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## FURTHER ADVANCES FOR THE SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

TIANJIAO DAI

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**FURTHER ADVANCES FOR THE SEQUENTIAL MULTIPLE  
ASSIGNMENT RANDOMIZED TRIAL (SMART)**

A

THESIS Presented to the Faculty of  
The University of Texas  
MD Anderson Cancer Center UHealth  
Graduate School of Biomedical Sciences  
in Partial Fulfillment  
of the Requirements  
for the Degree of  
DOCTOR OF PHILOSOPHY

by

Tianjiao Dai, M.S.

Houston, Texas

May, 2017

## **DEDICATION**

To all my family, my mentors and my friends,  
who have stood beside me throughout this time,  
for their help, support and love;  
I couldn't have done this without you.

## **ACKNOWLEDGEMENTS**

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I thank Dr. William Mattox, Dr. Andrew Bean, Ms. Brenda Gaughan, Ms. Lourdes Perez, and other staff members from UTHHealth-GSBS for their great help and support as I pursued my Ph.D. during the past several years.

I'm grateful for the unconditional support and love of my family. They have provided constant encouragement for me to freely pursue my academic research career. A special word of thanks also goes to my friends for their friendship and companionship. Finally, I would like to dedicate this thesis to Don Hadwin. I have been extremely fortunate in my life to have him as a teacher and friend. He has given me unconditional love and support. The relationships and bonds that I have with Don hold an enormous amount of meaning to me. He helped me build my confidence and encouraged me to pursue my Ph.D. studies in statistics. He has always been there for me through my ups and downs. I would not have made it this far without him. I hope I have made him proud.

## **ABSTRACT**

# **FURTHER ADVANCES FOR THE SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)**

Tianjiao Dai, M.S.

Advisory Professor: Sanjay Shete, Ph.D.

Sequential multiple assignment randomized trial (SMART) designs have been developed these years for studying adaptive interventions. In my Ph.D. study, I mainly investigate how to further improve SMART designs and optimize the interventions for each individual in the trial. My dissertation has focused on two topics of SMART designs.

1) Developing a novel SMART design that can reduce the cost and side effects associated with the interventions and proposing the corresponding analytic methods. I have developed a time-varying SMART design in which the time of the intervention varies among participants and contains part of the information regarding the intervention effect. We proposed two analytic approaches for analyzing the data from this type of SMART design. Based on simulations, we suggest using joint modeling as a data analysis method since it can well utilize the information of the intervention effect contained in the treatment (also referred to as intervention) time and estimate the model parameters better than the single mixed effect model. We also showed that the

proposed time-varying SMART design is more efficient than the existing standard SMARTs with respect to the cost and side effects associated with the interventions, while maintaining the same power as the standard SMART design when selecting the optimal embedded adaptive intervention.

2) Developing a new allocation strategy for SMART designs using a response-adaptive, covariate-balanced and optimal-decision-consistent randomization probability under the Bayesian framework. This method applied the existing randomization strategies in clinical trials to SMART designs by accounting for its special framework. In addition, it takes into account the optimization of the individual's intervention using a Q-learning approach in addition to being response-adaptive and balancing covariates between competing interventions at each SMART stage. This approach also takes advantage of the Bayesian framework. Using simulation studies, we compared the proposed allocation strategy to other possible and existing allocation strategies in clinical trials.

The research on SMART designs I conducted in my Ph.D. study will benefit the community of researchers in the areas of clinical trial design and social behavioral research. The novel design and analysis I proposed will increase the efficiency of SMARTs in terms of the time and cost and reduce the side effects associated with the interventions while promoting a better understanding of the optimal individualized intervention strategy. The new randomization strategy I developed for SMART designs increases the consistency of the optimal intervention strategy for each individual in the

trial, which suggests an advantage over other existing randomization methods in clinical trials that can be applied to SMART designs.



