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Micro-Randomized Trial with Flexible Design and Sample Size Considerations

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Summary

Technological advancements have made it possible to deliver mobile health interventions to individuals. A novel framework that has emerged from such advancements is the just-in-time adaptive intervention (JITAI), which aims to suggest the right support to the individuals when their needs arise. The micro-randomized trial (MRT) design has been proposed recently to test the proximal effects of these JITAIIs. In an MRT, participants are repeatedly randomized to one of the intervention categories of various components, at a scale of hundreds or thousands of decision-points over the study. However, the extant MRT framework only considers the components with a fixed number of categories. We propose a novel extension of the MRT design, by allowing flexible addition of more categories to the components during the study, in a spirit analogous to adaptive platform trials. Accordingly, we develop a methodology to allow for simultaneous comparisons of varying numbers of categories over a given study period. The proposed methodology is motivated by collaboration on the DIAMANTE study, which learns to adaptively deliver multiple complex kinds of text messages to encourage physical activity among the patients with Diabetes and Depression. We apply a methodology similar to the generalized estimating equation approach on the longitudinal data arising from the proposed MRT, to develop novel test statistics for assessing the proximal effects and deriving the associated sample size calculators. We conduct simulation studies to evaluate the sample size calculators, based on both power and precision. We have developed an R shiny application of the sample size calculators.

KEYWORDS:
mHealth, Just-In-Time Adaptive Intervention, Micro-Randomized Trial, Generalized Estimating Equation, Longitudinal Data

1 INTRODUCTION

Life is getting increasingly digital. The ubiquitous mobile devices are increasingly indispensable in our daily lives. They are not only used for communication, but are also used for a wide range of purposes such as calendar reminders, entertainment, activities tracking, and health monitoring, among many others. Mobile health (mHealth) is a term used for the practice of medicine and health supported by mobile devices or wearables. They can better reach areas, people, and healthcare practitioners with limited exposure to certain aspects of healthcare. They are used across the health fields and include treatments of chronic diseases (e.g.,...
managing HIV\textsuperscript{3}, increasing physical activity\textsuperscript{11}, supplement counseling or pharmacotherapy in treatment for substance use\textsuperscript{4}, and to support recovery from alcohol dependence\textsuperscript{5}. Mobile interventions for anti-retroviral therapy and smoking cessation have shown sufficient effectiveness and replicability in trials and have been recommended for inclusion in standard health services\textsuperscript{6}.

Mobile interventions not only provide convenient health support, but also can potentially be designed to deliver the support “just-in-time” due to the increasingly ubiquitous access and powerful sensing capabilities of mobile devices and wearables. This novel intervention design is known as the “just in time adaptive intervention” (JITAI), which aims to provide the right type or amount of support, at the right time\textsuperscript{7,8}, adapting according to an individual’s changing internal and contextual state. Nahum-Shani \textit{et al.}\textsuperscript{9} bridge the gap between the growing technological capabilities for delivering JITAI and research on the development and evaluation of these interventions.

JITAI for mHealth is intended to have proximal or short-term effects. A state-of-the-art experimental design proposed for testing the proximal effects of the intervention categories in JITAI is called the micro-randomized trial (MRT) design\textsuperscript{10}. The corresponding analysis plan and sample size calculation for current MRT designs have been derived by Liao \textit{et al.}\textsuperscript{11}. In an MRT, there are numerous decision time points (up to hundreds or even thousands) for each participant throughout the study period. At each decision time point, the participant is randomly assigned to one of the available intervention options. This sequential randomization captures the causal modeling of an intervention component’s time-varying proximal main effect as well as modeling of time-varying proximal moderation effect with another intervention component, similar to that of the factorial designs with multi-component intervention\textsuperscript{12}. Note that the classical factorial designs do not consider the time-varying aspects in the main and moderating effects of the intervention components. There are several existing research studies using the MRT design, for example, ‘HeartSteps’ for promoting physical activity (e.g., walking) among sedentary people\textsuperscript{13} to prevent heart diseases; ‘Sense2Stop’ for managing stress in newly abstinent smokers\textsuperscript{14}; ‘JOOL’ for engaging in self-monitoring using the proposed mHealth apps among office workers\textsuperscript{15}; ‘DIAMANTE’ for promoting physical activity (e.g., walking) among co-morbid diabetes and depression patients; ‘Stay Well at Home’\textsuperscript{16} for managing people’s mental wellness during COVID-19 pandemic period; ‘HEART’\textsuperscript{17} is to promote physical activity and healthy diets for managing cardiovascular diseases.

In a conventional MRT design, the number of intervention categories within an intervention component is predetermined and fixed during the trial. For example in the HeartSteps study, the Activity Suggestions component includes both the walking and anti-sedentary intervention message categories. Though the proximal effect sizes of both the walking and anti-sedentary message categories were estimated by Klasnja \textit{et al.}\textsuperscript{18}, the calculated sample size was only sufficient to detect the proximal effect size of the pooled active message types. As an experimental design extension of MRTs, it is possible to propose new intervention categories during the study period as in platform clinical trials\textsuperscript{19}. With the corresponding extension in sample size calculation extension of MRTs, it is possible to separate the proximal effect sizes of both the walking and anti-sedentary message categories\textsuperscript{20}.

In practice, there is a possibility that the candidate message categories are not all proposed at the beginning of the study\textsuperscript{21}. Therefore in this paper, we develop a novel flexible version MRT design (named “FlexiMRT”) with sample size consideration. The flexibility allows newly proposed intervention messages added not only initially but also later during the study period. With the corresponding sample size calculation, instead of estimating one proximal effect from each message component (i.e., the “pooled” active intervention message categories versus the control category), the proximal effects of individual message categories within each component versus no message (control) can be estimated. The individual message effect sizes will be interesting if they are expected to be different in magnitudes or directions. Novel test statistics are derived to detect the proximal effects from the FlexiMRT data. We derive the corresponding sample size calculators so that the trials can be sized to either detect the standardized proximal effect sizes at a nominal power and a nominal type-I error rate, or estimate the standardized proximal effect sizes within a precision or margin of error (e.g., the half-width of the confidence interval) at a nominal confidence level. The latter approach is useful in a pilot study scenario, when prior information on the proximal effects are very limited. In addition to the constant, linear, and quadratic trends for the proximal effect proposed by Liao \textit{et al.}\textsuperscript{11} for the HeartSteps study, we also consider a linear-plateau trend, which is a combination of linear and constant trends similar to a linear spline. It captures a potential scenario when the proximal effect is increased or decreased until reaching the maximum or minimum value respectively, and then maintaining it.

This work is motivated by our collaboration on the Diabetes and Mental Health Adaptive Notification Tracking and Evaluation (DIAMANTE) study\textsuperscript{22}, where it uses a multi-category MRT. The DIAMANTE study aims to understand the workings and optimal strategy to deliver text message programs to motivate regular exercise behavior in individuals. The “DIAMANTE” mHealth app, empowered by a text-messaging platform “HealthySMS”, sends multiple text messages to encourage physical
activity (i.e. walking) among co-morbid diabetes and depression patients from low-income and ethnic minority backgrounds served in the San Francisco Health Network.

We summarize the three main contributions of the paper. First, we proposed a novel FlexiMRT design, which allows for intervention categories to be added later during the course of the study, as in adaptive platform clinical trials. Second, we consider the sample size calculation methods for the proposed design, not only the traditional power-based but also precision-based that account for both full-fledged and pilot trial scenarios respectively. Finally, the proposed methodology has been applied to the aforementioned DIAMANTE study, a complex mHealth study of high relevance to modern healthcare systems.

The rest of the paper is organized as follows. Section 2 describes the proposed FlexiMRT design, the statistical analysis and sample size calculation methods for DIAMANTE. Section 3 demonstrates an application of the proposed sample size calculator based on the data analysis results from a version of the DIAMANTE study. Section 4 investigates the finite-sample performance of the proposed sample size calculation methods through simulation studies. Finally, the paper ends with a discussion in Section 5. Supplementary materials, consisting of detailed derivations and demonstrating the implementation of the proposed sample size calculator are relegated to the Appendix.

2 MICRO RANDOMIZED TRIAL WITH FLEXIBLE DESIGN: STATISTICAL MODEL ESTIMATION AND SAMPLE SIZE CALCULATION

In this section, we describe the proposed flexible micro-randomized trial (FlexiMRT) design, the corresponding analysis plan and sample size calculation methods.

2.1 Micro-Randomized Trial Design and The DIAMANTE Study

The micro-randomized trial (MRT) is a cutting-edge trial design suitable to take care of the time-varying, sequential nature of the multi-component interventions, akin to a sequential full-factorial design. At each decision time, participants are randomized to an intervention category. The MRT focuses on binary categories for the interventions (e.g., the intervention is on or off, see Liao et al.\textsuperscript{11}). In this paper, multiple categories are considered. For example, a message component includes \((1 + M)\) categories, which are no-message, type-1 message,..., type-M message.

The FlexiMRT design is motivated by a study named ‘DIAMANTE’ (Diabetes and Mental Health Adaptive Notification Tracking and Evaluation). It develops and employs a mobile health application (app), also named ‘DIAMANTE’ (https://diamante.healthysms.org). It uses mobile device technology to deliver physical activity promoting interventions, focusing on the cohort of patients with co-morbid diabetes and depression from low-income and ethnic minority families in the San Francisco Health Network. An example of the features of the DIAMANTE app is displayed in Figure 1. The current DIAMANTE study uses a MRT design with “multi-category” component and is summarized in Figure 2 which is explained below.

The study period is six months long with one decision time point per day, so the participants may be randomized approximately 180 decision time points in the study. On each day of the study period, each participant, who is available for intervention, is randomized to one of the categories of each of three multi-category components (factors), namely, Time Window (4 categories), Feedback Message (5 categories), and Motivational Message (4 categories). Thus, the DIAMANTE study allocates interventions according to a \(4 \times 5 \times 4\) factorial design each day. In other words, each participant receives one of the messages from each of Feedback Message and Motivational Message intervention components, at most one time per day as per the category of the Time Window, if that participant is available for intervention during the allocated Time Window category. The two different messages are sent one minute apart. See the following for more details about the various categories of the 3 intervention components.

**Factor 1: The Time Window component** (four categories, i.e., \(A_T=0, 1, 2, 3\)) suggests when to send the messages, i.e. category-0 (9:00 am - 11:30 am), category-1 (11:30 am - 14:00 pm), category-2 (14:00 pm - 16:30 pm) and category-3 (16:30 pm - 19:00 pm). A participant is randomly assigned to one of the time windows on each day of the study period. Unlike most MRTs, the DIAMANTE study investigates the proposed message intervention effects at different time windows of each study day.

**Factor 2: The Feedback Message component** (five categories, i.e., \(A_F=0, 1, 2, 3, 4\)) has a reference category-0 (i.e. no message or control) and four active intervention categories, i.e. category-1 (reaching goal, e.g., “Yesterday, you did not reach your goal.”), category-2 (steps walked yesterday, e.g., “Yesterday, you walked 3824 steps.”), category-3 (walked more or less
yesterday than the day before, e.g., “Yesterday, you walked more than day before.”), category-4 (steps walked yesterday plus a positive/negative message, e.g., “You walked 8000 steps yesterday. Great job!”).

**Factor 3: The Motivational Message component** is similar to the Feedback Message (four categories, i.e. $A^M=0, 1, 2, 3$), has a reference category-0 (i.e. no message or control) and three active intervention categories, i.e. category-1 (benefit, e.g., “Doing more physical activity can help reduce feelings of fatigue.”), category-2 (self-efficacy, e.g., “You have made changes to improve your health before, you can do it again.”) and category-3 (opportunity, e.g., “Is there a local park you have been waiting to visit? Use it as an opportunity to get out of the house and do more steps!”).

The primary outcome measure ($Y$) is the increase in step-count, i.e., the steps walked on the day when intervention messages were sent minus the steps walked on the day before, measured by the participants’ phone pedometer. The effects of the messages on steps change over 24-hours are examined.

The availability indicator ($I$) codes one if a participant is available to receive intervention messages at the assigned decision time point for each day of the study, otherwise it codes zero. The DIAMANTE study assumes the value of $I$ to be one for each participant at each decision time point (i.e. 100% availability). This is a reasonable assumption because the proximal outcome in this study is the change in daily steps after messages are sent, thus participants have sufficient time to respond to both the feedback and motivational messages at the randomly selected decision time points. This is in contrast with the HeartSteps study, which includes both the Activity Suggestions and Planning Support components. The availability indicator is considered for the former component but not for the latter one. The Activity Suggestions component suggests a participant to take action immediately after a message sent, i.e. measuring the walking steps within the next 30 minutes. The participants can be considered unavailable for intervention due to several reasons, e.g., driving, already walking and activity notification is off. For the Planning Support component, a message is sent at a convenient time selected by the participant, thus the participant is always considered available.

The current phase of DIAMANTE trial is a conventional MRT where all the intervention categories are added at the beginning of the trial. Even though we focus on the MRT design employed in the DIAMANTE study, at the macro level, this study involves a 3-group randomized control trial (RCT), i.e. the uniform random intervention (URI), adaptive intervention (AI) and control groups. An MRT design is embedded both within the URI and AI groups. The participants of the URI group receive the different message types and associated timings with equal probability while the participants of the AI group receive the message types and associated timings learned adaptively by a reinforcement learning algorithm in order to reach and maintain the maximum value of the proximal effects. Though both the URI and AI groups can be modified into a FlexiMRT design, the proposed sample size calculator can be only used to the uniform random intervention group.

For the statistical analysis plan and sample size calculators proposed through Sections 2.2 to 2.5, we consider the long format of the longitudinal dataset for the DIAMANTE study. Each row represents a participant at a particular day of the study, with the availability indicator $I$, the intervention dummy variables $A^I_1, A^I_2, A^I_3, A^I_4, A^F_1, A^F_2, A^F_3, A^M_1, A^M_2, A^M_3$, and the proximal response $Y$. For example, $A^I_1, A^I_2, A^I_3, A^F_4$ are the dummy variables of $A^I$, such that if the participant on that day receives control (or category-0) from the Feedback Message component, then the indicators give $A^I_1 = A^I_2 = A^I_3 = A^F_4 = 0$. The observation of participant $i$ on day $d$ is

$$\{I_{id}, A^I_{1id}, A^I_{2id}, A^I_{3id}, A^I_{4id}, A^F_{1id}, A^F_{2id}, A^F_{3id}, A^F_{4id}, A^M_{1id}, A^M_{2id}, A^M_{3id}, Y_{id}\}.$$  

### 2.2 Statistical Model

In this section, we first extend the statistical model proposed by Liao et al.\[13\] for micro-randomized trial (MRT)\[10\] to accommodate multi-category intervention components. Instead of estimating the proximal effect between two categories (active versus control), we estimate such effects for multiple intervention categories with reference to a control category. Multiple categories approach can be used to recognize whether the differences of effect sizes among the intervention message categories in magnitudes (see Section 3) or opposite direction of signs exist. To allow for the flexible addition of new intervention categories during the trial, we further remove the restriction on fixed allocation in the model. A regression model considering the proximal effect of a single component can be defined as below. We assume one decision time point per day, i.e. $T = 1$ for participant $i$ on day $d$, the proximal outcome is denote by $Y_{id}$.

First, we define the proximal effect size of message category $m$ on day $d$ from a particular component. It is denoted by a function $b_m(d; \beta_m)$, i.e.

$$b_m(d; \beta_m) = Z_{md}^T \beta_m = [1, d-1, \ldots, (d-1)^{p_m-1}] \beta_m,$$

(1)
where \( m = 1, \ldots, M \), \( d = 1, \ldots, D \) (the study period in days) and parameter \( \beta_m = (\beta_{m1}, \ldots, \beta_{mp_m})^T \) with a \((p_m - 1)\)th order. Note that \( Z^T_{md} \) in equation (1) corresponds to one decision time point per day (consistent with the DIAMANTE study in this paper), which can be extended to a more general form by involving the number of decision time points \( T \) per day, i.e.

\[
Z^T_{md} \beta_m = \left( 1, \frac{(d-1)T + t - 1}{T}, \ldots, \frac{(d-1)T + t - 1}{T}^{p_m-1} \right) \beta_m,
\]

where \( t = 1, \ldots, T \). The proximal effect sizes for different message categories on different days can be varied. They may follow the constant, linear, or quadratic trends, corresponding to \( p_m = 1, 2 \) or 3 respectively. The proximal effect trend for intervention category-\( m \) can also be described as having both the linear and constant trends, where it increases or decreases linearly until reaching the turning point on day \( d^m_{\text{turn}} \) and plateaus afterwards. We name it as the “linear-plateau” trend. In this case, we can define the proximal effect size using a linear spline, i.e.

\[
Z^T_{md} \beta_m = \left( 1, \left[ \min \left[ d^m_{\text{turn}} - 1, d - 1 \right] \frac{T + t - 1}{T} \right] \right) \beta_m,
\]

where we have \( \beta_m^T = (\beta_{m1}, \beta_{m2}) \).

