Planning SMARTs: Sample size estimation for comparing dynamic treatment regimens using longitudinal count outcomes with excess zeros

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Summary

In many health domains such as substance-use, outcomes are often counts with an excessive number of zeros (EZ) – count data having zero counts at a rate significantly higher than that expected of a standard count distribution (e.g., Poisson). However, an important gap exists in sample size estimation methodology for planning sequential multiple assignment randomized trials (SMARTs) for comparing dynamic treatment regimens (DTRs) using longitudinal count data. DTRs, also known as \textit{treatment algorithms} or \textit{adaptive interventions}, mimic the individualized and evolving nature of patient care through the specification of decision rules guiding the type, timing and modality of delivery, and dosage of treatments to address the unique and changing needs of individuals. To close this gap, we develop a Monte
Carlo-based approach to sample size estimation. A SMART for engaging alcohol and cocaine-dependent patients in treatment is used as motivation.

Key words: correlated count data; dynamic treatment regimen; longitudinal data analysis; sample size estimation; sequential multiple assignment randomized trial; zero-inflation

1. Introduction

A dynamic treatment regimen (DTR) is characterized by a sequence of treatments provided at different stages and individualized based on tailoring variables – baseline and ongoing information from the individual used to guide whether and how to modify treatment for the individual (Collins, Murphy, and Bierman, 2004). As a means to operationalize the sequential and individualized decision making in the provision of patient care, particularly in the treatment of chronic behavioral or physical health conditions, DTRs enable effective resource allocation and hold promise in decreasing the economic burden of poor health.

The sequential multiple assignment randomized trial (SMART) is a useful experimental approach for obtaining the empirical evidence necessary for the construction of an effective DTR. A SMART (Lavori and Dawson, 2000; Murphy, 2005) involves multiple stages of randomization with each stage beginning with a decision point in which some or all individuals are randomized among the appropriate intervention options. As an example, consider the SMART in Figure 1 to develop a DTR for engaging alcohol and cocaine-dependent patients in treatment. Intensive Outpatient Programs (IOPs) are the most common kind of treatment programs offered to individuals with relatively severe substance-use disorders. However, many individuals do not attend the IOP therapy sessions and hence are less likely to benefit from the program (McKay et al., 2015). The purpose of this study was to determine whether at the first intervention stage, it is better to offer motivational interviewing (MI)-based outreach efforts that
focus on helping the individual to engage in the IOP (MI-Engage) or MI-based outreach efforts that includes offering the individual additional customization options (MI-Choice), and to determine the best second-stage course of action for participants who do not respond to the initial outreach efforts. Alcohol and cocaine-dependent individuals were recruited when they entered IOP treatment, and their treatment attendance was tracked for 8 weeks. Those who failed to engage in the IOP by the 2nd week entered into the SMART and were randomized to MI-Engage or MI-Choice. At month 2 (i.e., two months after entering IOP treatment), participants showing signs of non-response were re-randomized to either MI-Choice or no further contact; all participants showing signs of response received no further contact (i.e., responders were not re-randomized). This experimental design has four DTRs embedded (EDTRs) within the design, and resulted in 6 cells, labeled A-F in Figure 1.

A longitudinal outcome assessing the number of past-month cocaine-use days was collected at the end of months 1 to 6. For ease of exposition, throughout, we will assume that randomization to the first-stage intervention options in the ENGAGE SMART instead occurred immediately after the end of month 1 (i.e., one month after entering IOP treatment), coinciding with the first measurement occasion. Among individuals who follow the six paths leading to cells A-F in Figure 1, means, variances, and rates of zeros (i.e., proportion of individuals having no cocaine-use days in the past month) across measurement occasions range from 0.51 to 7.71, 3.77 to 112.07, and 0.36 to 0.89, respectively. These summary statistics exemplify count data with excess zeros (EZ) which are characteristic of outcomes in a wide variety of health domains (e.g., counts of past-month heavy drinking days (Lei et al., 2012).

A variety of sample size planning resources have been developed for SMARTs having continuous-, binary-, or survival- type end-of-study or longitudinal outcomes (e.g., Li and
Murphy, 2011; Kidwell et al., 2018; Seewald, et al., 2020). However, a gap in the literature remains concerning sample size planning resources for the comparison of EDTRs in SMARTs using longitudinal count outcomes, particularly those having EZ. To our knowledge, this is the first manuscript proposing an approach to fill this gap.

We begin by describing the inferential target for longitudinal count outcomes with EZ (Section 2) and considerations in developing a Monte Carlo-based approach to sample size estimation for comparing EDTRs using longitudinal count data with EZ (Section 3). The proposed approach to sample size estimation is introduced (Section 4), simulation studies investigating its validity are described (Section 5 and 6). Finally, directions for future research are discussed (Section 7).

2. Hypothesis tests for comparing DTRs embedded in a SMART

In this manuscript, we will focus on one of the most common SMART designs exemplified by the ENGAGE study: a two-stage restricted SMART. In this design, there are two first-stage intervention options, and two second-stage intervention options where the decision on whether to randomize individuals to second-stage intervention options is determined based on a tailoring variable. In the most common type of SMART, the tailoring variable is the individual’s response status – an indicator for whether sufficient progress was achieved during the first stage of treatment – and only individuals classified as non-responders are re-randomized to second-stage intervention options.

2.1 Focusing on overall means of EZ vs. means for two distinct sub-populations

Count data with EZ are often postulated to be drawn from a mixture of two distinct subpopulations of individuals: one set of individuals for whom it would not be possible to observe non-zero counts (i.e., the non-susceptible subpopulation), and another set of individuals
for whom it would be possible to observe either zero or non-zero counts (i.e., the susceptible subpopulation). Hence, count data with EZ is sometimes described using a mixture model that contains two parts: one model for the probability of belonging to the non-susceptible subpopulation and another model for the mean of outcomes in the susceptible subpopulation. However, it has been noted by various authors (e.g., (Albert, Wang, and Nelson, 2014) that primary scientific questions in clinical trials typically do not concern the source of the excess zeros, but rather, the overall mean across the two sources, i.e., the treatment effect in the entire population. Hence, this manuscript focuses on developing an approach to sample size estimation for the case when EDTRs are compared based on overall means of a longitudinal count outcome.

2.2 Notation for quantities associated with EDTRs

Denote an EDTR in Figure 1 by \((a_1, a_2^{NR})\) where \(a_1\) is a first-stage intervention option and \(a_2^{NR}\) is a second-stage intervention option offered to non-responders; \(a_1 = \{+1, -1\}\) and \(a_2^{NR} = \{+1, -1\}\). Let \(t_j\) denote the time of the \(j^{th}\) measurement occasion where \(j = 1, \ldots, K, \ldots, T\). Here, we use \(K\) to represent the specific time point immediately before the second randomization occurs and \(T\) to represent the total number of measurement occasions. We assume that all individuals have measurements at each \(t_j\). Let \(Y_{i,t_j}\) denote a count outcome of an individual \(i\) that was observed during the actual conduct of the trial at time \(t_j\) (e.g., number of cocaine-use days over month \(t_j\)). Let \(Y_{i,t_j}^{(a_1,a_2^{NR})}\) denote a count outcome of an individual \(i\) that would have been observed at time \(t_j\) had the individual followed EDTR \((a_1, a_2^{NR})\). The outcome \(Y_{i,t_j}^{(a_1,a_2^{NR})}\) is also known as the potential outcome (Rubin, 2005) of individual \(i\) at time \(t_j\) under EDTR \((a_1, a_2^{NR})\). Finally, we define the mean trajectory of EDTR \((a_1, a_2^{NR})\) as \(\mathcal{T}^{(a_1,a_2^{NR})} := \{\mu_{t_j}^{(a_1,a_2^{NR})}: j = 1, \ldots, K, \ldots, T\}\) where \(\mu_{t_j}^{(a_1,a_2^{NR})}\) denotes \(E\{Y_{i,t_j}^{(a_1,a_2^{NR})}\}\).
2.3 Primary aims of a SMART

The comparison of a pair of EDTRs based on difference in end-of-study means is the most common primary aim in SMARTs. While not as popular, the comparison of a pair of EDTRs based on difference in Area Under the Curve (AUC) (Lu et al., 2016) is an appealing alternative primary aim that accounts for how mean trajectories of EDTRs evolve over time.

AUC is defined as the total area under $\mathcal{F}(a_1, a_2^{NR})$ between time $t_{j_1}$ and time $t_{j_2}$. Approximating AUC between $t_1$ and $t_T$ using the trapezoidal rule, $AUC(a_1, a_2^{NR}) := \sum_{j=1}^{T-1} \frac{1}{2} \left[ \mu_{t_j}^{(a_1, a_2^{NR})} + \mu_{t_{j+1}}^{(a_1, a_2^{NR})} \right] (t_{j+1} - t_j)$. In contrast to end-of-study outcomes, AUC captures the process of change in the longitudinal outcome over time. For example, when the longitudinal outcome is the number cocaine-use days in the past month prior to time $t_j$, average AUC between time $t_1$ and time $t_T$, defined as $AUC_{t_T-t_1}$, is the average number of past-month cocaine-use days over a period of length $t_T - t_1$. More generally, any particular pair of EDTRs $(a_1', a_2^{NR'})$ and $(a_1'', a_2^{NR''})$ can be compared based on the difference $\Delta_Q := \sum_{j=1}^{T} l_j \mu_{t_j}^{(a_1', a_2^{NR'})} - \sum_{j=1}^{T} l_j \mu_{t_j}^{(a_1'', a_2^{NR''})}$ where $l_j$’s are real valued constants. $\Delta_Q$ can be viewed as the difference of weighted sums with weights given by the $l_j$’s, which need not sum to 1. The choice of $l_j$’s can make $\Delta_Q$ equivalent to end-of-study means (e.g., by setting the $T^{th}$ weight to be equal to 1 and all other weights equal to zero), AUC (e.g., by setting the $1^{st}$ weight to be equal to $\left(\frac{t_2-t_1}{2}\right)$, the $T^{th}$ weight to be equal to $\left(\frac{t_{T}-t_{T-1}}{2}\right)$, and all other weights to be equal to $\left(\frac{t_{j+1}-t_{j-1}}{2}\right)$), or other estimands. Here, we propose an approach to estimate sample size required to attain power of $1 - \eta$ to reject the null hypothesis $H_0: \Delta_Q = 0$ against the alternative $H_a: \Delta_Q \neq 0$ at type-I error $\alpha$. 
2.4 Modeling and estimation of EDTR mean trajectories

Let \( I(\cdot) \) denote an indicator function. We utilize a piece-wise model for \( \mu_{t_j}^{(a_1,a_{2NR})} \) expressed in terms of stage-specific quantities and displayed in Equation 1 where mean trajectories of all EDTRs in a SMART are constrained to share the same intercept while the mean trajectories of a pair of EDTRs that only differ in \( a_2^{NR} \) are constrained to be identical until time \( t_K \), but allowed to differ after time \( t_K \). The parameters in Equation 1 can be estimated using the inverse probability weighted and replicated estimator (IPWRE) proposed by Lu and colleagues (Lu et al., 2016). In other words, for each EDTR, each measurement occasion \( j \) is given its own parameter in Equation 1.

