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

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Summary

Dynamic treatment regimens (DTRs), also known as treatment algorithms or adaptive interventions, play an increasingly important role in many health domains. DTRs are motivated to address the unique and changing needs of individuals by delivering the type of treatment needed, when needed, while minimizing unnecessary treatment. Practically, a DTR is a sequence of decision rules that specify, for each of several points in time, how available information about the individual should be used in practice to decide which treatment (e.g., type or intensity) to deliver. The sequential multiple assignment randomized trial (SMART) is an experimental design that is widely used to empirically inform the development of DTRs. Existing sample size planning resources for SMART studies are suitable for continuous, binary, or survival outcomes. However, an important gap exists in sample size estimation methodology for planning SMARTs with longitudinal count outcomes. Further, in many
health domains, count data are *overdispersed* – that is, having variance greater than their mean. To close this gap, this manuscript describes the development of a Monte Carlo-based approach for sample size estimation. Simulation studies were employed to investigate various properties of this approach. Throughout, a SMART for engaging alcohol and cocaine-dependent patients in treatment is used as motivation.

*Key words: dynamic treatment regimen (DTR); longitudinal data; overdispersed count data; sample size estimation; sequential multiple assignment randomized trial (SMART)*

1. Introduction

Dynamic treatment regimens (DTRs) are increasingly viewed as a powerful tool for improving people’s health in a resource efficient manner (Riley, et al., 2015). DTRs are motivated to address the unique and changing needs of individuals by delivering the type of treatment needed, when needed, while minimizing unnecessary treatment (Collins, Murphy, and Bierman, 2004). A DTR includes a sequence of decision rules that specify, at a decision point (i.e., point in time in which treatment decisions should be made), whether and how to modify the type, intensity, or modality of treatment based on available information about the individual, i.e., *tailoring variables*. Intended to provide a replicable guide for the delivery of individualized sequences of treatments in actual clinical practice, DTRs enable effective resource allocation and hold promise in decreasing the economic burden of poor health (Nahum-Shani, et al., 2020).

The sequential multiple assignment randomized trial (SMART) (Lavori and Dawson, 2000; Murphy, 2005) is a useful experimental approach for obtaining the empirical evidence necessary to construct effective DTRs. A SMART involves multiple stages of randomization with each stage beginning with a decision point in which some or all individuals are randomized among appropriate treatment options. As an example, consider the ENGAGE study (McKay et al., 2015) in which a SMART was conducted 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 treatment sessions regularly and are hence less likely to benefit from the program (McKay et al., 2015). Investigators of the study sought to determine whether at the first intervention stage, it is better to offer motivational interviewing (MI)-based outreach efforts that directly focus on helping the individual to engage in the IOP (MI-Engage) or MI-based outreach efforts that facilitate personal choice by highlighting possible treatment options (MI-Choice). They also sought 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 resulted in 6 cells, labeled A-F in Figure 1, and has four DTRs embedded (EDTRs) within the design (see Table 1). For ease of exposition, throughout, we will assume that randomization to the first-stage treatments in the SMART occurred immediately after the end of month 1 (i.e., one month after entering IOP treatment), coinciding with the first measurement occasion.

Many SMART studies are motivated to compare EDTRs in terms of a longitudinal outcome that counts the number of specific events or experiences. For example, in the context of the ENGAGE study, possible longitudinal outcomes could be the number of therapy sessions attended in the past month or the number of alcohol-use days in the past month. Existing empirical evidence from the ENGAGE study indicates that both of these count
variables are overdispersed, showing variance higher than their mean (e.g., means 6.5 - 8.0 and variances 85.0 - 141.9 for the number of sessions attended across 3 months; and means 1.7 - 3.7 and variances 12.8 - 58.5 for the number of alcohol use days across 6 months).

Sample size planning resources have been developed for SMARTs having continuous, binary-, or survival- end-of-study or longitudinal outcomes (e.g., Li and Murphy, 2011; Kidwell et al., 2018; Seewald, et al., 2020). However, a gap remains concerning sample size planning resources for the comparison of EDTRs in SMARTs using longitudinal count outcomes, particularly those having overdispersion. 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 (Section 2) and considerations in developing an approach to sample size estimation using longitudinal count data (Section 3). Section 4 describes the proposed approach. Simulation studies investigating its properties are described in Sections 5 and 6. Finally, directions for future research are discussed (Section 7).

2. Hypothesis tests for comparing DTRs embedded in a SMART

This manuscript focuses on one of the most common SMART designs exemplified by the ENGAGE study: a two-stage restricted SMART. In this design, there are two possible first-stage treatments, and two possible second-stage treatments where the decision on whether to randomize individuals to second-stage treatments 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 treatments.

2.1 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 treatment option and \(a_2^{NR}\) is a second-stage treatment option offered to non-responders; \(a_1 \in \{+1, -1\}\) and
\( a_{2}^{NR} \in \{+1, -1\} \). 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. Let \( Y_{t,t_j} \) denote a count outcome of an individual \( i \) that was observed during the actual conduct of the trial at time \( t_j \). Let \( Y_{t,t_j}^{(a_1,a_{2}^{NR})} \) 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 \( Y_{t,t_j}^{(a_1,a_{2}^{NR})} \) 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 \( E\{Y_{t,t_j}^{(a_1,a_{2}^{NR})}\} \).

### 2.2 Focusing on pairwise comparisons of EDTRs

The pairwise comparison of two EDTRs is the focus of this manuscript, analogous to existing sample size estimation literature for SMARTs (Kidwell et al., 2018; Seewald et al., 2020). Other analyses involving omnibus comparisons are possible (Ertefaie et al., 2016), but planning sample size for a scientifically justified pairwise comparison is a good starting point.

The comparison of EDTRs based on differences in end-of-study means is a common goal of SMARTs. However, EDTRs may also be compared based on differences in Area Under the Curve (AUC). In contrast to end-of-study means, AUC accounts for how mean trajectories of EDTRs evolve over time. This estimand is important in health domains where achieving sustained health behavior change over a longer period of time represents a clinically significant milestone (e.g., consistent therapy session attendance over three months) or a clinically significant risk factor (e.g., consistently high alcohol use over six months). AUC is defined as the total area under \( \mathcal{T}^{(a_1,a_{2}^{NR})} \) between \( t_1 \) and \( t_T \) and can be approximated using the trapezoidal rule as 

\[
\text{AUC}^{(a_1,a_{2}^{NR})} := \sum_{j=1}^{T-1} \frac{1}{2} \left[ \mu_{t_j}^{(a_1,a_{2}^{NR})} + \mu_{t_{j+1}}^{(a_1,a_{2}^{NR})} \right] (t_{j+1} - t_j).
\]

More generally,
a pair of EDTRs \((a_1', a_2^{NR'})\) and \((a_1'', a_2^{NR''})\) can be compared based on the contrast 
\[ \Delta_Q = \sum_{j=1}^T l_j \mu_{t_j}^{a_1', a_2^{NR'}} - \sum_{j=1}^T l_j \mu_{t_j}^{a_1'', a_2^{NR''}} \]
where \(l_j\)'s are real valued constants which need not sum to 1. \(\Delta_Q\) can be viewed as the difference of weighted sums with weights given by the \(l_j\)'s.

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 1st weight to be equal to \(\frac{t_2-t_1}{2}\), the \(T\)th weight to be equal to \(\frac{t_T-t_{T-1}}{2}\), and all other weights to be equal to \(\frac{t_j-t_{j-1}}{2}\)), 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 hypothesis \(H_a: \Delta_Q \neq 0\) at type-I error rate \(\alpha\).

2.3 Modeling and estimation of EDTR mean trajectories

Let \(I(\cdot)\) denote an indicator function. We utilize a model for \(\mu_{t_j}^{(a_1,a_2^{NR})}\) 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 \(t_K\). In other words, for each EDTR, each measurement occasion \(j\) is given its own parameter in Equation 1. The parameters in Equation 1 can be estimated using the inverse probability weighted and replicated estimator (IPWRE) (Lu et al., 2016).

\[
\log \left( \mu_{t_j}^{(a_1,a_2^{NR})} \right) = \beta_{1,j} + I(a_1 = +1) \cdot I(1 < j \leq K) \cdot \beta_{2,j} \\
+ I(a_1 = -1) \cdot I(1 < j \leq K) \cdot \beta_{3,j} \\
+ I(a_1 = +1, a_2^{NR} = +1) \cdot I(K < j \leq T) \cdot \beta_{4,j} \\
+ I(a_1 = +1, a_2^{NR} = -1) \cdot I(K < j \leq T) \cdot \beta_{5,j} \\
+ I(a_1 = -1, a_2^{NR} = +1) \cdot I(K < j \leq T) \cdot \beta_{6,j} \\
+ I(a_1 = -1, a_2^{NR} = -1) \cdot I(K < j \leq T) \cdot \beta_{7,j} 
\]
2.4 Hypothesis testing and power of the test

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

Theorem 2.1: $Z := \frac{\hat{\Delta}_Q^{IPWRE} - \Delta_Q}{\text{Var}(\hat{\Delta}_Q^{IPWRE})^{1/2}}$ is Normal$(0,1)$ distributed.

Let $z_q$ denote the $q^{th}$ percentile of the standard normal distribution. A Z-test is to reject $H_0$ if

$$\left| \frac{\Delta_Q^{IPWRE}}{\sqrt{\text{Var}(\hat{\Delta}_Q^{IPWRE})}} \right| > z_{1-\alpha/2}. \text{ The power of the test is thus } \Pr_{H_1} \left\{ \left| \frac{\Delta_Q^{IPWRE}}{\sqrt{\text{Var}(\hat{\Delta}_Q^{IPWRE})}} \right| > z_{1-\alpha/2} \right\}. $$

3. Considerations in developing an approach to sample size estimation

Deriving a convenient closed-form sample size formula requires expressing the variance term in the denominator of the $Z$-statistic in terms of quantities which are interpretable (and hence can be informed) by investigators. However, this term is impractical to express in a convenient formula, particularly when the total number of measurement occasions, $T$, is large. Hence, this manuscript adopts a Monte Carlo-based approach to enable investigators to estimate sample size for arbitrary number of measurement occasions $T$.

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 based on response status, ordering of the sequential randomizations in a SMART in relation to the timing of repeated measurements, and
dependency between response status 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 overdispersed count data.

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 realistic in practice (e.g., see Lei et al., 2012). In other approaches (e.g., Appendix 3 of Seewald, et al., 2020), quantities at the level of an EDTR are required as inputs to generate data. In the authors’ experience planning SMARTs, investigators typically find quantities (e.g., means) at the level of an EDTR more abstract and difficult to specify relative to quantities at the level of an Embedded Treatment Sequence (ETS). In contrast to an EDTR, an ETS refers to a sequence of treatments actually offered to an individual by time $t_j$. That is, starting at time $t_K$, an ETS is conditional on response status while an EDTR is marginal over response status. In particular, the mean of a longitudinal outcome at the level of an ETS is conditional on $a_1, a_2^{NR}$, and response status together, but the mean of a longitudinal outcome at the level of an EDTR is conditional on $a_1, a_2^{NR}$ and marginal over response status. Hence, another consideration is ensuring interpretability of design parameters – parameters that serve as inputs to sample size estimation.

