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A mixed model approach to estimate the survivor average causal effect in cluster-randomized trials

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Summary

In many medical studies, the outcome measure for some study participants becomes informatively truncated (censored, missing, or unobserved) due to death or other forms of drop out, creating a nonignorable missing data problem. In such cases, imputation methods that fill in unmeasureable QOL values for those who died rely on strong and untestable assumptions and may be conceptually unappealing to certain stakeholders when estimating a treatment effect. Composite outcomes that apply a value for death in the QOL distribution (such as the worst value) are a popular solution to account for death, but create treatment effects that can be difficult to interpret. The survivor average causal effect (SACE) is an alternative causal estimand that surmounts some of these issues. While principal stratification has been applied to estimate the SACE in individually-randomized trials, methods for estimating the SACE in cluster-randomized trials are currently limited. We develop a mixed model approach with an expectation-maximization algorithm to estimate the SACE in cluster-randomized trials. We model the continuous outcome measure with random effects to account for the intracluster correlations due to cluster-level randomization. In simulations we compare the performance of our approach with the existing fixed-effects approach without random effects, observing that our new approach has a smaller mean squared error of estimating the SACE and the associated confidence interval estimator provides closer to the nominal 95% level coverage. Our methodology is then illustrated in a cluster-randomized trial of telecare and assistive technology on health-related QOL in the elderly.

KEYWORDS:

Cluster randomized trials; Linear mixed models; Expectation-maximization; Potential outcomes; Principal stratification; Survivor average causal effect

1 | INTRODUCTION

The informative “truncation" or “censoring" by death problem is a challenge in many studies. When death occurs, the non-mortality outcome can not be measured or defined for those who die before the time of planned study measurement. Further, as the reason for the inability to measure an important study outcome is known and itself meaningful (i.e., nonignorable or missing not at random), this truncation is informative and can bias inference with statistical models that assume missing completely at random (MCAR) or missing at random (MAR)[1,2,3,4]. A common example of this problem in the medical literature is missing quality of life (QOL) measures due to death. Researchers have a limited number of options in such settings[3,4]. Composite outcomes (e.g., applying the worst possible QOL value to those who die) are a popular solution, but can be difficult to interpret and similar summary values of a composite outcome in different studies may represent very different combinations of clinical outcomes[5,6]. Imputation strategies are another potential solution, but also raise conceptual challenges as any imputed value for an informatively unmeasured outcome results in an explicit or implicit valuation of that health state to equal a value observed among those who did not die which may not be appealing or logical to certain stakeholders. Other potential approaches, such as a survivors only or complete case analysis, produce estimates that do not have a clear causal interpretation under the counterfactual outcome framework. In these frameworks, those who survive under treatment and control can be systematically different, and this obscures the target estimand[7,8].

In this manuscript, we focus on the survivor average causal effect (SACE) as a potential solution for the truncation-by-death problem. Under the potential outcomes framework, Frangakis and Rubin[9] first considered the principal stratification framework to estimate the SACE with independent and identically distributed data. The principal stratification framework has been demonstrated as a useful tool to address a wide range of similar problems beyond truncation-by-death, including noncompliance (e.g., using the related complier average causal effect[10]) and surrogate outcomes[11]. The framework (detailed more fully in Section 2) allows researchers to consider cohort members as belonging to at least four strata (Table 1). Two strata indicate those who would or would not survive regardless of treatment: these are the *always survivors* and *never survivors* stratum. The other two stratum indicate those who would only respond under treatment or control, classified as *compliant/protected* and *defiant/harmed* survivors. Because the pair of counterfactual non-mortality outcomes are only both well-defined for those who would survive under both treatment and control, the SACE is defined as the effect of an intervention on the outcome among the always survivors.

Principal stratification and the SACE framework have been used in a number of settings. For example, Zhang and Rubin[1] used the SACE to examine the impact of an educational program on test scores when the scores were not possible to collect among those who dropped out of school before taking the test. The SACE framework has also been used to gain insight into the effect of intensive care unit-based interventions for critically ill patients[12,13,14]. Bounds of the SACE providing the smallest and the largest possible values have been derived[1,15,16]. In practice, however, the bounds may be too wide to be informative for deciding whether the effect is positive or negative[17]. Further, in many studies, it is often of interest to have a point estimate of the SACE. Zhang et al[18] developed a likelihood-based method for SACE point estimation using the expectation-maximization (EM) algorithm[19] to estimate the wage effect of a job training program using principal stratification in a setting where wages are only meaningfully defined for employed individuals. Other approaches for estimating the SACE point estimate include the use of a sensitivity analysis procedure[20], a pretreatment covariate[17], a nonparametric structural equations model[21], and a substitution variable in the always survivors stratum[22].

The aforementioned approaches focus on randomized trials or observational studies where treatment or exposure assignment is at the individual level. However, many multicenter studies where the SACE would be useful must deal with clustering by

study sites, and methods for estimating the SACE in such settings are currently limited with a few exceptions for estimating the complier average causal effect. Specifically, principal stratification has been applied in clustered encouragement designs where the treatment encouragement is assigned at the cluster level[23,24] to address treatment non-compliance. In this article, we develop a mixed model-based estimator to support the estimation of SACE under the framework of principal stratification in cluster-randomized trials (CRTs). In CRTs, groups of subjects, instead of individuals, are randomized to treatment arms. Due to shared features among subjects within clusters, it is likely that the outcomes in the same cluster are more similar than those from different clusters[25,26]. The resulting similarity (or homogeneity) of patients (and thus their outcomes) within the same cluster then induces a positive intracluster correlation that must be accounted for in the analysis of the trial to ensure valid statistical inference. To explicitly account for the possible intracluster correlations when estimating the SACE, we develop a clustered mixture model by introducing cluster-level random effects into the stratum-specific potential outcome models (Section 3).

We adopt the multinomial logistic regression to model the membership probability in each principal stratum[18] to differentiate the latent strata in the trial population. Conditional on the random effects, each individual's observed outcome in a treated cluster can come from the always survivor stratum or the protected stratum, and thus is in a mixture model form[27,28,18]. Similarly, in a control cluster, a non-survivor whose outcome is not observed has a mixture model formulation. To estimate the model parameters and therefore the SACE, we develop an EM type algorithm[19,29,30,31,32] that maximizes the conditional log-likelihood function of the complete data given the observed data. For simplicity, we follow the conventional monotonicity assumption (Assumption 2 in Section 2.3) in our derivation. We note that without this assumption, an estimator can still be developed[18] but the likelihood function can be much flatter and so may engender less stable estimates. Our proposed model differs from the standard finite mixture model with random effects such as those in[33,34] because the potential outcomes may not be defined in certain mixture strata due to truncation. For example, due to the truncation by death, non-survivors' outcomes are not observed which then leads to a complicated form of the likelihood function.