\[
\log \left( \mu_{t_j}^{(a_1,a_{2NR})} \right) = \beta_{1,1} + I(a_1 = +1) \cdot I(1 < j \leq K) \cdot \beta_{2,j} \\
+ I(a_1 = -1) \cdot I(1 < j \leq K) \cdot \beta_{3,j} \\
+ I(a_1 = +1, a_2^{NR} = +1) \cdot I(K < j \leq T) \cdot \beta_{4,j} \\
+ I(a_1 = +1, a_2^{NR} = -1) \cdot I(K < j \leq T) \cdot \beta_{5,j} \\
+ I(a_1 = -1, a_2^{NR} = +1) \cdot I(K < j \leq T) \cdot \beta_{6,j} \\
+ I(a_1 = -1, a_2^{NR} = -1) \cdot I(K < j \leq T) \cdot \beta_{7,j}
\]

(1)

2.5 Hypothesis testing and power of the test

Let \( \beta \) denote a vector whose components are the \( 4T - 2K - 1 \) parameters of Equation 1 and \( \hat{\beta}_{IPWRE} \) and \( \Delta_Q^{IPWRE} \) denote an estimate of \( \beta \) and \( \Delta_Q \), respectively, obtained using IPWRE. Lu and colleagues (see Theorem I.2 in Supplementary Material of Lu and colleagues (Lu et al., 2016)) showed that \( \hat{\beta}_{IPWRE} \) is consistent and asymptotically multivariate normal (MVN) distributed. Based on this work, and using the delta method (Taylor linearization), we show that
the quantity $\hat{V} \equiv \text{Var} (\hat{\Delta}_{Q}^{PWRE})$ can be expressed in terms of $\hat{V} \equiv \text{Var} (\hat{\beta}^{PWRE})$ and that Theorem 2.1 holds (see Web Appendix A and Web Appendix B for details).

**Theorem 2.1:** $Z := \frac{\hat{\Delta}_{Q}^{PWRE} - \Delta_{Q}}{\sqrt{\hat{V} \equiv \text{Var} (\hat{\Delta}_{Q}^{PWRE})}}$ is Normal$(0,1)$ distributed.

Let $z_q$ denote the $q^{th}$ percentile of the standard normal distribution, $\alpha$ denote type-I error rate, $\eta$ denote type II error rate. A Z-test is to reject $H_0$ if $\left| \frac{\hat{\Delta}_{Q}^{PWRE}}{\sqrt{\hat{V} \equiv \text{Var} (\hat{\Delta}_{Q}^{PWRE})}} \right| > z_{1-\alpha/2}$. The power of the test is thus $1 - \eta \approx \Pr_{H_0} \left\{ \left| \frac{\hat{\Delta}_{Q}^{PWRE}}{\sqrt{\hat{V} \equiv \text{Var} (\hat{\Delta}_{Q}^{PWRE})}} \right| > z_{1-\alpha/2} \right\}$.

3. Considerations in developing a Monte Carlo-based approach to sample size estimation

Deriving a closed-form sample size formula necessarily involves expressing the variance term in the denominator of the Z-statistic in terms of quantities which are interpretable by clinical/behavioral experts. This variance term, which was derived by Lu and colleagues (see Theorem I.2 in Supplementary Material of Lu and colleagues (Lu et al., 2016)), is not analytically tractable as functions of the model parameters of interest, particularly when the total number of measurement occasions, $T$, is large. Hence, this manuscript adopts a Monte Carlo-based approach to enable clinical/behavioral experts to estimate sample size for arbitrary $T$.

**3.1 Considerations relating to the planned SMART design**

It is important for the data generation step in a Monte Carlo-based approach to accommodate salient features of realistic SMART designs, including the multiple sequential randomizations, re-randomization of non-responders based on a tailoring variable, ordering of the sequential randomizations in a SMART in relation to the timing of repeated measurements, and dependency between the tailoring variable and the repeated measurements. These features,
which are not typical of RCTs with longitudinal data, introduce substantial complexity to the data generation step, particularly when simulating counts with EZ. Another consideration is ensuring interpretability of design parameters – parameters that serve as inputs to sample size estimation – based on existing evidence (e.g., pilot studies, published scientific literature, practical considerations). In the authors’ collective experience planning SMARTs, clinical/behavioral experts typically have found the overall means at the EDTR-level abstract and difficult to specify, but specification of the overall means at the level of Embedded Treatment Sequences (ETS) more tractable. In contrast to an EDTR, an ETS refers to a sequence of intervention options offered in practice to an individual by time \( t_j \). That is, starting at time \( t_K \), an ETS is conditional on the tailoring variable while an EDTR is marginal over the tailoring variable.

In the SMART literature, approaches for generating longitudinal outcomes from two-stage restricted SMARTs are limited in various aspects. For example, in some simulation studies (e.g., (Miyahara and Wahed, 2012; Lu et al., 2016), data is generated such that the repeated measurements prior to the second-stage randomization are treated as independent of the tailoring variable. However, this is not a realistic assumption in practice (e.g., see (Lei et al., 2012)). In other cases (e.g., Appendix 3 in (Seewald, et al., 2020)), the tailoring variable is closely related to the repeated measurements, but EDTR-level quantities are required as inputs to generate data.

3.2 Considerations relating to the distribution of count data

Our approach to sample size estimation will be described using a negative binomial (NB) distribution, given by Equation 2 where a univariate random variable \( Y \) denotes the number of events during specified time period, e.g., counts of cocaine-use days within the past one-month, and \( \Gamma(\cdot) \) is the gamma function. When the distribution of \( Y \) is given by Equation 2, i.e.,
$Y \sim \text{NB}(\mu, \zeta)$, the dispersion parameter is $\zeta$, while the mean and variance of $Y$ are $\mu$ and $\mu + \zeta \mu^2$, respectively. Further, the probability of zero counts in $Y$ is

$$f_{\text{NB}}(\mu, \zeta)(y) = \frac{\Gamma(\zeta^{-1} + y)!}{\Gamma(\zeta^{-1})! y!} \pi(\zeta^{-1})(1 - \pi)^y$$

where $\pi = \frac{\zeta^{-1}}{\mu + \zeta^{-1}}$.

(2)

Although the NB distribution has been conventionally used to characterize overdispersion in count data, we argue that the NB distribution can also serve as a parsimonious characterization of EZ. Too see why this can be the case, observe that higher values in the dispersion parameter $\zeta$ impose increased variance (i.e., $\mu + \zeta \mu^2$ approaches infinity) and increased proportion of zeros (i.e., $(\frac{\zeta^{-1}}{\mu + \zeta^{-1}})^{\zeta^{-1}}$ approaches 1) relative to a Poisson distribution with the same mean.

4. Methods

We use ideas from two areas in the statistical literature, namely, the potential outcome framework and copulas to devise an approach to simulate count data with EZ from a two-stage restricted SMART. Copulas are functions that link together marginal univariate cumulative distribution functions to form a multivariate cumulative distribution function (CDF) (e.g., see (Song, 2000)). Copulas can be utilized in a data-generative model to simulate multivariate non-normal random variables whose marginal univariate distributions could be specified independently of the targeted correlation structure prior to data generation. Although a variety of copulas exist in the literature, the Gaussian copula was selected due to practical considerations relating to computational efficiency. Equation 3 defines a Gaussian copula; $X_1, \ldots, X_d$ represent random variables comprising the components of the multivariate random variable of interest, $F_{X_i}$’s are marginal univariate CDFs of the $X_i$’s, $\Phi_d$ denotes the standard $d$-dimensional
multivariate normal CDF, \( \phi \) denotes the univariate standard normal CDF, and \( \Lambda_d \) denotes a 
\( d \times d \) positive definite symmetric matrix that governs the dependence among the \( X_i \)'s.

\[
F_{X_1 \ldots X_d}(x_1 \ldots x_d) = \Phi_d \left( \phi^{-1} \left( F_{X_1}(x_1) \right) \cdots \phi^{-1} \left( F_{X_d}(x_d) \right); \Lambda_d \right) \tag{3}
\]

The notion of copulas in a data-generative model to simulate non-normal potential outcomes is not new. Outside the SMART setting, several authors (e.g., (Albert and Nelson, 2011)) have used a Gaussian copula (Song, 2000) to specify the joint distribution of non-normal potential outcomes. Using copulas in data generation will require generating each component of a multivariate random variable at the same time. Although it is impossible to determine the sequence of interventions that would actually be offered to an individual prior to first-stage randomization, it is possible to enumerate an individual’s full set of potential outcomes with respect to each ETS prior to data generation, a fact that is exploited in our proposed approach.

4.1 Notation for quantities associated with ETS

We let \( Y^s_{i,t_j} \) denote a count outcome of individual \( i \) that would have been observed at time \( t_j \) had the individual undergone a particular ETS \( s \) and let \( \mu_{i,t_j}^s \) denote \( E \left\{ Y^s_{i,t_j} \right\} \). We note that there are four EDTRs in the SMART design we consider, regardless of time. However, the number of ETSs associated with time \( t_j \) is determined by when \( t_j \) occurred in relation to first-stage randomization and second-stage randomization. Prior to first-stage randomization (i.e., at time \( t_1 \) ) an individual would not be offered any of the intervention options, hence, we denote this as (\( \cdot \)) and observe that Figure 1 displays only one ETS by the end of time \( t_1 \). After first-stage randomization but prior to second-stage randomization (i.e., when \( t_2 \leq t_j \leq t_K \) ) only the first-stage intervention would have been offered; hence, we denote this as \( (a_1) \) and observe that Figure 1 displays two possible ETSs at time \( t_j \). After the assessment of response status (i.e.,
when \( t_{K+1} \leq t_j \leq t_T \), second-stage intervention options would have been offered to non-responders, whereas responders would not get re-randomized. Hence, we denote the ETS as \((a_1, r, a_2^{NR})\) and observe that Figure 1 displays six ETSs at time \( t_j \). By convention, we set \( a_2^{NR} = 0 \) if response \((r=1)\) to \( a_1 \) was observed; \( a_2^{NR} = \pm 1 \) if non-response \((r=0)\) was observed.