3.2 Considerations relating to the distribution of overdispersed count data

Our approach to sample size estimation will be described using a negative binomial (NB) distribution, which has often been used to characterize the distribution of overdispersed count data when estimating sample size for randomized trials (e.g., see Li, Zhang, and Cao, 2019 and references cited therein). The NB distribution is given by Equation 2 where a univariate random variable $Y$ denotes the number of events during a specified time period
(e.g., number of therapy sessions attended or of alcohol-use days in the past month), \( \Gamma(\cdot) \) is the gamma function, and \( \zeta \) is the dispersion parameter. When the distribution of \( Y \) is given by Equation 2, its mean and variance are \( \mu \) and \( \mu + \zeta \mu^2 \), respectively, and we write \( Y \sim \text{NB}(\mu, \zeta) \).

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

(2)

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 overdispersed count data 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. Equation 3 defines a Gaussian copula; \( X_1, \ldots, X_d \) represent random variables comprising the components of the multivariate random variable of interest, \( F_{X_{\ell}}'s \) are marginal univariate CDFs of the \( X_{\ell} 's \), \( \Phi_d \) 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 \( X_{\ell} 's \).

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

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 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 $Y_{i,t_j}^s$ 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 $\mu_{i,j}^s$ denote $E\{Y_{i,t_j}^s\}$. There are four EDTRs in the SMART design we consider, regardless of time (see Table 1). However, the number of ETSs associated with time $t_j$ is determined by when $t_j$ occurred in relation to first- and second-stage randomization. Prior to first-stage randomization (i.e., at time $t_1$) an individual would not be offered any of the treatment 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 treatment 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 treatment 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 by the end of the study. 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

We assume that a given individual may be classified as a responder if the outcome immediately prior to the second randomization at time $t_K$ falls within a specific range of values. In Table 2, we display three examples of ways response status can be operationalized when designing SMARTs with overdispersed count data. From here onward, we describe our proposed approach using example (a) in Table 2, but our proposed approach can accommodate all three with minor modifications. Thus, for simplicity of exposition, 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 treatment \( a_1 \), then \( R_i^{(a_1)} = I(Y_{i,t_K}^{(a_1)} \leq c) \). Similarly, for observed outcomes, let \( R_i = I(Y_{i,t_K} \leq c) \). 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 \( \mu_t s \)'s (either directly or indirectly) from investigators allows the determination of the desired magnitude of \( \Delta_Q \) in the planned SMART.

\[
\Delta_Q := \sum_{j=2}^{K} l_j \left\{ \mu_t^{(a_1')} \right\} - \sum_{j=2}^{K} l_j \left\{ \mu_t^{(a_1'')} \right\} \\
+ \sum_{j=K+1}^{T} l_j \cdot \left\{ p \mu_t^{(a_1',1,0)} + (1-p) \mu_t^{(a_1',0,a_2K')} \right\} \\
- \sum_{j=K+1}^{T} l_j \cdot \left\{ q \mu_t^{(a_1'',1,0)} + (1-q) \mu_t^{(a_1'',0,a_2K''')} \right\}
\]

4.3 Data generation

To simplify exposition, within Section 4.3, we suppose that only three measurement occasions are to be collected (i.e., \( T=3 \)), but the approach is applicable to more measurement occasions. Specifically, suppose that in a planned two-stage restricted SMART with design depicted in Figure 1, measurements are to be collected 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 \( (t_T; T = 3) \). Parameters serving as inputs to data generation 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 treatment options.

3. The means of the longitudinal count outcome for all ETSs \(s\) and time points \(t_j\), i.e., the quantities \(\mu_{s,t_j}^c\) for all ETSs \(s\) and time points \(t_j\).

4. \(\tau_{MAX}\), the maximum within-person correlation among longitudinal outcomes \(Y_{i,t_j}^s\) across all pairs of ETSs \(s'\) and \(s''\) and pairs of time points \(t_j'\) and \(t_j''\). That is, \(\tau_{MAX} = \max_{s',t_j',t_j'',s''} \{\text{Corr}(Y_{i,t_j'}^s, Y_{i,t_j''}^{s''})\}\).

5. The dispersion parameter in the longitudinal count outcome for all ETSs \(s\) and time points \(t_j\), i.e., the quantities \(\zeta_{i,t_j}^s\) for all ETSs \(s\) and time points \(t_j\).

From these parameters, the proportion of responders to first-stage treatment (i.e., \(p\) and \(q\)) is implied since \(\Pr\{R_i^{(a_1)} = 1\} = \Pr\{Y_{i,t_j}^{(a_1)} \leq c\} = \sum_{y=0}^{c} f_{NB(\mu_{i,t_j}^{(a_1)}, \zeta_{i,t_j}^{(a_1)})}(y)\).

The quantities in items 1-4 may be elicited directly from investigators. Investigators may opt to either specify the dispersion parameter (item 5) directly based on data from prior studies. In the absence of prior studies, the value of the dispersion parameter can be determined indirectly either by having investigators specify either the variance or proportion of zeros in the longitudinal outcome for all ETSs \(s\) and time points \(t_j\), i.e., the quantities \(\text{Var}\{Y_{i,t_j}^s\}\) or \(\Pr\{Y_{i,t_j}^s = 0\}\), respectively, for all ETSs \(s\) and time points \(t_j\). In our experience, variances are more challenging to specify than proportion of zeros. Hence, we recommend eliciting the latter. Subsequently, the value of the dispersion parameter can then be obtained by solving the equation \(\Pr\{Y_{i,t_j}^s = 0\} = \left(\frac{1}{\zeta_{i,t_j}^s}\right)^{1/\zeta_{i,t_j}^s}\), which follows from Equation 2.

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

We noted earlier that it is possible to enumerate an individual’s full set of potential outcomes with respect to each ETS prior to data generation. This can be accomplished by
viewing each individual entering a SMART as belonging to one of several mutually exclusive subgroups, and subsequently, enumerating potential outcomes that would be feasible for individuals belonging to each subgroup.

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 treatment 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 \( Y_{i,t_j}^{S'} \’s \) 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 \( \theta_{i,j}^f \) 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 \( \theta_{i,j}^f \) such that the marginal distributions, i.e., the univariate distribution of a specific
component of $\boldsymbol{\theta}_i^j$ marginal over all the other components of $\boldsymbol{\theta}_i^j$, adhere to a desired univariate CDF (e.g., a NB CDF). In this way, $\boldsymbol{\theta}_i^j$ can be viewed as a non-linear transformation of a latent MVN-distributed variable, a property which will be leveraged later. Since the dimension of $\boldsymbol{\theta}_i^j$ differs across subgroups, a different copula should be specified for each subgroup. Specifically, $\boldsymbol{\theta}_i^j$ 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 ($j=4$).

The univariate CDFs $F_{X_\ell}$’s in Equation 3 must reflect design constraints. Because response status is defined in terms of a cut-point, the maximum or minimum possible value of the potential outcome under either first-stage treatment at the time of the $K^{th}$ measurement occasion (i.e., at $t_2$ in this case) is constrained. 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 the value of the cut-point $c$ while the value of $Y_{i,t_K}^{(-1)}$ is greater than the value of the cut-point $c$. 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 (i.e., the $F_{X_\ell}$’s) in the subgroup-specific 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. For Equation 5 with $c=0$, $f(w)$ reduces to a point mass at zero. For potential outcomes corresponding to ETS $s$ at any of the other measurement occasions, we choose a NB CDF defined by $F(w^*) := \Pr[W \leq w^*] = \sum_{w=0}^{w^*} f_{NB}(\mu_j^{s},\xi_j^{s})(w); j \neq K$. The complete specification of the univariate CDFs of the copula for each subgroup is displayed in Web Table 4 and 5.
Now, we turn our attention to $\mathbf{A}_d$ to complete the specification of a joint distribution for $\mathbf{\theta}_i$. We let $\mathbf{Z}_i$ denote the latent MVN-distributed variable associated with $\mathbf{\theta}_i$. Note that the correlation between the $X_i$’s in Equation 3 is determined not only by the choice of $\mathbf{A}_d$, 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 (see (Song, 2000)). To simplify this numerical estimation, we will specify either an autoregressive of order 1 (AR1) or an exchangeable structure for components of $\mathbf{Z}_i$ corresponding to potential outcomes in $\mathbf{\theta}_i$ lying along the same path leading to cells A-F in Figure 1.

Specifically, when an AR1 structure and an exchangeable structure is specified,

$$
corr(Z_{i,t_1}^{s'}, Z_{i,t_2}^{s''}) = \rho_{|t_1-t_2|} \text{ or } corr(Z_{i,t_1}^{s'}, Z_{i,t_2}^{s''}) = \rho,
$$

respectively, for all ETSs $s'$ and $s''$ lying along the same path leading to cells A-F in Figure 1 (e.g., the ETS $s' = (+1)$ at $t_2$ and the ETS $s'' = (+1,0,+1)$ at $t_3$ lie along the same path leading to cell B). Here, the parameter $\rho$, which we will refer to as the dependence parameter, is shared across all four subgroups for simplicity of elicitation. Finally, to complete our specification of the structure of correlation among components of $\mathbf{\theta}_i$, we set $corr(Z_{i,t_1}^{s'}, Z_{i,t_2}^{s''}) = \eta$, for all ETSs $s'$ and $s''$ lying along different paths in Figure 1 (e.g., the ETS $s' = (+1)$ at $t_2$ lies along the path leading to cell B but the ETS $s'' = (-1,0,+1)$ at $t_3$ lies along the path leading to cell E). In this way, we conceptually differentiate dependence between outcomes which can be feasibly observed together from outcomes which cannot (i.e., outcomes under ETS on different paths) in the conduct of a trial. As the complete set of potential outcomes of individuals belonging to
subgroup 4 is \( \Theta^j_t = \left( Y_{i,t_1}^{(c)}, Y_{i,t_2}^{(+1)}, Y_{i,t_2}^{(-1)}, Y_{i,t_3}^{(+1,0,+1)}, Y_{i,t_3}^{(-1,0,-1)} \right)^T \), the complete structure of \( \Lambda_4 \) is given by Equation 7 when an AR1 structure is specified.

\[
\Lambda_4 = \text{corr} \begin{pmatrix} Z_{i,t_1}^{(c)} \\ Z_{i,t_2}^{(+1)} \\ Z_{i,t_2}^{(-1)} \\ Z_{i,t_3}^{(+1,0,+1)} \\ Z_{i,t_3}^{(+1,0,-1)} \\ Z_{i,t_3}^{(-1,0,+1)} \\ Z_{i,t_3}^{(-1,0,-1)} \end{pmatrix} = \begin{pmatrix} 1 & \rho & \rho & \rho^2 & \rho^2 & \rho^2 & \rho^2 \\ \rho & 1 & \eta & \rho & \rho & \eta & \eta \\ \rho & \eta & 1 & \eta & \eta & \rho & \rho \\ \rho^2 & \rho & \eta & 1 & \eta & \eta & \eta \\ \rho^2 & \rho & \eta & \eta & 1 & \eta & \eta \\ \rho^2 & \eta & \rho & \eta & \eta & 1 & \eta \\ \rho^2 & \eta & \rho & \eta & \eta & \eta & 1 \end{pmatrix}
\]

The complete structure of \( \Lambda_1, \Lambda_2, \Lambda_3 \) for subgroups 1, 2, 3, respectively, can be analogously written. In Web Appendix H, we show that given a particular value of \( \rho \), power is not sensitive to the actual value of \( \eta \) (i.e., the actual extent of dependence between potential outcomes corresponding to ETSs which cannot be feasibly observed together in the conduct of a trial). Hence, throughout, we set \( \eta = \rho^2 \). When an exchangeable structure is specified for components of \( Z^i_t \), the complete structure of \( \Lambda_1, \Lambda_2, \Lambda_3, \Lambda_4 \) can be analogously written.