The rest of the article is organized as follows. Section 2 presents our study setup, and our models and the estimation procedure are in Sections 3 and 4 separately. In Section 5, we conduct a simulation study to compare our approach of estimating SACE with the approach of no random effects as in[18]. We illustrate the proposed method to estimate SACE in a CRT evaluating a telehealth program in Section 6. Section 7 concludes.

2 | NOTATION AND SETUP

In the following, we review the framework of the potential outcomes, and then the principal stratification framework to guide our work in the context of a parallel-arm CRT. We use the same subscript i to indicate the i-th cluster, either treatment or control, and the same subscript j to indicate the j-th subject in that cluster. Thereafter, we outline the common assumptions used to support estimation of the SACE in CRTs.

2.1 | Potential outcomes

In a CRT, subjects within the same cluster share the same treatment status. Let $D_i \in \{0, 1\}$ be the binary treatment assignment for the i-th cluster, with $D_i = 1$ indicating treatment and $D_i = 0$ indicating control. Let $S_{ij}(D_i)$ be the potential survival status that would be observed under the treatment assignment D_i. Let $Y_{ij}(D_i)$ be the potential outcome that would be observed under D_i. The outcome $Y_{ij}(D_i)$ is defined only for a survivor, i.e., $S_{ij}(D_i) = 1$.

TABLE 1 The four principal strata of trial participants using principal stratification.

ss	always survivors	$\{S_{ij}(1) = 1, S_{ij}(0) = 1\}$
sn	protected	$\{S_{ij}(1) = 1, S_{ij}(0) = 0\}$
ns	harmed	$\{S_{ij}(1) = 0, S_{ij}(0) = 1\}$
nn	never survivors	$\{S_{ij}(1) = 0, S_{ij}(0) = 0\}$

2.2 | Principal stratification

Each subject has two potential survivor status under treatment and control. Based on them, the framework of principal stratification[9] suggests that each subject can be classified into one of the four principal strata, defined by the joint potential values of the survival status (Table 1). Specifically, we let "s" stand for "survivor" and "n" stand for "non-survivor". We use "ss" to represent the always-survivors stratum (i.e., $\{S_{ij}(1) = 1, S_{ij}(0) = 1\}$) where a subject would survive regardless of the treatment assignment. We let "sn" indicate the protected stratum (i.e., $\{S_{ij}(1) = 1, S_{ij}(0) = 0\}$), where a subject would survive under treatment but would not survive under control. We use "ns" to represent the harmed stratum (i.e., $\{S_{ij}(1) = 0, S_{ij}(0) = 1\}$), where subjects would not survive under treatment but would survive under control. Finally, we let "nn" indicate the never-survivors stratum (i.e., $\{S_{ij}(1) = 0, S_{ij}(0) = 0\}$), where subjects would not survive in either treatment or control.

In practice, we cannot observe both $S_{ij}(1)$ and $S_{ij}(0)$ for each subject, i.e., we observe only one of $S_{ij}(1)$ and $S_{ij}(0)$ depending on the assigned treatment status. However, we are able to track the principal stratum to some degree based on the observed treatment assignment and the observed survival status. In a treatment cluster with $D_i = 1$, a survivor is in either the "ss" stratum or the "sn" stratum, whereas a non-survivor is in either the "ns" or the "nn" stratum. In a control cluster with $D_i = 0$, a survivor is in the "ss" stratum while a non-survivor is in the "sn" or the "nn" stratum. In general, the potential outcomes $Y_{ij}(1)$ and $Y_{ij}(0)$ can be only well-defined if the patient survives until the end of the study. Therefore, a common estimand of interest, SACE, in the presence of truncation, can be defined in a CRT as an participant-level average of potential outcome contrasts among the always-survivors, or equivalently,

$$\text{SACE} = E[Y_{ij}(1) - Y_{ij}(0)|S_{ij}(1) = S_{ij}(0) = 1] \tag{1}$$

2.3 | Assumptions

We assume that the cluster-level treatment assignment is independent of potential outcomes and the survival status of subjects within a cluster. This assumption holds by cluster randomization design and we formally spell the assumption below.

Assumption 1. *The treatment assignment D_i is independent of the collection of potential outcomes for each cluster, $\{Y_{ij}(1), Y_{ij}(0), S_{ij}(1), S_{ij}(0), j = 1, \ldots, m_i\}$, and m_i is the number of individuals in cluster i.*

In addition, we assume monotonicity such that there is no harmed patients who would survive under control arm but would die otherwise. This is often plausible in many CRT applications with system-level interventions which are perceived to be beneficial for patients.

Assumption 2. *For each subject j in cluster i, $S_{ij}(1) \geq S_{ij}(0)$, i.e., the cluster-level treatment does not lead to worse survival for each subject.*

Under this monotonicity assumption, there is no harmed stratum “ns" (which is an assumption that we revisit in the discussion). Each subject is therefore able to be classified into one of the three principal strata, “ss", “sn", or “nn", prior to the treatment assignment. However, the “ss" stratum is the only group for which both $Y_{ij}(1)$ and $Y_{ij}(0)$ are well-defined due to the absence of death truncation. Inference regarding the causal effect of treatment on the outcome will then be drawn only for the always-survivors where the SACE is well-defined in equation (1). As a more concrete illustration, Table 2 shows the relationship between each principal stratum and the observed survival status where the outcome is not defined for non-survivors (denoted by an asterisk, *).

TABLE 2 Three key principal strata and a tabulation of the possibly observed non-mortality outcomes in each stratum.

Principal stratum			$D_i = 1, S_{ij} = 1$	$D_i = 0, S_{ij} = 1$
ss:	always survivors,	$\{S_{ij}(1) = 1, S_{ij}(0) = 1\}$	$Y_{ij}(1)$	$Y_{ij}(0)$
sn:	protected,	$\{S_{ij}(1) = 1, S_{ij}(0) = 0\}$	$Y_{ij}(1)$	*
nn:	never survivors,	$\{S_{ij}(1) = 0, S_{ij}(0) = 0\}$	*	*

3 | PARAMETRIC MODELS FOR CLUSTER-RANDOMIZED TRIALS

In the following, we use subscripts “ss", “sn" or “nn" to denote the principal stratum specific parameters or variables. An extra subscript “1" or “0" respectively refers to a treated cluster or a control cluster.