Now, we consider the scenario where new message categories are added during the study. Let \( M_0 \) be the number of intervention message categories initially on day \( d_0 \) (e.g., the beginning of the study \( d = 1 \)), \( M_1 \) be the number of message categories added on day \( d_1 \) (first adding day after the beginning of the study), \( M_2 \) be the number of categories added at the last adding day \( d_k \), where we have \( d_0 \leq 1 < d_1 < \ldots < d_k \leq D \). Therefore, we have \( M = \sum_{j=0}^k M_j \). We assume that the participants have the same length of time until each new message category is added. This ensures that all added messages have the same duration for each participant to estimate their proximal effects. This is similar to a multi-arm multi-stage design (e.g., the STAMPEDE trial, a clinical study in prostate cancer), the adding intervention categories days are the number of days after the study started (i.e. day one). Note that the effect size for each of the new message categories is undefined before their adding days. Suppose \( d = d_1, m = M_0 + 1, T = 1 \) and \( p_m = 2 \), the proximal effect of category \( M_0 + 1 \) on day \( d_1 \) can be computed by \( b_{M_0+1}(d_1; \beta_{M_0+1}) = \beta_{M_0+1}^T \beta_M(1) \) based on equation (1), where \( b_{M_0+1}(d_1; \beta_{M_0+1}) \) is undefined before day \( d_1 \). Given that participant \( i \) is available for randomization on day \( d_1 \), we denote the intervention message categories by \( A_i = (A_{i1}, \ldots, A_{iM_0+1}, \ldots, A_{iM_0+1}^M) \) which follows a multinomial distribution, i.e. Multinomial(1, \( \sum_{m=0}^k \pi_{md}^i \)), where \( \pi_{md}^i \) denotes the randomization probability corresponding to \( A_i \). Note that before the first adding day (i.e. \( d < d_1 \)), the message categories \( M_0 + 1 \) to \( \sum_{j=0}^k M_j \) are not available. Thus, the category indicators \( A_{i(M_0+1)}^i \), \( A_{i(M_0+1)}^i \) and their corresponding randomization probabilities \( \pi_{i(M_0+1)d}, \pi_{i(M_0+1)d}^i \) have zero values. We then denote the proximal effects of all the intervention message categories on day \( d \) to be \( Z_{id}^T \beta_1, \ldots, Z_{id}^T \beta_{M_0}, \ldots, Z_{id}^T \beta_{k+1}, \ldots, Z_{id}^T \beta_{k+1} \). The working model is written as

\[
Y_{id} = B_d^T \alpha + \left[ (A_{i1d} - \pi_{i1d}) Z_{1d}^T \beta_1 + \ldots + (A_{iM_0+1d} - \pi_{iM_0+1d}) Z_{M_0+1d}^T \beta_{M_0} \right] + \left[ (A_{i(M_0+1)d} - \pi_{i(M_0+1)d}) Z_{(M_0+1)d}^T \beta_{M_0+1} + \ldots + (A_{i(M_0+M_1)d} - \pi_{i(M_0+M_1)d}) Z_{(M_0+M_1)d}^T \beta_{M_0+M_1} \right] + \ldots + \left[ (A_{i(M_0+1)d} - \pi_{i(M_0+1)d}) Z_{(M_0+1)d}^T \beta_{M_0+1} + \ldots + (A_{i(M_0+1)d} - \pi_{i(M_0+1)d}) Z_{(M_0+1)d}^T \beta_{M_0+M_1} \right] + \epsilon_{id},
\]

where \( B_d^T \alpha \) is a function of \( d \) and covariates that are unaffected by intervention categories. For example, we can define a \((q - 1)\)th-order function of \( d \) for \( B_d^T \alpha \) with parameters \( \alpha^T = (\alpha_1, \ldots, \alpha_q) \) and \( B_d^T = (1, d - 1, \ldots, (d - 1)^{q-1}) \), the parameters of interest for the \( m \)th intervention message category. \( \epsilon_{id} \) is the error term, and \( \epsilon = (\epsilon_1, \ldots, \epsilon_D)^T \) follows a multivariate normal distribution with zero mean, variance \( \sigma^2 \) and correlation coefficient \( \rho \), for \( i = 1, \ldots, N \).

We define the model parameter \( Y = (Y_{i1}, \ldots, Y_{iD})^T \) for \( i = 1, \ldots, N \) by \( \theta = (\alpha^T, \beta^T)^T \), where \( \beta^T = (\beta_{m1}, \ldots, \beta_{mp_m}) \). The least squares (LS) estimator \( \hat{\theta} \) is obtained by minimizing the squared error criterion,

\[
SEC(\theta) = \frac{1}{N} \sum_{i=1}^{N} \sum_{d=1}^{D} I_{id} \left[ Y_{id} - X_{id}^T \theta \right]^2,
\]

(3)
where $N$ is the sample size, $D$ is the study period in days; $I_{id}$ is the availability indicator for participant $i$ on day $d$ with expectation $E(I_{id}) = r_d$, see e.g., Liao et al. (2016)\textsuperscript{11} Boruvka et al. (2018)\textsuperscript{12} and Seewald et al. (2019)\textsuperscript{13} and $X$ is the design matrix for the regression model of $Y$. Note that the DIAMANTE study assumes the participants to be always available (i.e. $r_d = 1$). The LS estimator can be obtained by solving the equation

$$
\frac{\partial}{\partial \theta} SEC(\theta) = \frac{-2}{N} \sum_{i=1}^{N} \sum_{d=1}^{D} I_{id} [Y_{id} - X_{id}^T \theta] X_{id} = 0.
$$

Therefore the LS estimator is

$$
\hat{\theta} = \left( \frac{1}{N} \sum_{i=1}^{N} \sum_{d=1}^{D} I_{id} X_{id} X_{id}^T \right)^{-1} \frac{1}{N} \sum_{i=1}^{N} \sum_{d=1}^{D} I_{id} Y_{id} X_{id},
$$

i.e. $\hat{\theta} = (\hat{\alpha}^T, \hat{\beta}_m^T)^T$ with dimension $(q + \sum_{m=1}^{M} p_m) \times 1$, where $\hat{\alpha}$ is a vector that includes the first $q$ elements of $\hat{\theta}$ while $\hat{\beta}_m$ is a vector that includes the rest of the $\sum_{m=1}^{M} p_m$ elements of $\hat{\theta}$.

### 2.3 Test Statistics

This section proposes the hypothesis tests and derives the test statistics for the model in Section 2.2. We propose a null hypothesis

$$
H_0 : b_m(d; \beta_m) = 0,
$$

for all $m$ and $d$, and an alternative hypothesis

$$
H_1 : \text{not all } b_m(d; \beta_m) = 0,
$$

where $m$ indicates the $m$th intervention message category, i.e. $m = 1, \ldots, M_0, \ldots, M_1, \ldots$, $\sum_{j=0}^{k} M_j = M$, $\beta_m = (\hat{\beta}_{m1}, \ldots, \hat{\beta}_{mp})^T$; $d$ is the day during the study period, i.e. $d = 1, \ldots, D$; and $Z_{md}$ is defined in equation (1). We have the control category at $m = 0$.

In order to derive the test statistic distributions, the following assumptions are required.

1. Let $\Theta$ be the parameter space for $\theta$, where $\Theta$ is a compact subset of $R^{q + \sum_{m=1}^{M} p_m}$.
2. $E(SEC(\theta))$ exists and has a unique minimum value at $\hat{\theta} \in \Theta$.
3. $SEC(\theta)$ is continuous, bounded, and differentiable in the neighbourhood of $\hat{\theta}$.
4. The matrix $\sum_{d=1}^{D} E(I_{id} X_{id} X_{id}^T)$ in equation (5) is invertible.

First we present the following lemma of consistency and asymptotic normality for the least squares estimator $\hat{\theta}$. The proof is deferred to the Appendix.

**Lemma 1.** The least squares estimator $\hat{\theta}$ is a consistent estimator of $\tilde{\theta}$. Under standard moment conditions and assumptions 1 - 4, we have $\sqrt{N}(\tilde{\theta} - \hat{\theta}) \rightarrow \text{Normal}(0, \Sigma_\theta)$.

When the sample size $N$ is large, the sample mean within the estimator (5) is replaced by its expectation, i.e.

$$
\tilde{\theta} = \left[ \sum_{d=1}^{D} E(I_{id} X_{id} X_{id}^T) \right]^{-1} \sum_{d=1}^{D} E(I_{id} Y_{id} X_{id}),
$$

i.e. $\tilde{\theta} = (\tilde{\alpha}^T, \tilde{\beta}_m^T)^T$. In other words, it turns out that $\tilde{\theta} \rightarrow \hat{\theta}$ when $N \rightarrow \infty$. More details about equation (5) are covered in the Appendix. The asymptotic covariance matrix $\Sigma_\theta$ is defined by

$$
\Sigma_\theta = \left[ \sum_{d=1}^{D} E(I_{id} X_{id} X_{id}^T) \right]^{-1} E \left( \sum_{d=1}^{D} I_{id} \tilde{e}_{id} X_{id} \sum_{d=1}^{D} I_{id} \tilde{e}_{id} X_{id}^T \right) \left[ \sum_{d=1}^{D} E(I_{id} X_{id} X_{id}^T) \right]^{-1},
$$

where $E \left( \sum_{d=1}^{D} I_{id} \tilde{e}_{id} X_{id} \sum_{d=1}^{D} I_{id} \tilde{e}_{id} X_{id}^T \right)$ is defined in Appendix A. Thus the asymptotic distribution of $\hat{\beta}$ converges to normal, i.e. $\sqrt{N}(\hat{\beta} - \tilde{\beta}) \rightarrow \text{Normal}(0, \Sigma_\beta)$ with covariance matrix $\Sigma_\beta$; see the Appendix for its derivation. The asymptotic covariance matrix can be expressed as $\Sigma_\theta = Q^{-1} W Q^{-1}$. We have square matrices $Q$ and $W$, which are the lower right $\sum_{m=1}^{M} p_m \times \sum_{m=1}^{M} p_m$ blocks of $\sum_{d=1}^{D} E(I_{id} X_{id} X_{id}^T)$ and $E \left( \sum_{d=1}^{D} I_{id} \tilde{e}_{id} X_{id} \sum_{d=1}^{D} I_{id} \tilde{e}_{id} X_{id}^T \right)$, respectively.
Next we define the test statistic function $C_N$ (·), i.e., $C_N(\hat{\delta}) \bowtie N \hat{\beta}^T \Sigma_{\beta}^{-1} \hat{\beta}$, which follows a $\chi^2(\sum_{m=1}^M p_m)$ distribution when the null hypothesis is true and $N$ is large.\cite{Tu2004} We have $\hat{\delta} = \beta / \hat{\sigma}$, where $\hat{\sigma}$ is the average of the residual variance over all the decision time points, i.e. $\hat{\sigma} = \sum_{i=1}^D \text{Var}(e_{id}) / D$. Tu et al.\cite{Tu2004} proposes a sample size calculation method based on power under the GEE approach for longitudinal data. Leveraging on this, we define the power function as follows. If $H_0$: $\beta = 0$ is true, and the type-I error rate is defined by

$$\Pr \left( X_{\sum_{i=1}^m p_m} > \chi^2_{\sum_{i=1}^m p_m} \right) = \alpha, \tag{7}$$

where $X_{\sum_{i=1}^m p_m}$ presents a random variable that follows a central Chi-squared distribution with degrees of freedom $\sum_{m=1}^M p_m$ while $\chi^2_{\sum_{i=1}^m p_m}$ represents its $1 - \alpha$ quantile. We reject $H_0$ at $\alpha$ level of significance if $X_{\sum_{i=1}^m p_m} > \chi^2_{\sum_{i=1}^m p_m}$. If $H_1$: $\beta = \hat{\beta} \neq 0$ is true, then

$$\Pr \left( X_{\sum_{i=1}^m p_n, C_N(\hat{\delta})} > \chi^2_{\sum_{i=1}^m p_m} \right) = \text{Power}, \tag{8}$$

where $X_{\sum_{i=1}^m p_n, C_N(\hat{\delta})}$ represents a random variable that follows a Chi-squared distribution with degrees of freedom $\sum_{m=1}^M p_m$ and non-centrality parameter $C_N(\hat{\delta})$. Note that Tu et al.\cite{Tu2004} does not define the distribution of $C_N(\hat{\delta})$ for a small sample size.

When $N$ is small, $\Sigma_{\beta}$ is replaced by the sample estimate $\hat{\Sigma}_{\beta}$, which is derived by Mancl et al.\cite{Mancl2001}, and the test statistic follows Hotelling’s $T^2$ distribution; see, e.g., Hotelling\cite{Hotelling1931} and Li and Redden\cite{Li2015}. We define the small-sample estimator by $\hat{\Sigma}_{\beta} = \hat{\Omega}^{-1} \hat{W} \hat{Q}^{-1}$. Let

$$\hat{e}_{id} = Y_{id} - X_{id}^T \hat{\beta} \tag{9}$$

$$\hat{e}_{i} = (\hat{e}_{1}, \ldots, \hat{e}_{D}), \tag{10}$$

$$X_{i} = \left[ \begin{array}{c} X_{i1}^T I_{i1} \\ X_{iD}^T I_{iD} \end{array} \right]_{D \times (q + \sum_{m=1}^M p_m)} \tag{11}$$

$$H_{i} = X_{i}^T \sum_{i=1}^N X_{i} X_{i}^T \left( \hat{\Omega}^{-1} \hat{Q}^{-1} \right), \tag{12}$$

The matrix $\hat{Q}^{-1}$ is given by the lower right $\sum_{m=1}^M p_m \times \sum_{m=1}^M p_m$ block of $[\sum_{i=1}^N X_{i} X_{i}^T / N]^{-1}$; the matrix $\hat{W}$ is given by the lower right $\sum_{m=1}^M p_m \times \sum_{m=1}^M p_m$ block of $[\sum_{i=1}^N X_{i}(I_{D \times D} - H_{i})^{-1} \hat{e}_{i} (I_{D \times D} - H_{i})^{-1} X_{i}^T] / N$, where $I_{D \times D}$ is the identity matrix with dimension $D \times D$.

Liao et al.\cite{Liao2016} suggests that the test statistic follows a Hotelling’s $T^2$ distribution with dimension $\sum_{m=1}^M p_m$ and degrees of freedom $N - q - 1$, i.e.,

$$C_N(\hat{\delta}) = N \hat{\beta}^T \Sigma_{\beta}^{-1} \hat{\beta} \sim T_{\sum_{m=1}^M p_m, N-q-1}^2 = \sum_{m=1}^M p_m (N - q - 1) \sum_{m=1}^M p_m F_{\sum_{m=1}^M p_m, N-q-1, \sum_{m=1}^M p_m}. \tag{13}$$

Thus,

$$\frac{N - q - \sum_{m=1}^M p_m}{\sum_{m=1}^M p_m (N - q - 1)} C_N(\hat{\delta}) \sim F_{\sum_{m=1}^M p_n, N-q-\sum_{m=1}^M p_n, \sum_{m=1}^M p_n} \tag{14}$$

if $H_0$: $\beta = 0$ is true, and the type-I error rate ($\alpha$) is defined by

$$\Pr \left( F_{\sum_{m=1}^M p_n, N-q-\sum_{m=1}^M p_n} > f_{\sum_{m=1}^M p_n, N-q-\sum_{m=1}^M p_n, \sum_{m=1}^M p_n} \right) = \alpha, \tag{15}$$

where $F_{\sum_{m=1}^M p_n, N-q-\sum_{m=1}^M p_n}$ represents a random variable that follows a central $F$ distribution with degrees of freedom $\sum_{m=1}^M p_m$ and $N - q - \sum_{m=1}^M p_m$ while $f_{\sum_{m=1}^M p_n, N-q-\sum_{m=1}^M p_n}$ represents its $1 - \alpha$ quantile. We reject $H_0$ at $\alpha$ level of significance if $F_{\sum_{m=1}^M p_n, N-q-\sum_{m=1}^M p_n} > f_{\sum_{m=1}^M p_n, N-q-\sum_{m=1}^M p_n}$. If $H_1$: $\beta = \hat{\beta} \neq 0$ is true, then

$$\frac{N - q - \sum_{m=1}^M p_m}{\sum_{m=1}^M p_m (N - q - 1)} C_N(\hat{\delta}) \sim F_{\sum_{m=1}^M p_n, N-q-\sum_{m=1}^M p_n, C_N(\hat{\delta})}. \tag{16}$$
i.e. a non-central $F$ distribution with non-centrality parameter $C_N(\delta)$. Therefore

$$\Pr \left( \frac{F_{\sum_{m=1}^{M} p_m N - q - \sum_{m=1}^{M} p_m C_N(\delta)}}{F_{\sum_{m=1}^{M} p_m N - q - \sum_{m=1}^{M} p_m \alpha}} > \frac{f_{\sum_{m=1}^{M} p_m N - q - \sum_{m=1}^{M} p_m \alpha}}{f_{\sum_{m=1}^{M} p_m N - q - \sum_{m=1}^{M} p_m \alpha}} \right) = \text{Power},$$

(14)

where $F_{\sum_{m=1}^{M} p_m N - q - \sum_{m=1}^{M} p_m C_N(\delta)}$ represents a random variable following a non-central $F$ distribution with degrees of freedom $\sum_{m=1}^{M} p_m$ and $N - q - \sum_{m=1}^{M} p_m$ and non-centrality parameter $C_N(\delta)$. Note that Liao et al. did not provide any mathematical proofs for the distribution of the test statistic.