Finally, completing the specification of the \( \Lambda_d \)'s requires that a specific value for \( \rho \) be selected. Here, the selected value of \( \rho \) will be the specific value associated with the maximum expected correlation among outcomes, i.e., the specific value of \( \tau_{MAX} \) provided by investigators. Since an analytical formula relating \( \rho \) and \( \tau_{MAX} \) is generally unavailable, their relationship needs to be numerically estimated (see Web Appendix D for details).

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

Once the specification of a copula for each subgroup is complete, a method proposed by Madsen and Birkes (Madsen and Birkes, 2013), can then be directly applied to simulate multivariate non-normal data according to a pre-specified distribution of the multivariate (potential) outcome \( \Theta^j_t \) (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. Thus, for the particular set of values \((a_1)\) and \((a_1, r, a_2^NR)\) pertaining to individual \( i \), we have that \( Y_{i,t_1} = Y^{(i)}_{i,t_1} \), that \( Y_{i,t_2} = Y^{(a_1)}_{i,t_2} \), that \( R_i = R_i^{(a_1)} \), that \( Y_{i,t_3} = Y^{(a_1,1,0)}_{i,t_3} \) if \( R_i = 1 \), and \( Y_{i,t_3} = Y^{(a_1,0,a^2_{NR})}_{i,t_3} \) if \( R_i = 0 \).

Specifying the number of individuals to generate per subgroup

Let \( n_j \) denote the number of individuals that would belong to subgroup \( j \) and let \( \lceil \cdot \rceil \) denote the ceiling function. 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 treatment, i.e., \( n_4 = \min\{N(1-p),N(1-q)\} \), the number of individuals to generate for each subgroup can then be calculated as \( \lceil n_j \rceil \) where the \( n_j \)'s satisfy the following simple equations: \( N = \sum_{j=1}^{4} n_j \), \( p = \frac{n_1 + n_2}{N} \), \( q = \frac{n_1 + n_3}{N} \), and \( n_4 = \min\{N(1-p),N(1-q)\} \). Our working assumption is equivalent to setting \( n_4 \) to its maximum possible value; the minimum is zero. We show in Web Appendix I that power is not sensitive to the actual value of \( n_4 \).

4.4 Power calculation for a fixed sample size \( N \)

Let \( \mathbb{P}_M \) denote an empirical mean across \( M \) simulated datasets. We may estimate power by \( 1 - \eta \approx \mathbb{P}_M \left\{ I \left( \frac{\Delta^{PWRE}}{\sqrt{\overline{\alpha}r(\Delta^{PWRE})}} > z_{1-\alpha/2} \right) \right\} \) (see Web Appendix E for details).

5. Simulation Study Design

We consider a prototypical two-stage restricted SMART as in Figure 1 where response status is defined using the cut-point \( c = 0 \). 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 \( \left( \text{i.e.,} \Delta_{\text{EOS}} = E\{Y_{t,t_6}^{(+1,+1)}\} - E\{Y_{t,t_6}^{(-1,+1)}\} \right) \) or difference in AUC \( \left( \text{i.e.,} \Delta_{\text{AUC}} = \text{AUC}^{(+1,+1)} - \text{AUC}^{(-1,+1)} \right) \), each at a desired type-I error rate of \( \alpha = 0.05 \).

In **Simulation Study 1**, we investigate how power changes as \( \Delta_{\text{EOS}} \) and \( \Delta_{\text{AUC}} \) increase. Across all scenarios, proportions of responders \( p \) and \( q \), ETS proportion of zeros, and \( \rho \) were held constant as power was calculated across the grid 100, 150, 200, … 550 for total sample size \( N \). Ten scenarios corresponding to increased magnitude of \( \Delta_{\text{EOS}} \) and \( \Delta_{\text{AUC}} \) were considered. Table 3 displays the varying values of parameters used in this simulation study (top panel) and the dispersion parameter at each ETS and time point (bottom panel).

Altogether, these values imply the following values of \( \Delta_{\text{EOS}} \) and \( \Delta_{\text{AUC}} \) in scenarios 1-10: \( \Delta_{\text{EOS}} = 0.28 \) (scenario 1), 0.56 (scenario 2), 0.84 (scenario 3), 1.12 (scenario 4), 1.4 (scenario 5), 1.68 (scenario 6), 1.96 (scenario 7), 2.24 (scenario 8), 2.52 (scenario 9), 2.8 (scenario 10); and \( \Delta_{\text{AUC}} = 0.7 \) (scenario 1), 1.41 (scenario 2), 2.11 (scenario 3), 2.81 (scenario 4), 3.52 (scenario 5), 4.22 (scenario 6), 4.92 (scenario 7), 5.63 (scenario 8), 6.33 (scenario 9), 7.03 (scenario 10). Two sets of power curves were calculated, one for an AR1 structure and another for an exchangeable structure, respectively. Finally, we repeated the scenarios described above, but increased the value of \( \rho \). The magnitudes of \( \Delta_{\text{EOS}} \) and \( \Delta_{\text{AUC}} \) remained unchanged even at increased values of \( \rho \). \( M = 5000 \) Monte Carlo samples were used to calculate power.

In **Simulation Study 2**, we investigate whether our simulation approach was able to generate data that is consistent with the correlation structure (AR1 or exchangeable) and within-person correlation \( (\tau_{\text{MAX}}) \) specified by investigators. Here, we estimated
\[
\text{Corr} \left( Y_{t,t_j}^{s'}, Y_{t,t_j}^{s''} \right)
\]
for all pairs of ETSs \( s' \) and \( s'' \) and pairs of time points \( t_j' \) and \( t_j'' \) by
calculating their average value across all simulated datasets generated using scenarios identical to Simulation Study 1, except that the total sample size \( N \) was fixed to 1000. \( M = 5000 \) Monte Carlo samples were used to estimate the correlations.

### 6. Simulation Study Results

The results for **Simulation Study 1** are summarized in Figure 2 and 3. Results for scenario 1 (i.e., when \( \Delta_{\text{EOS}} = 0.28 \) [left panel]; when \( \Delta_{\text{AUC}} = 0.7 \) [right panel]) are displayed as solid dots on the bottom-most dashed horizontal line, results for scenario 2 (i.e., when \( \Delta_{\text{EOS}} = 0.56 \) [left panel]; when \( \Delta_{\text{AUC}} = 1.41 \) [right panel]) are displayed as solid dots on the 2\(^{nd}\) dashed horizontal line from the bottom. Analogously, results for scenarios 3-10 are displayed as solid dots on the 3\(^{rd}\) through 10\(^{th}\) dashed horizontal line from the bottom. The power curves indicate that power increases as \( \Delta_{\text{EOS}} \) or \( \Delta_{\text{AUC}} \) increases, with similar trends observed when \( \rho \) is fixed to 0.2, 0.4, and 0.6.

Results from **Simulation Study 2** show that when an AR1 structure is utilized and \( \rho \) was 0.2, 0.4, 0.6, the corresponding value of \( \tau_{\text{MAX}} \) was 0.15, 0.32, 0.52 in all scenarios. On the other hand, when an exchangeable structure was utilized, identical values were also observed in all scenarios (i.e., \( \rho \) was 0.2, 0.4, 0.6, the corresponding value of \( \tau_{\text{MAX}} \) was 0.15, 0.32, 0.52 in all scenarios). In all scenarios utilizing either type of correlation structure (i.e., AR1 or exchangeable), a monotone relationship between \( \rho \) and \( \tau_{\text{MAX}} \) was observed.

We display the estimated correlation structure only for the case when \( \rho = 0.6 \) in scenario 10 in Figure 4 and 5; the estimated correlation structures for all other scenarios are similar and hence omitted. In Figure 4 and 5, panels (a) through (f) display the estimated value of \( \text{Corr} \left( Y_{s,t}^{s'}, Y_{t}^{s''} \right) \) corresponding to pairs of ETS \( s' \) and \( s'' \) lying on the same path leading to cell A through F, respectively, in Figure 1. The results demonstrate that the specification of AR1 or exchangeable structure among components of the latent MVN...
variable \( Z_i^j \) leads to near-AR1 or near-exchangeable structure for the observed variable, although the strength of the correlation is bounded above, but not identical to, the specified \( \rho \).

Together, the results of Simulation Study 1 and 2 show that higher values of within-person correlation (i.e., \( \rho \), or equivalently of \( \tau_{MAX} \)) can lead to higher power for detecting differences in end-of-study means. However, we have seen that these gains were observed primarily when an exchangeable structure is utilized, and not an AR1 structure (Top Panels, Figure 6). On the other hand, higher values of \( \tau_{MAX} \) can lead to attenuation in power for detecting differences in AUC. This attenuation was observed in both AR1 and exchangeable structures (Bottom Panels, Figure 6). We provide an explanation for this result below.

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 outcomes having overdispersion. This approach is designed to require only specification of parameters that investigators can meaningfully interpret and can hence draw on existing empirical evidence and practical considerations to specify. Simulations show anticipated increases in power as the difference \( \Delta_{EOS} \) and the difference \( \Delta_{AUC} \) between embedded DTRs increase and little sensitivity to violations of working assumptions on \( n_4 \) and \( \eta \) (see Web Appendix H and I).

Higher values of \( \tau_{MAX} \) (i.e., the maximum within-person correlation among longitudinal outcomes) can lead to attenuation in power for detecting differences in AUC. This is because AUC is analogous to a within-cluster average and high within-person correlation represents less independent information per cluster (here, per person). In contrast, comparing end-of-study means with randomized data, under the assumption of group equivalence prior to randomization, is more similar to analysis of covariance where higher within-person correlation leads to an attenuation in standard error.
Although gains in power were observed for detecting differences in end-of-study means when an exchangeable structure was utilized, no gains in power were observed when an AR1 structure was utilized. The latter observation can be attributed to the fact that correlation between outcomes having increased time-separation (e.g., outcomes at $t_1$ and $t_6$) are generally near-zero (e.g., $0.52^{6-1} = 0.04$). Although within-person correlation often decrease with increased time-separation among measurement occasions, within-person correlation rarely approaches zero, even if they are taken many years apart (Fitzmaurice, Laird and Ware, 2012). Hence, utilizing an exchangeable structure in the data-generation process may more closely mimic data collected from a broader number of SMART studies compared to an AR1 structure. Particularly when more frequent measurement occasions are anticipated, practitioners employing our proposed approach may consider using an exchangeable structure but calculate power across different values for $\tau_{MAX}$ as a kind of sensitivity analysis.