3.1 | Principal strata membership models

Let each of the elements of the random vector $\mathbf{Z}_{ij} = (Z_{ss,ij}, Z_{sn,ij}, Z_{nn,ij})'$ be the binary indicator of the corresponding principal stratum. For example, $\mathbf{Z}_{ij} = (1, 0, 0)'$ means the (i, j)-th subject is in the “ss" stratum. Let $p_{ss,ij} = \mathrm{E}(Z_{ss,ij})$, and similarly we define $p_{sn,ij}$ and $p_{nn,ij}$. Let $\mathbf{x}_{ij}$ be a column vector of measured covariates (including the intercept) of the j-th subject in the i-th cluster. We consider a multinomial logistic membership model such that the reference “nn" stratum membership model is $p_{nn,ij} = 1/(1 + \exp\{\mathbf{x}'_{ij}\boldsymbol{\alpha}_{ss}\} + \exp\{\mathbf{x}'_{ij}\boldsymbol{\alpha}_{sn}\})$, where $\boldsymbol{\alpha}_{ss}$ and $\boldsymbol{\alpha}_{sn}$ are the regression coefficient vectors. We further have $p_{ss,ij} = p_{nn,ij}\exp\{\mathbf{x}'_{ij}\boldsymbol{\alpha}_{ss}\}$, $p_{sn,ij} = p_{nn,ij}\exp\{\mathbf{x}'_{ij}\boldsymbol{\alpha}_{sn}\}$.

3.2 | Outcome models in principal strata

Let $\mathcal{N}$ denote a normal density function. In the i-th treated cluster and under the treatment condition, we model the potential outcomes in the always-survivors stratum (“ss") with the random effect u_{1i} to account for the cluster-level random effects as

$$y_{ij}(1) = \mathbf{x}'_{ij}\boldsymbol{\beta}_{ss,1} + u_{1i} + \epsilon_{ij},\ u_{1i} \sim \mathcal{N}(0, \tau^2),\ \epsilon_{ij} \sim \mathcal{N}(0, \sigma^2), \tag{2}$$

and the outcome in the protected stratum ("sn") as

$$y_{ij}(1) = \mathbf{x}'_{ij}\boldsymbol{\beta}_{sn} + u_{1i} + \epsilon_{ij},\ u_{1i} \sim \mathcal{N}(0, \tau^2),\ \epsilon_{ij} \sim \mathcal{N}(0, \sigma^2). \tag{3}$$

We assume the observed outcome of a survivor follows a mixture distribution with the probability $p_{ss,ij}$ from the model (2), and with the probability $p_{sn,ij}$ from the model (3). That is, conditional on u_{1i}, the density of a survivor's outcome in the i-th treated cluster has the mixture model form

$$f(y_{ij}|u_{1i}) = \mathcal{N}(\mathbf{x}'_{ij}\boldsymbol{\beta}_{ss,1} + u_{1i}, \sigma^2)p_{ss,ij} + \mathcal{N}(\mathbf{x}'_{ij}\boldsymbol{\beta}_{sn} + u_{1i}, \sigma^2)p_{sn,ij}. \tag{4}$$

In the i-th control cluster where $D_i = 0$, we model the potential outcome in the "ss" stratum with the random effect u_{0i} as

$$y_{ij}(0) = \mathbf{x}'_{ij}\boldsymbol{\beta}_{ss,0} + u_{0i} + \epsilon_{ij},\ u_{0i} \sim \mathcal{N}(0, \tau^2),\ \epsilon_{ij} \sim \mathcal{N}(0, \sigma^2). \tag{5}$$

The outcome is not defined for a non-survivor who has the probability $p_{sn,ij}$ from the "sn" stratum, and the probability $p_{nn,ij}$ from the "nn" stratum. For simplicity, we assume the outcome models share the same variance/covariance parameters τ^2 and σ^2. Under the above parameterization, the intra-cluster correlation (ICC) among the always-survivors is given by $\tau^2/(\tau^2 + \sigma^2)$. Our model can be extended to accommodate the heterogeneity of distinct variance/covariance parameters of the outcomes.

3.3 | Likelihood function of the complete data

Table 3 shows the possible components of an individual's likelihood function. The observed outcome density in the treatment group follows a mixture model formulation as in (4). The observed data consist of the observed outcomes and the survival status of all the subjects. The missing data include the principal stratum indicator variables $\mathbf{Z}_{ij}$'s and the random effects u_{1i}'s and u_{0i}'s.

TABLE 3 Contribution of each subject's likelihood function given the survival status and the treatment assignment conditional on the random effects.

Observation	Principal stratum		Treatment ($D_i = 1$)	Control ($D_i = 0$)
Survivor	ss:	always-survivors	$p_{ss,ij}\mathcal{N}(\mathbf{x}'_{ij}\boldsymbol{\beta}_{ss,1} + u_{1i}, \sigma^2)$	$p_{ss,ij}\mathcal{N}(\mathbf{x}'_{ij}\boldsymbol{\beta}_{ss,0} + u_{0i}, \sigma^2)$
	sn:	protected	$p_{sn,ij}\mathcal{N}(\mathbf{x}'_{ij}\boldsymbol{\beta}_{sn} + u_{1i}, \sigma^2)$	*
Non-survivor	sn:	protected	*	$p_{sn,ij}$
	nn:	never-survivors	$p_{nn,ij}$	$p_{nn,ij}$

To arrive at the likelihood function, we now write f a generic density function. Suppose there are $m_{1,i}$ subjects in the i-th treated cluster. Let $\mathbf{y}_i = (y_{i1}\ \cdots\ y_{i\,m_{1,i}})'$ be the observed outcome vector. The likelihood of the complete data $(\mathbf{Z}_{ij}, \mathbf{y}_i, u_{1i})$, assuming the random-effects are observed, in the i-th treated cluster is

$$\prod_{j=1}^{m_{1,i}} \left\{ p_{ss,ij}^{Z_{ss,ij}} f_{ss,1}(y_{ij}|u_i)^{Z_{ss,ij}} \right\} \left\{ p_{sn,ij}^{Z_{sn,ij}} f_{sn}(y_{ij}|u_i)^{Z_{sn,ij}} \right\} \left\{ f(u_i)^{Z_{ss,ij}+Z_{sn,ij}} \right\} \left\{ p_{nn,ij}^{Z_{nn,ij}} \right\},$$

where $f_{ss,1}(y_{ij}|u_i) = \mathcal{N}(\mathbf{x}'_{ij}\boldsymbol{\beta}_{ss,1} + u_{1i}, \sigma^2)$ and $f_{sn}(y_{ij}|u_i) = \mathcal{N}(\mathbf{x}'_{ij}\boldsymbol{\beta}_{sn} + u_{1i}, \sigma^2)$ are from (2) and (3). Suppose there are $m_{0,i}$ subjects in the i-th control cluster. Let $f_{ss,0}(y_{ij}|u_i) = \mathcal{N}(\mathbf{x}'_{ij}\boldsymbol{\beta}_{ss,0} + u_{0i}, \sigma^2)$ from (5). Similarly, in the i-th control cluster, the

likelihood of the complete data, according to Table 3, is

$$\prod_{j=1}^{m_{0,i}} \left\{ p_{ss,i}^{Z_{ss,ij}} f_{ss,0}(y_{ij}|u_i)^{Z_{ss,ij}} \right\} \left\{ f(u_i)^{Z_{ss,ij}} \right\} \left\{ p_{sn,ij}^{Z_{sn,ij}} \right\} \left\{ p_{nn,ij}^{Z_{nn,ij}} \right\}.$$