In this paper, we further suggest an alternative distribution for $C_N(\delta)$, see Corollary 1 below, and provide certain mathematical derivations in Appendix C.

**Corollary 1.** According to Lemma 1 under a finite sample, the test statistic $C_N(\delta) = N \hat{\beta}^T \sum_{j=1}^{M} \hat{\beta} \sim \text{T}^2_{\sum_{m=1}^{M} p_m N}$

This distribution can be defined by

$$C_N(\delta) = N \hat{\beta}^T \sum_{j=1}^{M} \hat{\beta} \sim \text{T}^2_{\sum_{m=1}^{M} p_m N} = \frac{\sum_{m=1}^{M} p_m (N)}{N - \sum_{m=1}^{M} p_m + 1} \sum_{m=1}^{M} p_m N - \sum_{m=1}^{M} p_m + 1$$

under $H_0$. The corresponding type-I error rate ($\alpha$) can be defined by

$$\Pr \left( \frac{F_{\sum_{m=1}^{M} p_m N - \sum_{m=1}^{M} p_m + 1} > f_{\sum_{m=1}^{M} p_m N - \sum_{m=1}^{M} p_m + 1, \alpha}}{f_{\sum_{m=1}^{M} p_m N - \sum_{m=1}^{M} p_m + 1}} \right) = \alpha.$$  

(15)

We reject $H_0$ if

$$\frac{F_{\sum_{m=1}^{M} p_m N - \sum_{m=1}^{M} p_m + 1} > f_{\sum_{m=1}^{M} p_m N - \sum_{m=1}^{M} p_m + 1, \alpha}}{f_{\sum_{m=1}^{M} p_m N - \sum_{m=1}^{M} p_m + 1}}$$

at a significance level of $\alpha$, respectively. In addition if $H_1$: $\beta = \hat{\beta} \neq 0$ is true, then the power function can be defined by

$$\Pr \left( \frac{F_{\sum_{m=1}^{M} p_m N - \sum_{m=1}^{M} p_m + 1, C_N(\delta)} > f_{\sum_{m=1}^{M} p_m N - \sum_{m=1}^{M} p_m + 1, \alpha}}{f_{\sum_{m=1}^{M} p_m N - \sum_{m=1}^{M} p_m + 1}} \right) = \text{Power}$$

(16)

respectively. Simulation study results in Section 3 show that the proposed test statistics provide better estimates for both power and coverage probability than the test statistic of Liao et al. (2016) when the sample size is small.

### 2.4 Power-Based Sample Size Calculation

The power-based sample size calculation method should only be used if the goal of the study is to perform a hypothesis test as is typical in a confirmatory study. This method requires a working knowledge of the standardized proximal effect sizes of intervention categories (i.e. $b_m(d; \delta_m) = Z_m \delta_m$, where $\delta_m = \beta_m / \sigma$, for $m = 1, \ldots, M$) as input parameters. Thus, given the desired power (i.e., Power, in the above equations) and minimum detectable standardized $\beta$ (or) intended, the sample size $N$ can be computed by solving for either equation (8), (14), or (16), depending on the choice of test statistic. For example, assuming a linear-plateau trend, $\delta$ can be derived by the standardized initial ($b_m(d; \delta_m)$) and average ($\frac{1}{D - (d_j - 1) \sum_{d=1}^{D} b_m(d; \delta_m)}$) proximal effect sizes and the day $d_{\text{turn}}$ reaching turning point, where category-$m$ is added on day $d_j$, for $m = 1, \ldots, M$ and $j = 0, 1, \ldots, k$. Therefore, the calculated $N$ is the minimum integer that gives the estimated power not lower than its nominal value. In a study, different intervention components may have different number of category and different effect sizes, resulting in different sample sizes calculated.

### 2.5 Precision-Based Sample Size Calculation

Due to the novelty and recency of MRT, prior information on the proximal effects of the individual categories are often limited. Hence, conducting a pilot MRT to assess the feasibility and acceptability of the intervention categories can benefit researchers before conducting the full-scale study, similar to pilot studies for sequential multiple assignment randomized trials (SMARTS).

In order to operationalize the sample size calculation for pilot MRT, we suggest the sample size to be calculated in order to achieve certain level of accuracy or precision for the estimates of $\beta$’s; see, e.g., Kelley et al. or Maxwell et al. for discussions in the classical settings. The rationale and benefit of this approach in the relatively recent context of pilot SMARTs has been described in Yan et al.

For the precision-based method, based on the test statistic of Liao et al. with Hotelling’s $T^2$ distribution in equation (14), which assumes a small sample size $N$, we define the coverage probability or confidence level $(1 - \alpha)$ in terms of sample size $N$
and precision $\hat{\beta} - \beta$ for estimator $\hat{\beta}$.

$$\Pr\left(0 < (\hat{\beta} - \beta)^{\top} \Sigma_{\hat{\beta}}^{-1} (\hat{\beta} - \beta) < \frac{\sum_{m=1}^{M} p_m (N - q - 1)}{N (N - q - \sum_{m=1}^{M} p_m)} f_{\sum_{m=1}^{M} p_m, N - q - \sum_{m=1}^{M} p_m, a'} = 1 - \alpha, \right.$$

(17)

assuming $N > q + \sum_{m=1}^{M} p_m$. Let $\beta^* - \hat{\beta}$ denotes the pre-specified desired precision and $\Sigma_{\beta}^*$ denote the covariance matrix for $\hat{\beta}$ at $\hat{\beta} = \beta^*$. Hence $N$ can be calculated by solving the following equation,

$$(\beta^* - \hat{\beta})^{\top} (\Sigma_{\beta}^*)^{-1} (\beta^* - \hat{\beta}) > \frac{\sum_{m=1}^{M} p_m (N - q - 1)}{N (N - q - \sum_{m=1}^{M} p_m)} f_{\sum_{m=1}^{M} p_m, N - q - \sum_{m=1}^{M} p_m, a'}$$

(18)

In other words, $N$ is computed by limiting the upper bound of the random quantity $(\hat{\beta} - \beta)^{\top} \Sigma_{\hat{\beta}}^{-1} (\hat{\beta} - \beta)$ not higher than a pre-specified value, i.e. $(\beta^* - \hat{\beta})^{\top} (\Sigma_{\beta}^*)^{-1} (\beta^* - \hat{\beta})$. Note that $N$ is varied only due to $\beta^* - \hat{\beta}$ and everything else is fixed in equation (18). Under different test statistics in equations (4) and (16), $N$ can be calculated respectively using

$$(\beta^* - \hat{\beta})^{\top} (\Sigma_{\beta}^*)^{-1} (\beta^* - \hat{\beta}) > \frac{1}{N} \tilde{\chi}^2_{\sum_{m=1}^{M} p_m, a'}$$

(19)

and

$$(\beta^* - \hat{\beta})^{\top} (\Sigma_{\beta}^*)^{-1} (\beta^* - \hat{\beta}) > \frac{\sum_{m=1}^{M} p_m (N - q - 1)}{N (N - \sum_{m=1}^{M} p_m + 1)} f_{\sum_{m=1}^{M} p_m, N - \sum_{m=1}^{M} p_m + 1, a'}$$

(20)

The test statistic with $\chi^2$ distribution in equation (19) assumes a large $N$. $N$ can be computed by selecting the minimum value that gives the estimated coverage probability not lower than its nominal value ($1 - \alpha$). Note that given the other quantities are the same, $N$ increases as the magnitude of $| \beta^* - \hat{\beta} |$ decreases (i.e. estimate becomes more precise).

## 3 | DIAMANTE STUDY WITH STUDENT POPULATION EXAMPLE

A smaller study involving the DIAMANTE app and text-messages was already conducted in a university student population[22], where the intervention components, message categories, and primary outcome are the same as the main DIAMANTE study among co-morbid diabetes and depression patients described in Section 2.1. It includes 93 undergraduate and postgraduate students from the University of California, Berkeley. Only 27 of them received the adaptive intervention message program while the remaining 66 participants received the uniform random intervention message program. The study period was 45 days and thus there are 44 decision time points and proximal outcome measures (change in step counts from yesterday on each of days 2 to 45). In this section, we use the results from this student dataset to demonstrate the proposed sample size calculator for the FlexiMRT design. Note that the proposed sample size calculator is only applicable to the uniform random intervention group.

For the power analysis purpose, the proximal effects of the message categories are estimated using only the complete cases in the dataset and we assume 100% availability as reasoned in Section 2.1. For each participant, we delete the days when the messages were not sent due to systematic errors or when the outcome measures were not collected due to non-respond of the participant. It is important that the data collection systems are able to distinguish between missing outcome due to technical issue that prevents the message from being sent and disengagement (i.e. the message sent but the participant did not respond[23]). However, the technical missingness can be dealt with using imputation[23].

Here, we give an example using the Motivational Message component. It has three active intervention categories ($M = 3$), which were all proposed before the trial. The randomization probability ($\pi$) for each category (including the control category) was 0.25. According to the working model of $Y_{id}$ defined in Section 2.2, we considered the constant ($q = p_m = 1$), linear ($q = p_m = 2$) and quadratic ($q = p_m = 3$) trends for the intervention categories, where $m = 1, 2, 3$. The regression coefficients ($\beta$) can be estimated by equation (4). We denote the initial and average proximal effect sizes of the intervention categories using $\beta^0$ and $\hat{\beta}$ respectively, where $\hat{\beta}$ is defined by equation (1). The corresponding standardized effect sizes are denoted by $\delta^0 (\beta^0 / \hat{\beta})$ and $\delta^0 (\beta^0 / \hat{\sigma})$ respectively, where $\hat{\sigma}$ is the average of the residual variance over all the decision time points. Similarly, the standardized precision of the initial and average proximal effect sizes are denoted by $\Delta \delta^0 (\Delta \beta^0 / \hat{\beta})$ and $\Delta \delta^0 (\Delta \beta^0 / \hat{\sigma})$ respectively.

Under the constant trend assumption, the initial and average proximal effect sizes and the corresponding standardized effect sizes are the same. Note that this is because the effect sizes are marginalized over the study days and the historical variables not considered in the model (see Qian et al[23]). We have $\beta = (357, 589, 526)^\top = \beta^0 = \hat{\beta}$ and $\hat{\sigma} = 4869$ or
\[ \delta^0 - \delta^0 = (0.073, 0.121, 0.108)^T \], where the second category ‘self-efficacy’ message is statistically significant (p=0.048). Assuming uniform randomization, 100% availability, 44 decision time points, 5% type-I error rate, 80% power, and using the Chi-squared distributed test statistic \( \chi^2 \), the sample size required to detect the estimated standardized proximal effect size is 113. If we use the more conservative Hotelling’s T-squared distributed test statistic \( T^2 \), the sample size required is 117. For the uniform random intervention group, a message component with three intervention categories, a sample size of 117 participants is sufficient to detect the average standardized proximal effect sizes of the categories i.e. 0.073, 0.121 and 0.108, given the number of decision time points 44, at 5% type-I error rate and 80% power. This calculation has been mentioned by Figueroa et al. (2021).\[12\]

Though the student version DIAMANTE study did not consider adding messages during the study period, the analysis results can be also used to demonstrate the sample size calculation when more messages (pre-determined at the start of trial) are added during the study (i.e. FlexiMRT). For example, we assume constant trends for the proximal effect sizes for the motivational message categories, and two categories are added at halfway (i.e. the 23rd decision point). Suppose we use the same proximal effect sizes for the first three categories and \( \delta \) estimated above, and assume the proximal effect sizes are 300 for both categories, 100% availability, 5% type-I error rate, and 80% power, Hotelling’s T-squared distributed test statistic (i.e. equation \( T^2 \)) calculates a sample size of 163. Suppose the availability is not always 100%, for example, some participants may turn off the activity notification for some particular days. The calculated sample sizes are 230 and 319 for 70% and 50% expected availabilities, respectively.

Suppose we pool the individual intervention categories in the intervention components, so that there are effectively only two categories, similar to the ‘HeartSteps’ study. An important assumption would be that the effect sizes of each individual intervention messages within the components are equal. In this study, the standardized average proximal effect size of Motivational Message with two categories (i.e. no message versus pooled intervention messages) is 0.101 based on constant trend. This proximal effect is not significant (i.e. \( p = 0.051 \)). The calculated sample size that detects this effect at 80% power, 5% type-I error rate and 100% availability is 72. In comparison, if we use the non-pooled three categories in the Motivational Message, which are ‘benefit’, ‘self-efficacy’ and ‘opportunity’, the corresponding standardized average proximal effect sizes are 0.073, 0.121 and 0.108 respectively, where ‘self-efficacy’ effect is significant (i.e. \( p = 0.048 \)). Although the calculated sample size to detect these three intervention message categories at the same time (i.e. 117) is 60% higher than detecting the combined intervention categories, this multi-category approach can be used to recognize the effect size differences among the individual message types, which cannot be recognized by the two-category approach.

Assuming linear and quadratic trends, we have the initial proximal effect size vectors \((609, 441, 869)^T\) and \((662, 718, 1394)^T\), the average proximal effect size vectors \((338, 598, 512)^T\) and \((378, 621, 530)^T\), \( \bar{\delta} = 4867 \) and \( 4866 \), respectively. The corresponding standardized initial proximal effect size vectors are \((0.125, 0.091, 0.178)^T\) and \((0.136, 0.148, 0.287)^T\), while the corresponding standardized average proximal effect size vectors are \((0.069, 0.123, 0.105)^T\) and \((0.078, 0.128, 0.109)^T\), respectively. For the quadratic trend, the shape of the proximal effect size of the first message category ‘benefit’ is concave down with local maximum point at the 36-th decision time point after the study started while both the second ‘self-efficacy’ and third ‘opportunity’ message categories are concave up with local minimum points at the 17-th and 26-th decision time points, respectively, after the study started. Therefore, given the number of decision time points 44 and 100% availability, at 5% type-I error rate, and 80% power, the calculated sample sizes for both the linear and quadratic trends are 116 and 101 respectively based on the Hotelling’s T-squared distributed test statistics, i.e. equation \( T^2 \). Note that the estimated initial proximal effect sizes using the quadratic trend were larger than the effect sizes using the constant and linear trends, and hence the required sample size under the quadratic trend assumption turns out to be the smallest among the three considered trends.

Figure 3 shows the average steps change from yesterday in the study, and by observation, it is likely that the proximal effect sizes follow the constant trend. We have demonstrated some examples of sample size calculation using the power-based methods. Here we also demonstrate an example using a precision-based method, under the constant trend assumption for the precision of the proximal effect sizes. We specify the standardized precision for both the initial and average proximal effect sizes to be \( \Delta \delta_0 = \Delta \delta_0 = (0.073, 0.121, 0.108)^T \). Note that unlike the power-based method, the precision-based method does not consider the possible proximal effect sizes, and it only considers the precision or margin of error of the proximal effect size of each intervention category. Thus, given uniform randomization, 100% availability, 44 decision time points, 95% coverage probability, and using the Hotelling’s \( T^2 \) test statistic \( T^2 \), the sample size required to cover the specified proximal effect size precision is 86.
4 | SIMULATION STUDY

In this section, we present simulation studies to investigate the performance of the proposed sample size formulas based on power (i.e., equations (8), (13) and (16)) and precision (i.e., equations (19), (18) and (20)). For each simulation study, we generate 1000 Monte Carlo data sets with a desired power at 80% and a Type-I error rate at \( \alpha = 0.05 \). The performance of each sample size formula is measured by comparing the difference between the formulae and Monte Carlo estimates of either power or coverage probability, based on the calculated sample size \( N \). We consider the situations of both with and without mis-specifications of the outcome model.

The Monte Carlo data generation steps are given below. These steps include generating the random variables availability indicators \( I_{id} \), intervention categories \( A_{id} \), error term \( e_{id} \) and outcome measure \( Y_{id} \) for each participant \( i \), \( i = 1, \ldots, N \), on each day \( d \), \( d = 1, \ldots, D \), over the study period. In this section, we have \( D = 180 \) and \( 90 \) and the number of decision time point per day is 1, i.e. \( T = 1 \), since each participant receives each of the intervention components once per day.

**Step 1.** The availability indicators \( I_{id} \) are generated as binomial random variables, i.e. \( I_{id} \sim \text{Binomial}(r_{id}, 1) \) for each \( i \) and \( d \). Although the DIAMANTE study assumes that each individual is available at each decision time point, we fix the availability rates at 100% and 70% in our simulations, for more comprehensive illustrations.