4.2 Criterion for non-response

For simplicity, we assume that in the SMART being planned, a given individual will be classified as a responder if the outcome immediately prior to the second randomization at time \( t_K \) does not exceed a pre-specified cut-point \( c \), and a non-responder otherwise. In other words, let \( R_i^{(a_1)} \) denote response status for an individual \( i \) that would have been observed had the individual undergone first-stage intervention \( a_1 \), then \( R_i^{(a_1)} = I(Y_{i,t_K}^{(a_1)} \leq c) \). Similarly, for observed outcomes, let \( R_i = I(Y_{i,t_K} \leq c) \). In the health domain of substance-use, choosing the cut-point to be zero can be interpreted as classifying individuals who failed to abstain from past-month substance-use at time \( t_K \) as non-responders. Once a criterion for non-response has been defined, the magnitude of \( \Delta Q \) can be re-expressed in terms of quantities associated with ETSs as in Equation 4 where \( p \) and \( q \) denote the probabilities \( Pr\{R_i^{(a_1')} = 1\} \) and \( Pr\{R_i^{(a_1'')} = 1\} \), respectively. Equation 4 displays the equation by which eliciting \( p, q, \) and \( \mu_{s_j}'s \) (either directly or indirectly) from clinical/behavioral experts allows the determination of the desired magnitude \( \Delta Q \) in the planned SMART.
\[ \Delta_Q := \sum_{j=2}^{K} l_j \{ \mu_{t_j}^{(a_1^*')} \} - \sum_{j=2}^{K} l_j \{ \mu_{t_j}^{(a_1^'')} \} + \sum_{j=K+1}^{T} l_j \cdot \left\{ p \mu_{t_j}^{(a_1^' , 1, 0)} + (1 - p) \mu_{t_j}^{(a_1^'* , 0, a_2^{NR})} \right\} \]

\[ - \sum_{j=K+1}^{T} l_j \cdot \left\{ q \mu_{t_j}^{(a_1^'' , 1, 0)} + (1 - q) \mu_{t_j}^{(a_1^{**} , 0, a_2^{NR''})} \right\} \]

4.3 Data generation

To simplify exposition, within Section 4.3, we suppose that only three measurement occasions are to be collected (i.e., \( T = 3 \)) in a planned two-stage restricted SMART with design depicted in Figure 1: prior to first-stage randomization \((t_1)\), prior to second-stage randomization \((t_K; \ K = 2)\), and post-second stage randomization at end-of-study \((t_T; \ T = 3)\). However, the approach is applicable to more measurement occasions; design parameters required are:

1. Total number of individuals \( N \); the criterion \( \Delta_Q \); desired type-I error rate \( \alpha \).
2. \( c \), the cut-point used to determine response status to first-stage intervention options.
3. The means of the longitudinal EZ count outcome for all ETSs \( s \) and time points \( t_j \), i.e., the quantities \( \mu_{it_j}^s \) for all ETSs \( s \) and time points \( t_j \).
4. The proportion of zeros in the longitudinal EZ count outcome for all ETSs \( s \) and time points \( t_j \), i.e., the quantities \( Pr \{ Y_{it_j}^s = 0 \} \) for all ETSs \( s \) and time points \( t_j \).
5. \( \tau_{MAX} \), the maximum within-person correlation among longitudinal outcomes \( Y_{it_j}^s \) across all pairs of ETSs \( s' \) and \( s'' \) and pairs of time points \( t_{j'} \) and \( t_{j''} \). That is, \( \tau_{MAX} := \max_{s',s'',\ t_{j'},t_{j''}} \{ Corr \{ Y_{it_j}^{s'} , Y_{it_j}^{s''} \} \} \).

Enumerating an individual’s complete set of potential outcomes

The proposed approach to generating data assumes that each individual entering a SMART belongs to one of several mutually exclusive subgroups. Specifically, under the
potential outcome framework, each individual entering a two-stage restricted SMART depicted in Figure 1 can be thought of as belonging to one of four mutually exclusive subgroups based on whether they would respond to each first-stage intervention option: subgroup 1 refers to those who would respond to both $a_1 = +1$ and $a_1 = -1$; subgroup 2 refers to those who would respond to $a_1 = +1$ but not to $a_1 = -1$; subgroup 3 refers to those who would not respond $a_1 = +1$ but would respond to $a_1 = -1$; subgroup 4 refers to those who would not respond to either $a_1 = +1$ and $a_1 = -1$. This is similar to the notion of “always survivor”, “never survivor”, “protectable”, and “defier” subgroups introduced by Frangakis and colleagues (Frangakis, et al., 2007), although with different group definitions suited to the SMART context. Now, observe that it is impossible for individuals who are members of subgroup 1 to undergo the sequence $(a_1 = +1, r = 0, a_2^{NR} = +1)$ by the end of the third measurement occasion $t_3$ and hence, the potential outcome $Y_{i,t_3}^{(a_1=+1,r=0,a_2^{NR}=+1)}$ is undefined for these individuals. An analogous observation could be made involving other subgroups and measurement occasions (see Web Table 2). Hence, an individual’s complete set of potential outcomes can be enumerated by specifying all the potential outcomes $Y_{i,t_j}^{j}$’s that would be feasible for the individual, contingent on their subgroup membership.

**Specification of the joint distribution of an individual’s complete set of potential outcomes**

Let $\theta_i^j$ denote a vector of potential outcomes of individual $i$ belonging to subgroup $j$. A Gaussian copula is used to specify a multivariate cumulative distribution function (CDF) for $\theta_i^j$ such that the marginal distributions, i.e., the univariate distribution of a specific component of $\theta_i^j$ marginal over all the other components of $\theta_i^j$, adhere to a desired univariate CDF (e.g., a NB CDF). Since the dimension of $\theta_i^j$ differs across subgroups, a different Gaussian Copula should be
specified for each subgroup. Specifically, $\theta_i^j$ is a 5-dimensional for subgroup 1 (j=1), 6-dimensional for subgroups 2 and 3 (j=2 and 3), 7-dimensional for subgroup 4 (j=4). For each subgroup, the univariate CDFs $F_{X_i}$’s in Equation 3 are chosen to be the CDFs of count distributions. While there is flexibility in the choice of these univariate CDFs, the fact that response status is defined in terms of a cut-point constrains the maximum or minimum possible value of the potential outcome under either first-stage intervention at time of the $K^{th}$ measurement occasion (i.e., at $t_2$ in this case). For example, for individuals who belong to Subgroup 2 (i.e., those individuals who would respond to $a_1 = +1$ but not to $a_1 = -1$), the value of $Y_{i,t_K}^{(+1)}$ is at most $c$ while the value of $Y_{i,t_K}^{(-1)}$ is greater than $c$, i.e., $Y_{i,t_K}^{(+1)} \leq c$ and $Y_{i,t_K}^{(-1)} > c$. The constraints on $Y_{i,t_K}^{(+1)}$ and $Y_{i,t_K}^{(-1)}$ for the remaining subgroups can be analogously specified (see Web Table 3). The constraints on $Y_{i,t_K}^{(+1)}$ and $Y_{i,t_K}^{(-1)}$ for each subgroup thus inform our choice of univariate CDFs $F_{X_i}$’s to utilize in the specification of a subgroup-specific Gaussian copula. Specifically, for potential outcomes corresponding to ETS $s$ at the $K^{th}$ measurement occasion (i.e., at $t_2$ in this case), we choose a truncated NB CDF defined by $F(w^*) = \Pr\{W \leq w^*\} = \sum_{i=0}^{w^*} f(w)$. Equation 5 and Equation 6 define the function $f(w)$ if the constraints on $Y_{i,t_K}^s$ involve ‘$\leq$’ or ‘$>$’, respectively. We note that when $c=0$, $f(w)$ reduces to a point mass at zero if the constraint on $Y_{i,t_K}^s$ in involves ‘$\leq$’.

$$f(w) = \frac{f_{NB}(\mu_{t_K}^s, \zeta_{t_K}^s)(w)I(w \leq c)}{\sum_{y=0}^{c} f_{NB}(\mu_{t_K}^s, \zeta_{t_K}^s)(y)}$$

$$f(w) = \frac{f_{NB}(\mu_{t_K}^s, \zeta_{t_K}^s)(w)I(w > c)}{1 - \sum_{y=0}^{c} f_{NB}(\mu_{t_K}^s, \zeta_{t_K}^s)(y)}$$
On the other hand, for potential outcomes corresponding to ETS $s$ at any of the other measurement occasions, we choose a NB CDF defined by $F(w^*) := \Pr\{W \leq w^*\} = \sum_{w=0}^{w^*} f_{NB}(\mu_{ts}^j, \xi_{ts}^j)(w); j \neq K$. The complete specification of the univariate CDFs of the Gaussian copula for each subgroup is displayed in Web Table 4 and Web Table 5.

Now, we turn our attention to $\Lambda_d$ to complete the specification of a joint distribution for $\theta_i^j$. Note that the correlation between the $X_i$’s in Equation 3 is determined not only by the choice of $\Lambda_d$, but also by the marginal univariate CDFs (i.e., the $F_{X_i}$’s); in general, the correlation between the $X_i$’s is unavailable in closed-form but can be estimated using Monte Carlo methods (e.g., see (Song, 2000)). Hence, to enable tractability of this numerical estimation, we will use an exchangeable matrix for $\Lambda_d$ with $\rho$ on its off-diagonals; the same parameter $\rho$, which we will refer to as the dependence parameter in the copula, will be utilized across all four subgroups. A grid search (see Web Appendix D for details) will be employed to determine the value of $\rho$ to utilize in the Gaussian copula (i.e., Equation 3) for each subgroup; the grid search considers a range of values for $\rho$ within $-1$ to $1$ such that $\Lambda_d$ will be positive definite, e.g., when $-0.16 \leq \rho \leq 1$, $\Lambda_5, \Lambda_6$, and $\Lambda_7$ will be positive definite.

*Generating an individual’s complete set of potential outcomes*

Once the specification of a Gaussian copula for each subgroup is complete, a method proposed by Madsen and Birkes (Madsen and Birkes, 2013), which involves initially drawing from a MVN distribution and applying a series of non-linear transformations, can then be directly applied to simulate multivariate non-normal data according to a pre-specified distribution of the multivariate (potential) outcome $\theta_i^j$ (see Web Appendix C for details).
Simulating sequential randomizations to generate an individual’s observed outcomes

Once the complete set of potential outcomes for each of the $N$ individuals have been generated, observed outcomes are chosen based on simulated sequential randomizations and the potential outcome framework’s consistency assumption (Rubin, 2005). This assumption states that an individual’s observed outcome is equal to their potential outcome under the intervention that was offered during the actual conduct of the trial. This implies that for the particular set of values $(a_1)$ and $(a_1, r, a_2^{NR})$ pertaining to individual $i$, we have that $Y_{i,t_1} = Y_{i,t_1}^{(c)}$, that $Y_{i,t_2} = Y_{i,t_2}^{(a_1)}$, that $Y_{i,t_3} = Y_{i,t_3}^{(a_1,1,0)}$ if $R_i = 1$, and $Y_{i,t_3} = Y_{i,t_3}^{(a_1,0,a_2^{NR})}$ if $R_i = 0$.

Specifying the number of individuals to generate per subgroup

We describe how the number of individuals generated per subgroup is determined based on the design parameters specified above (at the onset of Section 4.3). First, the specified values for $Pr\{Y_{i,t_K}^{(+1)} = 0\}$, $\mu_{i,t_K}^{(+1)}$, $Pr\{Y_{i,t_K}^{(-1)} = 0\}$, and $\mu_{i,t_K}^{(-1)}$ and the NB density displayed in Equation 2 can be used to solve for the corresponding value of the dispersion parameters $\tilde{\phi}_{i,t_K}^{(+1)}$ and $\tilde{\phi}_{i,t_K}^{(-1)}$.

Subsequently, the probability of response to either first-stage intervention given a particular cut-point $c$, i.e., $Pr\{Y_{i,t_K}^{(a_1)} \leq c\}$ can now be calculated using the NB density displayed in Equation 2. Next, let $n_j$ denote the number of individuals that would belong to subgroup $j$ and $\lceil \cdot \rceil$ denote the ceiling function, respectively. Under the working assumption that the number of individuals in subgroup 4 is equal to the minimum of the number of non-responders to either first-stage intervention, i.e., $n_4 = \min\{N(1 - p), N(1 - q)\}$, the number of individuals to generate for each subgroup can then be obtained by solving for the $n_j$’s in Equation 7 and then calculated as $\lceil n_j \rceil$.