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**1 Introduction**

## **1.1 Experimental designs in clinical trials**

The design of experiments (DOE)(1-3) in clinical study is a formulation process with the goal of assessing the efficacy(4-6), safety(7) and causal mechanism(8,9) of medical products such as drugs or devices that are under development or evaluation. It is often used as a “reference standard” when judging all other types of designs. Specifically, in a DOE, we evaluate the effect of one or more factors (also called variables or covariates) on one or more response variables so that the data obtained can be analyzed to yield valid and objective conclusions. For example, in a test of a new vaccine which is developed to immunize people against the common cold, treatment condition (i.e., placebo or vaccine) is the factor to be evaluated and the number of colds reported in each treatment condition is the response variable. In the study of the effects of vitamin C and vitamin E on health, dosage of vitamin C and vitamin E are the two factors to be studied and the response variable is the number of days hospitalized. Usually, the conditions of the experiment (i.e., the levels of factors) can be manipulated (e.g. amount of dosage of vitamin C and vitamin E in the above example) and the factors (e.g. individuals’ diet) that are not of primary interest to the research objectives are controlled throughout the experiment while the results of the experiment are unknown in advance. Research goals, target populations and sampling strategies are specified before defining and conducting an experimental design. Key components of an experimental design are the experimental unit (person or community that is studied), types of variables (background, intermediate, primary

and uncontrollable), treatment structure (levels and combinations of treatments) and design structure (define the grouping of the experimental units into clusters).

Generally, the data we observe or measurements we obtain are the additive composite of the true level/value of the respondent on that measure and random error by “true score theory”(10,11), which is analogous to signal and noise in engineering. Experimental observations consist of the true effects of all variables on an outcome (signal) and the random error from the experimental technique (noise). Experimental designs are used to maximize the signal-to-noise ratio, i.e., enhance the signal or reduce the noise to improve the research quality. Among all types of experimental designs, factorial designs(12-16), randomized controlled trials(17-21) (RCTs) and crossover designs(22-28) are three of the most commonly used designs.

### **1.1.1 Factorial design**

A factorial design is often used to study the combined effects of two or more variables on an outcome by varying several factors simultaneously within a single experiment. It is a useful analytic method for cases in which the factors are interdependent. This type of design consists of several factors, each with discrete levels or values, and experimental units that take on all possible combinations (full factorial design(29-33)) or part of (fractional factorial design(12,15,34-38)) these levels across all such factors. For example, we would like to study the two intervention components-keeping a food diet(yes or no) and increasing activity(yes or no) with a factorial design, the two factors are the two interventions components

and each of them has two levels. Therefore, this is a  $2 \times 2$  (or  $2^2$ ) factorial design. Factorial designs are efficient for evaluating the effects of various combinations of factors as well as their interaction effects in one study rather than conducting a series of independent studies(39). However, factorial designs with more than two factors or many levels may suffer some difficulty because of the large number of different experimental conditions to manipulate. A meticulous plan is needed when operating a factorial design as an error in one of the levels will jeopardize the whole work.

### **1.1.2 Randomized controlled trial (RCT)**

Instead of comparing individual conditions to each other as is the goal in a factorial design, a randomized controlled trial(40-43) (RCT) is generally used when there are only two or three experimental conditions and the primary research goal is to directly compare the individual experimental conditions to each other. The two-group experimental design(18,44,45) is the simplest form of RCT, and the two groups are referred to as the experimental group and the control group. This type of RCT is used to conduct a specific study of an intervention (e.g., a medicine, therapy, diagnostic procedure, or surgical procedure) against a control (i.e., placebo or best existing treatment) by randomizing patients between the two corresponding groups. The primary interest of this type of design is to determine whether the two groups are different after the clinical application. The comparison of the two groups is based on the assumption that the two groups are comparable, which is ensured by random assignment. A secondary goal of an RCT can be to identify factors that