While Monte Carlo-based approaches are generally known to come at a cost of losing some generality, particularly with respect to the distribution of the longitudinal outcome, our approach can be viewed as general framework which can accommodate various parametric distributions for overdispersed, underdispersed (i.e., variance is less than the mean), or equidispersed (i.e., variance is equal to the mean) count data. To apply this approach to other distributions, one may have the CDF of the $\ell^{th}$ component ($\ell = 1, \ldots, d$) in Equation 3 specified to be the CDF of the desired (marginal) distribution instead of the CDF of a NB distribution. For example, one might also consider the mean-parametrized Conway-Maxwell Poisson (CMP) distribution (Huang, 2017). In contrast to the NB distribution, the CMP distribution can accommodate two types of dispersion: overdispersion and underdispersion. Finally, one may use the classical Poisson distribution in the choice of CDFs in Equation 3 to accommodate count outcomes which are equidispersed. Of course, using other distributions
would require modifications to the parameters elicited from investigators, which we outlined earlier.

The Z-test presented in Theorem 2.1 was evaluated in finite sample sizes ranging from 100 to 550 (see Web Appendix F). Generally, empirical type-I error rate was either nominal or slightly above nominal (i.e., about 0.05 to 0.07) when comparing EDTRs based on differences in end-of-study means. However, when comparing EDTRs based on differences in AUC, empirical type-I error rate was somewhat above nominal (i.e., between 0.07 to 0.09) in scenarios where overdispersion was more extreme but sample size remained modest at 200 or less. This occurs because the estimate $\hat{\text{Var}}(\Delta_{IPWRE})$, obtained from Taylor series arguments, can be biased in such extreme scenarios (see Web Appendix G). A bootstrap-based approach to estimating $\text{Var}(\Delta_{IPWRE})$ might improve accuracy (see e.g., Chakraborty, Laber, and Zhao, 2013) and is thus an area of future work.

While we have not considered missing data thus far, the possibility of missing data clearly must be considered when planning a SMART. Since it is likely to be difficult to elicit models for realistic missing data mechanisms from substantive researchers (due to challenges in specifying every possible cause of missingness in advance), a more practical approach might be to perform a sensitivity analysis of power under working missing completely at random or missing at random (MCAR or MAR; Little and Rubin, 2002) assumptions. Web Appendix J provides a sketch of an approach to estimate sample size when missing data is anticipated in a planned SMART. This approach builds on our proposed approach to data generation (Section 4.3) and power calculation (section 4.4). It includes an additional step in the data generation process to induce missing values in the $M$ simulated datasets and applying standard corrections (e.g., see pp. 86-87, Little and Rubin, 2002) to the Z-test in Theorem 2.1 to account for uncertainty due to the multiple imputations (e.g., see Little and Rubin, 2002; Shortreed et al., 2014). This is expected to lead to an attenuation in power.
Finally, our proposed approach enables investigators to plan sample size only for pairwise comparisons of EDTRs. Developing an approach to estimate sample size based on a multiple comparison with the best test, extending the work of Ertefaie and others (Ertefaie et al., 2016), is an important direction for future research.

Supplementary Material

The reader is referred to the online Supplementary Materials for web appendices, web figures, and web tables. R code implementing our proposed approach and accompanying documentation is available at https://github.com/jamieyap/CountSMART/releases/tag/v2.0.0

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Figures

Figure 1: The ENGAGE SMART design. Solid black circles represent randomization to treatment options.
Figure 2: Results of Simulation Study 1 when an AR1 structure is utilized in the specification of the latent MVN-distributed variable.
Figure 3: Results of Simulation Study 1 when an exchangeable structure is utilized in the specification of the latent MVN-distributed variable.
Figure 4: Results of Simulation Study 2 when an AR1 structure is utilized in the specification of the latent MVN-distributed variable.

A display of empirical within-person correlation among simulated count outcomes when $\rho = 0.6$ in Scenario 10, averaged across $M = 5000$ Monte Carlo samples. Panels (a), (b), (c), (d), (e), (f) display correlation of count outcomes was calculated among those which correspond to ETS lying on the path leading to cell A, B, C, D, E, F in Figure 1, respectively.

| Panel | Correlation Matrix |
|-------|--------------------|
| (a)   | ![Correlation Matrix](image) |
| (b)   | ![Correlation Matrix](image) |
| (c)   | ![Correlation Matrix](image) |
| (d)   | ![Correlation Matrix](image) |
| (e)   | ![Correlation Matrix](image) |
| (f)   | ![Correlation Matrix](image) |
Figure 5: Results of Simulation Study 2 when an exchangeable structure is utilized in the specification of the latent MVN-distributed variable.

A display of empirical within-person correlation among simulated count outcomes when \( \rho = 0.6 \) in Scenario 10, averaged across \( M = 5000 \) Monte Carlo samples. Panels (a), (b), (c), (d), (e), (f) display correlation of count outcomes was calculated among those which correspond to ETS lying on the path leading to cell A, B, C, D, E, F in Figure 1, respectively.
Figure 6: Results of Simulation Study 1 when an AR1 and exchangeable structure is utilized in the specification of the latent MVN-distributed variable are displayed on the left and right panels, respectively. For space considerations, only select power curves for difference in AUC are displayed.
Tables

Table 1: EDTRs embedded in the two-stage SMART design in Figure 1

| \((a_1, a_2^{NR})\) | EDTR | Example from ENGAGE |
|----------------------|------|---------------------|
| **Choice-Throughout’ DTR:** | Offer the individual MI-Choice at \(t_1\). | If the individual is regarded as a responder \(t_K\), then do nothing; else, offer \(a_2^{NR} = +1\) at \(t_K\). |

(1) \((+1, +1)\) Offer the individual treatment \(a_1 = +1\) at \(t_1\). If the individual is regarded as a responder \(t_K\), then do nothing; else, offer \(a_2^{NR} = +1\) at \(t_K\). **Choice-Initially’ DTR:** Offer the individual treatment MI-Choice at \(t_1\). If the individual is regarded as a responder \(t_K\), then have no further contact; else, offer MI-Choice at \(t_K\). |

(2) \((+1, -1)\) Offer the individual treatment \(a_1 = +1\) at \(t_1\). If the individual is regarded as a responder \(t_K\), then do nothing; else, offer \(a_2^{NR} = +1\) at \(t_K\). **Delayed-Choice’ DTR:** Offer the individual treatment MI-Engage at \(t_1\). If the individual is regarded as a responder \(t_K\), then have no further contact; else, offer MI-Choice at \(t_K\). |

(3) \((-1, +1)\) Offer the individual treatment \(a_1 = -1\) at \(t_1\). If the individual is regarded as a responder \(t_K\), then do nothing; else, offer \(a_2^{NR} = +1\) at \(t_K\). **No-Choice’ DTR:** Offer the individual treatment MI-Engage at \(t_1\). If the individual is regarded as a responder \(t_K\), then have no further contact; else, offer MI-Engage at \(t_K\). |

(4) \((-1, -1)\) Offer the individual treatment \(a_1 = -1\) at \(t_1\). If the individual is regarded as a responder \(t_K\), then do nothing; else, offer \(a_2^{NR} = -1\) at \(t_K\).
Table 2: Examples of how response status can be defined in a SMART with a longitudinal count outcome.

| Definition of response status | Example |
|------------------------------|---------|
| \( R_i = I(Y_{i,t_K} \leq c) \) | An individual is regarded as a responder if at \( t_K \), the number of alcohol-use days they had in the past-month (i.e., \( Y_{i,t_K} \)) does not exceed the cut-point \( c \). |
| \( R_i = I(Y_{i,t_K} > c) \) | If the cut-point \( c \) is selected by study designers to be equal to 0, then an individual is regarded as a responder if at \( t_K \) they abstained from any alcohol-use in the month prior to \( t_K \). |
| \( R_i = I(c_1 \leq Y_{i,t_K} \leq c_2) \) | An individual is regarded as a responder if at \( t_K \), the number of therapy sessions they attended in the past-month (i.e., \( Y_{i,t_K} \)) exceeds the cut-point \( c \). |
|                              |          |
|                              |          | If the cut-point \( c \) is selected by study designers to be equal to 0, then an individual is regarded as a responder if at \( t_K \) they attended at least one therapy session in the month prior to \( t_K \). |
|                              |          |
|                              |          | An individual is regarded as a responder if at \( t_K \), the number of times they adhered to a clinician-prescribed regimen of medication in the past-month (i.e., \( Y_{i,t_K} \)) range between \( c_1 \) and \( c_2 \). |
|                              |          | That is, going beyond the cut-point \( c_2 \) signifies that the individual deviated from the prescribed regimen by taking more than what was prescribed. |
|                              |          | On the other hand, going below the cut-point \( c_1 \) signifies that the individual deviated from the prescribed regimen by taking less than what was prescribed. |
Table 3: Parameter values in simulation studies. Below, $\pi_{i,t,j}^S$ denotes $Pr\{Y_{i,t,j}^S = 0\}$. For brevity, we omit the subscript $i$ in expressions for $\mu_{i,t,j}^S$, $\pi_{i,t,j}^S$ and $\zeta_{i,t,j}^S$.

| Total Sample Size | ETS Proportion of Zeros |
|-------------------|--------------------------|
| N=100, 150, 200, …, 550 | $\pi_{i,t,j}^S = 0.40, \pi_{i,t,j}^{\text{nominal}} = 0.40, \pi_{i,t,j}^{-1} = 0.40$ |
| $\rho = 0.2, 0.4, 0.6$ | $\pi_{i,t,j}^{100} = 0.40, \pi_{i,t,j}^{150} = 0.40, \pi_{i,t,j}^{200} = 0.40$ |
| Proportion of Responders | $\pi_{i,t,j}^{100} = 0.40, \pi_{i,t,j}^{150} = 0.40, \pi_{i,t,j}^{200} = 0.40$ |
| $p = 0.40$ and $q = 0.40$ | $\pi_{i,t,j}^{550} = 0.40, \pi_{i,t,j}^{250} = 0.40, \pi_{i,t,j}^{150} = 0.40$ |

**Variied across scenarios:**

| ETS Means |
|-----------|
| For all $\mu_{i,t,j}^S = 2.5, \mu_{i,t,j}^{\text{nominal}} = 2.6, \mu_{i,t,j}^{-1} = 2.75, \mu_{i,t,j}^{2} = 2.8 |

**Scenarios 1-10**

| For $i=1$: $\mu_{i,t,j}^S$ takes on the following values |
|------------------------------------------------------|
| For all $\mu_{i,t,j}^S = 2.5, \mu_{i,t,j}^{\text{nominal}} = 2.6 |

The value of $\mu_{i,t,j}^{(1.0)}, \mu_{i,t,j}^{(-1.0)}$, and $\mu_{i,t,j}^{(2.0)}$ was increased by about 7%, 14%, 28%, …, 70% respectively, from the values specified in the ‘Base Case’ above, but the value of $\mu_{i,t,j}^{(-1.0)}, \mu_{i,t,j}^{(1.0)}$, and $\mu_{i,t,j}^{(-2.0)}$ was retained from the values specified in the ‘Base Case’ above.