We note that our working assumption is equivalent to setting $n_4$ to its maximum possible value; the actual range of possible values for $n_4$ is between 0 to $\min\{N(1 - p), N(1 - q)\}$.
\begin{align}
N &= n_1 + n_2 + n_3 + n_4 \\
p &= \frac{n_1 + n_2}{N} \\
q &= \frac{n_1 + n_3}{N} \\
n_4 &= \min\{N(1 - p), N(1 - q)\}
\end{align}

(7)

4.4 Power calculation for a fixed sample size N

Let \(P_M\) denote an empirical mean across \(M\) simulated datasets. We estimate power using

\[
P_M \left\{ I \left( \left| \frac{\Delta_{PWRE}^I}{\sqrt{\text{Var}(\Delta_{PWRE}^I)}} \right| > z_{1-\alpha/2} \right) \right\}
\]

, calculated as follows:

1. Values for design parameters under the alternative hypothesis (\(H_a\)) are specified.
2. Select an appropriate value of the copula dependence parameter \(\rho\) (see Web Appendix D for more detail).
3. A large number of simulated SMART datasets, \(M\), consisting of \(N\) individuals each would be generated based on these values; the method of data-generation would follow that described in Section 4.3. For each of the \(M\) simulated datasets, data from all \(N\) individuals will be used to calculate \(\Delta_{PWRE}^I\) and \(\text{Var}(\Delta_{PWRE}^I)\).
4. Finally, power is calculated as the proportion of simulated datasets for which the inequality

\[
\left| \frac{\Delta_{PWRE}^I}{\sqrt{\text{Var}(\Delta_{PWRE}^I)}} \right| > z_{1-\alpha/2}
\]

holds.

When power calculation is repeated for a grid of sample sizes, e.g., 100, 150, \(\ldots\), 600, to produce a power curve, the sample size needed to attain power, say 0.80, can be determined by selecting the value of \(N\) where power first exceeds 0.80.
5. Simulation Study Design

Throughout this section, we consider a prototypical two-stage restricted SMART as in Figure 1 where response status is defined using the cut-point $c = 0$ (i.e., cocaine abstainers are responders). The longitudinal outcome will be measured at the end of each month, over a six-month period (i.e., $T = 6$), and randomization of non-responders occur immediately after the second measurement occasion (i.e., $K = 2$) where the pair of EDTRs $(+1,+1)$ and $(-1,+1)$ are compared using either difference in end-of-study means ($i.e., \Delta_{EOS} = E\{Y_{i,t_6}^{(+1,+1)}\} - E\{Y_{i,t_6}^{(-1,+1)}\}$) or difference in AUC ($i.e., \Delta_{AUC} = \text{AUC}^{(+1,+1)} - \text{AUC}^{(-1,+1)}$), each at a desired type-I error rate of $\alpha = 0.05$. $M = 5000$ Monte Carlo samples were used to calculate power.

5.1 Simulation Study 1

Although the Z-test derived from Theorem 2.1 is expected to perform well asymptotically, it is valuable to use simulations to investigate its performance with finite sample sizes. Simulation Study 1 is designed to evaluate the test’s performance by examining the empirical type-I error rate when $\Delta_{EOS} = 0$ and $\Delta_{AUC} = 0$. Across all scenarios, total sample size $N$, proportion of responders $p$ and $q$, ETS means, and $\tau_{MAX}$ were held constant. Three scenarios corresponding to increased ETS proportion of zeros were considered. Table 1 displays the varying values of parameters used in Simulation Study 1.

5.2 Simulation Study 2

Simulation Study 2 is designed to investigate how power changes as $\Delta_{EOS}$ and $\Delta_{AUC}$ increase. Across all scenarios, proportions of responders $p$ and $q$, ETS proportion of zeros, and $\tau_{MAX}$ were held constant as power was calculated across the grid 100, 150, 200, … 550, 600 for total sample size $N$. Ten scenarios corresponding to increased magnitude of $\Delta_{EOS}$ and $\Delta_{AUC}$ were considered. Table 1 displays the varying values of parameters used in Simulation Study 2;
altogether, these values imply the following values for $\Delta_{EOS}$ and $\Delta_{AUC}$ in scenarios 1-10: $\Delta_{EOS} = 0$ (scenario 1), 0.195 (scenario 2), 0.390 (scenario 3), 0.585 (scenario 4), 0.780 (scenario 5), 0.975 (scenario 6), 1.170 (scenario 7), 1.365 (scenario 8), 1.560 (scenario 9), 1.755 (scenario 10); and $\Delta_{AUC} = 0$ (scenario 1), 0.892 (scenario 2), 1.785 (scenario 3), 2.677 (scenario 4), 3.570 (scenario 5), 4.463 (scenario 6), 5.355 (scenario 7), 6.248 (scenario 8), 7.140 (scenario 9), 8.033 (scenario 10). Additionally, to investigate how power changes as $\tau_{MAX}$ increases, we repeated the scenarios described above, but increased the values of $\tau_{MAX}$. We note that throughout scenarios 1-10, the magnitude of $\Delta_{EOS}$ and $\Delta_{AUC}$ remained identical even at increased values of $\tau_{MAX}$.

5.3 Simulation Study 3

Simulation Study 3 is designed to investigate whether power is sensitive to violation of the working assumption made with respect to subgroup 4, namely that the number of individuals in subgroup 4 ($n_4$) is equal to the minimum number of non-responders to either of the 2 initial interventions. Ten scenarios identical to those described in Simulation Study 2 were considered, except that the total sample size $N$ was fixed to 500 and $\tau_{MAX}$ was fixed to 0.7. Within each scenario, the working assumption was violated by calculating power when $n_4$ was set to 0, 10, 20, 30, 40 …, 180, 190 (i.e., the maximum possible value of $n_4$).

5.4 Simulation Study 4

Rather than unrealistically requiring clinical/behavioral experts to specify a large number of different correlations in advance, our proposed approach only requires eliciting the maximum within-person correlation (i.e., $\tau_{MAX}$) as an input to power calculation. However, this approach might lead to a degree of misspecification. In order to provide practical guidance to trial planners on the selection of a value for the copula dependence parameter $\rho$, Simulation Study 4 is designed to investigate the minimum ($\tau_{MIN}$) and maximum ($\tau_{MAX}$) within-person correlation
\( \text{Corr} \left( Y_{i,t}^{s'} , Y_{i,t}^{s''} \right) \) possible given specific values of \( \rho \). We consider the three scenarios identical to that described in Simulation Study 1. In each of the three scenarios, we fix the value of \( \rho \) to the values 0.05, 0, 0.05, 0.10, 0.15…, 0.95, 1, and then calculate \( \tau_{\text{MIN}} \) and \( \tau_{\text{MAX}} \) for each value of \( \rho \) (see Web Appendix D for more detail).

6. Simulation Study Results

The results for Simulation Study 1 are summarized in Figure 2 where total sample size \( N \) (x-axis) is plotted against the empirical type-I error rate (y-axis). The results show slightly above nominal empirical type-I error rate (i.e., 0.05 to 0.07) when the proportion of zeros are relatively low (ranging from 0.52 to 0.65; top panels) and slightly below nominal empirical type-I error rate (i.e., 0.04 to 0.05) when the proportion is zeros is relatively high (ranging from 0.60 to 0.87; bottom panels).

The results for Simulation Study 2 are summarized in Figure 3 where total sample size \( N \) (x-axis) is plotted against power (y-axis). Scenarios 1-10 are represented by the solid dots on the first through tenth layer, respectively. The power curves indicate that power increases as \( \Delta_{\text{EOS}} \) and \( \Delta_{\text{AUC}} \) increase, with similar trends observed when \( \tau_{\text{MAX}} \) is fixed to 0.4, 0.7 and 0.1. Further, the results show that given a particular value for \( \Delta_{\text{EOS}} \), high within-person correlation can increase power for detecting differences in end-of-study means. For example, consider scenario 10 where \( \Delta_{\text{EOS}} = 1.755 \): when \( \tau_{\text{MAX}} = 0.7 \), a sample size of \( N=450 \) is required to achieve power of 0.80 (see top panel), but when \( \tau_{\text{MAX}} = 0.1 \), a sample size of \( N=500 \) is required to achieve power of 0.80 (see bottom panel). In contrast, given a particular value for \( \Delta_{\text{AUC}} \), high within-person correlation can decrease power for detecting differences in AUC. For example, consider scenario 10 where \( \Delta_{\text{AUC}} = 8.033 \): when \( \tau_{\text{MAX}} = 0.7 \) (see top panel), a sample size of \( N=400 \) is
required to achieve power of 0.80, but when \( \tau_{MAX} = 0.1 \) (see bottom panel), a sample size of \( N=250 \) is required to achieve power of 0.80.

The results for Simulation Study 3 are summarized in Figure 4 where \( n_4 \) (x-axis) is plotted against power (y-axis). Scenarios 1-10 are represented by the solid dots on the first through tenth layer, respectively. The results show that across the ten scenarios, power is not sensitive to the actual value of \( n_4 \).

Finally, the results for Simulation Study 4 are summarized in Figure 5 where for each fixed value of \( \rho \) (x-axis), the corresponding value of \( \tau_{MIN} \) and \( \tau_{MAX} \) (y-axis) are displayed. The results show that across all values of \( \rho \), the difference between \( \tau_{MIN} \) and \( \tau_{MAX} \) does not exceed 0.10, 0.17, and 0.33 for scenarios with low, moderate, and high zeros, respectively.

7. Discussion

The current manuscript addresses an important gap in sample size planning for SMARTs by introducing a Monte Carlo-based approach for estimating the sample size needed to compare two DTRs embedded in a SMART using longitudinal count outcome data with EZ. This approach is designed to require only specification of parameters that clinical/behavioral experts can meaningfully interpret and can hence draw on existing empirical evidence and practical consideration to specify. Simulation studies indicate that this method generally performs well in terms of empirical type-I error rate, showing anticipated increases in power as the difference between embedded DTRs increase, and little sensitivity to violation of working assumptions. The results also show that while high within-person correlation increases power for detecting differences in end-of-study means, it decreases power for detecting differences in AUC. These results are expected given that the AUC is analogous to a within-cluster average, such that high within-person correlation represents less independent information per cluster (here, a person).
Meanwhile, comparing end-of-study means with randomized data, under the assumption of group equivalence prior to randomization, is more similar to analysis of covariance, such that high within-person correlation allows baseline variance to be accounted for and reduce standard error for the difference.