influence the effects of the treatment(s) under study(46-48). The RCT has been considered to be the gold standard for treatment evaluation over the past several decades because of its advantages in reducing bias through good randomization, producing results that can be analyzed with well-known statistical tools, and its clear identification of participating individuals. However, the RCT also has drawbacks as such trials are time- and cost-intensive(49), and have relatively poor performance in assessing the benefit from complex interventions that account for individual preferences or adherence, or in tailoring interventions to individual needs(50). In addition, the traditional RCT ignores the cumulative information obtained during the trial that can potentially be used to improve the results(50-53). RCTs do not allow for the manipulation of subjects or interventions during the trial, which results in a lack of heterogeneity and makes the results vulnerable to confounders. Over time, the pre-fixed and unchanged treatments that are typically used in RCTs are being replaced by adaptive interventions(54-56) in clinical and behavioral studies.

### **1.1.3 Crossover design**

In the crossover design (22,57,58), each patient receives a different treatment at a different time period during the trial. In contrast to a factorial design and most RCTs, in which patients are randomized to a treatment and remain on that treatment throughout the trial duration, patients in crossover designs switch from one treatment to another during the trial. Crossover designs are often used to study treatments to alleviate symptoms of a chronic and stable disease, with the advantage of reducing the influence of confounding factors and reducing the sample size while attaining the same level of statistical power or precision as other types of

designs(57). Although different treatments can be applied to the same patient in the crossover design, the sequence of the treatments is determined before the trial is conducted with a fixed time of administration for each treatment. Therefore, this type of design is also non-adaptive and does not take into account the patients' responses during the trial(58,59).

## **1.2 Adaptive intervention**

Adaptive interventions(60,61) are developed to allow for greater individualization and adaptation of intervention options than in the traditional fixed-intervention approach that is typical of RCTs. In some statistical literature, adaptive interventions are referred to as dynamic treatment regimes/regimens (DTRs)(62-70), tailored treatment regimens(71) or adaptive treatment strategies(72). They are operationalized as a sequence of decision rules that specify how intervention options (e.g., type, intensity, dosage of treatment) should be adapted to an individual's characteristics and changing needs as well as covariate history and response at critical decision points during the course of care. With the goal of optimizing the long-term effectiveness of the treatment, the interventions are repeatedly adjusted over time because responses differ from person to person. Adaptive interventions are particularly useful for chronic disorders for which there is no uniformly or widely effective treatment because of their ability to accommodate high heterogeneity in patients(66,72-75).

Compared to the commonly fixed interventions in RCT, in which the composition and dosage of interventions are defined before the trial is conducted and are offered uniformly to all participants, adaptive interventions can better accommodate the individualized needs of patients and therefore have the potential to be optimized. The major difference between fixed intervention and adaptive intervention is that the adaptive intervention consists of not only the treatments, but also other systemic components that can moderate the treatment effects (76). In adaptive interventions, there is interdependency among treatments, factors that moderate treatment effects, decision rules, and implementation of decision rules. Therefore, for the cases where significant variation in treatment effects is expected to be a function of identifiable tailoring variables, across participants and/or within participants over time, an adaptive intervention can be employed as an alternative approach to a fixed intervention. Conversely, if treatment effects do not vary systematically across individuals, an adaptive intervention is unlikely to show advantages over a fixed intervention.

There are four basic elements in an adaptive intervention: (1) intervention stages: each beginning with a decision of intervention, (2) intervention options at each stage regarding the types, dosages and other tactical options such as augmenting, switching or maintaining, (3) tailoring variables that contain the individual information that can be used for making decisions, and (4) a decision rule that links the tailoring variable as the input to specific intervention options as the output. There are typically two types of tailoring variables(77,78): (1) baseline tailoring variables that include information regarding an individual's characteristics



or information that is obtained before the first intervention stage, which can be used at the first stage or at subsequent stages, and (2) intermediate tailoring variables that are obtained during any decision stage and can be used to make decisions at subsequent stages. There are generally three types of research aims(79) with adaptive interventions: (1) evaluating a particular adaptive intervention; (2) finding the best tailoring variables and/or decision rules; (3) implementing the decision rules (i.e., testing or generating hypotheses to build an adaptive intervention).