4 | ESTIMATION VIA EXPECTATION-MAXIMIZATION

Parameters in our models include $\{\boldsymbol{\beta}_{ss,1}, \boldsymbol{\beta}_{sn}, \boldsymbol{\beta}_{ss,0}, \boldsymbol{\alpha}_{ss}, \boldsymbol{\alpha}_{sn}, \sigma^2, \tau^2\}$. To estimate these parameters, we developed an EM algorithm approach[19]. The details of the iterative estimation procedure is provided in the supplementary material (Section S1), and we only outline the main steps below. We obtain the complete data log-likelihood based on the calculation in Section 3.3. In the E-step, we calculate the conditional expectation of the complete data log-likelihood given the observed data and the estimates from the previous iteration. The calculation relies on the conditional mean of $Z_{ss,ij}$ and $Z_{sn,ij}$, and the conditional mean and variance of u_{1i} and u_{0i}. We make the plausible assumption that each of $Z_{ss,ij}$ and $Z_{sn,ij}$ is conditionally independent of u_{i1} or u_{i0} given the observed data.

In the M-step, we find estimates of $\boldsymbol{\beta}_{ss,1}$ and $\boldsymbol{\beta}_{sn}$ by maximizing the conditional complete data log-likelihood of the treated clusters, and similarly estimate $\boldsymbol{\beta}_{ss,0}$ in the control clusters. We estimate the remaining parameters using data from both treated clusters and control clusters. After obtaining the parameter estimates, we also derive an estimator of the SACE and propose to use the cluster-bootstrap method to construct the confidence intervals.

4.1 | E-step

In the i-th treated cluster, we can compute

$$\eta_{ss,ij} \equiv \mathrm{P}(Z_{ss,ij} = 1|y_{ij}) = \frac{\mathcal{N}(\mathbf{x}'_{ij}\boldsymbol{\beta}_{ss,1}, \sigma^2 + \tau^2) p_{ss,ij}}{\mathcal{N}(\mathbf{x}'_{ij}\boldsymbol{\beta}_{ss,1}, \tau^2 + \sigma^2) p_{ss,ij} + \mathcal{N}(\mathbf{x}'_{ij}\boldsymbol{\beta}_{sn}, \tau^2 + \sigma^2) p_{sn,ij}},$$

and $\mathrm{P}(Z_{sn,ij} = 1|y_{ij}) = 1 - \eta_{ss,ij}$. In the i-th control cluster, we have

$$\eta_{sn,ij} \equiv \mathrm{P}(Z_{sn,ij} = 1|S_{ij} = 0) = \frac{p_{sn,ij}}{p_{sn,ij} + p_{nn,ij}},\ \mathrm{P}(Z_{ss,ij} = 1|y_{ij}) = 1.$$

To find the conditional mean and variance of u_{1i}, we perform a Monte Carlo E-step calculation[32]. Suppose there are $m_{1,i,1}$ survivors in the i-th treated cluster. We find the joint density of $(u_{1i}, \mathbf{y}_i)$, and the marginal density of $\mathbf{y}_i$ respectively as

$$f(u_{1i}, \mathbf{y}_i) = \left\{ \prod_{j=1}^{m_{1,i,1}} f(y_{ij}|u_{1i}) \right\} f(u_{1i}),\ f(\mathbf{y}_i) = \int f(u_{1i}, \mathbf{y}_i) \mathrm{d}u_{1i}.$$

We randomly sample a large number of (e.g., 100) u_{1i}'s from $N(0, \sigma^2)$ given the estimates from the previous iteration. Then we calculate $\mathrm{E}(u_{i1}|\mathbf{y}_i)$ and $\mathrm{Var}(u_{i1}|\mathbf{y}_i)$ numerically based on the conditional or posterior density of the random effect, $f(u_{1i}|\mathbf{y}_i) = f(u_{1i}, \mathbf{y}_i)/f(\mathbf{y}_i)$. Specifically, under the linear mixed modeling, we obtain the conditional mean and variance of u_{0i} in closed forms. Let $\mathbf{X}_i = (\cdots\ \mathbf{x}_{ij}\ \cdots)$ be a matrix whose number of columns is equal to the number of subjects in the cluster. Let $\mathbf{1}_i$ be a column vector of 1's of appropriate order. Let $m_{0,i,1}$ be the number of survivors in the i-th control cluster. We can arrive at $\mathrm{E}(u_{0i}|\mathbf{y}_i) = \tau^2 \mathbf{1}'_i(\mathbf{y}_i - \mathbf{X}'_i\boldsymbol{\beta}_{ss,0})/(m_{0,i,1}\tau^2 + \sigma^2)$ and $\mathrm{Var}(u_{0i}|\mathbf{y}_i) = \tau^2\sigma^2/(m_{0,i,1}\tau^2 + \sigma^2)$.