For $i=6$: $\mu_{i,t,j}^S$ takes on the following values |

The value of $\mu_{i,t,j}^{(1.0)}, \mu_{i,t,j}^{(-1.0)}$, and $\mu_{i,t,j}^{(2.0)}$ was increased by about 10%, 20%, 30%, …, 100% respectively, from the values specified in the ‘Base Case’ above, but the value of $\mu_{i,t,j}^{(-1.0)}, \mu_{i,t,j}^{(1.0)}$, and $\mu_{i,t,j}^{(-2.0)}$ was retained from the values specified in the ‘Base Case’ above.

| Value of dispersion parameter $\zeta_{i,t,j}$ implied by choice of values for $\mu_{i,t,j}^S$ and $\pi_{i,t,j}^S$: |
|---------------------------------------------------------------------------------------------------------------------------------|
| For $j=1$: $\zeta_{i,t,j}$ takes on the following values throughout Scenarios 1-10 |
| For all $\zeta_{i,t,j}^{1.0} = 1.92, \zeta_{i,t,j}^{\text{nominal}} = 2.98 |
| For $j = 3.4.5.6$: $\zeta_{i,t,j}$ takes on the following values throughout Scenarios 1-10 |
| $\zeta_{i,t,j}^{(-1.0)} = \zeta_{i,t,j}^{(-1.0)} + \zeta_{i,t,j}^{(-1.0)} = 1.98 $ |
| $\zeta_{i,t,j}^{(-1.0)} = \zeta_{i,t,j}^{(-1.0)} + \zeta_{i,t,j}^{(-1.0)} = 2.05 $ |
| $\zeta_{i,t,j}^{(-1.0)} = \zeta_{i,t,j}^{(-1.0)} + \zeta_{i,t,j}^{(-1.0)} = 2.09 $ |
| $\zeta_{i,t,j}^{(-1.0)} = \zeta_{i,t,j}^{(-1.0)} + \zeta_{i,t,j}^{(-1.0)} = 2.11 $ |

For $j=3$: $\zeta_{i,t,j}$ takes on the following values throughout Scenarios 2-10, $\zeta_{i,t,j}^{(-1.0)} = \zeta_{i,t,j}^{(-1.0)}$ |

The value of $\zeta_{i,t,j}^{(-1.0)}$ was increased by about 5%, 10%, 14%, …, 36% respectively from the values in Scenario 1.

For $j=4$: $\zeta_{i,t,j}$ takes on the following values throughout Scenarios 2-10, $\zeta_{i,t,j}^{(-1.0)} = \zeta_{i,t,j}^{(-1.0)}$ |

The value of $\zeta_{i,t,j}^{(-1.0)}$ was increased by about 5%, 9%, 14%, …, 34% respectively from the values in Scenario 1.

For $j=5$: $\zeta_{i,t,j}$ takes on the following values throughout Scenarios 2-10, $\zeta_{i,t,j}^{(-1.0)} = \zeta_{i,t,j}^{(-1.0)}$ |

The value of $\zeta_{i,t,j}^{(-1.0)}$ was increased by about 5%, 9%, 13%, …, 34% respectively from the values in Scenario 1.

For $j=6$: $\zeta_{i,t,j}$ takes on the following values throughout Scenarios 2-10, $\zeta_{i,t,j}^{(-1.0)} = \zeta_{i,t,j}^{(-1.0)}$ |

The value of $\zeta_{i,t,j}^{(-1.0)}$ was increased by about 6%, 12%, 17%, …, 42% respectively from the values in Scenario 1.
Planning SMARTs: Sample size estimation for comparing dynamic treatment regimens using longitudinal count outcomes with overdispersion

Supplementary Material

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\textbf{Web Appendix A. Estimation of $\Delta Q$ using a longitudinal 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 and did not provide details on how analyses may be carried out when the longitudinal outcome is count. In brief, after a model for the mean trajectory of EDTRs has been specified, e.g., as in Equation 1 (displayed below), the steps required to obtain $\hat{\beta}_{IPWRE}$ using a longitudinal count outcome are analogous to the approach one would employ when using either a longitudinal continuous or binary outcome (see Dziak, et al., 2019; Nahum-Shani, et al., 2020; Seewald, et al., 2020). Similar to the exposition of Dziak and colleagues (Dziak, et al, 2019), Nahum-Shani
and colleagues (Nahum-Shani, et al, 2020), and Seewald and colleagues (Seewald, et al, 2020), our model of EDTR means in Equation 1 constrains the mean trajectories of EDTRs sharing the same first-stage treatment to be identical, but allows the mean trajectories of EDTRs having different second-stage treatments to diverge; in contrast, however, our model for EDTR means do not assume a specific parametric form for the EDTR mean trajectories (e.g., quadratic as a function of time).

Equation 1 below displays a specific example of how we would specify a particular model for EDTR means given specific values for $K$ and $T$. In equation 1, $K = 2, T = 6$ and EDTR means implied by Equation 1 are given by Web Table 1.

$$\log\left(\mu_{t_j}^{(a_1,a_2^{NR})}\right) = \beta_{1,1} + I(a_1 = +1) \cdot \beta_{2,2}$$

$$+ I(a_1 = -1) \cdot \beta_{3,2}$$

$$+ I(a_1 = +1, a_2^{NR} = +1) \cdot I(2 < j \leq 6) \cdot \beta_{4,j}$$

$$+ I(a_1 = +1, a_2^{NR} = -1) \cdot I(2 < j \leq 6) \cdot \beta_{5,j}$$

$$+ I(a_1 = -1, a_2^{NR} = +1) \cdot I(2 < j \leq 6) \cdot \beta_{6,j}$$

$$+ I(a_1 = -1, a_2^{NR} = -1) \cdot I(2 < j \leq 6) \cdot \beta_{7,j}$$

Much of the details provided next concern how to express $\Delta Q$ as a non-linear function of the unknown parameters in Equation 1 using matrix algebra.

**Result A.1:** 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 2.

$$\Delta Q = \text{Lexp} \left[ C^{(a_1',a_2^{NR'})} \beta \right] - \text{Lexp} \left[ C^{(a_1'',a_2^{NR''})} \beta \right]$$
In Equation 2, $\boldsymbol{\beta}$ denotes a vector having $4T - 2K - 1$ components, $\mathbf{C}^{(a_1, a_2^{NR})}$ 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; $\mathbf{L}$ is a $1 \times T$ matrix whose elements are the real-valued constants $l_j$’s.

The specific form of $\mathbf{C}^{(a_1, a_2^{NR})}$ is chosen so that the term $\exp \left[ \mathbf{C}^{(a_1, a_2^{NR})} \mathbf{\beta} \right]$, which we denote more succinctly by $\mathbf{U}_\beta^{(a_1, a_2^{NR})}$, results in a diagonal matrix having means under EDTR $(a_1, a_2^{NR})$ as elements on its diagonal.

Finally, we note that in the specific example of using Equation 1 as a model for EDTR means, the matrices in Equation 2 are specified as follows: $\mathbf{\beta}$:

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

where $\mathbf{\beta}^{(+1,+1)} = \begin{pmatrix} \beta_{1,2} \\ \beta_{4,3} \\ \beta_{4,5} \\ \beta_{6,3} \\ \beta_{6,4} \\ \beta_{6,6} \end{pmatrix}$, $\mathbf{\beta}^{(-1,+1)} = \begin{pmatrix} \beta_{1,5} \\ \beta_{5,3} \\ \beta_{5,4} \\ \beta_{7,3} \\ \beta_{7,4} \end{pmatrix}$, and $\mathbf{\beta}^{(-1,-1)} = \begin{pmatrix} \beta_{1,6} \\ \beta_{5,5} \\ \beta_{5,6} \\ \beta_{7,5} \\ \beta_{7,6} \end{pmatrix}$ and the matrices $\mathbf{C}^{(+1,+1)}$, $\mathbf{C}^{(+1,-1)}$, $\mathbf{C}^{(-1,+1)}$, $\mathbf{C}^{(-1,-1)}$ are defined as:

\[
\begin{align*}
\mathbf{C}^{(+1,+1)} &:= (\mathbf{M}^{(+1)}) \quad \mathbf{0}_{6 \times 12} \quad \mathbf{\mathbf{C}}^{(+1,-1)} := (\mathbf{M}^{(+1)}) \quad \mathbf{0}_{6 \times 4} \quad \mathbf{M} \quad \mathbf{0}_{6 \times 8} \\
\mathbf{C}^{(-1,+1)} &:= (\mathbf{M}^{(-1)}) \quad \mathbf{0}_{6 \times 8} \quad \mathbf{M} \quad \mathbf{0}_{6 \times 4} \quad \mathbf{\mathbf{C}}^{(-1,-1)} := (\mathbf{M}^{(-1)}) \quad \mathbf{0}_{6 \times 12} \quad \mathbf{M}
\end{align*}
\]

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

\[
\begin{align*}
\mathbf{M}^{(+1)} &:= \begin{pmatrix}
1 & 0 & 0 \\
1 & 1 & 0 \\
1 & 0 & 0 \\
1 & 0 & 0 \\
1 & 0 & 0 \\
1 & 0 & 0
\end{pmatrix}, \quad \mathbf{M}^{(-1)} := \begin{pmatrix}
1 & 0 & 0 \\
1 & 0 & 0 \\
1 & 0 & 1 \\
1 & 0 & 0 \\
1 & 0 & 0 \\
1 & 0 & 0
\end{pmatrix}, \quad \mathbf{M} := \begin{pmatrix}
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
1 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 \\
0 & 0 & 1 & 0 \\
0 & 0 & 0 & 1
\end{pmatrix}
\end{align*}
\]
Web Appendix B. Proof of Theorem 2.1

The proof of Theorem 2.1 involves using two results: first, that $\sqrt{N}(\hat{\beta}_{IPWRE} - \beta)$ is asymptotically Multivariate Normal (MVN)-distributed (see Theorem I.2 in Supplementary Material (Lu et al., 2016)) and the multivariate delta method (Taylor linearization); the latter result is used to justify that $\sqrt{N}(\hat{\Delta}_Q - \Delta_Q)$ is asymptotically MVN. The remaining details of the proof express the calculations in terms of matrix algebra.