Generally, adaptive interventions are developed with the goal of enhancing the strength of the adaptive intervention and maximizing replicability. Specifically, a well-designed intervention should include well-chosen and well-measured tailoring variables, and should be able to produce the same results on different samples with respect to the treatment effects(79). However, in practice, we usually do not have sufficient empirical evidence or knowledge to build a high-quality adaptive intervention for choosing the intervention stages, treatment options, useful variables and decision rules. In order to obtain the optimal interventions for each individual, sequential multiple assignment randomized trials (SMARTs)(80) are developed and applied.

### **1.3 Sequential Multiple Assignment Randomized Trial (SMART)**

#### **1.3.1 Definition and empirical examples of the SMART design**

SMART is the trial in which each individual goes through multiple stages with a critical decision point corresponding to each stage. Specifically, it involves an initial

stage in which participants are randomized to all the available intervention options such as different types of medical or behavioral treatments, followed by subsequent stages in which some or all of the individuals are re-randomized to intervention options available at that stage. Re-randomizations and intervention options at each subsequent stage depend on the information obtained from previous stages such as patient adherence or response status. Because the complexity of the SMART design increases with the number of stages, a two-stage SMART is the most commonly used design for its simplicity and ability to study various clinical problems.

According to the extent and form of incorporated tailoring variables, a two-stage SMART design can be categorized into the following four types(76). (1) SMARTs with no embedded tailoring variables, in which the intervention strategies are applied to all participants at the second stage regardless of any information observed prior to the second-stage randomization. Interventions in this type of design are actually non-adaptive because there are no embedded tailoring variables. (2) A SMART study in which re-randomization to the second-stage intervention options depends on an intermediate outcome, i.e., a participant is re-randomized or not in the second stage depending on his/her response status (responder/non-responder) to the first-stage intervention. (3) SMARTs in which re-randomization to different second-stage intervention options depends on an intermediate outcome, i.e., intervention options of the second stage are different for responders and non-responders to the first stage. (4) SMARTs in which the determination of whether to re-randomize or not depends on both an intermediate

outcome and prior treatment, which uses more information obtained before the second stage than the other three types of SMARTs described here.

Several empirical examples that have used SMART designs are listed here:

(1) A study of smoking cessation(78) in which a two-stage SMART was conducted to find an optimal multi-factor behavioral intervention to help smokers quit smoking and follow-up strategies for them; (2) An adaptive treatment study of children with attention deficit hyperactivity disorder (i.e., ADHD)(76,77,80), with the primary aim of choosing the initial treatment between pharmacological and behavioral interventions and the secondary aim of choosing a second-stage intervention for children who have insufficient response; (3) A study of adaptive reinforcement-based treatment for pregnant drug abusers (RBT)(81,82) to choose an intervention that intensifies, decreases, or is supplemented on the basis of patient response; (4) A SMART design for comparing attendance-based prize contingency management (CM) to treatment without incentives as well as testing the length and timing of CM(83).

### **1.3.2 SMART and MOST**

Multiphase Optimization Strategy (MOST)<sup>(84)</sup> was proposed by Collins et al. as a new approach to systematically and efficiently optimize behavioral interventions. MOST consists of three phases: a screening phase for selecting active intervention components, a refining phase for fine tuning and optimizing the selected components, and a confirming phase for evaluating the efficacy of the optimized interventions. MOST, like SMART, is based on randomized experimentation. Although MOST and SMART can be seen as two separate approaches for building

optimal interventions for patients, SMART can also be integrated into MOST to increase the potency of adaptive interventions. Because the refining phase in MOST features the same goal as that of SMART, a SMART can be used to identify the best adaptive intervention strategy by choosing the intervention types and levels. The best adaptive intervention selected through a SMART is then tested and evaluated by RCTs in the confirming phase of MOST.