**Step 2.** The intervention categories \( A_{id} = (A_{1id}, \ldots, A_{M_d id}) \) are generated as multinomial random variables, i.e. \( A_{id} \sim \text{Multinomial}(1, \sum_{m=1}^{M_d} \pi_{md}, \pi_{1id}, \ldots, \pi_{(\sum_{m=1}^{M_d} M_d) id}) \). Note that \( \pi_{md} \) is the randomization probability of intervention category-\( m \) on day \( d \) while \( 1 - \sum_{m=1}^{M_d} \pi_{md} \) is the randomization probability of control category. We consider \( M=4 \) intervention categories, where \( M_0 = 3 \) categories are added at the beginning of the study (consistent with the Motivational Message component in DIAMANTE study) and \( M_1 = 1 \) category is added at half-way of the study. The initial randomization probability of either the control or intervention category is 0.25 and the probability changes to 0.2 after a new category is added.

**Step 3.** The error term \( e_i = (e_{i1}, \ldots, e_{id})^\top \) are generated by the multivariate normal distribution, i.e., \( e_{id} \sim \text{MVN}(0_{D \times 1}, \text{COV}(e_{id})) \), where \( \text{COV}(e_{id}) \) is the covariance matrix of \( e_{id} \) with a dimension of \( D \times D \) with diagonal entries \( \sigma^2 \) and off-diagonal entries \( \rho \sigma^2 \).

**Step 4.** The outcome measure \( Y_{id} \) are computed by \( Y_{id} = X_{id}^\top \theta + e_{id} \), where \( \theta = (\alpha^\top, \beta^\top)^\top \), \( i = 1, \ldots, N \) and \( d = 1, \ldots, D \). We have \( X_{id} = [B_{id}^\top, (A_{1id} - \pi_{1id})Z_{id}^\top, \ldots, (A_{M_d id} - \pi_{M_d id})Z_{id}^\top] \), where we have the constant, linear, quadratic or linear-plateau trends (see Section 2.2) for both \( B_{id} \) and \( Z_{md} \) at \( m=1, 2, 3 \) and 4. We consider the linear-plateau trend for the standardized proximal effect sizes of the intervention categories, see equation (2), at \( T = 1 \). We define \( d_{\text{turn}}^m = 28 \) for the intervention categories added at the beginning of the study, i.e. \( m=1, 2 \) and 3 while we define \( d_{\text{turn}}^m = 118 \) when \( D = 180 \) or \( d_{\text{turn}}^m = 73 \) when \( D = 90 \) for the intervention category added at the half-way through the study, i.e. \( m=4 \). In this simulation study, we have \( B_{id} = (1, \min[28 - 1, d - 1]) \).

On day \( d \), the standardized proximal effect size of the intervention category-\( m \) satisfies \( \delta_m(d, \delta_m) = Z_{md}^\top \delta_m \), where \( \delta_m = \beta_m / \sigma \) and \( m = 1, \ldots, 4 \). Note that we have \( \delta^2 = \sigma^2 \). For \( m=1, 2 \) and 3, we define: a) the initial standardized proximal effect sizes \( (\delta_m(1, \delta_m)) \) to be 0.001; b) the precision (standardized margin of error) of initial proximal effect sizes \( (\delta_m(1, \delta_m) - \delta_m(1, \delta_m)) \) to be 0.001; c) the average standardized proximal effect sizes \( \frac{1}{D} \sum_{d=1}^{D} \delta_m(d, \delta_m) \) to be 0.1 and 0.06; and d) the precision of the average standardized proximal effect sizes \( \frac{1}{D} \sum_{d=1}^{D} \delta_m(d, \delta_m) \) to be 0.10 and 0.06. Similarly, for \( m=4 \), the initial standardized proximal effect size, the precision (standardized margin of error) of initial proximal effect size, the average standardized proximal effect size and the precision of the average standardized proximal effect size are defined by \( \delta_m([0.5 D] + 1, \delta_m) = 0.001, \delta_m([0.5 D] + 1, \delta_m) - \delta_m([0.5 D] + 1, \delta_m) = 0.10, \frac{1}{D - [0.5 D]} \sum_{d=[0.5 D] + 1}^{D} \delta_m(d, \delta_m) = 0.01 \) and 0.06, and \( \frac{1}{D - [0.5 D]} \sum_{d=[0.5 D] + 1}^{D} \delta_m(d, \delta_m) = 0.10 \) and 0.060 respectively.

4.1 | Correctly specified working model

This section assumes that the working models for outcome measure \( Y_{id} \) are correctly specified. The Table I presents a list of sample sizes calculated by the power-based method, with the corresponding formulae and Monte Carlo estimated powers. Similarly, Table II presents a list of sample sizes calculated by the precision-based method, with
the corresponding formula-based and Monte Carlo estimated coverage probabilities. We observe that both the Monte Carlo and formula-based estimates of either power or coverage probabilities are almost the same, except for the power-based method when the total decision time points is 180 and the test statistic is Hotelling’s $T^2_{\sum_{m=1}^q N_q^{m-1}}$. We further illustrate the interpretation of the sample sizes, powers and coverage probabilities calculated in Tables 1 and 2. For example, in Table 1 given 100% availability, a total number of decision time points of 180, a test statistic following the Hotelling’s $T^2_{M_p,N}$ distribution, at 5% level of significance, detecting the average standardized proximal effect size of 0.1 for each of the intervention categories at a sample size of 54 achieves a power of 80%. The second example is from Table 2 given 100% availability, a total number of decision time points of 180, a test statistic following the Hotelling’s $T^2_{M_p,N}$ distribution and a sample size of 59, the average standardized proximal effect size for each of the intervention categories achieves a precision of 0.1 and 95% coverage probability.

We further consider the effect of the number of intervention categories ($M = 1, \ldots, 10$) on the sample size. Assuming all the intervention categories are added at the start of the study, we calculate the power-based sample size using inputs set at at $a = 0.05$, power = 80%, $D = 180$, $T = 1$ for one decision time point per day, standardized proximal effect size of 0.1 and initial standardized proximal effect size of 0.001 for each intervention category, linear-plateau trend with turning point on the 28-th day, and 100% availability. The error term of the corresponding statistical model follows a standard normal distribution. The test statistics follow Hotelling’s $T^2_{\sum_{m=1}^q N_q^{m-1}}$. Figure 4 shows the sample size ($N$) increases with the number of intervention categories ($M$) in a particular component.

In general, when the working model is correctly specified, the proposed sample size calculator provides accurate power and coverage probability estimated. In the following sub-sections, we calculate sample sizes by considering some working model mis-specifications for outcome $Y_{id}$.

### 4.2 Mis-specified trend for proximal effect

We calculate the sample sizes and the corresponding formulated powers or coverage probabilities assuming either the constant, linear or quadratic trend for the proximal effect of the intervention categories. However, the corresponding Monte Carlo (MC) powers or coverage probabilities are estimated from the MC datasets generated using a linear-plateau trend (i.e., we let the true trend be linear-plateau).

The shape differences among the constant, linear, quadratic and linear-plateau trends can be observed in Figure 5. It presents the plots of time (days) versus estimated standardized proximal effect sizes ($Z^T_{md} \delta_m$) based on different trends, for the intervention categories proposed both at the beginning (i.e. $m=1, 2, 3$) and at half-way (i.e. $m=4$) of the study. The average standardized proximal effect size ($\frac{1}{180} \sum_{d=1}^{180} Z^T_{md} \delta_m$ for $m=1, 2, 3$ and $\frac{1}{90} \sum_{d=91}^{180} Z^T_{md} \delta_m$ for $m=4$) is 0.1 and the initial standardized proximal effect size ($\delta_m(1, \delta_m)$ for $m=1, 2, 3$ and $\delta_m(91, \delta_m)$ for $m=4$) is 0.01 for each of the intervention categories.

Table 3 presents a list of sample sizes calculated by the power-based method, with the corresponding formula-based and Monte Carlo estimated powers. We observe that the formula-based power estimates are very close to the desired power 80%. The Monte Carlo estimated powers are lower than 80%, due to the smaller sample sizes (under-powered) calculated using the mis-specified proximal effect trends compared to the sample sizes in Table 4 that are calculated based on the correct trend. The difference between the corresponding sample sizes between these two tables are the largest when assuming the constant trend. The sample sizes are similar between the linear and quadratic trends. The large sample size differences are due to the large shape differences, see Figure 5. These findings are different from the simulation results of Liao et al. (2011), because they used the mis-specified proximal effect trends, which have similar shape to the real ones. Another reason is that the proposed method also considers adding categories during the study period. Similarly, Table 4 presents a list of sample sizes calculated by the precision-based method, with the corresponding formula-based and Monte Carlo estimated coverage probabilities. We observe that the formula-based coverage estimates are very close to the desired value 95%. For the MC estimates, the mis-specified quadratic trend performs best with slightly higher values, followed by the linear trend, while the constant trend performs the worst with much lower values.

### 4.3 Mis-specified number of intervention categories

In this section, we calculate the sample sizes and the corresponding formulated powers and coverage probabilities, where the numbers of intervention categories added both at the beginning ($M_0$) and half-way through ($M_1$) are mis-specified. Note that $M = M_0 + M_1$. The first mis-specification considers the case when both $M_0$ and $M_1$ are mis-specified, where only one intervention category is added initially, i.e. $M_0 = 1$ and $M_1 = 0$. This is exactly the same as Liao et al. (2011) under power-based
approach. The second mis-specification considers that all the categories added at the beginning of the study, i.e. \( M_0 = 3 \) and \( M_1 = 0 \). Note that the MC datasets are generated assuming the correctly specified number of categories, \( M_0 = 3 \) and \( M_1 = 1 \) (i.e. the true design), and the MC powers and coverage probabilities are estimated accordingly.

Table 5 presents a list of sample sizes calculated by the power-based method, with the corresponding formula-based and Monte Carlo estimated powers. We observe that the formula-based power estimates are very close to the desired power 80%. The Monte Carlo estimated powers are lower than 80%, due to smaller sample sizes (under-powered) calculated based on the mis-specified \( M \), which are lower than the true values, compared to the sample sizes in Table 1 that are calculated based on the correct \( M \). The difference between the corresponding sample sizes between these two tables are the largest when assuming mis-specification of \( M_0 = 1 \) and \( M_1 = 0 \), followed by \( M_0 = 3 \) and \( M_1 = 0 \). The large sample size differences are due to the mis-specified \( M \) values being further away from the real values. Similarly, Table 6 presents a list of sample sizes calculated by the precision-based method, with the corresponding formula-based and Monte Carlo estimated coverage probabilities. We observe that the formula-based coverage estimates are very close to the desired value 95%. The Monte Carlo estimates are lower than the desired values when the mis-specified \( M \) is smaller than the true \( M \).

Based on both Tables 5 and 6, we conclude that for a particular intervention component with multiple categories, where some are proposed half-way through the study, underestimating the number of intervention categories added either initially or half-way through, or both, calculates a lower sample size \( N \) that underestimates either the power or coverage probability.

4.4 Mis-specified variance of error term

In this section, we calculate the sample sizes and the corresponding formulated power or coverage probability under a situation that the error term \( \epsilon_i = (\epsilon_{i1}, \ldots, \epsilon_{id})^T \) are generated by the multivariate normal distribution, i.e., \( \epsilon_i \sim \text{MVN}(0, \text{COV}(\epsilon_i)) \), where \( \text{COV}(\epsilon_i) \) is the covariance matrix of \( \epsilon_i \) with dimension of \( D \times D \). Instead of a constant variance \( \sigma^2 \), we define the variance of \( \epsilon_{id} \) to be \( \sigma^2_d \), for \( d = 1, \ldots, D \), which varies in \( d \) over the study. See Figure 6 for both the linearly increasing (i.e. \( \sigma^2_d = 0.9^d + 0.0021 \times (d - 1) \)) and decreasing (i.e. \( \sigma^2_d = 1.19^d - 0.0021 \times (d - 1) \)) trends of \( \sigma^2_d \). Note that for both trends, we have \( \overline{\sigma}^2 = \frac{1}{D} \sum_{d=1}^{D} \sigma^2_d = 1 \).

Table 7 presents a list of sample sizes calculated by the power-based method, with the corresponding formula-based and Monte Carlo estimated powers. We observe that the formula-based power estimates are very close to the desired power 80%. The Monte Carlo estimated powers are also close to the desired values under both the increasing and decreasing trends of \( \sigma^2_d \). Similarly, Table 8 presents a list of sample sizes calculated by the precision-based method, with the corresponding formula-based and Monte Carlo estimated coverage probabilities. The formula-based coverage probability estimates are very close to the desired value 95%. The Monte Carlo estimates are close to the formula-based estimates under both the increasing and decreasing trends of \( \sigma^2_d \). Therefore, based on the simulation results, we observe that the proposed sample size calculator is still accurate when the outcome measure variances are not constant over the study period.

4.5 Mis-specified autocorrelation of error term

In this section, we calculate the sample sizes and the corresponding formulated power or coverage probability, when the error term \( \epsilon_i = (\epsilon_{i1}, \ldots, \epsilon_{id})^T \) follows a normal AR(1) process, e.g., \( \epsilon_{id} = \phi \epsilon_{i,d-1} + \nu_{id} \), where \( \phi = 0.5 \) and \( -0.5 \) and \( \nu_{id} \) are i.i.d Normal(0, 0.75). Note that \( \epsilon_i \) follows a multivariate normal distribution with standardized normal for marginal distribution and non-zero correlation coefficients.

Table 9 presents a list of sample sizes calculated by the power-based method, with the corresponding formula-based and MC estimated powers. We observe that both the formula-based and MC power estimates are very close to the desired power 80%. Similarly, Table 10 presents a list of sample sizes calculated by the precision-based method, with the corresponding formula-based and Monte Carlo estimated coverage probabilities. We observe that both the formula-based and MC coverage probability estimates are very close to the desired value 95%.

Therefore, based on the simulation results, we observe that the proposed sample size calculator can be still accurate regardless of the autocorrelation structure for the outcome measures over time.
4.6 | Mis-specified trend of availability

It is common to calculate sample size under a simple assumption of constant trend for availability. However, the availability trend may not actually be constant in real data. Here, we demonstrate the robustness of the sample sizes, when the corresponding formulated power or coverage probability values are calculated based on a constant trend availability rate 70% i.e. $r_d = 0.7$. The datasets are generated based on linearly increasing (i.e. $r_d = 0.5+0.0022\times(d-1)$) and decreasing (i.e. $r_d = 0.9-0.0022\times(d-1)$) availability trends, for $d=1,\ldots,D$, where we have $\bar{r} = \frac{1}{D}\sum_{d=1}^{D} r_d = 0.7$, see Figure 7.

Table 11 presents a list of sample sizes calculated by the power-based method, with the corresponding formula-based and MC estimated powers. We observe that both the formula-based and MC power estimates are very close to the desired power 80%. Similarly, Table 12 presents a list of sample sizes calculated by the precision-based method, with the corresponding formula-based and MC estimated coverage probabilities. Both the formula-based and MC coverage probability estimates are very close to the desired value 95%.

5 | DISCUSSION

In this paper, we propose a FlexiMRT design. Within this framework, it is possible to allow intervention categories of some components (e.g., message types) to be added not only at the beginning, but also later during the study period as in a platform clinical trial. We derive the novel sample size calculation methods for FlexiMRT design based not only on power but also on the precision of proximal effect size estimates. For the power-based method, the required sample size is calculated to detect a standardized effect size at a nominal power and a specified significance level. For the precision-based method, the required sample size is calculated to achieve a precision at a nominal coverage probability. Our simulation study shows that the sample sizes obtained by the proposed method give the Monte Carlo estimates of power and coverage probability close to the corresponding formulated estimates, given that the specified working model is not too far from the true one. A sample size calculated by incorrectly using the MRT sample size calculator that only considers two-category components (i.e. Liao et al.11) does not provide sufficient power to detect the proximal effects of the components with more than one intervention category.

As mentioned, the DIAMANTE study is the primary motivation behind this paper. We have shown how the proposed sample size calculation method can be applied for the uniform random intervention group of the DIAMANTE study with university student population. However, it is worth noting that the calculated sample size is not aiming to select the optimal category, but to detect whether at least one of the active intervention categories is more effective than the control category. At the data analysis stage, we can still compare the proximal main (or moderated) effects of the intervention messages at different time windows over the study period.

We are currently collecting data through the DIAMANTE study, and performing interim data analysis, which can be used to further improve the experimental design, e.g., developing just-in-time adaptive intervention strategies for the intervention messages or applying reinforcement learning algorithm on randomization probabilities on the adaptive intervention group. When the data collection is completed, we can apply linear mixed model approach to investigate the between-person heterogeneity of the proximal effect of an intervention component. This is similar to the method of Qian et al.15. Based on the data analysis results of Bidargaddi et al.13, we could investigate whether an intervention category of a message component is more effective at midday on weekends than other decision time points. The approach by Boruvka et al.10 can also be used to identify the moderator effect of intervention categories of message components between the current and past decision time points on a subsequent response.