Proof of Theorem 2.1: We begin by observing that $Var(\hat{\Delta}_Q^{IPWRE})$ can be expressed in terms of the covariance of a matrix product involving the quantity $Cov(\hat{\beta}_{IPWRE})$, i.e., as

$$Var(\hat{\Delta}_Q^{IPWRE}) = Cov\left((DU_{\hat{\beta}_{IPWRE}}C) \cdot \hat{\beta}_{IPWRE}\right)$$

where $D$, $U_{\hat{\beta}_{IPWRE}}$, and $C$ are the block matrices defined below:

$$D = (L - L) \quad U_{\hat{\beta}_{IPWRE}} = \begin{pmatrix} U^{(a_1',a_2^{NR'})}_{\hat{\beta}_{IPWRE}} & 0_{T \times T} \\ 0_{T \times T} & U^{(a_1'',a_2^{NR''})}_{\hat{\beta}_{IPWRE}} \end{pmatrix} \quad C = \begin{pmatrix} C^{(a_1',a_2^{NR'})} \\ C^{(a_1'',a_2^{NR''})} \end{pmatrix}$$

For example, when $T = 6$, the EDTR means are given by Equation 2 and $U_{\beta}^{(+1,+1)}$ is then given by Equation 3.; 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 multivariate delta method, we have that $\sqrt{N}(\hat{\Delta}_Q^{IPWRE} - \Delta_Q)$ is asymptotically MVN with zero mean and covariance $\text{Var}(\sqrt{N} \hat{\Delta}_Q^{IPWRE})$, where $\text{Var}(\hat{\Delta}_Q^{IPWRE})$ can be expressed as in Equation 4. Hence, we have that $Z = \frac{\hat{\Delta}_Q^{IPWRE} - \Delta_Q}{\sqrt{\text{Var}(\hat{\Delta}_Q^{IPWRE})}}$ is Normal(0,1) distributed.

\[
\text{Var}(\hat{\Delta}_Q^{IPWRE}) = (DU_{\hat{\beta}_{IPWRE}}C) \cdot \text{Cov}(\hat{\beta}_{IPWRE}) \cdot (DU_{\hat{\beta}_{IPWRE}}C)^T \tag{4}
\]

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

\[
\text{Var}(\hat{\Delta}_Q^{IPWRE}) = (DU_{\hat{\beta}_{IPWRE}}C) \cdot \frac{\hat{\Sigma}_{\hat{\beta}_{IPWRE}}}{N} \cdot (DU_{\hat{\beta}_{IPWRE}}C)^T \tag{5}
\]

Again, by Slutsky’s Theorem, we have that $Z = \frac{\hat{\Delta}_Q^{IPWRE} - \Delta_Q}{\sqrt{\text{Var}(\hat{\Delta}_Q^{IPWRE})}}$ is Normal(0,1) distributed. This completes the proof. ■

**Web Appendix C. Approach to generate draws from the multivariate distribution of $\theta_i^j$**

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., $\Lambda_{d_j} = I_{d_j \times d_j} + \rho (1_{d_j \times 1}1_{d_j \times 1}^T - I_{d_j \times d_j})$
where \( \mathbf{1}_{m_1 \times m_2} \) denotes an \( m_1 \times m_2 \) matrix whose elements are all one and \( \mathbf{I}_{m_1 \times m_2} \) denotes an \( m_1 \times m_2 \) identity matrix.

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

That is, \( \left( \begin{array}{c} U_1^{(\ell)} \\ \vdots \\ U_{d_j}^{(\ell)} \end{array} \right) = \left( \begin{array}{c} \phi(Z_1^{(\ell)}) \\ \vdots \\ \phi(Z_{d_j}^{(\ell)}) \end{array} \right) \).

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

\[
\left( \begin{array}{c} X_1^{(\ell)} \\ \vdots \\ X_{d_j}^{(\ell)} \end{array} \right) = \left( \begin{array}{c} F_1^{-1}(U_1^{(\ell)}) \\ \vdots \\ F_{d_j}^{-1}(U_{d_j}^{(\ell)}) \end{array} \right).
\]

Hence, each \( \mathbf{X}^{(\ell)} \) is effectively a draw of \( \mathbf{\Theta}_j \) 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 \texttt{mvtnorm} \citep{GenzBretz2009,Genz2020} was utilized to draw from a multivariate normal (MVN) distribution.

**Web Appendix D. Approach to estimate the relationship between \( \rho \) and \( \tau_{MAX} \)**

Estimating the relationship between \( \rho \) and \( \tau_{MAX} \) involves generating simulated datasets using the approach described in Section 4.3 of the main manuscript, and then estimating

\[
\text{Corr} \left( Y_{s,t}^{s'}, Y_{s,t}^{s''} \right)
\]

for all pairs of ETSs \( s' \) and \( s'' \) and pairs of time points \( t_{j'} \) and \( t_{j''} \) by calculating their average value across all simulated datasets. Specifically, for each value of \( \rho \) in a
grid (e.g., 0, 0.05, 0.10, 0.15, ...), we estimate $\tau_{MAX}$ by using $\mathbb{P}_M\{\hat{\tau}_{MAX}\}$ 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 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, construct the following six vectors:
   - $\mathbf{Y}_i^A := \left( Y_{i,t_1}^{(\cdot)} \ldots Y_{i,t_K}^{(+1)} Y_{i,t_{K+1}}^{(+1,0)} \ldots Y_{i,t_T}^{(+1,1,0)} \right)^T$ using individuals belonging to subgroups 1 and 2
   - $\mathbf{Y}_i^B := \left( Y_{i,t_1}^{(\cdot)} \ldots Y_{i,t_K}^{(+1)} Y_{i,t_{K+1}}^{(+1,0,+1)} \ldots Y_{i,t_T}^{(+1,0,+1)} \right)^T$ using individuals belonging to subgroups 3 and 4
   - $\mathbf{Y}_i^C := \left( Y_{i,t_1}^{(\cdot)} \ldots Y_{i,t_K}^{(+1)} Y_{i,t_{K+1}}^{(+1,0,-1)} \ldots Y_{i,t_T}^{(+1,0,-1)} \right)^T$ using individuals belonging to subgroups 3 and 4
   - $\mathbf{Y}_i^D := \left( Y_{i,t_1}^{(\cdot)} \ldots Y_{i,t_K}^{(-1)} Y_{i,t_{K+1}}^{(-1,0)} \ldots Y_{i,t_T}^{(-1,0,0)} \right)^T$ using individuals belonging to subgroups 1 and 3
   - $\mathbf{Y}_i^E := \left( Y_{i,t_1}^{(\cdot)} \ldots Y_{i,t_K}^{(-1)} Y_{i,t_{K+1}}^{(-1,0,+1)} \ldots Y_{i,t_T}^{(-1,0,+1)} \right)^T$ using individuals belonging to subgroups 2 and 4
   - $\mathbf{Y}_i^F := \left( Y_{i,t_1}^{(\cdot)} \ldots Y_{i,t_K}^{(-1)} Y_{i,t_{K+1}}^{(-1,0,-1)} \ldots Y_{i,t_T}^{(-1,0,-1)} \right)^T$ using individuals belonging to subgroups 2 and 4

Using these vectors, a correlation matrix corresponding to $\mathbf{Y}_i^A, \mathbf{Y}_i^B, \mathbf{Y}_i^C, \mathbf{Y}_i^D, \mathbf{Y}_i^E, \mathbf{Y}_i^F$ will be estimated and the quantity $\hat{\tau}_{MAX}$ (defined below) could then be calculated.
\[ \hat{\tau}_{MAX} := \max_{s', s'', t'_j, t''_j} \left\{ \text{Corr} \left( Y_{it_j}', Y_{it_j}'' \right) \right\} \] (6)

When \( s' = s'' \), the calculation of the maximum above should exclude the terms where \( t'_j = t''_j \); for example, \( \text{Corr} \left( Y_{it_2}^{(1)}, Y_{it_2}^{(1)} \right) \) will be excluded.

3. Finally, \( \mathbb{P}_M \{ \hat{\tau}_{MAX} \} \) is calculated as the mean of \( \hat{\tau}_{MAX} \) across all simulated datasets. Let \( \hat{\tau}_{MAX}^\rho \) denote the value of \( \mathbb{P}_M \{ \hat{\tau}_{MAX} \} \) corresponding to a particular value of \( \rho \) which we calculate using the above-described approach. The value of \( \rho \) for which \( \hat{\tau}_{MAX}^\rho \) closest to the desired value of \( \tau_{MAX} \) will be selected and used to calculate power.

Web Appendix E. Power calculation for a fixed sample size \( N \)

Let \( \mathbb{P}_M \) denote an empirical mean across \( M \) simulated datasets. We estimate power using

\[
\mathbb{P}_M \left\{ \left. \left| \frac{\hat{\Delta}_Q^{IPWRE}}{\sqrt{\text{Var}(\hat{\Delta}_Q^{IPWRE})}} \right| > z_{1-\alpha/2} \right\} \]

calculated as follows:

1. Values for design parameters under the alternative hypothesis (\( H_a \)) are specified.
2. An appropriate value of the copula dependence parameter \( \rho \) (see Web Appendix D for more detail) is selected.
3. A large number of simulated SMART datasets, \( M \), consisting of \( N \) individuals each are generated based on these values; the method of data-generation would follow that described in Section 4.3 in the main manuscript. For each of the \( M \) simulated datasets, data from all \( N \) individuals will be used to calculate \( \hat{\Delta}_Q^{IPWRE} \) and \( \sqrt{\text{Var}(\hat{\Delta}_Q^{IPWRE})} \).
4. Finally, power is calculated as the proportion of simulated datasets for which the inequality \( \left| \frac{\hat{\Delta}_Q^{IPWRE}}{\sqrt{\text{Var}(\hat{\Delta}_Q^{IPWRE})}} \right| > z_{1-\alpha/2} \) holds.
When power calculation is repeated for a grid of sample sizes (e.g., 100, 150, 200, ...), 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.

**Web Appendix F. Simulation Study 3**

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 3 is designed to evaluate the test’s performance by examining the empirical type-I error rate when $\Delta_{EOS} = 0$ and $\Delta_{AUC} = 0$.

As in Simulation Study 1 and 2, we still consider a prototypical two-stage restricted SMART, as in Figure 1 of the main manuscript, and we assume that response status is defined using the cut-point $c = 0$. 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., $\Delta_{EOS} = E\{Y_{t,6}^{(+1,+1)}\} - E\{Y_{t,6}^{(-1,+1)}\}$) or difference in AUC (i.e., $\Delta_{AUC} = AUC^{(+1,+1)} - AUC^{(-1,+1)}$), each at a desired type-I error rate of $\alpha = 0.05$.

Web Table 6 displays the varying values of parameters used in the scenarios considered in Simulation Study 3. These parameters correspond to increased overdispersion from Scenarios 1-3. Across all scenarios, total sample size $N$, proportion of responders $p$ and $q$, ETS means, and $\rho$ were held constant; an AR1 correlation structure was specified. Three scenarios corresponding to increased values of the NB dispersion parameter were considered, in order to investigate whether higher overdispersion might lead to higher-than-nominal type-I error rates. Finally, we
repeated the scenarios described above, but increased the value of \( \rho \), in order to investigate whether higher within-person correlation might lead to higher-than-nominal type-I error rates. The magnitudes of \( \Delta_{EOS} \) and \( \Delta_{AUC} \) remained unchanged even at increased values of \( \rho \). \( M = 5000 \) Monte Carlo samples were used to calculate empirical type-I error rate.

The results for Simulation Study 3 are summarized in Web Figure 1 (for difference in end-of-study means) and Web Figure 2 (for difference in AUC) where total sample size \( N \) (x-axis) is plotted against the empirical type-I error rate (y-axis). Notably, when \( \Delta_{AUC} = 0 \), empirical type-I error rate ranges between 0.07 to 0.09 at more modest sample sizes (i.e., 200 or less) as overdispersion becomes more extreme (i.e., Scenarios 2 and 3). Otherwise, empirical type-I error rate was either nominal or slightly above nominal (i.e., about 0.05 to 0.07). Higher within-person correlation did not noticeably influence empirical Type-I error rate.