### **1.3.3 Similarities and differences between SMART and other experimental designs**

As a relatively new type of experimental design, SMART has some similarities to traditional designs (e.g., the factorial design and RCT). Although the randomization in SMART designs permits an unbiased comparison, which is true of the RCT and factorial design, it differs in terms of the actual conduct of the trial. In particular, randomization in a SMART occurs repeatedly (e.g. 2 or 3 times) over time to promote unbiased comparisons between the intervention components at each stage for developing an adaptive intervention. In addition, restrictions based on the intermediate outcome may apply to the randomization in SMART, which also differs from that of the factorial design and RCT.

When compared to adaptive designs in a clinical study, SMART designs involve different stages of intervention and/or experimentation and change based on the accumulating data(85), which is similar to the adaptive designs with prospectively planned time points for modification along the trial. However, the SMART design is different from the adaptive design in many aspects. First, each

participant in a SMART goes through multiple stages of intervention; while each stage in an adaptive design involves different participants. The application of a SMART develops an optimal dynamic treatment regimen that can benefit future patients; while adaptive designs mostly focus on the most efficacious treatment based on the current knowledge available at the time a participant is randomized to the trial. The sample size, randomization probabilities and intervention options are pre-specified in the SMART, which is also different from the adaptive design, in which the factors are adjustable for different groups of people in the trial. Adaptations to interventions in SMART designs are made within the participant; whereas adaptations to interventions in adaptive designs are made between participants. However, despite the differences between the two types of designs, elements in the adaptive design can be incorporated and used in the SMART design(86,87).

SMART designs also have some operational similarity with classical crossover trial designs(23,88) in which the patients cross from one treatment to another during the course of the trial. However, they have different design structures because crossover designs are typically used to contrast the effects of stand-alone treatments; whereas SMART designs are used to develop a DTR. Additionally, decisions of intervention options are typically made on the basis of the participants' intermediate outcomes in the SMART design; whereas participants receive all the candidate interventions in crossover trials. In a crossover trial, it is crucial to exclude the carryover effects(59,89-91), whereas SMARTs make use of carryover effects to construct optimal DTRs and improve the final outcomes.

### **1.3.4 Advantages of SMART designs**

The major advantage of the SMART design is that it facilitates the development of high-quality adaptive interventions by allowing researchers to test multiple potential adaptive interventions along with the available patient-specific variables. In SMART, interventions for participants are time-varying according to the information accumulating during the trial. Several critical decision points are built into the trial, each of which corresponds to a separate stage of intervention. The effectiveness of each stage can be assessed as the participants are randomized multiple times. Several adaptive interventions embedded within a SMART can be tested and the patient-specific variables can be assessed in relation to the intervention components in the same trial. All these features have increased the popularity of SMART designs in real-world clinical studies particularly for chronic disorders, as they allow clinicians to develop the best decision rules based on research rather than a priori decisions, which is the strategy applied in the traditional two-arm RCT. SMART designs can effectively accommodate heterogeneous samples as well as baseline measures and time-varying factors.

In a multiple arm, one-stage-at-a-time, randomized trial, synergistic effects are usually detected on the basis of retrospective information about the type and intensity of the interventions that participants received prior to their response/non-response. However, in SMART designs, the interventions are manipulated prospectively, with the type and intensity recorded during the trial.

A SMART design also has the advantage of comparing multiple intervention options at each single stage and within the context of what happens in later stages while taking into account the delayed intervention effects. Specifically, a SMART design can be used to study whether the effect of one intervention is enhanced by subsequent or prior interventions. A SMART design can reduce deleterious cohort effects(92-94) because participants who stay until the end of a SMART may be more representative of the population than participants who remain in single-stage trials. Many participants drop out of single-stage trials because the set of interventions are fixed over time, which means that some participants will lack beneficial treatment options and their adherence to the protocol will decrease. In this sense, SMART is expected to be able to recruit participants who better represent the relevant population as non-responders to the standard treatment are more motivated to adhere to a trial that offers multiple and varying treatments and are more receptive to the intervention(95).