4.2 | M-step

Let $m_{1,1} = \sum_{i:D_i=1} m_{1,i,1}$ be the total number of survivors in the treatment clusters, and $m_{0,1} = \sum_{i:D_i=0} m_{0,i,1}$ be the total number of survivors in the control clusters. We obtain the estimates at the current iteration in the following:

$$\hat{\boldsymbol{\beta}}_{ss,1} = \left\{ \sum_{i:D_i=1} \sum_{j\le m_{1,i,1}} \eta_{ss,ij}(\mathbf{x}_{ij}\mathbf{x}'_{ij}) \right\}^{-1} \sum_{i:D_i=1} \sum_{j\le m_{1,i,1}} \eta_{ss,ij}\mathbf{x}_{ij} \left\{ y_{ij} - \mathrm{E}(u_{1i}|\mathbf{y}_i) \right\}$$

$$\hat{\boldsymbol{\beta}}_{sn} = \left\{ \sum_{i:D_i=1} \sum_{j\le m_{1,i,1}} (1-\eta_{ss,ij})(\mathbf{x}_{ij}\mathbf{x}'_{ij}) \right\}^{-1} \sum_{i:D_i=1} \sum_{j\le m_{1,i,1}} (1-\eta_{ss,ij})\mathbf{x}_{ij} \left\{ y_{ij} - \mathrm{E}(u_{1i}|\mathbf{y}_i) \right\}$$

$$\hat{\boldsymbol{\beta}}_{ss,0} = \left\{ \sum_{i:D_i=0} \sum_{j\le m_{0,i,1}} (\mathbf{x}_{ij}\mathbf{x}'_{ij}) \right\}^{-1} \sum_{i:D_i=0} \sum_{j\le m_{0,i,1}} \mathbf{x}_{ij} \left\{ y_{ij} - \mathrm{E}(u_{0i}|\mathbf{y}_i) \right\}$$

To update the variance components parameters, we let $y_{ij,ss,1} = y_{ij} - \mathbf{x}'_{ij}\hat{\boldsymbol{\beta}}_{ss,1} - \mathrm{E}(u_{1i}|\mathbf{y}_i)$, $y_{ij,sn} = y_{ij} - \mathbf{x}'_{ij}\hat{\boldsymbol{\beta}}_{sn} - \mathrm{E}(u_{1i}|\mathbf{y}_i)$, and $y_{ij,ss,0} = y_{ij} - \mathbf{x}'_{ij}\hat{\boldsymbol{\beta}}_{ss,0} - \mathrm{E}(u_{0i}|\mathbf{y}_i)$, based on which we can derive

$$\begin{aligned}\hat{\sigma}^2 &= \frac{\sum_{i:D_i=1}\sum_{j\le m_{1,i,1}} \left\{ \eta_{ss,ij}\, y^2_{ij,ss,1} + (1-\eta_{ss,ij}) y^2_{ij,sn} + \mathrm{Var}(u_{1i}|\mathbf{y}_i) \right\}}{m_{1,1}+m_{0,1}} \\ &\quad + \frac{\sum_{i:D_i=0}\sum_{j\le m_{0,i,1}} \left\{ y^2_{ij,ss,0} + \mathrm{Var}(u_{0i}|\mathbf{y}_i) \right\}}{m_{1,1}+m_{0,1}}. \\ \hat{\tau}^2 &= \frac{\sum_{i:D_i=1} m_{1,i,1}\mathrm{E}(u^2_{1i}|\mathbf{y}_i) + \sum_{i:D_i=0} m_{0,i,1}\mathrm{E}(u^2_{0i}|\mathbf{y}_i)}{m_{1,1}+m_{0,1}}.\end{aligned}$$

Finally, we estimate the coefficient vectors $\boldsymbol{\alpha}_{ss}$ and $\boldsymbol{\alpha}_{sn}$ in the multinomial logistic regression using the Newton-Raphson algorithm. Based on the multinomial likelihood formulation, the first and second order derivatives of $\boldsymbol{\alpha}_{ss}$ are

$$\begin{aligned}&\sum_{i:D_i=1}\sum_{j\le m_{1,i,1}} \eta_{ss,ij}\mathbf{x}'_{ij} + \sum_{i:D_i=0}\sum_{j\le m_{0,i,1}} \mathbf{x}'_{ij} - \sum_{i:D_i=1}\sum_{j\le m_{1,i}} \frac{\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{ss})}{1+\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{ss})+\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{sn})}\mathbf{x}'_{ij} \\ &\quad - \sum_{i:D_i=0}\sum_{j\le m_{0,i}} \frac{\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{ss})}{1+\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{ss})+\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{sn})}\mathbf{x}'_{ij},\end{aligned}$$

and

$$\begin{aligned}&- \sum_{i:D_i=1}\sum_{j\le m_{1,i}} \frac{\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{ss})\left\{1+\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{sn})\right\}}{\left\{1+\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{ss})+\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{sn})\right\}^2}\mathbf{x}_{ij}\mathbf{x}'_{ij}. \\ &- \sum_{i:D_i=0}\sum_{j\le m_{0,i}} \frac{\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{ss})\left\{1+\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{sn})\right\}}{\left\{1+\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{ss})+\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{sn})\right\}^2}\mathbf{x}_{ij}\mathbf{x}'_{ij}.\end{aligned}$$

Similarly, the first and second order derivatives of $\boldsymbol{\alpha}_{sn}$ are

$$\begin{aligned}&\sum_{i:D_i=1}\sum_{j\le m_{1,i,1}} (1-\eta_{ss,ij})\mathbf{x}'_{ij} + \sum_{i:D_i=0}\sum_{j\le m_{0,i,0}} \eta_{sn,ij}\mathbf{x}'_{ij} \\ &\quad - \sum_{i:D_i=1}\sum_{j\le m_{1,i}} \frac{\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{sn})}{\left\{1+\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{ss})+\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{sn})\right\}}\mathbf{x}'_{ij} \\ &\quad - \sum_{i:D_i=0}\sum_{j\le m_{0,i}} \frac{\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{sn})}{\left\{1+\exp(\zeta_{ss}+\mathbf{x}'_{ij}\boldsymbol{\alpha}_{ss})+\exp(\zeta_{sn}+\mathbf{x}'_{ij}\boldsymbol{\alpha}_{sn})\right\}}\mathbf{x}'_{ij},\end{aligned}$$

and

$$-\sum_{i:D_i=1}\sum_{j\le m_{1,i}}\frac{\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{sn})\left\{1+\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{ss})\right\}}{\left\{1+\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{ss})+\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{sn})\right\}^2}\mathbf{x}_{ij}\mathbf{x}'_{ij}$$
$$-\sum_{i:D_i=0}\sum_{j\le m_{0,i}}\frac{\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{sn})\left\{1+\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{ss})\right\}}{\left\{1+\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{ss})+\exp(\mathbf{x}'_{ij}\boldsymbol{\alpha}_{sn})\right\}^2}\mathbf{x}_{ij}\mathbf{x}'_{ij}.$$

These derivatives will be used in the iterative updates using the Newton formula.

4.3 | Estimation and Inference for Survivor Average Causal Effect

Because the joint potential values of the survival status $S_{ij}(1), S_{ij}(0)$ are not simultaneously observable, it is not immediate as how to derive the SACE from the parameter estimates under our modeling assumptions. To proceed, we base our estimate on an equivalent form of the SACE below. We summarize the result in a proposition, and the proof is provided in the supplementary material (Section S1).