The simulation studies also point to several limitations in our approach and directions for future research. In Simulation Study 1, scenarios with relatively low rates of zeros show slightly above nominal type-I error rate. This is consistent with evidence outside the SMART setting showing inflated empirical type-I error rates in Wald tests concerning count data with EZ (e.g., (Yu, et al., 2013)). On the other hand, scenarios with relatively high rates of zeros show a slightly below nominal empirical type-I error rate. Further investigation into the results of Simulation Study 1 (see Web Appendix E) showed that estimates of $\sqrt{\text{Var}(\hat{\Delta}_{E_{OS}}^{IPWRE})}$ were unbiased but estimates of $\sqrt{\text{Var}(\hat{\Delta}_{AUC}^{IPWRE})}$ exhibited a pronounced downward bias when the total sample size N is below 200. This bias was attenuated as N was increased, particularly in the scenario with high rates of zero. Outside the SMART setting, other authors have observed that score tests using the Normal approximation may underestimate nominal type-I error rate (Jung, Jhun, and Lee, 2005). These results suggest that Taylor series arguments used by Lu and colleagues (Lu, et al., 2016) to derive an expression for $\sqrt{\text{Var}(\hat{\beta}_{IPWRE})}$ may not approximate well the true value $\text{Var}(\hat{\beta}_{IPWRE})$ in scenarios with relatively high rates of zeros. Nonetheless, the results of Simulation Study 1 indicate that type-I error rate was close to nominal (i.e., within the 0.04 to 0.06 range) in most conditions. If the available N is small or the proportion of zeroes is expected to be large, the use of bootstrap based approaches to approximating the variance of the estimated difference between embedded DTRs should be explored.
Finally, the results in Simulation Study 4 indicate that the shortcut of using the maximum expected correlation $\tau_{MAX}$ to select the value of the simulated data dependence parameter $\rho$ is adequate in many situations. However, this approach may not be appropriate in extreme conditions, such as scenarios with high rates of zeros, where the difference $\tau_{MAX} - \tau_{MIN}$ can be substantial. When such conditions are anticipated, trial planners may consider selecting the value of $\rho$ which will yield either much smaller or much larger value of $\tau_{MAX}$ than the actual value elicited from clinical/behavioral experts to correct for possible over-estimation or under-estimation of power, as a kind of sensitivity analysis.

Despite the limitations, the current manuscript provides a novel simulation strategy which addresses an important practical need in planning SMARTs with longitudinal outcomes using elicitable and interpretable parameters. The simulation strategy outlined here, combining use of principal stratification and copulas, can readily be extended to other types of outcome variables, such as binary outcomes, in addition to the count variables with EZ considered here.

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Supporting Information

Web Appendices, Tables, and Figures referenced in Sections 2, 4, 5, 6, 7 are available with this manuscript at the Biometrics website on Wiley Online Library. Code utilized for this manuscript is available at https://github.com/jamieyap/CountSMART
Figures

Figure 1: The ENGAGE SMART design
Figure 2: Results of Simulation Study 1. This figure appears in color in the electronic version of this article.

Total sample size (x-axis) vs. Empirical Type-I Error Rate (y-axis)

**Difference in end-of-study means**

- **Low Zeros**
- **Moderate Zeros**
- **High Zeros**

**Difference in AUC**

- **Low Zeros**
- **Moderate Zeros**
- **High Zeros**
Figure 3: Results of Simulation Study 2. This figure appears in color in the electronic version of this article.
Figure 4: Results of Simulation Study 3. This figure appears in color in the electronic version of this article.
Figure 5: Results of Simulation Study 4. This figure appears in color in the electronic version of this article.

Result of grid search using values of design parameters in Simulation Study 1: $\rho$ (x-axis) vs. $\hat{\tau}_{MIN}$ (y-axis; triangles) and $\rho$ (x-axis) vs $\hat{\tau}_{MAX}$ (y-axis; dots)

- $\tau_{max}$ (Low Zeros)
- $\tau_{max}$ (Moderate Zeros)
- $\tau_{max}$ (High Zeros)
- $\tau_{min}$ (Low Zeros)
- $\tau_{min}$ (Moderate Zeros)
- $\tau_{min}$ (High Zeros)

Low Zeros (when $\rho=0.80$: $\tau_{max}=0.73$, $\tau_{min}=0.67$)
Moderate Zeros (when $\rho=0.80$: $\tau_{max}=0.71$, $\tau_{min}=0.81$)
High Zeros (when $\rho=0.80$: $\tau_{max}=0.71$, $\tau_{min}=0.48$)
Tables

Table 1: Parameter values in simulation studies. Below, $\pi_{t_j}^{(s)}$ denotes $Pr\{Y_{i,t_j}^{S} = 0\}$.

| Simulation Study 1 | Simulation Study 2 |
|--------------------|--------------------|
| **Fixed across all scenarios:** | **Fixed across all scenarios:** |
| **Total Sample Size** | N=500 |
| **ETS Means** | $\mu_{t_1}^{(s)} = 0.5, \mu_{t_2}^{(s)} = 1.95, \mu_{t_3}^{(s)} = 2, \mu_{t_4}^{(s)} = 3, \mu_{t_5}^{(s)} = 2.95, \mu_{t_6}^{(s)} = 1.95$ |
| **Copula Dependence Parameter** | $\rho = 0.8$ (i.e., $\tau_{MAX} = 0.7$) |
| **Proportion of Responders** | $p = 0.60$ and $q = 0.62$ |

| **Varied across scenarios:** | **Varied across scenarios:** |
| **Scenario 1** | **Scenario 1** |
| **ETS Proportion of Zeros** | For all $s$: $\mu_{t_1}^{(s)} = 0.5, \mu_{t_2}^{(s)} = 1.95, \mu_{t_3}^{(s)} = 2, \mu_{t_4}^{(s)} = 3, \mu_{t_5}^{(s)} = 2.95, \mu_{t_6}^{(s)} = 1.95$ |
| $\pi_{t_1}^{(+1,0,0)} = 0.60, \pi_{t_2}^{(-1)} = 0.62$ | $\mu_{t_1}^{(s)} = 0.5, \mu_{t_2}^{(s)} = 1.95, \mu_{t_3}^{(s)} = 2$ |
| $\pi_{t_2}^{(+1,0,0)} = \pi_{t_3}^{(+1,0,0)} = \pi_{t_4}^{(+1,0,0)} = \pi_{t_5}^{(+1,0,0)} = 0.58$ | $\mu_{t_4}^{(s)} = 3, \mu_{t_5}^{(s)} = 2.95, \mu_{t_6}^{(s)} = 1.95$ |
| $\pi_{t_3}^{(+1,0,0)} = \pi_{t_4}^{(+1,0,0)} = \pi_{t_5}^{(+1,0,0)} = 0.56$ | |
| $\pi_{t_4}^{(+1,0,0)} = \pi_{t_5}^{(+1,0,0)} = 0.54$ | |
| $\pi_{t_7}^{(+1,0,0)} = \pi_{t_8}^{(+1,0,0)} = 0.52$ | |
| $\pi_{t_8}^{(+1,0,0)} = \pi_{t_9}^{(+1,0,0)} = 0.54$ | |
| $\pi_{t_9}^{(+1,0,0)} = \pi_{t_10}^{(+1,0,0)} = 0.54$ | |
| $\pi_{t_{10}}^{(+1,0,0)} = \pi_{t_11}^{(+1,0,0)} = 0.54$ | |
| **Scenarios 2-3** | **Scenarios 2-10** |
| **ETS Proportion of Zeros** | **ETS Means** |
| For $j = 1, 2$: $\pi_{t_j}^{(s)}$ takes on the following values | For $j = 1, 2$: $\mu_{t_j}^{(s)}$ takes on the following values |
| $\pi_{t_1}^{(+1,0,0)} = 0.60, \pi_{t_2}^{(-1)} = 0.62$ | $\mu_{t_1}^{(s)} = 0.5, \mu_{t_2}^{(s)} = 1.95, \mu_{t_3}^{(s)} = 2$ |
| For $j = 3, 4, 5, 6$: $\pi_{t_j}^{(s)}$ takes on the following values | $\mu_{t_4}^{(s)} = 3, \mu_{t_5}^{(s)} = 2.95, \mu_{t_6}^{(s)} = 1.95$ |
| The value of $\pi_{t_j}^{(+1,0,0)}$, $\pi_{t_j}^{(+1,0,0)}$, and $\pi_{t_j}^{(+1,0,0)}$ was increased by 25% and 50%, respectively, from scenario 1, while the value of $\pi_{t_j}^{(-1,0,0)}$, $\pi_{t_j}^{(-1,0,0)}$, and $\pi_{t_j}^{(-1,0,0)}$ was increased by 20% and 45%, respectively, from scenario 1. | The value of $\mu_{t_j}^{(+1,0,0)}$, $\mu_{t_j}^{(+1,0,0)}$, and $\mu_{t_j}^{(+1,0,0)}$ was increased by 10%, 20%, 30%, ..., 80%, 90% respectively, from scenario 1, but the value of $\pi_{t_j}^{(-1,0,0)}$, $\pi_{t_j}^{(-1,0,0)}$, and $\pi_{t_j}^{(-1,0,0)}$ was retained from scenario 1.
Web Appendix A. Estimation of $\Delta Q$ using a longitudinal EZ count outcome

Although IPWRE is applicable to many kinds of outcomes, the illustration and simulation studies of Lu and colleagues (Lu et al., 2016) focused on a continuous longitudinal outcome. Here, we provide details on estimation of $\Delta Q$ using IPWRE when the longitudinal outcome is count with EZ and a log-link function. We begin by noting that for any given pair of EDTRs $(a_1', a_2^{NR'})$ and $(a_1'', a_2^{NR''})$ and set of real-valued constants $l_j$’s, the quantity $\Delta Q$ can be re-expressed as in Equation 1.

$$\Delta Q = L \exp \left[ C(a_1', a_2^{NR'}) \beta \right] - L \exp \left[ C(a_1'', a_2^{NR''}) \beta \right]$$  \hspace{1cm} (1)

In Equation 1, $C(a_1, a_2^{NR})$ denotes a $T \times (4T - 2K - 1)$ matrix of 1’s and 0’s, specifying which of the $4T - 2K - 1$ parameters is associated with EDTR $(a_1, a_2^{NR})$; $\exp[\cdot]$ denotes element-wise exponentiation; $L$ is $1 \times T$ matrix whose elements are the real-valued constants
\( l_j \)'s. The specific form of \( C^{(a_1,a_2^{NR})} \) is chosen so that the term \( \exp \left[ C^{(a_1,a_2^{NR})} \beta \right] \), which we denote more succinctly by \( U_{\beta}^{(a_1,a_2^{NR})} \), results in a diagonal matrix having the mean trajectory of EDTR \( (a_1,a_2^{NR}) \), i.e., \( \tau^{(a_1,a_2^{NR})} \), as elements on its diagonal.