Compared to a multi-arm trial with a fully formed intervention for each arm, the SMART design enables us to understand the underlying mechanism of the intervention by using randomized comparisons. In contrast, the multi-arm trial only provides information on which arm is better. Building a multi-armed trial also requires a lot of effort and information such as clinical experience, a variety of well-established theoretical principles and results from prior trials. A SMART design can be used to identify useful patient-specific variables at each stage, which enables us to address questions of clinical and theoretical interest such as whether the

intervention provided to non-responding patients should differ depending on the patient's level of adherence to the initial intervention.

### **1.3.5 Scientific aims of SMART designs**

In a SMART design, each stage corresponds to a critical decision point and each individual many go through multiple stages. Participants are randomized one or more times according to their response status. The randomization occurs at the beginning of the intervention stages and is used to provide data for answering scientific questions concerning intervention options at that stage. The goal of a SMART is to inform the development of adaptive interventions. Three types of scientific aims that can be addressed using a SMART are (1) the main effect aim, which compares the overall effect for a treatment in a stage, (2) the embedded adaptive interventions aim, which studies the interactive effect between the intervention components between stages, and (3) the optimization aim, which finds a more optimal sequence of treatments for each individual.

Specifically, the main effect aim addresses questions such as, "What is the best initial treatment?" The answer to this question corresponds to the main effects of the first-stage intervention options. Another question is, "What is the best treatment option for non-responders?" Answering this question involves comparing the interventions among non-responders, averaging over the duration of the initial intervention, and corresponds to the main effect of the second-stage treatments. This aim is useful for finding the efficacious adaptive intervention as it provides



information, at each stage, on which intervention is more beneficial on average. Statistical hypothesis tests are generally involved in this process.

The embedded adaptive intervention aim focuses on how treatment components work with or against each other and determining the interactive effect between them. It studies all the intervention groups embedded in the SMART. The advantage of this aim is that the delayed effect can be captured when the long-term effect of earlier stages appears in later stages. It seeks to identify the best performing adaptive intervention rather than comparing two (or more) treatment options alone.

The third aim, the optimization aim, is to propose an optimal intervention for an individual based on a study of the patient-specific variables and tailored interventions available in the SMART. Patient-specific variables that can inform tailored interventions, other than those already embedded in the SMART, may be identified during this process, which may lead to sequential treatment options that are more specifically tailored to the individual patient and optimal interventions beyond the existing adaptive interventions embedded in the SMART design. Studies of this aim are very popular as it explores the potential for building a better adaptive intervention for each individual. The optimization aim identifies baseline variables that are useful for making decisions about the initial/first-stage treatment as well as other intermediate variables, other than response status, that might be useful in making decisions about the next treatment stage.

The primary aim in a SMART can be one of the three scientific aims discussed above. The choice depends on the scientific considerations specific to the area of study and application. For example, in a smoking cessation study, the primary aim is often to identify the most effective intervention at each stage, which can be accompanied by the secondary aims of studying the quality of life and cost-effectiveness associated with the interventions.

### **1.3.6 Designing a SMART**

At each critical decision point in a SMART, all information available up to that point can be viewed as the input of a certain systematic function for which the output is the recommendation about the intervention for the following stage. Specifically, participants in a SMART are assigned to their initial/first-stage intervention(s) according to their individual baseline variables. Then, at the end of the first stage, their response to the initial intervention, baseline variables and intermediate variables obtained up to that point can be used to tailor the second-stage treatment options. This process can continue to the third and even further stages while the intervention options can be further individualized by making use of the heterogeneity within the participants. The design of the SMART should follow the KISS principle(96): Keep it simple and straightforward at each intervention stage and critical decision point. Summary statistics or measurements for each stage should be low dimensional. Responder or adherence status is represented with binary indicators. The designed SMART should be easy to apply in actual clinical practice. And the treatment options in each stage should be restricted by feasibility or certain scientific considerations. Additionally, in order to develop an adaptive

intervention that is more specifically tailored to the individual patient, it is desirable to use auxiliary time-varying measures and moderators. Choosing a simple primary aim or primary aims in a SMART will aid the development of adaptive interventions while powering the SMART to test this hypothesis. Appropriate steps are important for developing a better SMART that can adapt to the needs of the individual participant.