Proposition 1. By Assumptions 1, we have

$$E[Y_{ij}(1)-Y_{ij}(0)|S_{ij}(1)=S_{ij}(0)=1]=\frac{\mathrm{E}[(\mathbf{x}'_{ij}\boldsymbol{\beta}_{ss,1}+u_{i1})p_{ss,ij}]}{\mathrm{P}[S_{ij}(1)=S_{ij}(0)=1]}-\frac{\mathrm{E}[(\mathbf{x}'_{ij}\boldsymbol{\beta}_{ss,0}+u_{i0})p_{ss,ij}]}{\mathrm{P}[S_{ij}(1)=S_{ij}(0)=1]}.$$

After we obtain the parameter estimates, we get the estimated $\hat{p}_{ss,ij}$ from the principal strata model. In the i-th treatment cluster, let $\hat{y}_{ij}=\mathbf{x}'_{ij}\hat{\boldsymbol{\beta}}_{ss,1}+\hat{\mathrm{E}}(u_{i1}|\mathbf{y}_i)$. In the i-th control cluster, let $\hat{y}_{ij}=\mathbf{x}'_{ij}\hat{\boldsymbol{\beta}}_{ss,0}+\hat{\mathrm{E}}(u_{i0}|\mathbf{y}_i)$. Proposition 1 suggests that we can estimate the SACE using the sample analogue

$$\frac{\sum_{i:D_i=1}\sum_{j=1}^{m_{1,i}}\hat{p}_{ss,ij}\hat{y}_{ij}}{\sum_{i:D_i=1}\sum_{j=1}^{m_{1,i}}\hat{p}_{ss,ij}}-\frac{\sum_{i:D_i=0}\sum_{j=1}^{m_{0,i}}\hat{p}_{ss,ij}\hat{y}_{ij}}{\sum_{i:D_i=0}\sum_{j=1}^{m_{0,i}}\hat{p}_{ss,ij}}. \tag{6}$$

Assumption 1 enables us to estimate the probability $\mathrm{P}[S_{ij}(1)=S_{ij}(0)=1]$ separately in the treatment group and in the control group. Finally, we obtain the confidence intervals of the estimate using the bootstrap method of sampling the clusters with replacement[35,36]. We randomly sample the treated clusters and the control clusters separately. In each bootstrap sample, we fit the model and obtain the SACE estimate. The 95% confidence intervals are obtained from the 2.5% and the 97.5% quantiles of the bootstrap estimates.

5 | SIMULATION STUDY

We conduct a simulation study to examine the finite-sample performance of the proposed procedure to estimate SACE in parallel CRTs. In addition, we also use the simulation to compare the proposed approach with a fixed-effects outcome modeling approach to demonstrate the necessity of accounting for clustering through the random effects in CRTs. In our simulation study, we examined settings with the number of clusters $n_c = 30$ and 60 in each arm to capture cluster numbers seen in a majority of cluster trials[37,38], and to capture small and medium-large cluster trial settings[38]. In each cluster, the number of subjects was simulated from a normal distribution after rounding with mean $s = 25$ and 50, and a standard deviation of 3. The variance parameters satisfy $\tau^2+\sigma^2=2$, and we used the ICC $\rho=\tau^2/(\tau^2+\sigma^2)=0.01$, 0.05, and 0.1, a common range of ICC informed by CRT literature[39,40,41,42]. These ICC values correspond to $\tau^2=0.02$, 0.1 and 0.2, and correspondingly $\sigma^2=1.98$, 1.9 and 1.8. We simulated two covariates independently from a Bernoulli distribution with a probability of success as 0.5, and from a standard normal distribution. Values of the fixed effects including the intercepts are $\boldsymbol{\beta}_{ss,1}=(-0.5\ 1\ 1.5)'$, $\boldsymbol{\beta}_{sn}=(-0.3\ 0.8\ 1.3)'$,

$\boldsymbol{\beta}_{ss,0} = (-0.2\ 1\ 1)'$, $\boldsymbol{\alpha}_{ss} = (1\ 2\ 1)'$, and $\boldsymbol{\alpha}_{sn} = (-0.5\ -1.5\ -1)'$. For each simulation setting, due to extensive computation time, we generated 200 simulated datasets and analyzed each dataset using 200 bootstrap samples to obtain interval estimate of the SACE.

The principal strata variable $\mathbf{Z}_{ij}$ is simulated from a multinomial distribution. Hence in each simulation, we observe the principal stratum status of each subject. Let $1_{\{Z_{ss,ij}=1\}}$ be the indicator function if the (i,j)-th subject is in the "ss" stratum. In each simulation, we compute the SACE as

$$\frac{\sum_{i:D_i=1}\sum_{j=1}^{m_{1,i,1}} y_{ij}(1)1_{\{Z_{ss,ij}=1\}}}{\sum_{i:D_i=1}\sum_{j=1}^{m_{1,i,1}} 1_{\{Z_{ss,ij}=1\}}} - \frac{\sum_{i:D_i=0}\sum_{j=1}^{m_{0,i,1}} y_{ij}(0)1_{\{Z_{ss,ij}=1\}}}{\sum_{i:D_i=0}\sum_{j=1}^{m_{0,i,1}} 1_{\{Z_{ss,ij}=1\}}}.$$

The true value of the SACE is then computed as the average of the 200 replicates. We examine the absolute value of the bias, the mean squared error (MSE) of estimation, and the coverage proportion of the bootstrap confidence intervals relative to the true SACE we obtain for each simulation scenario.

TABLE 4 Performance of the developed mixed-effects (ME) approach and the fixed effects (FE) approach in terms of the absolute value of the bias, the MSE of estimating SACE, and the coverage proportion of the bootstrap confidence intervals. The number of clusters is $n_c = 30, 60$, the average cluster size is $s = 25$ and 50, and the ICC $\rho = 0.01$, 0.05 and 0.1.