For example, when second-stage randomization occurs at the second measurement occasion and there are six measurement occasions in total i.e., \( K = 2, T = 6 \), then the mean trajectory of the longitudinal outcome can be modeled by Equation 2. In terms of the parameters \( \beta_{m,j} \)'s in Equation 2, the mean trajectory the EDTRs, i.e., \( \tau^{(+1,+1)}, \tau^{(+1,-1)}, \tau^{(-1,+1)} \), and \( \tau^{(-1,-1)} \), are then given by Web Table 1.

\[
\log \left( \mu_{t_j}^{(a_1,a_2^{NR})} \right) = \beta_{1,1} + I(a_1 = +1) \cdot \beta_{2,2} \\
+ I(a_1 = -1) \cdot \beta_{3,2} \\
+ I(a_1 = +1, a_2^{NR} = +1) \cdot I(2 < j \leq 6) \cdot \beta_{4,2} \\
+ I(a_1 = +1, a_2^{NR} = -1) \cdot I(2 < j \leq 6) \cdot \beta_{5,2} \\
+ I(a_1 = -1, a_2^{NR} = +1) \cdot I(2 < j \leq 6) \cdot \beta_{6,2} \\
+ I(a_1 = -1, a_2^{NR} = -1) \cdot I(2 < j \leq 6) \cdot \beta_{7,2} 
\]

After a model for the mean trajectory of EDTRs has been specified, e.g., as in Equation 2, the steps required to obtain \( \hat{\beta}^{IPWRE} \) using a longitudinal EZ count outcome is identical to the approach one would employ when using either a longitudinal continuous or binary outcome. We direct readers to literature providing details of the steps involved (see (Dziak, et al., 2019; Nahum-Shani, et al., 2020; Seewald, et al., 2020; Lu et al., 2016)); the R package geeM (McDaniel, Henderson, and Rathouz, 2013) was utilized in this manuscript’s implementation of IPWRE. Once an estimate for \( \beta \) has been obtained (i.e., \( \hat{\beta}^{IPWRE} \)), an estimate for \( \Delta Q \) can be simply calculated by substituting \( \beta \) with its estimate in Equation 2. In other words, once \( \hat{\beta}^{IPWRE} \)
has been obtained, $\Delta^\text{IPWRE}_q$ can simply be calculated by applying an appropriate matrix product to $\hat{\beta}^\text{IPWRE}$ (a matrix product based on Equation 1).

Finally, we note that in the specific example of using Equation 2 as a model for the mean trajectory of EDTRs, we specify the matrices in Equation 1 as follows: $\beta :=$

\[
\begin{pmatrix}
\beta_{1,1} & \beta_{2,2} & \beta_{3,2} & \beta^{(+1,+1)} & \beta^{(+1,-1)} & \beta^{(-1,+1)} & \beta^{(-1,-1)}
\end{pmatrix}^T
\]

where $\beta^{(+1,+1)} = (\beta_{4,3} \ \beta_{4,4} \ \beta_{4,5})^T$, $\beta^{(+1,-1)} = (\beta_{5,3} \ \beta_{5,4} \ \beta_{5,5} \ \beta_{5,6})^T$, and $\beta^{(-1,+1)} = (\beta_{6,3} \ \beta_{6,4} \ \beta_{6,5} \ \beta_{6,6})^T$, and the matrices $C^{(+1,+1)}$, $C^{(+1,-1)}$, $C^{(-1,+1)}$, $C^{(-1,-1)}$ are defined as:

\[
C^{(+1,+1)} := (M^{(+1)} M_0^{6\times12}) \quad C^{(+1,-1)} := (M^{(+1)} 0_{6\times4} M 0_{6\times8})
\]

\[
C^{(-1,+1)} := (M^{(-1)} 0_{6\times8} M 0_{6\times4}) \quad C^{(-1,-1)} := (M^{(-1)} 0_{6\times12} M)
\]

where $0_{m_1 \times m_2}$ denotes an $m_1 \times m_2$ matrix whose elements are all zero, and the matrices $M^{(+1)}$, $M^{(-1)}$, and $M$ are:

\[
M^{(+1)} := \begin{pmatrix}
1 & 0 & 0 \\
1 & 1 & 0 \\
1 & 0 & 0 \\
1 & 0 & 0
\end{pmatrix}, \quad M^{(-1)} := \begin{pmatrix}
1 & 0 & 0 \\
1 & 0 & 1 \\
1 & 0 & 0 \\
1 & 0 & 0
\end{pmatrix}, \quad M := \begin{pmatrix}
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
1 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 \\
0 & 0 & 1 & 0 \\
0 & 0 & 0 & 1
\end{pmatrix}
\]

Web Appendix B. Proof of Theorem 2.1

We begin by observing that $\text{Var}(\Delta^\text{IPWRE}_q)$ can be expressed in terms of the covariance of a matrix product involving the quantity $\text{Cov}(\hat{\beta}^\text{IPWRE})$, i.e., as $\text{Var}(\Delta^\text{IPWRE}_q) =$

\[
\text{Cov} \left( (DU_{\hat{\beta}^\text{IPWRE}} C) \cdot \hat{\beta}^\text{IPWRE} \right)
\]

where $D$, $U_{\hat{\beta}^\text{IPWRE}}$, and $C$ are the block matrices defined below:
\[
D = (L - L) \quad U_{\beta_{IPWRE}} = \begin{pmatrix}
U^{(a_1', a_2''R)}_{\beta_{IPWRE}} & 0_{T \times T} \\
0_{T \times T} & U^{(a_1'', a_2''R')}_{\beta_{IPWRE}}
\end{pmatrix} \quad C = \begin{pmatrix}
C^{(a_1', a_2''R')} \\
C^{(a_1'', a_2''R')}
\end{pmatrix}
\]

Here, \(U_{\beta}^{(+1, +1)}\) is then given by Equation 3 when \(T = 6\) and Equation 2 is utilized as a model for the EDTR mean trajectories; the matrices \(U_{\beta}^{(+1, +1)}, U_{\beta}^{(+1, -1)}, U_{\beta}^{(-1, +1)}, U_{\beta}^{(-1, -1)}\) are defined analogously for other values of \(K\) or \(T\).

\[
U_{\beta}^{(+1, +1)} = \begin{pmatrix}
e^{\beta_{1,1}} & 0 & 0 & 0 & 0 & 0 \\
0 & e^{\beta_{1,1} + \beta_{2,2}} & 0 & 0 & 0 & 0 \\
0 & 0 & e^{\beta_{1,1} + \beta_{3,3}} & 0 & 0 & 0 \\
0 & 0 & 0 & e^{\beta_{1,1} + \beta_{4,4}} & 0 & 0 \\
0 & 0 & 0 & 0 & e^{\beta_{1,1} + \beta_{4,5}} & 0 \\
0 & 0 & 0 & 0 & 0 & e^{\beta_{1,1} + \beta_{4,6}}
\end{pmatrix}
\]

By application of the delta method (Taylor linearization), we have that \(\sqrt{N}(\hat{\Delta}_{Q}^{IPWRE} - \Delta_{Q})\) is asymptotically MVN with zero mean and covariance \(Var(\sqrt{N}\hat{\Delta}_{Q}^{IPWRE})\), where \(Var(\hat{\Delta}_{Q}^{IPWRE})\) can be expressed as in Equation 4. Hence, we have that \(Z = \frac{\hat{\Delta}_{Q}^{IPWRE} - \Delta_{Q}}{\sqrt{Var(\hat{\Delta}_{Q}^{IPWRE})}}\) is Normally distributed.

\[
Var(\hat{\Delta}_{Q}^{IPWRE}) = (DU_{\beta_{IPWRE}}C) \cdot Cov(\hat{\beta}_{IPWRE}) \cdot (DU_{\beta_{IPWRE}}C)^T
\]

Now, let \(\hat{\Sigma}_{\beta_{IPWRE}}\) denote an estimator for \(Cov(\sqrt{N}\hat{\beta}_{IPWRE})\) proposed by Lu and colleagues (see Theorem I.2 in Supplementary Material [Lu et al., 2016]). Then by Slutsky’s Theorem, \(Var(\hat{\Delta}_{Q}^{IPWRE})\) is approximated by Equation 5.

\[
Var(\hat{\Delta}_{Q}^{IPWRE}) = (DU_{\beta_{IPWRE}}C) \cdot \frac{\hat{\Sigma}_{\beta_{IPWRE}}}{N} \cdot (DU_{\beta_{IPWRE}}C)^T
\]
Again, by Slutsky’s Theorem, we have that \( Z = \frac{\hat{\Delta}_Q^{PWRE} - \Delta Q}{\sqrt{\text{Var}(\hat{\Delta}_Q^{PWRE})}} \) is Normal(0,1) distributed. ■

Web Appendix C. Approach to generate draws from the multivariate distribution of \( \theta_i^{SGj} \)

Our application of the method proposed by Madsen and Birkes (Madsen and Birkes, 2013) consists of three steps. Here, \( d_j \) denotes the dimension of \( \theta_i^{j} \) and \( 0_{m_1 \times m_2} \) denotes an \( m_1 \times m_2 \) matrix whose elements are all zero.

1. Generate \( n_j \) independent draws from a multivariate standard normal distribution with mean \( 0_{d_j \times 1} \) and correlation matrix \( \Gamma_{d_j} \), i.e., \( Z^{(\ell)} \sim \text{MVN}(0_{d_j \times 1}, \Lambda_{d_j}) \), \( \ell = 1,2,\ldots,n_j \). In the manuscript, \( \Lambda_{d_j} \) is exchangeable, i.e., \( \Lambda_{d_j} = I_{d_j \times d_j} + \rho \left( 1_{d_j \times 1} 1_{d_j \times 1}^T - I_{d_j \times d_j} \right) \) where \( 1_{m_1 \times m_2} \) denotes an \( m_1 \times m_2 \) matrix whose elements are all zero and one and \( I_{m_1 \times m_2} \) denotes an \( m_1 \times m_2 \) identity matrix.

2. Denote the vectors \( Z^{(\ell)} \) and \( U^{(\ell)} \) by \( Z^{(\ell)} := \left( Z_1^{(\ell)} \ldots Z_{d_j}^{(\ell)} \right)^T \) and \( U^{(\ell)} := \left( U_1^{(\ell)} \ldots U_{d_j}^{(\ell)} \right)^T \). For each \( \ell = 1,2,\ldots,n_j \), generate a new vector \( U^{(\ell)} \) by applying a transformation using the univariate standard normal CDF to each component of \( Z^{(\ell)} \). That is, \( \left( U_1^{(\ell)} \ldots U_{d_j}^{(\ell)} \right) = \left( \phi \left( Z_1^{(\ell)} \right) \ldots \phi \left( Z_{d_j}^{(\ell)} \right) \right) \).

3. For each \( \ell = 1,2,\ldots,n_j \), generate a new vector \( X^{(\ell)} \) by applying a transformation using the inverse of the CDF of a univariate count distribution to each component of \( U^{(\ell)} \). That is, if \( X^{(\ell)} := \left( X_1^{(\ell)} \ldots X_{d_j}^{(\ell)} \right) \) and \( F_1,\ldots,F_{d_j} \) denotes an appropriate CDF of a univariate count distribution corresponding to components \( 1,\ldots,d_j \) respectively, of \( U^{(\ell)} \), then
\[
\left( X_1^{(\ell)} \ldots X_{d_j}^{(\ell)} \right) = \left( F_1^{-1} \left( U_1^{(\ell)} \right) \ldots F_{d_j}^{-1} \left( U_{d_j}^{(\ell)} \right) \right).
\]

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Hence, each $X^{(\ell)}$ is effectively a draw of $\theta^l_1$ from its multivariate distribution where the CDFs $F_1, ..., F_{d_j}$ are given by Web Table 4 and Web Table 5. The R package *mvtnorm* (Genz and Bretz, 2009; Genz, et al., 2020) was utilized to draw from a multivariate normal (MVN) distribution.