**Web Appendix G. Supplement to Simulation Study 3**

We investigate whether the slightly above nominal or below nominal empirical type-I error rates observed in Simulation Study 3 can be attributed to bias in estimates of \( \Delta_{EOS} \) and \( \Delta_{AUC} \), or bias in estimates of \( \sqrt{Var(\hat{\Delta}_{EOS}^{IPWRE})} \) and \( \sqrt{Var(\hat{\Delta}_{AUC}^{IPWRE})} \); we utilize values of design parameters identical to Simulation Study 3.

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

\[
\frac{1}{M} \cdot \sum_{j=1}^{M} (\hat{\Delta}_{EOS}^{(j)} - \Delta_{EOS}) \quad \text{and} \quad \frac{1}{M} \cdot \sum_{j=1}^{M} (\hat{\Delta}_{AUC}^{(j)} - \Delta_{AUC}),
\]

where \( \Delta_{EOS}^{(j)} \) and \( \Delta_{AUC}^{(j)} \) denotes 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 3 were specified such that \( \Delta_{EOS} = 0 \) and \( \Delta_{AUC} = 0 \). As Web
Figure 3 shows, estimates $\hat{\Delta}_{EOS}^{IPWRE}$ are unbiased. On the other hand, as Web Figure 4 shows, 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 $\frac{1}{M} \cdot \Sigma_{j=1}^{M} (\hat{\sigma}_{EOS}^{(j)} - \sigma_{EOS})$ and $\frac{1}{M} \cdot \Sigma_{j=1}^{M} (\hat{\sigma}_{AUC}^{(j)} - \sigma_{AUC})$, 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 Web Figure 5 shows, estimates of standard errors for differences in end-of-study means are unbiased. On the other hand, as Web Figure 6 shows, estimates of $\sqrt{Var(\hat{\Delta}_{AUC}^{IPWRE})}$ exhibit a pronounced downward bias when total sample size N is 200 or less; the bias attenuated as N was increased.

**Web Appendix H. Simulation Study 4**

We investigate whether power is sensitive to violation of the working assumption made with respect to $\eta$, namely that $\eta = \frac{\rho}{2}$.

As in Simulation Study 1 and 2, we still consider a prototypical two-stage restricted SMART, as in Figure 1 of the main manuscript, and we assume that response status is defined using the cut-point $c = 0$. 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 \( i.e., \Delta_{\text{EOS}} = E\{Y_{i,t_6}^{(+1,+1)}\} - E\{Y_{i,t_6}^{(-1,+1)}\} \) or difference in AUC (i.e., $\Delta_{\text{AUC}} = \text{AUC}^{(+1,+1)} - \text{AUC}^{(-1,+1)}$), each at a desired type-I error rate of $\alpha = 0.05$.

Ten scenarios identical to those described in Simulation Study 1 were considered, except that the total sample size $N$ was fixed to 500 and $\rho$ was fixed to 0.6. Within each scenario, the working assumption was violated by calculating power when $\eta$ was set to 0, 0.05, 0.10, 0.15, 0.20, $\ldots$, 0.45. $M = 5000$ Monte Carlo samples were used to calculate power. Throughout, an AR1 correlation structure was specified.

We note that investigating sensitivity of violations to this working assumption is only possible at pairs of values of $\rho$ and $\eta$ for which $\Lambda_1, \Lambda_2, \Lambda_3,$ and $\Lambda_4$ are positive definite. When $\rho$ was fixed to 0.6, values of $\eta$ equal to 0.50, 0.55, 0.60, 0.65, $\ldots$, 0.95, 1 will result in at least one of the $\Lambda_j$’s being non-positive-definite.

The results for Simulation Study 4 are summarized in Web Figure 7 where $\eta$ (x-axis) is plotted against power (y-axis). More specifically, results for scenario 1 (i.e., when $\Delta_{\text{EOS}} = 0.28$ [left panel]; when $\Delta_{\text{AUC}} = 0.7$ [right panel]) are displayed as solid dots on the bottom-most dashed horizontal line, results for scenario 2 (i.e., when $\Delta_{\text{EOS}} = 0.56$ [left panel]; when $\Delta_{\text{AUC}} = 1.41$ [right panel]) are displayed as solid dots on the 2nd dashed horizontal line from the bottom. Analogously, results for scenarios 3-10 are displayed as solid dots on the 3rd through 10th dashed horizontal line from the bottom. The results show that across the ten scenarios, power is not sensitive to the actual value of $\eta$. 

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Web Appendix I. Simulation Study 5

We 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 treatments.

As in Simulation Study 1 and 2, we still consider a prototypical two-stage restricted SMART, as in Figure 1 of the main manuscript, and we assume that response status is defined using the cut-point $c = 0$. 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 $\alpha = 0.05$.

Ten scenarios identical to those described in Simulation Study 1 were considered, except that the total sample size $N$ was fixed to 500 and $\rho$ was fixed to 0.6. Within each scenario, the working assumption was violated by calculating power when $n_4$ was set to 100, 150, 200, 250, 300 (i.e., the maximum possible value of $n_4$). $M = 5000$ Monte Carlo samples were used to calculate power. Throughout, an AR1 correlation structure was specified. The results for Simulation Study 5 are summarized in Web Figure 8 where $n_4$ (x-axis) is plotted against power (y-axis). More specifically, results for scenario 1 (i.e., when $\Delta_{EOS}=0.28$ [left panel]; when $\Delta_{AUC}=0.7$ [right panel]) are displayed as solid dots on the bottom-most dashed horizontal line, results for scenario 2 (i.e., when $\Delta_{EOS}=0.56$ [left panel]; when $\Delta_{AUC}=1.41$ [right panel]) are displayed as solid dots on the 2nd dashed horizontal line from the bottom. Analogously, results for
scenarios 3-10 are displayed as solid dots on the 3rd through 10th dashed horizontal line from the bottom. The results show that across the ten scenarios, power is not sensitive to the actual value of $n_4$.

**Web Appendix J. Estimating sample size when missing data is anticipated in a planned SMART**

An additional step in the data generating process (described in Section 4.3 of main manuscript) can be included to induce missing completely at random or missing at random (MCAR or MAR; Little and Rubin, 2002) values in each of the $M$ simulated datasets. Specifically, for each of the $M$ simulated datasets (say, $M = 5000$), MCAR values in the longitudinal count outcome can be subsequently generated by regarding each observed outcome $Y_{i,t,j}$ as missing when $O_{i,t,j} = 0$ and not missing when $O_{i,t,j} = 1$, where $O_{i,t,j}$ ~ Bernoulli($p$) and $p \in (0,1)$. In contrast, for each of the $M$ simulated datasets, MAR values in the longitudinal outcome can subsequently be generated by first specifying a logistic regression model for the (conditional) probability that $Y_{i,t,j}$ is not missing at $t_j$ (which we denote by $p_{t,j}$) in terms of variables observed prior to $t_j$, and then, regarding each observed outcome $Y_{i,t,j}$ as missing when $O_{i,t,j} = 0$ and not missing when $O_{i,t,j} = 1$, where $O_{i,t,j}$ ~ Bernoulli($p_{t,j}$) and $p_{t,j} \in (0,1)$. As a concrete example, consider the prototypical SMART in Figure 1 of the main manuscript. In this case, one possible model for a MAR missing data mechanism might be $\text{logit}(p_{t,j}) = \theta_0 + \theta_1 X + \theta_2 A_1 \cdot I(1 < j \leq T) + \theta_3 X A_1 \cdot I(1 < j \leq T)$ for all $j = 1, \ldots, T$ where $A_1 \in \{-1, +1\}$ is an indicator for first-stage randomization assignment and $X$ represents a binary baseline covariate (e.g., which may represent gender, race, etc.) defined as a deterministic function of the outcome at the first measurement occasion, e.g., $X = I(Y_{i,t_1} < \omega)$ for some cut-point $\omega > 0$. 

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We note that modeling more complex dependence between $X$ and $Y_{i,t_j}$’s may require eliciting additional parameters from domain experts; accounting for more complex dependence between $X$ and $Y_{i,t_j}$’s is an area of future work.

To deal with missing data in each of the $M$ simulated datasets, multiple imputation (e.g., see Little and Rubin, 2002; Shortreed et al., 2014) can be employed. Standard corrections (e.g., see pp. 86-87, Little and Rubin, 2002) can then be used to adjust the Z-test to account for uncertainty from multiple imputation. Finally, power can then be estimated by the proportion of times out of $M$ for which the null hypothesis is rejected using this adjusted test. That is, if $J$ denotes the total number of imputed datasets associated with each of the $M$ simulated datasets, then power can then be estimated by

$$\mathbb{P}_M \left\{ I \left( \frac{\hat{Z}_Q}{\hat{\sigma}_Q} > z_{1-\alpha/2} \right) \right\}$$

where the terms within the indicator function are given by equations 7, 8, and 9 below.

$$\bar{\Delta}_Q^I := \frac{1}{J} \sum_{j=1}^{J} \hat{\Delta}_Q^{(j)}$$  \hspace{7cm} (7)

$$\hat{\sigma}_Q^I := \sqrt{W + \left( 1 + \frac{1}{J} \right) \cdot B}$$  \hspace{5.5cm} (8)

$$W := \frac{1}{J} \sum_{j=1}^{J} \left( \hat{\sigma}_Q^{(j)} \right)^2 \text{ and } B := \frac{1}{J-1} \cdot \sum_{j=1}^{J} \left( \bar{\Delta}_Q^{(j)} - \bar{\Delta}_Q^I \right)^2$$  \hspace{2cm} (9)

In equations 7, 8, and 9 above, $\bar{\Delta}_Q^I$ and $\hat{\sigma}_Q^I$ denote the value of $\hat{\Delta}_Q^{IPWRE}$ and $\sqrt{\text{Var}(\hat{\Delta}_Q^{IPWRE})}$, respectively, estimated using the $j^{th}$ imputed dataset ($j = 1, \ldots, J$).
Web Appendix K. Software and Computation Time

The R package geeM (McDaniel, Henderson, and Rathouz, 2013) was utilized in this manuscript’s implementation of IPWRE; the R package mvtnorm (Genz and Bretz, 2019; Genz, et al., 2020) was utilized to obtain samples from a MVN distribution; the R package rootSolve was used for root-finding (Soetaert and Herman, 2009; Soetaert, 2009).

Computation time to complete calculation of power for one given set of parameters in Simulation Studies 1-5 did not go beyond 900 seconds (15 minutes) and decrease with smaller sample sizes. Actual computation time to complete calculation of power for particular sets of parameters considered displayed in a column named ‘elapsed.secs’ within files named ‘power.csv’ made available in the same repository containing R code implementing our proposed approach: https://github.com/jamieyap/CountSMART/releases/tag/v2.0.0

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Web Figures

Web Figure 1: Results of Simulation Study 3 in Web Appendix F – Empirical Type-I Error Rate when $\Delta_{EOS} = 0$.

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

Scenario 1
(Overdispersion is least extreme)

Scenario 2
(Overdispersion is more extreme)

Scenario 3
(Overdispersion is most extreme)

$\rho = 0.20$

$\rho = 0.40$

$\rho = 0.60$
Web Figure 2: Results of Simulation Study 3 in Web Appendix F – Empirical Type-I Error Rate when $\Delta_{AUC} = 0$.