			0.01		0.05		0.1	
		n_c	ME	FE	ME	FE	ME	FE
$s = 25$	|Bias| ($\times 10^{-2}$)	30	0.74	0.46	0.52	0.12	0.85	0.55
		60	0.58	0.41	0.38	0.16	0.76	0.15
	MSE ($\times 10^{-2}$)	30	1.46	1.49	1.72	1.82	2.96	3.13
		60	0.71	0.71	0.91	0.95	1.28	1.38
	Coverage (%)	30	94.0	93.5	95.5	89.0	92.0	82.5
		60	93.5	93.0	94.0	91.0	95.5	80.5
$s = 50$	|Bias| ($\times 10^{-2}$)	30	0.76	0.46	0.98	0.62	0.71	0.14
		60	0.51	0.29	0.92	0.57	1.02	0.34
	MSE ($\times 10^{-2}$)	30	0.96	0.99	1.20	1.24	2.07	2.23
		60	0.40	0.42	0.63	0.65	0.90	1.01
	Coverage (%)	30	92.0	90.5	95.5	86.0	93.0	75.0
		60	93.5	93.0	94.5	83.5	93.0	76.0

We compare our approach with the fixed effects approach of no random effects in the outcome models, but retain the same principal strata membership model. The corresponding SACE estimate is as in (6) but now setting $\hat{\mathrm{E}}(u_{i1}|\mathbf{y}_i) = \hat{\mathrm{E}}(u_{i0}|\mathbf{y}_i) = 0$. For this fixed-effects approach, we obtain the bootstrap confidence intervals by sampling the individuals with replacement. Comparison of the MSE and the coverage proportions of the fixed effects model parameters $\{\boldsymbol{\beta}_{ss,1}, \boldsymbol{\beta}_{sn}, \boldsymbol{\beta}_{ss,0}, \boldsymbol{\alpha}_{ss}, \boldsymbol{\alpha}_{sn}\}$ are provided in the supplementary material. Table 4 summarizes the SACE comparison between our approach (ME) and the fixed effects only (FE) approach. Though the fixed effects only approach has slightly lower bias overall, both approaches have small bias, nearly

all less than 1%. The developed approach has smaller MSE and close to the nominal 95% coverage. The coverage proportion of the fixed effects only approach deteriorates as the ICC increases. This comparison demonstrates the necessity of accounting for clustering in CRTs for more accurate inference with SACE, especially when the ICC becomes larger.

6 | APPLICATION TO THE WHOLE SYSTEMS DEMONSTRATOR (WSD) TELECARE QUESTIONNAIRE STUDY

To assess our methodology in a real-world trial setting, we reanalyzed the Whole Systems Demonstrator (WSD) Telecare Questionnaire Study, which was nested in the pragmatic cluster-randomised WSD telecare trial conducted to compare participant-reported outcomes between home-based telecare with the usual care across three local authority sites in England[43,44]. In the study, participants registered within a particular general practice and the general practice constituted the cluster-level unit of randomization. There are 201 clusters, 100 in the telecare arm and 101 in the usual care arm. There were unequal cluster sizes. The cluster sizes of the telecare group ranged from 1 to 20 with mean 5.24, and the cluster sizes in the usual care group ranged from 1 to 23 with mean 5.96. The analyzed sample size and cluster number reported herein varies very slightly from the original published analysis due to different analytic methods and use of the outcome data.

For our illustration we examined the physical quality of life outcome (PCS) of 1126 participants. The PCS was as assessed by the Short Form 12-item Survey (SF-12)[45]. The outcome measures for the trial were collected at the baseline and also at 12 months, which was the final time of data collection. However, those outcomes were not measured if participants withdrew from the study. The main reasons for formal withdrawal included death, moving to residential or nursing care, and deterioration in condition (physical or mental capacity)[45]. Among the 524 participants in the telecare arm, 45 (8.58%) of the outcomes were truncated. In the usual care arm, 82 (13.62%) of the 602 outcomes were truncated. The telecare arm has slightly higher mean and standard deviation of the PCS outcome, 27.63 vs. 27.21 and 8.50 vs. 8.30. Figure 1 shows the histograms and the QQ normal plots of the outcome for all participants and also by arms.

Each participant's demographic information was also recorded including age, gender, ethnicity, number of co-morbid conditions, level of education, and the Index of Multiple Deprivation score based on their postcode at the time of enrollment into the trial. We estimated the SACE for the PCS outcome adjusting for the baseline covaraites and also the baseline PCS measurement. Table 5 shows the estimates by the developed approach (ME) and the fixed effects only approach (FE) together with the 95% bootstrap confidence intervals from 500 bootstrap samples. The table also shows the estimated proportion of a principal stratum as an average of the individual probabilities. The estimated proportions are close to each other, and both confidence intervals of the SACE estimate cover the estimate of equality: 0.

We compared the two estimates with the one from the linear mixed-effects model approach that excludes the records without observed outcomes. We adjust for the same covariates in the model together with their first order interactions with the treatment variable, telecare or usual care. Based on the parameter estimates, we calculated two averages of the predicted outcomes among the survivors: one assuming everyone was in the telecare trial arm, and then assuming everyone received usual care. Our treatment effect estimate was then derived by taking the difference of these two counterfactual averages. Without using the information of the withdrawal from the study, the estimate is 0.08 with 95% bootstrap confidence interval $(-0.56, 1.02)$. Though the linear mixed-effects model approach produces a consistent result of no significant treatment effect, it excludes the 127 (11.28%)