The proposed FlexiMRT design has also been very recently applied to the “Stay Well at Home” study, where the intervention message categories are added at the beginning of the study; see Figueroa et al.15 for the study protocol. This study involves sending contextual text-messages to people, to manage their mental health while maintaining social distances in order to avoid COVID-19 transmission. The proximal outcome is mood rating (scored 0-9), which is measured three hours after the messages are sent. This outcome measure can be categorized into a dummy variable (e.g., 6 or below versus above 6). An important future work would be to develop a data analysis method, similar to the approach of Qian et al.15 for binary outcomes, under the proposed FlexiMRT design. We aim to pursue this in near future.

The proposed FlexiMRT design allows a specified number of new intervention message categories to be added half-way through the study. This design can be further extended using a decision-theoretic framework similar to Lee et al.50 to investigate when to add or not add a message categories based on the observed proximal outcomes. During the study period, a message category will be dropped if the proximal effect size is below the specified lower boundary, or the study will be stopped if effect
size of that category is above the specified upper boundary, at a particular time point. Otherwise, the intervention message category will be continued to the end of the study. The advantage of such an approach is mentioned by Magirr et al. (2012)\cite{Magirr2012}. It will improve the efficient evaluation of each proposed intervention message category under an MRT design.

The proposed sample size calculator of the FlexiMRT design can be extended to allow for adaptive randomization probabilities, determined by the proximal outcomes and message categories at previous decision time points, e.g., Wason and Trippa (2014)\cite{Wason2014}, with the aim of sending more effective messages to the participants. In other words, the sequential outcomes and randomization probabilities of the current message categories depend on the outcomes and message categories from previous decision time points, in order to achieve experimental objectives. In this type of design, we can estimate not only the current proximal effect, but also the delayed effect, of each intervention category of a particular message component. Similar to Dempsey et al. (2020)\cite{Dempsey2020}, we can extend the proposed FlexiMRT design to also consider stratifying strategies, where the inverse probability weighting techniques may be incorporated into the test statistic construction, which can be used to deal with more complex dependencies, i.e. the proximal outcome may depend on both treatments of today and yesterday. Another possible future research direction is extending the sample size calculator to also account for clustered effects. For example, it may be likely that the participants’ physical activity performance can be positively influenced by their peers in the same group.

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Conflict of interest

The authors declare no potential conflict of interests.

DATA AVAILABILITY STATEMENT

The students dataset from the adapted DIAMANTE study used to demonstrate the proposed sample size calculators in Section 3 is available from the co-author, Dr. Caroline Figueroa, c.a.figueroa@berkeley.edu, upon reasonable request.

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APPENDIX

A DERIVATION OF THE COVARIANCE MATRIX OF $\hat{\beta}$

This section derives the covariance matrix of the parameter estimator $\hat{\beta}$. First, we derive the expression for equation (5), i.e. $\hat{\theta} = \sum_{d=1}^{D} E (I_{id}X_{id}X_{id}^T)^{-1} \sum_{d=1}^{D} E (I_{id}Y_{id}X_{id})$, in more details. The expectation within the second summation can be...
expressed by

\[
E \left( I_{id} Y_{id} X_{id} \right) = \begin{bmatrix}
E(I_{id} Y_{id} B_d) \\
E(I_{id} Y_{id} (A_{i1d} - \pi_{1d}) Z_{1d}) \\
\vdots \\
E(I_{id} Y_{id} (A_{iM_{id}} - \pi_{M_{id}}) Z_{M_{id}})
\end{bmatrix} \\
= \begin{bmatrix}
E(I_{id} Y_{id} (A_{i1d} - \pi_{1d}) Z_{1d}) \\
E(I_{id} Y_{id} (A_{i1d} - \pi_{1d}) Z_{1d}) \\
\vdots \\
E(I_{id} Y_{id} (A_{i1d} - \pi_{1d}) Z_{1d})
\end{bmatrix} \sum_{j=0}^{k} M_{jd} Z_{\left(\sum_{j=0}^{k} M_{jd}\right)} \\
= \begin{bmatrix}
E(I_{id} E(Y_{id} B_d)) \\
E(I_{id} E(Y_{id} (A_{i1d} - \pi_{1d}) Z_{1d}) \\
\vdots \\
E(I_{id} E(Y_{id} (A_{i1d} - \pi_{1d}) Z_{1d})
\end{bmatrix} \sum_{j=0}^{k} M_{jd} Z_{\left(\sum_{j=0}^{k} M_{jd}\right)} \sum_{j=0}^{k} M_{jd} Z_{\left(\sum_{j=0}^{k} M_{jd}\right)} \\
\tau_d B_d \sum_{j=0}^{k} M_{jd} Z_{\left(\sum_{j=0}^{k} M_{jd}\right)} \\
\tau_d E(Y_{id} (A_{i1d} - \pi_{1d})) Z_{1d} \\
\vdots \\
\tau_d E(Y_{id} (A_{i1d} - \pi_{1d})) Z_{1d}
\end{bmatrix}
\]

where

\[
E(Y_{id} (A_{i1d} - \pi_{1d})) \\
= E \{ B_d \sum_{j=0}^{k} M_{jd} Z_{\left(\sum_{j=0}^{k} M_{jd}\right)} \sum_{j=0}^{k} M_{jd} Z_{\left(\sum_{j=0}^{k} M_{jd}\right)} \}
\]

\[
= \begin{bmatrix}
(A_{i1d} - \pi_{1d}) Z_{1d} \beta_1 \\
\vdots \\
(A_{i1d} - \pi_{1d}) Z_{1d} \beta_M_1 \\
\vdots \\
(A_{i1d} - \pi_{1d}) Z_{1d} \beta_0
\end{bmatrix}
\]

\[
= \begin{bmatrix}
\pi_{1d} (1 - \pi_{1d}) Z_{1d} \beta_1 - \pi_{1d} \pi_{M_{id}} Z_{M_{id}} \beta_M_1 \\
\vdots \\
\pi_{1d} (1 - \pi_{1d}) Z_{1d} \beta_0 \\
\vdots \\
\pi_{1d} (1 - \pi_{1d}) Z_{1d} \beta_M_1
\end{bmatrix}
\]

\[
+ \begin{bmatrix}
\pi_{1d} (1 - \pi_{1d}) Z_{1d} \beta_1 \\
\vdots \\
\pi_{1d} (1 - \pi_{1d}) Z_{1d} \beta_M_1 \\
\vdots \\
\pi_{1d} (1 - \pi_{1d}) Z_{1d} \beta_0
\end{bmatrix}
\]

\[
= \begin{bmatrix}
\pi_{1d} (1 - \pi_{1d}) Z_{1d} \beta_1 \\
\vdots \\
\pi_{1d} (1 - \pi_{1d}) Z_{1d} \beta_M_1 \\
\vdots \\
\pi_{1d} (1 - \pi_{1d}) Z_{1d} \beta_0
\end{bmatrix}
\]
Hence, in the similar way, we have

\[
E(Y_{i,d}(A_{1}^{k}(\sum_{j=0}^{k} M_{j})d - \pi_{(\sum_{j=0}^{k} M_{j})d}))
\]
\[
= \left[ -\pi_{(\sum_{j=0}^{k} M_{j})d} \beta_{1} - \cdots - \pi_{(\sum_{j=0}^{k} M_{j})d} \beta_{M} \right]
\]
\[
+ \left[ -\pi_{(\sum_{j=0}^{k} M_{j})d} \beta_{(M+1)} - \cdots - \pi_{(\sum_{j=0}^{k} M_{j})d} \beta_{(M+1)} \right]
\]
\[
\vdots
\]
\[
+ \left[ -\pi_{(\sum_{j=0}^{k} M_{j})d} \beta_{(\sum_{j=0}^{k} M_{j})d} + \pi_{(\sum_{j=0}^{k} M_{j})d} (1 - \pi_{(\sum_{j=0}^{k} M_{j})d}) \beta_{(\sum_{j=0}^{k} M_{j})d} \right]
\]

The expectation part for the first summation of equation (5) can be expressed by

\[
E(I_{id}X_{id}X_{id}^\top)
\]
\[
= \tau_d E \left[ \begin{array}{c}
B_d \\
(A_1^{k}d) \pi_{1d} \beta_{1} \\
\vdots \\
(A_1^{k}d) \pi_{(\sum_{j=0}^{k} M_{j})d} \beta_{(\sum_{j=0}^{k} M_{j})d}
\end{array} \right] \left[ \begin{array}{c}
B_d^\top \\
(A_1^{k}d) \pi_{1d} \beta_{1} \\
\vdots \\
(A_1^{k}d) \pi_{(\sum_{j=0}^{k} M_{j})d} \beta_{(\sum_{j=0}^{k} M_{j})d}
\end{array} \right]
\]
\[
= \tau_d E \left[ \begin{array}{cccc}
B_d & B_d^\top & \cdots & B_d^\top \\
0 & (A_1^{k}d) \pi_{1d} \beta_{1} & \cdots & (A_1^{k}d) \pi_{1d} \beta_{1} \\
\vdots & \vdots & \ddots & \vdots \\
0 & (A_1^{k}d) \pi_{(\sum_{j=0}^{k} M_{j})d} \beta_{(\sum_{j=0}^{k} M_{j})d} & \cdots & (A_1^{k}d) \pi_{(\sum_{j=0}^{k} M_{j})d} \beta_{(\sum_{j=0}^{k} M_{j})d}
\end{array} \right]
\]

Thus the estimators of equation (5) is \( \tilde{\theta} = (\tilde{\alpha}^\top, \tilde{\beta}^\top)^\top \), where \( \tilde{\alpha} \) is the first \( q \) elements of \( \tilde{\theta} \) while \( \tilde{\beta} \) is the rest \( \sum_{m=1}^{M} p_{m} \) elements of \( \tilde{\theta} \), i.e.

\[
\tilde{\alpha} = \left( \sum_{d=1}^{D} \tau_d B_d B_d^\top \right)^{-1} \sum_{d=1}^{D} \tau_d B_d^\top \alpha B_d
\]

and

\[
\tilde{\beta} = (\tilde{\beta}_{1}^\top, \cdots, \tilde{\beta}_{M}^\top)^\top, \quad \tilde{\beta}_{1}^\top = (\sum_{d=1}^{D} \tau_d (1 - \pi_{1d}) \beta_{1d}) \left( \sum_{d=1}^{D} \tau_d \right)^{-1}
\]

\[
\tilde{\beta}_{M}^\top = (\sum_{d=1}^{D} \tau_d (1 - \pi_{(\sum_{j=0}^{k} M_{j})d}) \beta_{(\sum_{j=0}^{k} M_{j})d}) \left( \sum_{d=1}^{D} \tau_d \right)^{-1}
\]
Next, we give detail expression for $\sqrt{N}(\hat{\theta} - \bar{\theta})$ by substituting equation (4) for the estimator $\hat{\theta}$, i.e.

$$\sqrt{N}(\hat{\theta} - \bar{\theta}) = \sqrt{N} \left\{ \frac{1}{N} \sum_{i=1}^{N} \sum_{d=1}^{D} I_{id} X_{id} X_{id}^T \right\}^{-1} \left\{ \frac{1}{N} \sum_{i=1}^{N} \sum_{d=1}^{D} I_{id} Y_{id} X_{id} - \bar{\theta} \right\}$$

$$= \sqrt{N} \left\{ \frac{1}{N} \sum_{i=1}^{N} \sum_{d=1}^{D} I_{id} X_{id} X_{id}^T \right\}^{-1} \left\{ \frac{1}{N} \sum_{i=1}^{N} \sum_{d=1}^{D} [I_{id} Y_{id} X_{id} - I_{id} X_{id} \bar{\theta}] \right\}$$

$$= \sqrt{N} \left\{ \sum_{d=1}^{D} E(I_{id} X_{id} X_{id}^T) \right\}^{-1} \left\{ \frac{1}{N} \sum_{i=1}^{N} \sum_{d=1}^{D} [I_{id} X_{id} \bar{\epsilon}_{id}] \right\} + o_p(1).$$

where $o_p(1) \to 0$, $\bar{\epsilon}_{id} = Y_{id} - B_1^{T} \bar{\theta} - (A_{1d} - \pi_{1d}) Z_{1d}^{T} \bar{B}_1 - \cdots -(A_{Md} - \pi_{Md}) Z_{Md}^{T} \bar{B}_M$ and $E(I_{id} X_{id} \bar{\epsilon}_{id}) = 0$. Therefore, the asymptotic covariance matrix of $\hat{\theta}$ (6) can be derived by

$$\Sigma_{\theta} = \sqrt{N} \left\{ \sum_{d=1}^{D} E(I_{id} X_{id} X_{id}^T) \right\}^{-1} E \left\{ \frac{1}{N} \sum_{i=1}^{N} \sum_{d=1}^{D} [I_{id} \bar{\epsilon}_{id} X_{id}] \right\} \sqrt{N} \left\{ \sum_{d=1}^{D} E(I_{id} X_{id} X_{id}^T) \right\}^{-1}$$

$$= \sqrt{N} \left\{ \sum_{d=1}^{D} E(I_{id} X_{id} X_{id}^T) \right\}^{-1} \frac{1}{N} E \left\{ \sum_{i=1}^{N} \sum_{d=1}^{D} I_{id} \bar{\epsilon}_{id} X_{id} \sum_{d=1}^{D} I_{id} \bar{\epsilon}_{id} X_{id} \right\} \sqrt{N} \left\{ \sum_{d=1}^{D} E(I_{id} X_{id} X_{id}^T) \right\}^{-1}$$

$$= \left\{ \sum_{d=1}^{D} E(I_{id} X_{id} X_{id}^T) \right\}^{-1} E \left\{ \sum_{d=1}^{D} I_{id} \bar{\epsilon}_{id} X_{id} \sum_{d=1}^{D} I_{id} \bar{\epsilon}_{id} X_{id} \right\} \left\{ \sum_{d=1}^{D} E(I_{id} X_{id} X_{id}^T) \right\}^{-1}.$$

We have

$$E(\sum_{d=1}^{D} I_{id} \bar{\epsilon}_{id} X_{id} \sum_{d=1}^{D} I_{id} \bar{\epsilon}_{id} X_{id}^T)$$

$$= E\left(\sum_{d=1}^{D} I_{id} \bar{\epsilon}_{id} \bar{\epsilon}_{id} X_{id}^T \sum_{d=1}^{D} I_{id} \bar{\epsilon}_{id} \bar{\epsilon}_{id} X_{id}^T\right) + \sum_{(d\neq d')}^{(D)} \sigma_{(d)(d')} \tau_{d} \tau_{d'}$$

$$= \sum_{d=1}^{D} \sigma_{d}^2 \sum_{d=1}^{d} \tau_{d} \tau_{d} + \sum_{(d\neq d')}^{(D)} \sigma_{(d)(d')} \tau_{d} \tau_{d'}$$

$$\approx \sigma^2 \sum_{d=1}^{D} \tau_{d} \tau_{d} + \sum_{(d\neq d')}^{(D)} \sigma_{(d)(d')} \tau_{d} \tau_{d'}.$$
where \( \hat{\sigma}^2 = \sum_{d=1}^{D} \text{Var}(\epsilon_{id})/D \). Thus, assuming constant variance \( \text{Var}(\epsilon_{id}) \) over \( d \), i.e. \( \hat{\sigma}^2 = \sigma^2 \), \( \sigma_{(d')}(d') = 0 \), or \( \epsilon_{id} \) and \( \epsilon_{i(d')} \) are independent, where \( (d) \neq (d') = 1, \ldots, D \), the asymptotic covariance matrix \( \hat{\Sigma}_\theta \) is the lower right \( \sum_{m=1}^{M} p_m \times \sum_{m=1}^{M} p_m \) block of the asymptotic covariance matrix \( \Sigma_\theta \), can be defined by

\[
\hat{\Sigma}_\theta \approx \sum_{d=1}^{D} \epsilon_d \left[ \begin{array}{c c c}
\kappa_{1d}(1 - \kappa_{1d})Z_{1d}Z_{1d}^T & \cdots & -\kappa_{1d}\kappa_{(\sum_{m=1}^{M} M_d)}(1 - \kappa_{1d})Z_{1d}Z_{1d}^T \\
-\kappa_{1d}\kappa_{(\sum_{m=1}^{M} M_d)}(1 - \kappa_{1d})Z_{1d}Z_{1d}^T & \cdots & \cdots \\
\vdots & \ddots & \vdots \\
-\kappa_{1d}\kappa_{(\sum_{m=1}^{M} M_d)}(1 - \kappa_{1d})Z_{1d}Z_{1d}^T & \cdots & \cdots \\
\end{array} \right]^{-1}
\]

\[
\hat{\sigma}^2 \sum_{d=1}^{D} \epsilon_d \left[ \begin{array}{c c c}
\kappa_{1d}(1 - \kappa_{1d})Z_{1d}Z_{1d}^T & \cdots & -\kappa_{1d}\kappa_{(\sum_{m=1}^{M} M_d)}(1 - \kappa_{1d})Z_{1d}Z_{1d}^T \\
-\kappa_{1d}\kappa_{(\sum_{m=1}^{M} M_d)}(1 - \kappa_{1d})Z_{1d}Z_{1d}^T & \cdots & \cdots \\
\vdots & \ddots & \vdots \\
-\kappa_{1d}\kappa_{(\sum_{m=1}^{M} M_d)}(1 - \kappa_{1d})Z_{1d}Z_{1d}^T & \cdots & \cdots \\
\end{array} \right]^{-1}
\]

\[
\hat{\sigma}^2 \sum_{d=1}^{D} \epsilon_d \left[ \begin{array}{c c c}
\kappa_{1d}(1 - \kappa_{1d})Z_{1d}Z_{1d}^T & \cdots & -\kappa_{1d}\kappa_{(\sum_{m=1}^{M} M_d)}(1 - \kappa_{1d})Z_{1d}Z_{1d}^T \\
-\kappa_{1d}\kappa_{(\sum_{m=1}^{M} M_d)}(1 - \kappa_{1d})Z_{1d}Z_{1d}^T & \cdots & \cdots \\
\vdots & \ddots & \vdots \\
-\kappa_{1d}\kappa_{(\sum_{m=1}^{M} M_d)}(1 - \kappa_{1d})Z_{1d}Z_{1d}^T & \cdots & \cdots \\
\end{array} \right]^{-1}
\]

B PROOF OF LEMMA 1

Proof: The proof of consistency requires the result of strong law of large numbers, such that \( \hat{\theta} \rightarrow \tilde{\theta} \), almost surely, and uniformly for \( \theta \in \Theta \) as \( N \rightarrow \infty \) and \( \tilde{\theta} \) being the unique minimum value of \( E(SEC(\theta)) \). To prove the asymptotic normality result, by the central limit theorem, \( \sqrt{N}(\hat{\theta} - \tilde{\theta}) \) converges in distribution to Normal(0, \( \Sigma_\theta \)).