Web Appendix D. Approach to estimate the relationship between $\rho$, $\tau_{\text{MIN}}$, and $\tau_{\text{MAX}}$

For each value of $\rho$ in a grid, e.g., 0, 0.05, ..., 0.95, 1, we estimate $\tau_{\text{MAX}}$ and $\tau_{\text{MIN}}$ by using $\mathbb{P}_M(\hat{\tau}_{\text{MAX}})$ and $\mathbb{P}_M(\hat{\tau}_{\text{MIN}})$, respectively, calculated using the procedure below.

1. A large number of simulated SMART datasets, $M$, consisting of a large number of individuals each, $N^*$, would be generated based on values of design parameters specified previously; data-generation would follow that described in Section 4.3, with only the final step on simulating sequential randomizations omitted.

2. For each simulated dataset, six vectors as follows:

- $Y^A_i = (Y_{i,t_1}^{(\cdot)} ... Y_{i,t_K}^{(+1)} Y_{i,t_{K+1}}^{(+1,1,0)} ... Y_{i,t_T}^{(+1,1,0)})^T$ using individuals belonging to subgroups 1 and 2
- $Y^B_i = (Y_{i,t_1}^{(\cdot)} ... Y_{i,t_K}^{(+1)} Y_{i,t_{K+1}}^{(+1,0,1)} ... Y_{i,t_T}^{(+1,0,1)})^T$ using individuals belonging to subgroups 3 and 4
- $Y^C_i = (Y_{i,t_1}^{(\cdot)} ... Y_{i,t_K}^{(+1)} Y_{i,t_{K+1}}^{(+1,0,-1)} ... Y_{i,t_T}^{(+1,0,-1)})^T$ using individuals belonging to subgroups 3 and 4
- $Y^D_i = (Y_{i,t_1}^{(\cdot)} ... Y_{i,t_K}^{(-1)} Y_{i,t_{K+1}}^{(-1,1,0)} ... Y_{i,t_T}^{(-1,1,0)})^T$ using individuals belonging to subgroups 1 and 3
- $Y^E_i = (Y_{i,t_1}^{(\cdot)} ... Y_{i,t_K}^{(-1)} Y_{i,t_{K+1}}^{(-1,0,1)} ... Y_{i,t_T}^{(-1,0,1)})^T$ using individuals belonging to subgroups 2 and 4
• \( \mathbf{Y}^F_i = (Y_{i,t_1}^{(0)} \ldots Y_{i,t_K}^{(-1)} Y_{i,t_{K+1}}^{(-1,0,-1)} \ldots Y_{i,t_T}^{(-1,0,-1)})^T \) using individuals belonging to subgroups 2 and 4

Using these vectors, a correlation matrix corresponding to \( \mathbf{Y}^A_i, \mathbf{Y}^B_i, \mathbf{Y}^C_i, \mathbf{Y}^D_i, \mathbf{Y}^E_i, \mathbf{Y}^F_i \) will be estimated and the quantities \( \hat{\tau}_{MAX} \) and \( \hat{\tau}_{MAX} \) (defined below) could then be calculated.

\[
\hat{\tau}_{MAX} := \max_{s',s'',t_j,t_j'} \{ \overline{Corr}(Y_{i,t_j}^{s'}, Y_{i,t_j'}^{s''}) \} \tag{6}
\]

\[
\hat{\tau}_{MIN} := \min_{s',s'',t_j,t_j'} \{ \overline{Corr}(Y_{i,t_j}^{s'}, Y_{i,t_j'}^{s''}) \} \tag{7}
\]

We note that in when \( s' = s'' \), the calculation of the maximum in and the minimum above will exclude the terms where \( t_j = t_j' \); for example, \( \overline{Corr}(Y_{i,t_2}^{(1)}, Y_{i,t_2}^{(1)}) \) will be excluded.

3. Finally, \( \mathbb{P}_M{\{\hat{\tau}_{MAX}\}} \) and \( \mathbb{P}_M{\{\hat{\tau}_{MIN}\}} \) is calculated as the mean of \( \hat{\tau}_{MAX} \) and \( \hat{\tau}_{MIN} \), respectively, across all simulated datasets.

Let \( \hat{\tau}^\rho_{MAX} \) and \( \hat{\tau}^\rho_{MIN} \) denote the value of \( \mathbb{P}_M{\{\hat{\tau}_{MAX}\}} \) and \( \mathbb{P}_M{\{\hat{\tau}_{MIN}\}} \) corresponding to a particular value of \( \rho \) which we calculate using the above-described approach. The value of \( \rho \) for which \( \hat{\tau}^\rho_{MAX} \) closest to the desired value of \( \tau_{MAX} \) will be selected and used to calculate power.

Web Appendix E. Supplement to Simulation Study 1

In Web Appendix E, we investigate whether the slightly above nominal or below nominal empirical type-I error rates observed in Simulation Study 1 can be attributed to bias in estimates of \( \Delta_{EOS} \) and \( \Delta_{AUC} \), or bias in estimates of \( \sqrt{Var(\hat{\Delta}^{IPWRE}_{EOS})} \) and \( \sqrt{Var(\hat{\Delta}^{IPWRE}_{AUC})} \); we utilize values of design parameters identical to Simulation Study 1.
First, bias in estimates of $\Delta_{EOS}$ and $\Delta_{AUC}$ were estimated by calculating the average of the difference between the estimated and true value of $\Delta_{EOS}$ and $\Delta_{AUC}$. That is, bias is calculated as

$$\frac{1}{M} \cdot \sum_{j=1}^{M} (\hat{\Delta}_{EOS}^{(j)} - \Delta_{EOS})$$

and

$$\frac{1}{M} \cdot \sum_{j=1}^{M} (\hat{\Delta}_{AUC}^{(j)} - \Delta_{AUC})$$

where $\hat{\Delta}_{EOS}^{(j)}$ and $\hat{\Delta}_{AUC}^{(j)}$ denote the value of $\Delta_{EOS}^{IPWRE}$ and $\Delta_{AUC}^{IPWRE}$, respectively, at the $j^{th}$ simulated dataset. Note that values of design parameters in Simulation Study 1 were specified such that $\Delta_{EOS} = 0$ and $\Delta_{AUC} = 0$. As the left panels of Web Figure 1 show, estimates $\hat{\Delta}_{EOS}^{IPWRE}$ are unbiased. On the other hand, as the right panels of Web Figure 1 show, estimates $\hat{\Delta}_{AUC}^{IPWRE}$ exhibit slight bias which attenuates as total sample size $N$ is increased.

Second, bias in estimates of $\sqrt{Var(\hat{\Delta}_{EOS}^{IPWRE})}$ and $\sqrt{Var(\hat{\Delta}_{AUC}^{IPWRE})}$ were estimated by calculating the average of the difference between the estimated value of $\sqrt{Var(\hat{\Delta}_{EOS}^{IPWRE})}$ and

$$\sqrt{Var(\hat{\Delta}_{AUC}^{IPWRE})}$$

and the empirical standard error of $\hat{\Delta}_{EOS}^{IPWRE}$ and $\hat{\Delta}_{AUC}^{IPWRE}$, respectively. Here, empirical standard error is calculated as the square root of the variance of $\hat{\Delta}_{EOS}^{IPWRE}$ and $\hat{\Delta}_{AUC}^{IPWRE}$ across all simulated datasets. That is, bias is calculated as

$$\frac{1}{M} \cdot \sum_{j=1}^{M} (\hat{\sigma}_{EOS}^{(j)} - \sigma_{EOS})$$

and

$$\frac{1}{M} \cdot \sum_{j=1}^{M} (\hat{\sigma}_{AUC}^{(j)} - \sigma_{AUC})$$

where $\hat{\sigma}_{EOS}^{(j)}$ and $\hat{\sigma}_{AUC}^{(j)}$ denotes the value of $\sqrt{Var(\hat{\Delta}_{EOS}^{IPWRE})}$ and

$$\sqrt{Var(\hat{\Delta}_{AUC}^{IPWRE})}$$

respectively, at the $j^{th}$ simulated dataset; $\sigma_{EOS}$ and $\sigma_{AUC}$ denotes the empirical standard error of $\hat{\Delta}_{EOS}^{IPWRE}$ and $\hat{\Delta}_{AUC}^{IPWRE}$, respectively. As the left panels of Web Figure 2 show, estimates of standard errors for differences in end-of-study means are unbiased. On the other hand, as the right panels of Web Figure 2 show, estimates of $\sqrt{Var(\hat{\Delta}_{AUC}^{IPWRE})}$ exhibit a
pronounced *downward* bias when total sample size \( N \) is below 200; the bias attenuated as \( N \) was increased, particularly in the ‘High Zeros’ scenario.

Taken together, these results suggest that Taylor series arguments used by Lu and colleagues (Lu et al., 2016) to derive an expression for \( \text{Var}(\hat{\beta}_{IPWRE}) \) do not well approximate the true value \( \text{Var}(\hat{\beta}_{IPWRE}) \) for modest sample sizes in a ‘High Zeros’ scenario. Subsequently, these results suggest that \( \text{Var}(\hat{\delta}_{IPWRE}) \) do not also well approximate the true value \( \text{Var}(\hat{\delta}_{IPWRE}) \) in a ‘High Zeros’ scenario. In the SMART setting, the bootstrap and its variants (e.g., adaptive m-out-of-n bootstrap) have been employed as a means to obtain valid inference when a Q-learning data-analytic approach is used to compare EDTRs in a SMART (Chakraborty, Murphy, and Strecher, 2010; Chakraborty, Laber, and Zhao, 2013), a situation when Taylor series arguments also lead to imprecise inference. Hence, developing a bootstrap-based approach to inference on marginal structural model-based data-analytic approaches such as the IPWRE is an area of future work which could subsequently be integrated with this manuscript’s proposed overall strategy for sample size estimation.

Web Appendix F. Supplement to Simulation Study 4

We consider ten scenarios identical to that described in Simulation Study 2. In each of the ten scenarios, we fix the value of \( \rho \) to the values -0.05, 0, 0.05, 0.10, 0.15…, 0.95, 1, and then calculate \( \tau_{MIN} \) and \( \tau_{MAX} \) for each value of \( \rho \) (see Web Appendix D for more detail). We note that the simulation study here in Web Appendix F differs from that of the simulation study in Section 5.4 in that here in Web Appendix F, ETS proportion of zeros were held constant across all scenarios while ETS means were varied; in contrast, in Section 5.4, ETS proportion of zeros were varied while ETS means were held constant across all scenarios. Additionally, we note that in both simulation studies, the value of \( M \) and \( N^* \) was set to 1000 and 2000, respectively.
Simulation results when design parameters in Simulation Study 1 were utilized are summarized in the plot in Web Figure 3 where $\rho$ (x-axis) is displayed against $\tau_{MIN}$ and $\tau_{MAX}$ (y-axis). Across all values of $\rho$, the difference between $\tau_{MIN}$ and $\tau_{MAX}$ not exceed 0.11 in all scenarios. These results suggest that, when selecting the value of $\rho$, trial planners should focus on the impact of ETS proportion of zeros on the difference between $\tau_{MIN}$ and $\tau_{MAX}$, rather than the impact of the magnitude of ETS means on the difference between $\tau_{MIN}$ and $\tau_{MAX}$.