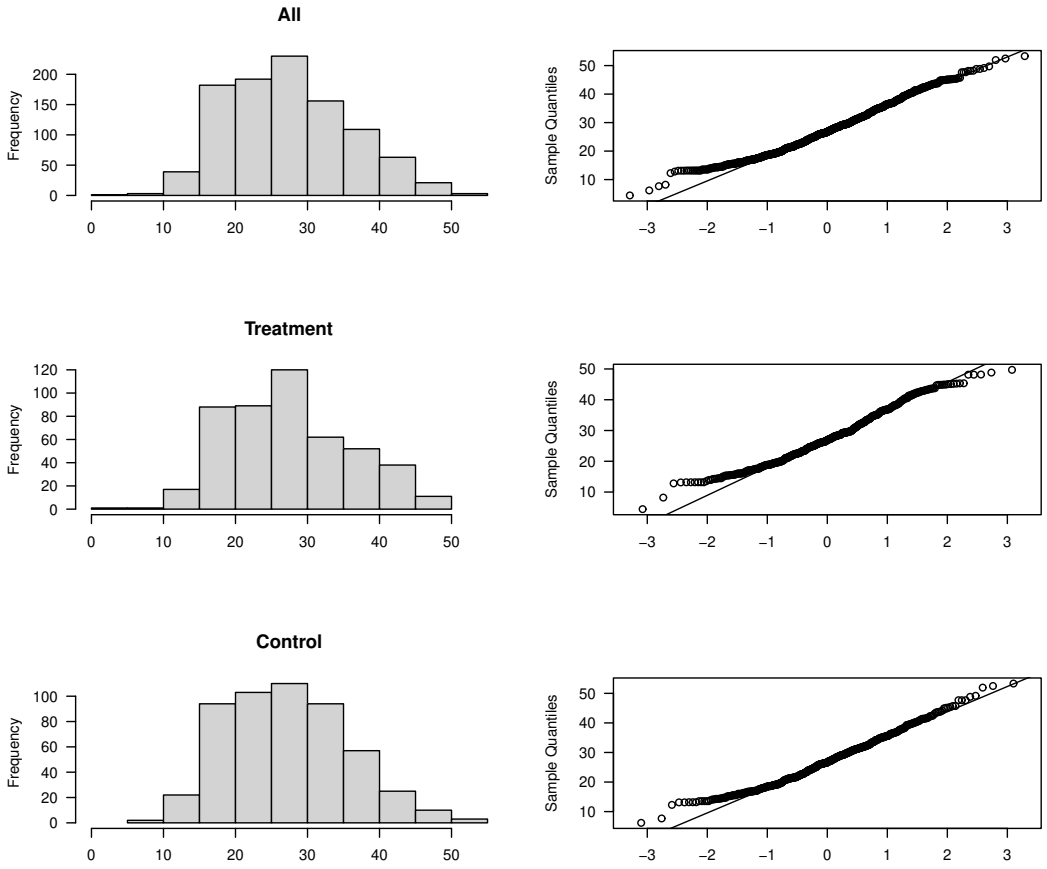

FIGURE 1 Histograms and QQ normal plots of the physical quality of life outcome (PCS), assessed by the Short Form 12-item Survey (SF-12) in the Whole Systems Demonstrator (WSD) Telecare Questionnaire Study.

TABLE 5 Estimation of the SACE and the proportion of a principal stratum by the developed mixed-effects (ME) approach and the fixed effects approach (FE).

	ME	FE
SACE	0.32 (-0.88,1.43)	0.21 (-0.99, 1.41)
ss: always survivors	0.84 (0.80, 0.86)	0.84 (0.80, 0.87)
sn: protected	0.05 (0.04, 0.12)	0.07 (0.04, 0.12)
nn: never survivors	0.11 (0.07, 0.12)	0.09 (0.06, 0.11)

subjects from the analysis. As a result, the estimated treatment effect is derived from a cohort that includes a subset of individuals who do not have a counterfactual outcome since they are not in the always survivors strata (Table 1). In contrast, the principal stratification framework allows us to estimate the SACE which provides a clear causal interpretation of the treatment effect.

7 | SUMMARY AND DISCUSSION

In many trials, both individually and clustered, participant outcomes will be unobserved due to truncation by death or other informative dropout reasons (e.g., migration of leaving school). In such settings, the SACE can provide valuable insight about treatment effects among a defined subset of subjects who would not experience truncation under either treatment or control. In this paper, we developed a new approach to estimate SACE in cluster-randomized trials under the linear mixed effects model framework. It is worth noting that our methodology allows for the inclusion of covariates and can be easily extended to observational data settings. Our method estimates the model parameters using the EM algorithm and constructs confidence intervals of the estimates using cluster-level bootstrap. In the simulation settings we examined, confidence intervals derived from the developed approach had closer to the nominal 95% coverage than the existing approach with fixed effects only. To support the use of our approach we have provided R code in the supplementary materials (see section S3).

A potential limitation of our models is that we assume the outcomes follow normal distributions. It may be of future interest to test the robustness of the normality assumption by simulating data from other distributions, and to derive the parameter estimates under other distribution assumptions. Finally, we have assumed monotonicity to derive the SACE estimate in CRTs. This assumption, while seemingly plausible for the WSD trial studying cluster-level treatment with perceived benefit against no intervention, may be less reasonable for other applications, such as comparative effectiveness trials that have two active treatments. Relaxing the monotonicity assumption to include the harmed strata may require addressing additional computational challenges given our mixed-effects outcome modeling structure for each strata. It would be of interest for future research to further explore this generalization to accommodate the harmed strata as a further sensitivity analysis strategy[18].

A final consideration for potential users of our method, or the SACE more generally in randomized trials (clustered or individually-randomized), emerges from the fact that the always-survivors stratum is a latent class of trial participants that cannot be identified until after randomization and the trial is completed. This has two direct consequences. First, as a subset of the intention to treat population, there will always be some concern for a loss of power due to the smaller sample size of this stratum. Thus, while the SACE may be a more attractive estimand, its use may may come with an empirical trade-off to certain approaches such as using a composite outcome (e.g., applying the worst value of QOL to those who died), that while challenging to interpret causally, could have less of a statistical power penalty than selecting the SACE. However, this concern may be partially offset in settings where the effect is likely to be larger among the always-survivors stratum than the overall population (i.e., average treatment effect[46]). Second, but related, without knowing the size or characteristics of the always-survivors stratum prior to completing a study, power calculations, and obtaining optimal power targets may be a challenge, particularly in settings where sample sizes are constrained and cannot be increased.

Given these considerations, at present, we believe we can offer three practical recommendations for those who may wish to use the SACE estimate in their trial. First, the SACE may be better as a pre-planned secondary analysis in trials with smaller available sample sizes, and only considered as the target trial estimand in larger pragmatic trials or in settings where effect sizes and always-survivors rates can be assumed with reasonable certainty to be in some range, and available sample sizes are adequate[46]. Second, as is recommended when working with other uncertain trial design elements[47,48], we recommend that Monte Carlo simulation studies be undertaken to assess statistical power (Jo[46] also provided additional design-based guidance on addressing treatment noncompliance but potentially relevant to the SACE). Finally, because our new method of adding a random intercept reduces power relative to fixed-effects approaches, but may do so variably across settings, future research should explore the relationship between precision (power) of the SACE estimator and commonly observed intracluster correlation coefficients with the goal of estimating design effects to assist investigators planning to use SACE estimates in CRTs.

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Author contributions

WW, FL, and MOH developed the idea for the manuscript, and WW wrote the first draft and lead the analysis. All authors provided feedback on the manuscript structure and content and provided edits. All authors approved of the final submitted manuscript.

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Conflict of interest

MOH has received consulting fees from Elsevier, the American Thoracic Society, Berkley Research Group, Pura Vida Investments, LLC, Guidepoint Advisers, and Trinity Life Science, all for work unrelated to the topics in this manuscript.

SUPPORTING INFORMATION

The following supporting information is available as part of the online article: proof of Proposition 1, the MSE and the coverage proportions of the fixed effects model parameters $\{\boldsymbol{\beta}_{ss,1}, \boldsymbol{\beta}_{sn}, \boldsymbol{\beta}_{ss,0}, \boldsymbol{\alpha}_{ss}, \boldsymbol{\alpha}_{sn}\}$ in the simulation study, and the R code to implement the developed approach.

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