Based on the proof Lemma 1 [1] we conclude that the asymptotic distribution of \( \sqrt{N}(\hat{\theta} - \tilde{\theta}) \) converges to Normal(0, \( \Sigma_\theta \)).

C PROOF OF COROLLARY 1

Based on the equations [9] to [12] defined in Section 2.3 and the covariance estimator of GEE regression coefficient derivation in Mancl and DeRouen (2001) [4], we have an approximation, i.e.

\[
E(\hat{\epsilon}_i^T \hat{\epsilon}_i^T) \approx (I_{D \times D} - H_i)(\text{COV}(Y_i))(I_{D \times D} - H_i)^T \quad (C1)
\]

and the covariance estimator of \( \hat{\theta} \), i.e.

\[
\hat{\Sigma}_\theta = \left( \sum_{i=1}^{N} X_iX_i^T / N \right)^{-1} \left( \sum_{i=1}^{N} X_i(I_{D \times D} - H_i)^{-1} \hat{\epsilon}_i^T (I_{D \times D} - H_i)^{-1} X_i^T \right) \left( \sum_{i=1}^{N} X_iX_i^T / N \right)^{-1}. \quad (C2)
\]

Based on equation (C1), assuming the second summation of equation (C2) can be approximated by

\[
\sum_{i=1}^{N} X_i(I_{D \times D} - H_i)^{-1} \hat{\epsilon}_i^T (I_{D \times D} - H_i)^{-1} X_i^T 
\approx \sum_{i=1}^{N} X_i\text{COV}(Y_i)X_i^T
\approx \sum_{i=1}^{N} X_i\epsilon_i^T X_i^T,
\]

\[ \Rightarrow \]

\[ \sum_{i=1}^{N} X_i\epsilon_i^T X_i^T, \]
where

\[
X_{i}e_{i} = \begin{bmatrix}
\sum_{d=1}^{D} I_{id}e_{id} \\
\sum_{d=1}^{D} I_{id}(d-1)^{q-1}e_{id} \\
\sum_{d=1}^{D} I_{id}(A_{1id} - \pi_{id})e_{id} \\
\vdots \\
\sum_{d=1}^{D} I_{id}(A_{iM_{id}} - \pi_{M_{id}})e_{id} \\
\sum_{d=1}^{D} I_{id}(A_{iM_{id}} - \pi_{M_{id}})(d-1)^{p_{M} - 1}e_{id} \\
\vdots \\
\sum_{d=1}^{D} I_{id}(A_{iM_{id}} - \pi_{M_{id}})(d-1)^{p_{M} - 1}e_{id} \\
\sum_{d=1}^{D} I_{id}(A_{iM_{id}} - \pi_{M_{id}})(d-1)^{p_{M} - 1}e_{id}
\end{bmatrix}
\]

with dimension \((q + \sum_{m=1}^{M} p_{m}) \times 1\). Hence, we can have \(\hat{\Sigma}_{p_{id}}\) approximated by

\[
U \left( \sum_{i=1}^{N} X_{i}X_{i}^{T} / N \right)^{-1} \left( \sum_{i=1}^{N} X_{i}e_{i}e_{i}^{T} + \sum_{i=1}^{N} X_{i}X_{i}^{T} / N \right) \left( \sum_{i=1}^{N} X_{i}X_{i}^{T} / N \right)^{-1} U^{T},
\]

where \(U\) is a rectangular matrix with dimension \((\sum_{m=1}^{M} p_{m}) \times (q + \sum_{m=1}^{M} p_{m})\), i.e., \(U = [U_{0}, U_{1}]\), where \(U_{0}\) is a zeros matrix with dimension \(\sum_{m=1}^{M} p_{m} \times q\) while \(U_{1}\) is an identity matrix with dimension \(\sum_{m=1}^{M} p_{m} \times \sum_{m=1}^{M} p_{m}\). Assuming \(X_{i}\) are given, but not \(\epsilon_{i}\) and hence \(X_{i}e_{i}\) are random, for \(i = 1, \ldots, N\). Therefore, the degrees of freedom for \(X_{i}e_{i}\) can be \(N\) when assuming no restrictions on \(X_{i}e_{i}\). Thus, when \(N\) is small, the test statistic follows a Hotelling's \(T^{2}\) distribution.

**D R IMPLEMENTATION**

**D.1 Implementation in R function**

In this section, we demonstrate the implementation of the R function `SampleSize_FlexiMRT` for sample size calculations via a simulation study. This function is available at [https://github.com/Kenny-Jing-Xu/FlexiMRT-SS/blob/master/SampleSizeFlexiMRT.R](https://github.com/Kenny-Jing-Xu/FlexiMRT-SS/blob/master/SampleSizeFlexiMRT.R).

The inputs of the function are defined in the following.

```r
SampleSize_FlexiMRT(days, occ_per_day, aa.day.aa, prob,
                    beta_shape, beta_mean, beta_initial, beta_quadratic_max,
                    tau_shape, tau_mean, tau_initial, tau_quadratic_max,
                    sigma, pow, sigLev, method, test, result, SS)
```

- `days`: the number of days during the study period
- `occ_per_day`: the number of decision time point per day during the study period. Note it is fixed at `occ_per_day=1` for DIAMANTE study
- `aa.day.aa`: the day of each proposed intervention category
- `prob`: the allocation probability matrix of the levels, with dimension of D by (M+1), where the first column are the allocation probabilities of control level
- **beta_shape**: the shape of \( b_m(d; \beta_m) \) in terms of \( d \), i.e. “constant”, “linear”, “linear and constant”, or “quadratic”
- **beta_mean**: the average of standardized proximal effect size of each intervention category over the study period
- **beta_initial**: the initial standardized proximal effect size of each intervention category
- **beta_quadratic_max**: the first value of \( d \) that gives the turning value of \( b_m(d; \beta_m) \) if the shape is “quadratic” or “linear and constant”.
- **tau_shape**: the shape of \( \tau_d \) in term of \( d \), i.e. “constant”, “linear”, “linear and constant”, or “quadratic”
- **tau_mean**: the average of \( \tau_d \) over the study period
- **tau_initial**: the initial \( \tau_d \)
- **tau_quadratic_max**: the value of \( d \) that gives the maximum value of \( \tau_d \) if the shape is quadratic
- **sigma**: \( \sigma \) or the standard deviation of the error term \( e \)
- **pow**: the power
- **sigLev**: the type-I error rate
- **method**: the method of sample size calculation, based on either power, i.e. “power” or confidence interval, i.e. “confidence interval”
- **test**: the test statistics, based on Chi-squared distribution, i.e. “chi”, Hotelling’s T-squared distribution with \( N - q - 1 \) degrees of freedom, i.e. “hotelling N-q-1”, Hotelling’s T-squared distribution with \( N - 1 \) degrees of freedom, i.e. “hotelling N-1”, or Hotelling’s T-squared distribution with \( N \) degrees of freedom, i.e. “hotelling N”
- **result**: the chosen calculated result, i.e “choice_sample_size”, “choice_power” or “choice_coverage_probability”
- **SS**: the specified sample size if the result of either power or coverage probability is chosen

The possible outputs are summarized below:
- \( N \), the estimated sample size;
- \( P \), the estimated power;
- \( CP \), the estimated coverage probability;
- \( d \), the consistent estimated \( \beta \);
- **Sig_bet_inv**, the inverse of the asymptotic covariance estimated for \( \beta \).

Here we present the R code for the sample size calculation corresponding to
- Test statistics=Hotelling’s \( T_{M_p,N-q-1}^2 \),
- \( M = 4 \), where \( M = M_0 + M_1 \), \( M_0 = 3 \) and \( M_1 = 1 \),
- \( D = 180 \),
- average proximal standardized effect=0.1 for each intervention category,
- proximal effects increased linearly at the beginning and maintained constant after 28-day,
- constant availability rate=70%.
# One decision time point per day during the study period
occ_per_day = 1

# The number of parameter of beta for each intervention category, i.e. p_m
pb = 2

# The study period of 180-day
days = 180

# Three intervention categories proposed at the beginning and
# another one proposed in the middle of the trial.
aa.each = c(3, 1)

# The first day, the middle day and the last day of the study period
aa.day = c(1, (floor(days/2) + 1), days)

# The number of days when the intervention categories are proposed in the trial
aa.freq = length(aa.day) - 1

# The days that each of the intervention categories are added to the trial, e.g., c(1,1,1,91)
aa.day.aa = rep( (aa.day)[1:aa.freq], aa.each)

# The allocation probability matrix
# Based on uniform random with dimension 180 by 5
# The first column are the allocation probability of control category.
# Other columns are the probabilities of intervention categories.
# Rows 1-90 are c(0.25, 0.25, 0.25, 0.25, 0).
# Rows 91-180 are c(0.2, 0.2, 0.2, 0.2, 0.2).
prob = matrix(0, days, (1 + sum(aa.each)))
for (l in 1:(length(aa.day) - 1)) {
    prob[aa.day[l + 0]:aa.day[l + 1] - 1, 1:(1 + cumsum(aa.each)[l])] = 1/(cumsum(aa.each)[l] + 1)
}
prob[aa.day[length(aa.day)]],
1:(1 + sum(aa.each)) = 1/(1 + sum(aa.each))
# Linear until 28-day then constant in term of d for the beta shape
beta_shape= "linear and constant"

# Average proximal standardised effect size for each intervention category
beta_mean=rep(0.1, sum( aa_each ) )

# Initial proximal standardised effect size for each intervention category
beta_initial=rep(0.01, sum( aa_each ) )

# Maximum proximal standardised effect day for each intervention category
beta_quadratic_max=aa.day.aa-1+28

# Constant shape for availability proportion
tau_shape= "constant"

# Average availability proportion
tau_mean=0.7

# Initial availability proportion
tau_initial=0.7

# Maximum availability day
tau_quadratic_max=28

# The power 0.8 and type-I error rate 0.05
pow=0.8
sigLev=0.05

# The standard deviation and correlation coefficient of the error term
sigma=1
rho=0

# The sample size calculated by power and test statistics with distribution
# of Hotelling’s T-squared with degrees of freedom N-q-1
method="power"
test = "hotelling N-q-1"
result = "choice_sample_size"

MRTN=SampleSize_FlexiMRT(days=days, occ_per_day=occ_per_day,
aa.day.aa = aa.day.aa,
prob=prob,
beta_shape=beta_shape, beta_mean=beta_mean,
beta_initial=beta_initial,
beta_quadratic_max=beta_quadratic_max,
tau_shape=tau_shape, tau_mean=tau_mean,
tau_initial=tau_initial,
tau_quadratic_max=tau_quadratic_max,
sigma=sigma, pow=pow, sigLev=sigLev,
method=method, test=test, result=result)

# The calculated sample size
N=MRTN$N

The above R codes calculate sample size 73. The formulated power achieved under this number of participants (0.80) can be calculated by substituting the inputs of result="choice_power" and SS=73 in the R function SampleSize_FlexiMRT.
D.2 Implementation using R shiny

Similar to the online sample size calculator (MRT-SS) for the micro-randomized trial created by Nicholas et al.[39], we create the proposed sample size calculator named “FlexiMRT-SS” using R shiny. The web link of this application is https://kennyxu.shinyapps.io/FlexiMRT-SS/. We explore each of its components briefly using Figure D1 based on the same example Section D.1.

Figure D1 describes a trial that has study period 180 days with only one decision time point per day. For a particular component, three intervention categories are proposed before the first day of study, and another one is added in the halfway through the study, i.e. after 90 days. At each decision time point, a participant is randomly allocated to either the control category or one of the active intervention categories based on uniform random intervention strategy. For example, the randomization probability for each category (control or intervention) is 1/4 for the first half of the study period, while the randomization probability for each level is 0.2 for the second half of the study period when one more category is added. The availability of each participant is expected 70% at all the decision time points. The sample size calculation method is based on power. The test statistic is assumed to follow a Hotelling’s $T^2$ distribution with denominator degrees of freedom $N - q - 1$. For the proximal effect, it is assumed to follow a trend of increasing linearly from day-1 to day-28 and then maintaining constantly at its maximum value. The initial and average values of the standardized proximal effect size for either intervention level are 0.01 and 0.1 respectively. In the ‘Result’ section, the sample size is calculated as the final output under a nominal 80% power and a level of significance 0.05. The output is presented by “The required sample size is 73 to attain 80% power when the significance level is 0.05,” after the ‘Get Result’ button is clicked. Alternatively, if ‘Power’ is selected in the ‘Result’ section, and 73 is specified in the ‘Number of Participants’ cell, the output is going to be “The sample size 73 gives 80% power when the significance level is 0.05”.
**FIGURE 1** Diabetes and Mental Health Adaptive Notification Tracking and Evaluation

| Time Window | Feedback Message | Motivational Message | Proximal outcome |
|-------------|-----------------|----------------------|------------------|
| C-0: 9:00 - 11:30am | C-0: control | | |
| C-1: 11:30am - 14:00pm | C-1: reaching goal | | |
| C-2: 14:00 - 16:30pm | C-2: steps walked yesterday | | |
| C-3: 16:30 - 19:00pm | C-3: walk more or less yesterday than day before | | |
| | C-4: steps walked yesterday plus an encouraging message | | |

Each day of the study

**FIGURE 2** Micro-Randomized Trial Design for Diabetes and Mental Health Adaptive Notification Tracking and Evaluation study; R=Randomization and C=Category. Each day during the study period, a Time Window is selected. At the selected Time Window, a Feedback message and a Motivational message are sent. The two messages are one minute apart. The primary outcome is the change in daily steps after the messages are sent.
**FIGURE 3** Average change of step counts from yesterday on each of days 2 to 45

**TABLE 1** Sample sizes calculation based on power (P) when the working model assumptions are correct. Note that we have $M = 4$, where $M_0 = 3$ and $M_1 = 1$, $\sigma = 1$ and $\rho = 0$. The significance level is 0.05. The desired P is 0.80. One decision time point per day and study periods are 180 and 90 days. At each time point, the expected availabilities are 100% and 70%. Linear increasing trend until reaching maximum at 28th day and constant trend afterwards for the standardized proximal effect size. The initial standardized proximal effect sizes are 0.001. We consider the average standardized proximal effect sizes (ES) 0.1 and 0.06.

| Availability | Test Statistics | Decision Time Point | Sample Size | Formulated P | Monte Carlo P |
|--------------|-----------------|---------------------|-------------|--------------|---------------|
|              |                 |                     | 0.10 | 0.06 | 0.10 | 0.06 | 0.10 | 0.06 |
| 100%         | $\chi^2_{\sum m p_m}$ | 180 | 46 | 127 | 0.81 | 0.80 | 0.81 | 0.81 |
|              |                 | 90  | 86 | 242 | 0.81 | 0.80 | 0.80 | 0.81 |
|              | Hotelling’s $T^2_{\sum m p_m, N}$ | 180 | 54 | 135 | 0.81 | 0.80 | 0.81 | 0.81 |
|              |                 | 90  | 93 | 249 | 0.80 | 0.81 | 0.79 |
|              | Hotelling’s $T^2_{\sum m p_m, N-q-1}$ | 180 | 54 | 135 | 0.80 | 0.81 | 0.77 | 0.78 |
|              |                 | 90  | 94 | 250 | 0.80 | 0.80 | 0.80 | 0.79 |
| 70%          | $\chi^2_{\sum m p_m}$ | 180 | 65 | 182 | 0.80 | 0.81 | 0.78 |
|              |                 | 90  | 122 | 345 | 0.80 | 0.80 | 0.77 | 0.80 |
|              | Hotelling’s $T^2_{\sum m p_m, N}$ | 180 | 73 | 190 | 0.80 | 0.80 | 0.78 | 0.80 |
|              |                 | 90  | 130 | 353 | 0.80 | 0.80 | 0.80 |
|              | Hotelling’s $T^2_{\sum m p_m, N-q-1}$ | 180 | 73 | 190 | 0.80 | 0.80 | 0.81 | 0.80 |
|              |                 | 90  | 130 | 353 | 0.80 | 0.81 | 0.81 |

Note: $\chi^2$, Hotelling’s $T^2$
FIGURE 4 Sample Sizes calculation based on Power when the standardized proximal effect size of intervention categories satisfy $\delta_m(d, \delta_m) = Z_{md}^T \delta_m$, where $\delta_m = \beta_m / \sigma$, for $m = 1, \ldots, M$. Note that we have $M = 1, \ldots, 10$, $\sigma = 1$ and $\rho = 0$. The significance level is 0.05. The desired power is 0.80. The total number of decision time points ($D$) is 180. The average standardized proximal effect sizes ($\frac{1}{D} \sum_{d=1}^{D} \delta_m(d, \delta_m)$) are 0.1. The initial standardized proximal effect sizes ($\delta_m(1, \delta_m)$) are 0.001. Quadratic trend reaching turning point on the 28th day and 100% availability at each time point are assumed.