Web Appendix G. Accommodation for Reproducibility of Results

In this section, we highlight notable features of the repository https://github.com/jamieyap/CountSMART that improve the likelihood of reproducibility of the results discussed in the current manuscript; from here onward, we will refer to this repository as the ‘CountSMART repository’.

The CountSMART repository houses R code (R Core Team, 2020) used in the development of our proposed approach to sample size estimation. The R package renv (Ushey, 2020) was utilized to record the collection of software dependencies (e.g., R package version numbers) in a file named renv.lock within the CountSMART repository. The process for utilizing the file renv.lock to recreate the software environment used in the current manuscript is described within the renv documentation (Ushey, 2020).

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Web Figures

Web Figure 1: Results of Supplement to Simulation Study 1 in Web Appendix E. This figure appears in color in the electronic version of this article.
Web Figure 2: Results of Supplement to Simulation Study 1 in Web Appendix E. This figure appears in color in the electronic version of this article.

Total sample size (x-axis) vs. Empirical Bias in estimates of \( \sqrt{\text{Var}(\hat{\Delta}_{EOS})} \) and \( \sqrt{\text{Var}(\hat{\Delta}_{AUC})} \) (y-axis)

Difference in end-of-study means
Low Zeros

Moderate Zeros

High Zeros

Difference in AUC
Low Zeros

Moderate Zeros

High Zeros
Web Figure 3: Results of Supplement to Simulation Study 4 in Web Appendix F. This figure
appears in color in the electronic version of this article.

Result of grid search using values of design parameters in Simulation Study 1: $\rho$ (x-axis) vs. $\hat{\tau}^\rho_{\text{MIN}}$ (y-axis; triangles) and $\rho$ (x-axis) vs. $\hat{\tau}^\rho_{\text{MAX}}$ (y-axis; dots)
Web Tables

Web Table 1: Rows display the mean trajectory of the longitudinal EZ count outcome under each of the four EDTRs in terms of the parameters $\beta_{m,j}$’s in Equation 2

| EDTR  | $E\{Y_{l,t_1}^{(a_1,a_{2}^{NR})}\}$ | $E\{Y_{l,t_2}^{(a_1,a_{2}^{NR})}\}$ | $E\{Y_{l,t_3}^{(a_1,a_{2}^{NR})}\}$ | $E\{Y_{l,t_4}^{(a_1,a_{2}^{NR})}\}$ | $E\{Y_{l,t_5}^{(a_1,a_{2}^{NR})}\}$ | $E\{Y_{l,t_6}^{(a_1,a_{2}^{NR})}\}$ |
|-------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| (+1, +1) | $\beta_{1,1}$ | $\beta_{1,1} + \beta_{2,2}$ | $\beta_{1,1} + \beta_{4,3}$ | $\beta_{1,1} + \beta_{4,4}$ | $\beta_{1,1} + \beta_{4,5}$ | $\beta_{1,1} + \beta_{4,6}$ |
| (+1, −1) | $\beta_{1,1}$ | $\beta_{1,1} + \beta_{2,2}$ | $\beta_{1,1} + \beta_{5,3}$ | $\beta_{1,1} + \beta_{5,4}$ | $\beta_{1,1} + \beta_{5,5}$ | $\beta_{1,1} + \beta_{5,6}$ |
| (−1, +1) | $\beta_{1,1}$ | $\beta_{1,1} + \beta_{3,2}$ | $\beta_{1,1} + \beta_{6,3}$ | $\beta_{1,1} + \beta_{6,4}$ | $\beta_{1,1} + \beta_{6,5}$ | $\beta_{1,1} + \beta_{6,6}$ |
| (−1, −1) | $\beta_{1,1}$ | $\beta_{1,1} + \beta_{3,2}$ | $\beta_{1,1} + \beta_{7,3}$ | $\beta_{1,1} + \beta_{7,4}$ | $\beta_{1,1} + \beta_{7,5}$ | $\beta_{1,1} + \beta_{7,6}$ |
Web Table 2: The first row of the table below enumerates all possible potential outcomes corresponding to the SMART design in Figure 1 when there are three measurement occasions. Below, the potential outcomes \( Y_{i,t_j}^{S} \)'s that would be feasible for an individual, contingent on their subgroup membership, are denoted by a check-mark (✓).

| Subgroup 1 | ✓ | ✓ | ✓ | ✓ | — | — | ✓ | — | — |
| Subgroup 2 | ✓ | ✓ | ✓ | ✓ | — | — | — | ✓ | ✓ |
| Subgroup 3 | ✓ | ✓ | ✓ | — | ✓ | ✓ | ✓ | — | — |
| Subgroup 4 | ✓ | ✓ | ✓ | — | ✓ | ✓ | — | ✓ | ✓ |
Web Table 3: Constraints on the values of $Y_{i,t_2}^{(+1)}$ and $Y_{i,t_2}^{(-1)}$ for the four subgroups in a SMART are listed; these constrains are based on response status defined as $R_{i}^{(a_1)} = I(Y_{i,t_K}^{(a_1)} \leq c)$ in this manuscript’s exposition of the proposed approach to data generation.

| Subgroup | Constraint on the value of $Y_{i,t_2}^{(+1)}$ | Constraint on the value of $Y_{i,t_2}^{(-1)}$ |
|----------|-------------------------------|----------------------------------|
| Subgroup 1 | $Y_{i,t_2}^{(+1)} \leq c$ | $Y_{i,t_2}^{(-1)} \leq c$ |
| Subgroup 2 | $Y_{i,t_2}^{(+1)} \leq c$ | $Y_{i,t_2}^{(-1)} > c$ |
| Subgroup 3 | $Y_{i,t_2}^{(+1)} > c$ | $Y_{i,t_2}^{(-1)} \leq c$ |
| Subgroup 4 | $Y_{i,t_2}^{(+1)} > c$ | $Y_{i,t_2}^{(-1)} > c$ |
Web Table 4: The complete specification of the marginal distribution of the components of $\mathbf{\theta}^{SG}_i$ for each subgroup is displayed.

Below, $c$ is a cut-point used in the definition of response status. The CDF of a negative binomial (NB), upper truncated negative binomial (UTNB), and lower truncated negative binomial (LTNB) distribution determined by $c$, $\mu^S_{i_j}$, and $\zeta^S_{i_j}$ is denoted by $F_{NB}(\mu^S_{i_j}, \zeta^S_{i_j})$, $F_{UpperTruncNB}(\mu^S_{i_j}, \zeta^S_{i_j}, c)$, and $F_{LowerTruncNB}(\mu^S_{i_j}, \zeta^S_{i_j}, c)$, respectively. In terms of the probability mass function (PMF) of a NB random variable $f_{NB}(\mu^S_{i_j}, \zeta^S_{i_j})$, the PMF of a UTNB random variable and a LTNB random variable is

$$f_{UpperTruncNB}(\mu^S_{i_j}, \zeta^S_{i_j}, c)(w) = \frac{f_{NB}(\mu^S_{i_j}, \zeta^S_{i_j})(w)I(w \leq c)}{\sum_{w=0}^{\infty} f_{NB}(\mu^S_{i_j}, \zeta^S_{i_j})(y)}$$

and

$$f_{LowerTruncNB}(\mu^S_{i_j}, \zeta^S_{i_j}, c)(w) = \frac{f_{NB}(\mu^S_{i_j}, \zeta^S_{i_j})(w)I(w > c)}{1 - \sum_{y=0}^{\infty} f_{NB}(\mu^S_{i_j}, \zeta^S_{i_j})(y)}$$

respectively. When $c=0$, the UTNB PMF reduces to a point mass at zero.

| Subgroup 1 | $F_{NB}(\mu^{(1)}_{i_1}, \zeta^{(1)}_{i_1})$ | $F_{UpperTruncNB}(\mu^{(1)}_{i_2}, \zeta^{(1)}_{i_2}, c)$ | $F_{UpperTruncNB}(\mu^{(-1)}_{i_2}, \zeta^{(-1)}_{i_2}, c)$ |
|------------|---------------------------------|---------------------------------|---------------------------------|
| Subgroup 2 | $F_{NB}(\mu^{(2)}_{i_1}, \zeta^{(2)}_{i_1})$ | $F_{UpperTruncNB}(\mu^{(2)}_{i_2}, \zeta^{(2)}_{i_2}, c)$ | $F_{LowerTruncNB}(\mu^{(2)}_{i_2}, \zeta^{(2)}_{i_2}, c)$ |
| Subgroup 3 | $F_{NB}(\mu^{(3)}_{i_1}, \zeta^{(3)}_{i_1})$ | $F_{LowerTruncNB}(\mu^{(3)}_{i_2}, \zeta^{(3)}_{i_2}, c)$ | $F_{UpperTruncNB}(\mu^{(3)}_{i_2}, \zeta^{(3)}_{i_2}, c)$ |
| Subgroup 4 | $F_{NB}(\mu^{(4)}_{i_1}, \zeta^{(4)}_{i_1})$ | $F_{LowerTruncNB}(\mu^{(4)}_{i_2}, \zeta^{(4)}_{i_2}, c)$ | $F_{LowerTruncNB}(\mu^{(-1)}_{i_2}, \zeta^{(-1)}_{i_2}, c)$ |
Web Table 5: Web Table 4, Continued

| Subgroup   | $F_{Y_i(t_3)}$ | $F_{Y_i(t_3)}^{(+1,0,+1)}$ | $F_{Y_i(t_3)}^{(+1,0,+1)}$ | $F_{Y_i(t_3)}^{(-1,0,+1)}$ | $F_{Y_i(t_3)}^{(-1,0,+1)}$ | $F_{Y_i(t_3)}^{(+1,0,-1)}$ |
|------------|----------------|----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Subgroup 1 | $F_{NB}(\mu_3^{(+1,0)}, \xi_3^{(+1,0)})$ | $-$ | $-$ | $F_{NB}(\mu_3^{(-1,0)}, \xi_3^{(-1,0)})$ | $-$ | $-$ |
| Subgroup 2 | $F_{NB}(\mu_3^{(+1,0)}, \xi_3^{(+1,0)})$ | $-$ | $-$ | $-$ | $F_{NB}(\mu_3^{(-1,0)}, \xi_3^{(-1,0)})$ | $F_{NB}(\mu_3^{(-1,0)}, \xi_3^{(-1,0)})$ |
| Subgroup 3 | $-$ | $F_{NB}(\mu_3^{(+1,0)}, \xi_3^{(+1,0)})$ | $F_{NB}(\mu_3^{(+1,0)}, \xi_3^{(+1,0)})$ | $F_{NB}(\mu_3^{(-1,0)}, \xi_3^{(-1,0)})$ | $-$ | $-$ |
| Subgroup 4 | $-$ | $F_{NB}(\mu_3^{(+1,0)}, \xi_3^{(+1,0)})$ | $F_{NB}(\mu_3^{(+1,0)}, \xi_3^{(+1,0)})$ | $-$ | $F_{NB}(\mu_3^{(-1,0)}, \xi_3^{(-1,0)})$ | $F_{NB}(\mu_3^{(-1,0)}, \xi_3^{(-1,0)})$ |