.26 (2.47)	0.11 (2.46)	0.26 (2.47)	0.11 (2.46)	0.24 (2.48)	0.11 (2.46)
S3	**Low (5)**	**Low (0.1)**	9.79 (2.47)	0.07 (2.46)	9.79 (2.47)	0.07 (2.46)	9.81 (2.48)	0.04 (2.46)
S4	**Low (5)**	**High (0.3)**	30.9 (2.58)	0.08 (2.46)	30.9 (2.58)	0.08 (2.46)	31.0 (2.58)	0.02 (2.46)
S5	**High (20)**	**High (0.3)**	125.3 (2.58)	0.01 (2.47)	125.3 (2.58)	0.01 (2.47)	125.3 (2.58)	0.03 (2.47)

Table V – Bias, variance, rMSE CI coverage and width of the INB for a scenario (S11) with a cluster-level prognostic relationship that differs by treatment arm (true INB=£1 000).

	SUR			MLM			TSB		
	Without covariate adjustment	Adjust for main effect only	Adjust for interaction*	Without covariate adjustment	Adjust for main effect only	Adjust for interaction	Without covariate adjustment	Adjust for main effect only	Adjust for interaction
Mean (SE) bias	421.9 (28.9)	167.9 (9.4)	3.93 (28.0)	422.3 (27.9)	167.5 (7.6)	3.51 (22.3)	423.9 (29.1)	168.2 (9.0)	4.71 (26.2)
variance	1 673 434	176 655	183 833	1 555 618	116 477	112 697	1 695 850	162 577	158 030
rMSE	1 361	453	438	1 317	380	367	1 369	437	425
CI coverage	0.808	0.879	0.885	0.790	0.919	0.947	0.809	0.875	0.881
Mean CI width	1 742	1 472	1 352	1 711	1 343	1 194	1 749	1 482	1 401

* ATE is reported at the covariate mean. This scenario is characterised by high ICCs (0.2), unequal numbers per cluster, and 20 clusters per treatment arm

Figure 1 – CI coverage of the INB (nominal level is 0.95) for adjusted methods for the following scenarios: base case (S5); confounding on costs (S6); imbalanced cluster-level covariate (S7); high ICCs (S8); high cluster size variation (S9); few clusters (S10)*.



*Each scenario includes the other characteristics of the preceding scenario.

Appendix 1 – Algorithm for the non-parametric TSB combined with SUR.

Suppose we have M_k clusters randomised to treatment (k=2) and control (k=1), with n_j individuals within each cluster j.

1. For i in 1 to n_j (individuals in cluster j)
2. For j in 1 to M_k (clusters in treatment k)
3. For k in 1 to 2 (treatments)
4. Calculate shrunken cluster means, $\hat{x}_j^c$ and $\hat{x}_j^e$, for cost and outcome[9].
5. Calculate standardized individual-level residuals, $\hat{z}_{cost,ji}$ and $\hat{z}_{effect,ji}$, for cost and outcome[10].
6. Randomly sample (with replacement) M_k pairs of cluster means, $x^*_{cost,j'}$ and $x^*_{effect,j'}$, from the shrunken cluster means calculated in step 4.
7. Within each resampled cluster, randomly sample (with replacement) $\sum_{j'=1}^{M_k} n_{j'}$ pairs of standardized residuals (step 5), $z^*_{cost,i'}$ and $z^*_{effect,i'}$, where i'=1... $\sum_{j'=1}^{M_k} n_{j'}$.
8. Re-construct the sample ($y^*_{cost,j'i'}$, $y^*_{effect,j'i'}$) by adding the shrunken cluster means from step 6 and the standardized residuals from step 7, i.e. $y^*_{cost,j'i'} = x^*_{cost,j'} + z^*_{cost,i'}$ where $i' = 1 \ldots n_{j'}$ and likewise for effects; call it a 'synthetic' sample.
9. Incorporate the covariate set ($w_{j'i'}$) into each synthetic sample: ($y^*_{cost,j'i'} + w_{j'i'}$, $y^*_{effect,j'i'} + w_{j'i'}$). Covariates can be different for costs versus outcomes.
10. Repeat steps 4 to 9 for each treatment arm and stack these 'synthetic' samples into a single bootstrap sample.
11. Replicate steps 6 to 10 R times to construct R bootstrap samples.
12. Apply SUR without robust standard error to each bootstrap sample generated in step 11, to estimate mean and standard error (SE) of incremental costs (ΔC), incremental outcomes (ΔE) and the covariance (ΔC,ΔE), adjusted for potential confounders.
13. Calculate the parameter of interest, e.g. INB, by averaging SUR estimates across the R replications: $\widehat{INB} = (\sum_{r=1}^{R} \widehat{\Delta \mathrm{E}}_\mathrm{r}\, \lambda - \widehat{\Delta \mathrm{C}}_\mathrm{r})/\mathrm{R}$, where λ is the willingness-to-pay for a QALY.
14. Applying the Central Limit Theorem, CIs for INB can be constructed as $\widehat{INB} \pm 1.96 SE(\widehat{INB})$ (Nixon et al., 2010) where,