FIGURE 5 The plots of estimated standardized proximal effect size $Z_{md}^T \delta_m$ on each day under different trends. We have days $d = 1, \ldots, 180$ and intervention categories $m=1, 2, 3, \text{ and } 4$, a) the categories 1 to 3 are proposed at the beginning and b) the category 4 is proposed on the half-way. The datasets are generated based on a linear-plateau trend, where $Z_{md}^T \delta_m$ increased with $d$ until the 28th day after the category proposed, then maintain the maximum value for the rest of study period. The average standardized proximal effect sizes are 0.1 ($\frac{1}{D} \sum_{d=1}^{D} Z_{md}^T \delta_m$ for $m=1, 2, 3$ and $\frac{1}{D - [0.5D]} \sum_{d=[0.5D]+1}^{D} Z_{md}^T \delta_m$ for $m=4$) for all the trends, where $D=180$. The initial standardized proximal effect sizes are 0.001 ($\delta_m(1, \delta_m)$ for $m=1, 2, 3$ and $\delta_m([0.5D]+1, \delta_m)$ for $m=4$) for all except the constant trend. Quadratic trend reaching maximum on the 90th day after the category proposed.
TABLE 2 Sample sizes calculation based on coverage probability (CP) when the working model assumptions are correct. Note that we have $M = 4$, where $M_0 = 3$ and $M_1 = 1$, $\sigma = 1$ and $\rho = 0$. The desired CP is 95%. One decision time point per day and study periods are 180 and 90 days. At each time point, the expected availabilities are 100% and 70%. Linear increasing trend until reaching maximum at 28th day and constant trend afterwards for the standardized proximal effect size. The precision of initial standardized proximal effect sizes are 0.001. We consider the precision of average standardized proximal effect sizes 0.10 and 0.06.

| Availability | Test Statistics | Decision Time Point | Sample Size | Formulated CP | Monte Carlo CP |
|--------------|----------------|---------------------|-------------|---------------|---------------|
|              |                |                     | 0.10  | 0.06  | 0.10  | 0.06  | 0.10  | 0.06  |
| 100%         | $\chi^2_{\sum_{m} p_m}$ | 180  | 47   | 132  | 0.95 | 0.95 | 0.94 | 0.96 |
|              | Hotelling’s $T^2_{\sum_{m} p_m, N}$ | 90   | 88   | 249  | 0.95 | 0.95 | 0.95 | 0.95 |
|              | Hotelling’s $T^2_{\sum_{m} p_m, N - q - 1}$ | 180  | 59   | 143  | 0.95 | 0.95 | 0.95 | 0.95 |
|              |                 | 90   | 100  | 261  | 0.95 | 0.95 | 0.96 | 0.95 |
| 70%          | $\chi^2_{\sum_{m} p_m}$ | 180  | 67   | 188  | 0.95 | 0.95 | 0.94 | 0.95 |
|              | Hotelling’s $T^2_{\sum_{m} p_m, N}$ | 90   | 126  | 356  | 0.95 | 0.95 | 0.95 | 0.95 |
|              | Hotelling’s $T^2_{\sum_{m} p_m, N - q - 1}$ | 180  | 79   | 199  | 0.95 | 0.95 | 0.96 | 0.96 |
|              |                 | 90   | 138  | 368  | 0.95 | 0.95 | 0.96 | 0.97 |

FIGURE 6 The plots of $\sigma^2_d$ on each day $d$ under both the linearly increasing and decreasing trends, where $d = 1, \ldots, 180$. 

a) Increasing  
b) Decreasing
TABLE 3 Sample sizes calculation based on power (P) when the standardized proximal effect size trends are mis-specified. The correct trends are linear increasing until reaching maximum at 28th day and constant trend afterwards. The mis-specified trends are constant, linear and quadratics. The initial standardized proximal effect sizes are 0.0001. We consider the average standardized proximal effect sizes (ES) 0.1 and 0.06. Note that we have $M = 4$, where $M_0 = 3$ and $M_1 = 1$, $\sigma = 1$ and $\rho = 0$. The significance level is 0.05. The desired P is 0.80. One decision time point per day and study periods are 180 days. At each time point, the expected availabilities are 100% and 70%.

| Mis-Specified Trend | Availability | Test Statistics | Sample Size | Formulated P | Monte Carlo P |
|---------------------|--------------|-----------------|-------------|--------------|---------------|
| Constant            | 100%         | $X^2_{\sum p_m}$ | 39          | 0.81         | 0.73          | 0.69          |
|                     |              | Hotelling’s $T^2_{\sum p_m N}$ | 43          | 0.80         | 0.64          | 0.70          |
|                     | 70%          | $X^2_{\sum p_m}$ | 44          | 0.81         | 0.66          | 0.66          |
|                     |              | Hotelling’s $T^2_{\sum p_m N−q−1}$ | 44          | 0.80         | 0.70          | 0.68          |
|                     |              | Hotelling’s $T^2_{\sum p_m N}$ | 55          | 0.80         | 0.64          | 0.69          |
|                     | 70%          | $X^2_{\sum p_m}$ | 60          | 0.81         | 0.69          | 0.71          |
|                     |              | Hotelling’s $T^2_{\sum p_m N−q−1}$ | 60          | 0.80         | 0.64          | 0.69          |
| Linear              | 100%         | $X^2_{\sum p_m}$ | 41          | 0.81         | 0.76          | 0.74          |
|                     |              | Hotelling’s $T^2_{\sum p_m N}$ | 49          | 0.81         | 0.77          | 0.77          |
|                     | 70%          | $X^2_{\sum p_m}$ | 49          | 0.80         | 0.73          | 0.76          |
|                     |              | Hotelling’s $T^2_{\sum p_m N−q−1}$ | 49          | 0.80         | 0.73          | 0.77          |
|                     |              | Hotelling’s $T^2_{\sum p_m N}$ | 58          | 0.80         | 0.73          | 0.77          |
|                     | 70%          | $X^2_{\sum p_m}$ | 66          | 0.80         | 0.73          | 0.73          |
|                     |              | Hotelling’s $T^2_{\sum p_m N−q−1}$ | 66          | 0.80         | 0.73          | 0.73          |
| Quadratic           | 100%         | $X^2_{\sum p_m}$ | 40          | 0.80         | 0.74          | 0.73          |
|                     |              | Hotelling’s $T^2_{\sum p_m N}$ | 51          | 0.80         | 0.73          | 0.76          |
|                     | 70%          | $X^2_{\sum p_m}$ | 52          | 0.81         | 0.76          | 0.71          |
|                     |              | Hotelling’s $T^2_{\sum p_m N−q−1}$ | 52          | 0.80         | 0.74          | 0.78          |
|                     |              | Hotelling’s $T^2_{\sum p_m N}$ | 57          | 0.80         | 0.74          | 0.78          |
|                     | 70%          | $X^2_{\sum p_m}$ | 68          | 0.80         | 0.74          | 0.76          |
|                     |              | Hotelling’s $T^2_{\sum p_m N−q−1}$ | 68          | 0.80         | 0.77          | 0.74          |

FIGURE 7 The plots of $r_d$ on each day $d$ under both the linearly increasing and decreasing trends, where $d = 1, \ldots, 180$. 

a) Increasing

b) Decreasing
TABLE 4 Sample sizes calculation based on coverage probability (CP) when the standardized proximal effect size trends are mis-specified. The correct trends are linear increasing until reaching maximum at 28th day and constant trend afterwards. The mis-specified trends are constant, linear and quadratics. The precision of initial standardized proximal effect sizes are 0.0001. We consider the precision of average standardized proximal effect sizes (ES) 0.1 and 0.06. Note that we have $M = 4$, where $M_0 = 3$ and $M_1 = 1$, $\sigma = 1$ and $\rho = 0$. The desired CP is 95%. One decision time point per day and study periods are 180 days. At each time point, the expected availabilities are 100% and 70%.

| Mis-Specified Trend | Availability | Test Statistics | Sample Size | Formulated CP | Monte Carlo CP |
|---------------------|--------------|-----------------|-------------|---------------|---------------|
|                     |              |                 | 0.1 0.06    | 0.1 0.06      | 0.1 0.06      |
| Constant            | 100%         | $\chi^2_{\sum p_m}$ | 31 85 0.95  | 0.95 0.75     | 0.73          |
|                     | 70%          | $\chi^2_{\sum p_m}$ | 37 91 0.95  | 0.95 0.69     | 0.69          |
|                     |              | Hotelling’s $T^2_{\sum p_m, N}$ | 38 92 0.95 | 0.95 0.73     | 0.73          |
|                     |              | Hotelling’s $T^2_{\sum p_m, N-q-1}$ | 44 121 0.95 | 0.95 0.75     | 0.75          |
| Linear              | 100%         | $\chi^2_{\sum p_m}$ | 42 120 0.95 | 0.95 0.92     | 0.93          |
|                     | 70%          | $\chi^2_{\sum p_m}$ | 54 132 0.95 | 0.95 0.92     | 0.94          |
|                     |              | Hotelling’s $T^2_{\sum p_m, N}$ | 54 132 0.95 | 0.95 0.93     | 0.94          |
|                     |              | Hotelling’s $T^2_{\sum p_m, N-q-1}$ | 60 171 0.95 | 0.95 0.93     | 0.92          |
| Quadratic           | 100%         | $\chi^2_{\sum p_m}$ | 49 140 0.96 | 0.95 0.97     | 0.97          |
|                     | 70%          | $\chi^2_{\sum p_m}$ | 65 156 0.95 | 0.95 0.98     | 0.97          |
|                     |              | Hotelling’s $T^2_{\sum p_m, N}$ | 66 157 0.95 | 0.95 0.97     | 0.97          |
|                     |              | Hotelling’s $T^2_{\sum p_m, N-q-1}$ | 69 199 0.95 | 0.95 0.95     | 0.94          |
|                     |              |                 |             |               |               |
|                     | 100%         | $\chi^2_{\sum p_m}$ | 85 216 0.95 | 0.95 0.97     | 0.97          |
|                     | 70%          | $\chi^2_{\sum p_m}$ | 86 216 0.95 | 0.95 0.98     | 0.97          |
TABLE 5 Sample sizes calculation based on power (P) when the numbers of intervention categories $M$ are mis-specified. We have $M = 4$, where $M_0 = 3$ and $M_1 = 1$, $\sigma = 1$ and $\rho = 0$. The mis-specified values of $M$ are $M_1 = 0$ with $M_0 = 1, 3$ and 4. The correct trends are linear increasing until reaching maximum at 28th day and constant trend afterwards. The initial standardized proximal effect sizes are 0.0001. We consider the average standardized proximal effect sizes (ES) 0.1 and 0.06. The significance level is 0.05. The desired P is 0.80. One decision time point per day and study periods are 180 days. At each time point, the expected availabilities are 100% and 70%.

| Mis-Specified $M$ | Availability | Test Statistics | Sample Size | Formulated P | Monte Carlo P |
|-------------------|--------------|-----------------|-------------|--------------|--------------|
| $M_0 = 1$ and $M_1 = 0$ | 100% | $\chi^2_{\sum p_m}$ | 21 | 0.81 | 0.42 | 0.39 |
| | | Hotelling’s $T^2_{\sum p_mN}$ | 24 | 0.81 | 0.30 | 0.34 |
| | | Hotelling’s $T^2_{\sum p_mN-q-1}$ | 24 | 0.80 | 0.26 | 0.36 |
| | 70% | $\chi^2_{\sum p_m}$ | 30 | 0.81 | 0.40 | 0.41 |
| | | Hotelling’s $T^2_{\sum p_mN}$ | 33 | 0.80 | 0.31 | 0.38 |
| | | Hotelling’s $T^2_{\sum p_mN-q-1}$ | 33 | 0.80 | 0.29 | 0.38 |
| $M_0 = 3$ and $M_1 = 0$ | 100% | $\chi^2_{\sum p_m}$ | 39 | 0.80 | 0.71 | 0.73 |
| | | Hotelling’s $T^2_{\sum p_mN}$ | 46 | 0.80 | 0.68 | 0.71 |
| | | Hotelling’s $T^2_{\sum p_mN-q-1}$ | 46 | 0.80 | 0.68 | 0.70 |
| | 70% | $\chi^2_{\sum p_m}$ | 56 | 0.80 | 0.73 | 0.75 |
| | | Hotelling’s $T^2_{\sum p_mN}$ | 62 | 0.80 | 0.71 | 0.71 |
| | | Hotelling’s $T^2_{\sum p_mN-q-1}$ | 62 | 0.80 | 0.71 | 0.72 |
| $M_0 = 4$ and $M_1 = 0$ | 100% | $\chi^2_{\sum p_m}$ | 50 | 0.80 | 0.84 | 0.85 |
| | | Hotelling’s $T^2_{\sum p_mN}$ | 58 | 0.80 | 0.84 | 0.85 |
| | | Hotelling’s $T^2_{\sum p_mN-q-1}$ | 59 | 0.80 | 0.82 | 0.86 |
| | 70% | $\chi^2_{\sum p_m}$ | 72 | 0.80 | 0.86 | 0.84 |
| | | Hotelling’s $T^2_{\sum p_mN}$ | 80 | 0.80 | 0.84 | 0.81 |
| | | Hotelling’s $T^2_{\sum p_mN-q-1}$ | 80 | 0.80 | 0.84 | 0.85 |
TABLE 6 Sample sizes calculation based on coverage probability (CP) when the numbers of intervention categories $M$ are mis-specified. We have $M = 4$, where $M_0 = 3$ and $M_1 = 1$, $\sigma = 1$ and $\rho = 0$. The mis-specified values of $M$ are $M_1 = 0$ with $M_0=1, 3$ and $4$. The correct trends are linear increasing until reaching maximum at 28th day and constant trend afterwards. The precision of initial standardized proximal effect sizes are 0.0001. We consider the precision of average standardized proximal effect sizes (ES) 0.1 and 0.06. The desired CP is 95%. One decision time point per day and study periods are 180 days. At each time point, the expected availabilities are 100% and 70%.

| Mis-Specified $M$ | Availability | Test Statistics | Sample Size | Formulated CP | Monte Carlo CP |
|-------------------|--------------|----------------|-------------|---------------|----------------|
| $M_0 = 1$ and $M_1 = 0$ | 100% | $\chi^2_{\sum p_n}$ | 13 | 0.95 | 0.95 | 0.18 | 0.18 |
| | | | 17 | 0.95 | 0.95 | 0.10 | 0.15 |
| | | Hotelling’s $T^2_{\sum p_n,N}$ | 18 | 0.96 | 0.95 | 0.14 | 0.15 |
| | 70% | | 19 | 0.96 | 0.95 | 0.18 | 0.16 |
| | | Hotelling’s $T^2_{\sum p_n,N-q-1}$ | 23 | 0.96 | 0.95 | 0.16 | 0.14 |
| | | | 23 | 0.96 | 0.95 | 0.15 | 0.16 |
| $M_0 = 3$ and $M_1 = 0$ | 100% | $\chi^2_{\sum p_n}$ | 36 | 0.95 | 0.95 | 0.82 | 0.86 |
| | | Hotelling’s $T^2_{\sum p_n,N}$ | 45 | 0.95 | 0.95 | 0.85 | 0.82 |
| | | Hotelling’s $T^2_{\sum p_n,N-q-1}$ | 46 | 0.95 | 0.95 | 0.86 | 0.86 |
| | 70% | | 52 | 0.95 | 0.95 | 0.82 | 0.85 |
| | | Hotelling’s $T^2_{\sum p_n,N}$ | 61 | 0.95 | 0.95 | 0.86 | 0.83 |
| | | Hotelling’s $T^2_{\sum p_n,N-q-1}$ | 61 | 0.95 | 0.95 | 0.84 | 0.86 |
| $M_0 = 4$ and $M_1 = 0$ | 100% | $\chi^2_{\sum p_n}$ | 52 | 0.95 | 0.95 | 0.97 | 0.97 |
| | | Hotelling’s $T^2_{\sum p_n,N}$ | 64 | 0.95 | 0.95 | 0.97 | 0.98 |
| | | Hotelling’s $T^2_{\sum p_n,N-q-1}$ | 64 | 0.95 | 0.95 | 0.98 | 0.97 |
| | 70% | | 74 | 0.95 | 0.95 | 0.97 | 0.98 |
| | | Hotelling’s $T^2_{\sum p_n,N}$ | 86 | 0.95 | 0.95 | 0.98 | 0.97 |
| | | Hotelling’s $T^2_{\sum p_n,N-q-1}$ | 86 | 0.95 | 0.95 | 0.98 | 0.97 |
TABLE 7 Sample sizes calculation based on power (P) when \( \sigma_d^2 \) is not constant over \( d \), i.e. linearly increasing or decreasing over \( d \). We have \( M = 4 \), where \( M_0 = 3 \) and \( M_1 = 1 \) and \( \rho = 0 \). The correct trends are linear increasing until reaching maximum at 28th day and constant trend afterwards. The initial standardized proximal effect sizes are 0.0001. We consider the average standardized proximal effect sizes (ES) 0.1 and 0.06. The significance level is 0.05. The desired P is 0.80. One decision time point per day and study periods are 180 days. At each time point, the expected availabilities are 100% and 70%.