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

Scenario 1 (Overdispersion is least extreme)

Scenario 2 (Overdispersion is more extreme)

Scenario 3 (Overdispersion is most extreme)

$\rho = 0.20$

$\rho = 0.40$

$\rho = 0.60$
Web Figure 3: Results of Supplement to Simulation Study 3 in Web Appendix G – Bias when $\Delta_{EOS} = 0$. 

Total sample size (x-axis) vs. Empirical Bias in estimates of $\Delta_{EOS}^{IPWRE}$ (y-axis)

Scenario 1
(Overdispersion is least extreme)

Scenario 2
(Overdispersion is more extreme)

Scenario 3
(Overdispersion is most extreme)

$\rho = 0.20$

$\rho = 0.40$

$\rho = 0.60$
Web Figure 4: Results of Supplement to Simulation Study 3 in Web Appendix G – Bias when $\Delta_{AUC} = 0$.

Total sample size (x-axis) vs. Empirical Bias in estimates of $\Delta_{AUC_I^{PWRE}}$ (y-axis)

Scenario 1
(Overdispersion is least extreme)

Scenario 2
(Overdispersion is more extreme)

Scenario 3
(Overdispersion is most extreme)

\[
\begin{align*}
\rho &= 0.20 \\
\rho &= 0.40 \\
\rho &= 0.60
\end{align*}
\]
Web Figure 5: Results of Supplement to Simulation Study 3 in Web Appendix G – Bias when $\Delta_{EOS} = 0$.
Web Figure 6: Results of Supplement to Simulation Study 3 in Web Appendix G – Bias when $\Delta_{AUC} = 0$.

Total sample size (x-axis) vs. Empirical Bias in estimates of $\sqrt{\text{Var} \left( \Delta_{AUC}^{IPWRE} \right)}$ (y-axis)

Scenario 1
(Overdispersion is least extreme)

Scenario 2
(Overdispersion is more extreme)

Scenario 3
(Overdispersion is most extreme)
Web Figure 7: Results of Simulation Study 4 – Sensitivity of power to violations in working assumption on $\eta$

Web Figure 8: Results of Simulation Study 5 – Sensitivity of power to violations in working assumption on $n_4$
Web Tables

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

| EDTR  | $E\left\{Y_{i,t_{1}}^{(a_{1},a_{2}^{NR})}\right\}$ | $E\left\{Y_{i,t_{2}}^{(a_{1},a_{2}^{NR})}\right\}$ | $E\left\{Y_{i,t_{3}}^{(a_{1},a_{2}^{NR})}\right\}$ | $E\left\{Y_{i,t_{4}}^{(a_{1},a_{2}^{NR})}\right\}$ | $E\left\{Y_{i,t_{5}}^{(a_{1},a_{2}^{NR})}\right\}$ | $E\left\{Y_{i,t_{6}}^{(a_{1},a_{2}^{NR})}\right\}$ |
|-------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| (+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 (√).

|                | $Y_{i,t_1}^{(-)}$ | $Y_{i,t_2}^{(+)}$ | $Y_{i,t_2}^{(-)}$ | $Y_{i,t_3}^{(+1,0)}$ | $Y_{i,t_3}^{(+1,0,+1)}$ | $Y_{i,t_3}^{(+1,0,+1)}$ | $Y_{i,t_3}^{(-1,0)}$ | $Y_{i,t_3}^{(-1,0,+1)}$ | $Y_{i,t_3}^{(-1,0,+1)}$ |
|----------------|------------------|------------------|------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| 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 $K_{i}^{(a_1)} = I(Y_{i,t_K}^{(a_1)} \leq c)$ 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 $\btheta^*_i$ 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, $\mu_{i1}^s$, and $\xi_{i1}^s$ is denoted by $F_{NB}(\mu_{i1}^s, \xi_{i1}^s)\text{.}$

$F_{UpperTruncNB}(\mu_{i1}^s, \xi_{i1}^s, c)$, and $F_{LowerTruncNB}(\mu_{i1}^s, \xi_{i1}^s, c)$, respectively. In terms of the probability mass function (PMF) of a NB random variable $f_{NB}(\mu_{i1}^s, \xi_{i1}^s)$, the PMF of a UTNB random variable and a LTNB random variable is $f_{UpperTruncNB}(\mu_{i1}^s, \xi_{i1}^s)(w) = \frac{f_{NB}(\mu_{i1}^s, \xi_{i1}^s)(w)I(w\leq c)}{\Sigma_{y=0} f_{NB}(\mu_{i1}^s, \xi_{i1}^s)(y)}$ and $f_{LowerTruncNB}(\mu_{i1}^s, \xi_{i1}^s, c)(w) = \frac{f_{NB}(\mu_{i1}^s, \xi_{i1}^s)(w)I(w>c)}{1-\Sigma_{y=0} f_{NB}(\mu_{i1}^s, \xi_{i1}^s)(y)}$, respectively. When c=0, the UTNB PMF reduces to a point mass at zero.

|              | $F_{v_{i1}}$ | $F_{v_{i1}}^{(+1)}$ | $F_{v_{i1}}^{(-1)}$ |
|--------------|-------------|-----------------|-----------------|
| Subgroup 1   | $F_{NB}(\mu_{i1}^{(1)}, \xi_{i1}^{(1)})$ | $F_{UpperTruncNB}(\mu_{i1}^{(1)}, \xi_{i1}^{(1)}, c)$ | $F_{UpperTruncNB}(\mu_{i1}^{(1)}, \xi_{i1}^{(1)}, c)$ |
| Subgroup 2   | $F_{NB}(\mu_{i1}^{(1)}, \xi_{i1}^{(1)})$ | $F_{UpperTruncNB}(\mu_{i1}^{(1)}, \xi_{i1}^{(1)}, c)$ | $F_{LowerTruncNB}(\mu_{i1}^{(1)}, \xi_{i1}^{(1)}, c)$ |
| Subgroup 3   | $F_{NB}(\mu_{i1}^{(1)}, \xi_{i1}^{(1)})$ | $F_{UpperTruncNB}(\mu_{i1}^{(1)}, \xi_{i1}^{(1)}, c)$ | $F_{LowerTruncNB}(\mu_{i1}^{(1)}, \xi_{i1}^{(1)}, c)$ |
| Subgroup 4   | $F_{NB}(\mu_{i1}^{(1)}, \xi_{i1}^{(1)})$ | $F_{LowerTruncNB}(\mu_{i1}^{(1)}, \xi_{i1}^{(1)}, c)$ | $F_{LowerTruncNB}(\mu_{i1}^{(1)}, \xi_{i1}^{(1)}, c)$ |
Web Table 5: Web Table 4, Continued

|                  | $F_{y,i,t_3}^{(+1,1,0)}$ | $F_{y,i,t_3}^{(+1,0,+1)}$ | $F_{y,i,t_3}^{(+1,0,-1)}$ | $F_{y,i,t_3}^{(-1,1,0)}$ | $F_{y,i,t_3}^{(-1,0,+1)}$ | $F_{y,i,t_3}^{(+1,0,-1)}$ |
|------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| **Subgroup 1**   | $F_{NB}^{(+1,0,0)}(\mu_{t_3},\epsilon_{t_3})$ | $-$                       | $-$                       | $F_{NB}^{(-1,1,0)}(\mu_{t_3},\epsilon_{t_3})$ | $-$                       | $-$                       |
| **Subgroup 2**   | $F_{NB}^{(+1,0,0)}(\mu_{t_3},\epsilon_{t_3})$ | $-$                       | $-$                       | $-$                       | $F_{NB}^{(-1,0,+1)}(\mu_{t_3},\epsilon_{t_3})$ | $F_{NB}^{(-1,0,-1)}(\mu_{t_3},\epsilon_{t_3})$ |
| **Subgroup 3**   | $-$                       | $F_{NB}^{(+1,0,0)}(\mu_{t_3},\epsilon_{t_3})$ | $F_{NB}^{(-1,0,+1)}(\mu_{t_3},\epsilon_{t_3})$ | $F_{NB}^{(-1,0,-1)}(\mu_{t_3},\epsilon_{t_3})$ | $-$                       | $-$                       |
| **Subgroup 4**   | $-$                       | $F_{NB}^{(+1,0,0)}(\mu_{t_3},\epsilon_{t_3})$ | $F_{NB}^{(+1,0,0)}(\mu_{t_3},\epsilon_{t_3})$ | $-$                       | $F_{NB}^{(-1,0,+1)}(\mu_{t_3},\epsilon_{t_3})$ | $F_{NB}^{(-1,0,-1)}(\mu_{t_3},\epsilon_{t_3})$ |
Web Table 6: Parameter values in Simulation Study 3. Below, $\pi_{i,t_j}^S$ denotes $Pr\{Y_{i,t_j}^S = 0\}$.

For brevity, we omit the subscript $i$ in expressions for $\mu_{i,t_j}^S$, $\pi_{i,t_j}^S$ and $\xi_{i,t_j}^S$.

| Fixed across all scenarios: | ETS Means |
|-----------------------------|-----------|
| Total Sample Size           | N=100, 150, 200, ..., 550 |
| Copula Dependence Parameter | $\rho = 0.2, 0.4, 0.6$ |
| Proportion of Responders    | $p = 0.40$ and $q = 0.40$ |

| Varied across scenarios: | Scenario 1 | Scenario 2 | Scenario 3 |
|--------------------------|------------|------------|------------|
| ETS Proportion of Zeros  | $\pi_{1,t} = 0.40, \pi_{2,t} = 0.40, \pi_{1,t} = 0.40, \pi_{2,t} = 0.20$ | $\pi_{1,t} = 0.40, \pi_{2,t} = 0.40, \pi_{1,t} = 0.40, \pi_{2,t} = 0.40$ | $\pi_{1,t} = 0.40, \pi_{2,t} = 0.40, \pi_{1,t} = 0.40, \pi_{2,t} = 0.60$ |
| For all s: $\mu_{s,t}^i = 4.8, \mu_{s,t}^j = 2.6, \mu_{s,t}^i = 2.7, \mu_{s,t}^j = 2.75, \mu_{s,t}^i = 2.8$ |

Value of dispersion parameter $\xi_{i,t}^S$ implied by choice of values for $\mu_{s,t}^i$ and $\pi_{s,t}^j$:

| Scenario 1 | Scenario 2 | Scenario 3 |
|------------|------------|------------|
| For all s: $\xi_{t}^S = 0.51, \xi_{t}^S = 1.18, \pi_{1,t}^S = 0.55, \pi_{2,t}^S = 0.60, \mu_{s,t}^i = 0.62, \mu_{s,t}^j = 0.63.$ | For all s: $\xi_{t}^S = 1.92, \xi_{t}^S = 2.98, \xi_{t}^S = 1.98, \xi_{t}^S = 2.05, \mu_{s,t}^i = 2.08, \mu_{s,t}^j = 2.11.$ | For all s: $\xi_{t}^S = 5.15, \xi_{t}^S = 6.91, \xi_{t}^S = 5.26, \xi_{t}^S = 5.36, \mu_{s,t}^i = 5.41, \mu_{s,t}^j = 5.46.$ |