$$SE(\widehat{INB}) = \sqrt{[\sum_{r=1}^{R} \mathrm{SE}(\widehat{\Delta \mathrm{E}}_\mathrm{r})^2\, \lambda^2 + \mathrm{SE}(\widehat{\Delta \mathrm{C}}_\mathrm{r})^2 - 2\lambda \mathrm{cov}(\widehat{\Delta \mathrm{E}}_\mathrm{r}, \widehat{\Delta \mathrm{E}}_\mathrm{r})]/\mathrm{R}}.$$

---

[9] $\hat{x}_j^c = c\bar{y}_{..}^c + (1-c)\bar{y}_j^c$ where c is given by $(1-c)^2 = \frac{M_k}{M_k - 1} - \frac{SS_W}{b(b-1)SS_B}$; SS_w= within-sum of squares and SS_B = between-sums of squares, b = average cluster size (a formulation akin to the harmonic mean is used here (Smeeth and Ng, 2002)).

[10] $\hat{z}_{cost,ji} = \frac{y_{cost,ji} - \bar{y}_{cost,j.}}{\sqrt{1-b^{-1}}}$, where $y_{cost,ji}$ is the observed cost for the i-th individual in cluster j. These are similarly calculated for outcomes and separately for the two treatments.

Appendix 2 – Bias (True INB=£1 000), variance and rMSE of the INB for adjusted methods, across scenarios S5-S10*.

	Bias			Variance			rMSE		
	SUR	**MLM**	**TSB+SUR**	**SUR**	**MLM**	**TSB+SUR**	**SUR**	**MLM**	**TSB+SUR**
Base-case (S5)	0.04 (2.47)	0.01 (2.47)	0.26 (2.47)	12 168	12 172	12 174	110.3	110.3	110.3
Confounding on costs (S6)	1.77 (2.65)	1.78 (2.65)	1.59 (2.65)	14 092	14 092	14 073	118.7	118.7	118.6
Cluster-level covariate (S7)	0.06 (2.69)	0.06 (2.69)	3.24 (2.67)	14 475	14 468	14 258	120.3	120.2	119.4
High ICCs (S8)	7.84 (7.06)	8.11 (7.05)	8.25 (7.05)	99 431	99 549	99 431	315.5	315.3	315.4
High cluster size variation (S9)	10.3 (9.54)	2.04 (7.76)	9.07 (9.22)	182 142	120 300	169 880	426.8	346.8	412.2
Few clusters (S10)	0.15 (15.5)	0.56 (12.8)	1.48 (14.5)	478 875	329 378	422 329	691.8	573.8	649.7

* Each scenario includes the other characteristics of the preceding scenario.