| Trend of \( \sigma_d^2 \) | Availability | Test Statistics | Sample Size | Formulated P | Monte Carlo P |
|---------------------------|--------------|----------------|-------------|--------------|--------------|
|                           |              |                | 0.1         | 0.06         | 0.06         | 0.1          | 0.06         | 0.06         |
| Increasing                | 100%         | \( \sum p_m \) | 46          | 127          | 0.81         | 0.80         | 0.80         | 0.80         |
|                           |              | Hotelling’s \( T_{\sum p_m, N}^2 \) | 54          | 135          | 0.81         | 0.80         | 0.78         | 0.77         |
|                           |              | Hotelling’s \( T_{\sum p_m, N-q-1}^2 \) | 54          | 135          | 0.80         | 0.78         | 0.77         | 0.78         |
|                           | 70%          | \( \sum p_m \) | 65          | 182          | 0.80         | 0.80         | 0.78         | 0.80         |
|                           |              | Hotelling’s \( T_{\sum p_m, N}^2 \) | 73          | 190          | 0.80         | 0.78         | 0.78         | 0.78         |
|                           |              | Hotelling’s \( T_{\sum p_m, N-q-1}^2 \) | 73          | 190          | 0.80         | 0.78         | 0.78         | 0.78         |
| Decreasing                | 100%         | \( \sum p_m \) | 46          | 127          | 0.81         | 0.81         | 0.80         | 0.80         |
|                           |              | Hotelling’s \( T_{\sum p_m, N}^2 \) | 54          | 135          | 0.81         | 0.80         | 0.79         | 0.79         |
|                           |              | Hotelling’s \( T_{\sum p_m, N-q-1}^2 \) | 54          | 135          | 0.80         | 0.79         | 0.79         | 0.80         |
|                           | 70%          | \( \sum p_m \) | 65          | 182          | 0.80         | 0.80         | 0.82         | 0.80         |
|                           |              | Hotelling’s \( T_{\sum p_m, N}^2 \) | 73          | 190          | 0.80         | 0.80         | 0.78         | 0.81         |
|                           |              | Hotelling’s \( T_{\sum p_m, N-q-1}^2 \) | 73          | 190          | 0.80         | 0.78         | 0.78         | 0.81         |

TABLE 8 Sample sizes calculation based on coverage probability (CP) when \( \sigma_d^2 \) is not constant over \( d \), i.e. linearly increasing or decreasing over \( d \). We have \( M = 4 \), where \( M_0 = 3 \) and \( M_1 = 1 \) and \( \rho = 0 \). The correct trends are linear increasing until reaching maximum at 28th day and constant trend afterwards. The precision of initial standardized proximal effect sizes are 0.0001. We consider the precision of average standardized proximal effect sizes (ES) 0.1 and 0.06. The desired CP is 95%. One decision time point per day and study periods are 180 days. At each time point, the expected availabilities are 100% and 70%.

| Trend of \( \sigma_d^2 \) | Availability | Test Statistics | Sample Size | Formulated CP | Monte Carlo CP |
|---------------------------|--------------|----------------|-------------|--------------|--------------|
|                           |              |                | 0.1         | 0.06         | 0.06         | 0.1          | 0.06         | 0.06         |
| Increasing                | 100%         | \( \sum p_m \) | 47          | 132          | 0.95         | 0.95         | 0.96         | 0.95         |
|                           |              | Hotelling’s \( T_{\sum p_m, N}^2 \) | 59          | 143          | 0.95         | 0.95         | 0.95         | 0.95         |
|                           |              | Hotelling’s \( T_{\sum p_m, N-q-1}^2 \) | 59          | 143          | 0.95         | 0.95         | 0.96         | 0.95         |
|                           | 70%          | \( \sum p_m \) | 67          | 188          | 0.95         | 0.95         | 0.95         | 0.95         |
|                           |              | Hotelling’s \( T_{\sum p_m, N}^2 \) | 79          | 199          | 0.95         | 0.95         | 0.96         | 0.95         |
|                           |              | Hotelling’s \( T_{\sum p_m, N-q-1}^2 \) | 79          | 200          | 0.95         | 0.95         | 0.94         | 0.95         |
| Decreasing                | 100%         | \( \sum p_m \) | 47          | 132          | 0.95         | 0.95         | 0.94         | 0.94         |
|                           |              | Hotelling’s \( T_{\sum p_m, N}^2 \) | 59          | 143          | 0.95         | 0.95         | 0.95         | 0.96         |
|                           |              | Hotelling’s \( T_{\sum p_m, N-q-1}^2 \) | 59          | 143          | 0.95         | 0.95         | 0.96         | 0.96         |
|                           | 70%          | \( \sum p_m \) | 67          | 188          | 0.95         | 0.95         | 0.95         | 0.94         |
|                           |              | Hotelling’s \( T_{\sum p_m, N}^2 \) | 79          | 199          | 0.95         | 0.95         | 0.95         | 0.95         |
|                           |              | Hotelling’s \( T_{\sum p_m, N-q-1}^2 \) | 79          | 200          | 0.95         | 0.95         | 0.96         | 0.95         |
TABLE 9  Sample sizes calculation based on power (P) when $e_{id} = \phi e_{i,d-1} + \nu_{id}$, where $\phi=0.5$ and $-0.5$ and $\nu_d$ are i.i.d Normal(0, 0.75). We have $M = 4$, where $M_0 = 3$ and $M_1 = 1$ and $\rho = 0$. The correct trends are linear increasing until reaching maximum at 28\textsuperscript{th} day and constant trend afterwards. The initial standardized proximal effect sizes are 0.0001. We consider the average standardized proximal effect sizes (ES) 0.1 and 0.06. The significance level is 0.05. The desired P is 0.80. One decision time point per day and study periods are 180 days. At each time point, the expected availabilities are 100% and 70%.

| $\phi$ | Availability | Test Statistics | Average standardized proximal effect size |
|--------|--------------|----------------|------------------------------------------|
|        |              |                | Formulated P | Monte Carlo P |                      |
|        |              | Sample Size    | 0.1  | 0.06 | 0.06 | 0.1  | 0.06 |                      |
| 0.5    | 100%         | $\chi^2_{\sum p_{\text{Ne}}}$ | 46   | 127  | 0.81 | 0.80 | 0.82 |                      |
|        |              | Hotelling’s $T^2_{\sum p_{\text{Ne}},N}$ | 54   | 135  | 0.81 | 0.80 | 0.78 | 0.77                  |
|        |              | Hotelling’s $T^2_{\sum p_{\text{Ne}},N-q-1}$ | 54   | 135  | 0.80 | 0.80 | 0.78 |                      |
| 0.5    | 70%          | $\chi^2_{\sum p_{\text{Ne}}}$ | 65   | 182  | 0.80 | 0.80 | 0.79 | 0.81                  |
|        |              | Hotelling’s $T^2_{\sum p_{\text{Ne}},N}$ | 73   | 190  | 0.80 | 0.80 | 0.79 | 0.78                  |
|        |              | Hotelling’s $T^2_{\sum p_{\text{Ne}},N-q-1}$ | 73   | 190  | 0.80 | 0.80 | 0.77 | 0.79                  |
| -0.5   | 100%         | $\chi^2_{\sum p_{\text{Ne}}}$ | 46   | 127  | 0.81 | 0.80 | 0.80 | 0.81                  |
|        |              | Hotelling’s $T^2_{\sum p_{\text{Ne}},N}$ | 54   | 135  | 0.81 | 0.80 | 0.83 | 0.79                  |
|        |              | Hotelling’s $T^2_{\sum p_{\text{Ne}},N-q-1}$ | 54   | 135  | 0.80 | 0.80 | 0.80 | 0.77                  |
| -0.5   | 70%          | $\chi^2_{\sum p_{\text{Ne}}}$ | 65   | 182  | 0.80 | 0.80 | 0.80 | 0.82                  |
|        |              | Hotelling’s $T^2_{\sum p_{\text{Ne}},N}$ | 73   | 190  | 0.80 | 0.80 | 0.78 | 0.82                  |
|        |              | Hotelling’s $T^2_{\sum p_{\text{Ne}},N-q-1}$ | 73   | 190  | 0.80 | 0.80 | 0.79 | 0.78                  |

TABLE 10  Sample sizes calculation based on coverage probability (CP) when $e_{id} = \phi e_{i,d-1} + \nu_{id}$, where $\phi=0.5$ and $-0.5$ and $\nu_d$ are i.i.d Normal(0, 0.75). We have $M = 4$, where $M_0 = 3$ and $M_1 = 1$. The correct trends are linear increasing until reaching maximum at 28\textsuperscript{th} day and constant trend afterwards. The precision of initial standardized proximal effect sizes are 0.0001. We consider the precision of average standardized proximal effect sizes (ES) 0.1 and 0.06. The desired CP is 95%. One decision time point per day and study periods are 180 days. At each time point, the expected availabilities are 100% and 70%.

| $\phi$ | Availability | Test Statistics | Average standardized proximal effect size |
|--------|--------------|----------------|------------------------------------------|
|        |              |                | Formulated CP | Monte Carlo CP |                      |
|        |              | Sample Size    | 0.1  | 0.06 | 0.06 | 0.1  | 0.06 |                      |
| 0.5    | 100%         | $\chi^2_{\sum p_{\text{Ne}}}$ | 47   | 132  | 0.95 | 0.95 | 0.96 | 0.95                  |
|        |              | Hotelling’s $T^2_{\sum p_{\text{Ne}},N}$ | 59   | 143  | 0.95 | 0.95 | 0.95 | 0.94                  |
|        |              | Hotelling’s $T^2_{\sum p_{\text{Ne}},N-q-1}$ | 59   | 143  | 0.95 | 0.95 | 0.95 | 0.96                  |
| 0.5    | 70%          | $\chi^2_{\sum p_{\text{Ne}}}$ | 67   | 188  | 0.95 | 0.95 | 0.96 | 0.95                  |
|        |              | Hotelling’s $T^2_{\sum p_{\text{Ne}},N}$ | 79   | 199  | 0.95 | 0.95 | 0.95 | 0.95                  |
|        |              | Hotelling’s $T^2_{\sum p_{\text{Ne}},N-q-1}$ | 79   | 200  | 0.95 | 0.95 | 0.95 | 0.95                  |
| -0.5   | 100%         | $\chi^2_{\sum p_{\text{Ne}}}$ | 47   | 132  | 0.95 | 0.95 | 0.94 | 0.95                  |
|        |              | Hotelling’s $T^2_{\sum p_{\text{Ne}},N}$ | 59   | 143  | 0.95 | 0.95 | 0.95 | 0.95                  |
|        |              | Hotelling’s $T^2_{\sum p_{\text{Ne}},N-q-1}$ | 59   | 143  | 0.95 | 0.95 | 0.95 | 0.96                  |
| -0.5   | 70%          | $\chi^2_{\sum p_{\text{Ne}}}$ | 67   | 188  | 0.95 | 0.95 | 0.95 | 0.94                  |
|        |              | Hotelling’s $T^2_{\sum p_{\text{Ne}},N}$ | 79   | 199  | 0.95 | 0.95 | 0.95 | 0.95                  |
|        |              | Hotelling’s $T^2_{\sum p_{\text{Ne}},N-q-1}$ | 79   | 200  | 0.95 | 0.95 | 0.95 | 0.95                  |
TABLE 11 Sample sizes calculation based on power (P) when \( \tau_d \) is not constant over \( d \), i.e. linearly increasing or decreasing over \( d \). We have \( M = 4 \), where \( M_0 = 3 \) and \( M_1 = 1 \) and \( \rho = 0 \). The correct trends are linear increasing until reaching maximum at 28\(^{th} \) day and constant trend afterwards. The initial standardized proximal effect sizes are 0.0001. We consider the average standardized proximal effect sizes (ES) 0.1 and 0.06. The significance level is 0.05. The desired P is 0.80. One decision time point per day and study periods are 180 days. The average expected availability over all time point is 70%.

| Trend of \( \tau_d \) | Test Statistics | Sample Size | Formulated P | Monte Carlo P |
|------------------------|-----------------|-------------|--------------|--------------|
|                        |                 | 0.1 | 0.06 | 0.1 | 0.06 | 0.1 | 0.06 | 0.1 | 0.06 |
| Increasing             | \( \chi^2_{\sum p_n} \) | 65  | 182  | 0.80 | 0.80 | 0.80 | 0.79 |
|                        | Hotelling’s \( T^2_{\sum p_n N} \) | 73  | 190  | 0.80 | 0.82 | 0.79 |
|                        | Hotelling’s \( T^2_{\sum p_n N - q - 1} \) | 73  | 190  | 0.80 | 0.80 | 0.78 |
| Decreasing             | \( \chi^2_{\sum p_n} \) | 65  | 182  | 0.80 | 0.80 | 0.79 | 0.79 |
|                        | Hotelling’s \( T^2_{\sum p_n N} \) | 73  | 190  | 0.80 | 0.78 | 0.77 |
|                        | Hotelling’s \( T^2_{\sum p_n N - q - 1} \) | 73  | 190  | 0.80 | 0.77 | 0.80 |

TABLE 12 Sample sizes calculation based on coverage probability (CP) when \( \tau_d \) is not constant over \( d \), i.e. linearly increasing or decreasing over \( d \). We have \( M = 4 \), where \( M_0 = 3 \) and \( M_1 = 1 \) and \( \rho = 0 \). The correct trends are linear increasing until reaching maximum at 28\(^{th} \) day and constant trend afterwards. The precision of initial standardized proximal effect sizes are 0.0001. We consider the precision of average standardized proximal effect sizes (ES) 0.1 and 0.06. The desired CP is 95%. One decision time point per day and study periods are 180 days. The average expected availability over all time point is 70%.

| Trend of \( \tau_d \) | Test Statistics | Sample Size | Formulated CP | Monte Carlo CP |
|------------------------|-----------------|-------------|--------------|--------------|
|                        | Precision of average standardized proximal effect size | 0.1 | 0.06 | 0.1 | 0.06 | 0.1 | 0.06 |
| Increasing             | \( \chi^2_{\sum p_n} \) | 67  | 188  | 0.95 | 0.95 | 0.94 | 0.95 |
|                        | Hotelling’s \( T^2_{\sum p_n N} \) | 79  | 199  | 0.95 | 0.95 | 0.95 | 0.96 |
|                        | Hotelling’s \( T^2_{\sum p_n N - q - 1} \) | 79  | 200  | 0.95 | 0.96 | 0.96 |
| Decreasing             | \( \chi^2_{\sum p_n} \) | 67  | 188  | 0.95 | 0.95 | 0.94 | 0.95 |
|                        | Hotelling’s \( T^2_{\sum p_n N} \) | 79  | 199  | 0.95 | 0.95 | 0.95 | 0.94 |
|                        | Hotelling’s \( T^2_{\sum p_n N - q - 1} \) | 79  | 200  | 0.95 | 0.94 | 0.95 | 0.95 |
FIGURE D1  
a) The study duration is 180 days with 1 decision time point a day.  
b) The number of intervention category added at the first day is 3 and added half-way through the study in days is 1.  
c) The randomization probability is based on uniform random intervention.  
d) The expected availability of each participant at each decision time point is 70%.  
e) The sample size calculation method is based on power.  
f) The test statistics is Hotelling’s $T^2$ distributed with denominator degrees of freedom $N - q - 1$.  
g) The proximal effect is increased linearly until 28-day then maintaining constantly at its maximum value. 
The initial and average values of the standardised proximal effect size for any of the intervention levels are 0.01 and 0.1 respectively.  
h) The required sample size is calculated at a nominal power of 80% and level of significance 5%.