### **1.3.7 Analytical methods of SMARTs**

Analytic methods and strategies for SMART designs depend on scientific aims. Since there are typically two or more intervention stages in a SMART and the outcomes of interest are measured after each stage, standard longitudinal data analysis methods, such as linear mixed-effect models (LMM), can be used(97). In addition, as the SMART design is also a type of factorial experimental design, analytic methods for factorial experiments that were developed for behavioral interventions can be applied. Specifically, the outcomes of participants from different subgroups can be pooled to analyze the main effects of an intervention at each stage by using a single indicator with levels that represent the types of main effects.

If there are only two types of main effects to compare, the analysis is identical to that used to analyze data arising from the RCT. A similar strategy can be applied for an analysis associated with embedded adaptive interventions. However, unlike the standard regression analyses to compare the main effects, a weighted-and-replicated regression approach is generally involved in this analysis as an

adjustment to produce valid statistical results. The weights are used to accommodate over- or under-representation of outcomes if the number of randomizations are different or the randomization probabilities are not equal across participants (for which the corresponding weights are inversely proportional to the probability of being assigned a particular intervention sequence), or participants are randomized to different numbers of intervention options(98-100). On the other hand, replication is used for the application of standard software when observations for participants are consistent with more than one embedded adaptive intervention.

Data analyses associated with the optimization aim can use the strategies applied to standard moderator analysis for data arising from RCTs. Baseline covariates can be included in the regression to help identify the effects of interventions and explain for whom the intervention effects are stronger, which is a typical approach used for RCT. Strategies for identifying useful variables to use in building better adaptive interventions in a SMART are similar to those for regressions with interactions between covariates and treatments, but with the focus on exploring not only baseline variables but also intermediate variables. Various types of machine learning strategies(101,102) can be applied for this type of optimization analysis. Q-Learning(103) and A-learning(104,105) are two main approaches for estimating the optimal treatment regime.

Q-learning uses backwards steps to construct a sequence of decision rules that link the patient-specific variables and response status to past interventions to the most efficient intervention option that can maximize the long-term primary

outcome for each individual. Each step of Q-learning corresponds to an optimization of the Q-function for that stage. Typically, the Q-function for each stage of a SMART corresponds to a regression model, including all candidate patient-specific variables available up to that stage. The optimal intervention decision for the current stage is then chosen by maximizing or minimizing the corresponding Q-function, conditional on the fact that optimal adaptive decisions are achieved for all subsequent stages. At the end of Q-learning analysis, an optimal adaptive intervention that consists of the options for each stage is proposed. This adaptive intervention can go beyond the existing adaptive interventions that are embedded in the SMART. It is common in practice to use linear regression models for the Q-functions, but they can be applied to complex relationships. There is a compromise between choosing an interpretable and relatively simple model and mitigating the risk of model misspecification through various approaches such as using flexible models and support vector regression models(106).

As an alternative method to Q-learning, advantage learning(105) (i.e., A-learning) has been developed to identify the optimal regime without specifying the Q-function. A-learning is either contrast-based or regret-based. In contrast-based A-learning, contrast functions are specified and the g-estimation(107,108) method is applied; whereas in regret-based A-learning, regret functions are implemented using iterative minimization(108). A-learning relies on correct specification of the contrast or regret functions to identify the optimal treatment regime. Although it also involves the same recursive strategy as Q-learning, A-learning may be more robust to model misspecification for consistently estimating the optimal treatment regime

since models in A-learning are only posited for contrast and regret functions for the part of the outcome regression. Nonetheless, Q-learning may be more efficient relative to A-learning in parameter estimation when the Q-functions are correctly specified. In addition, Q-learning may have practical advantages as it allows for the use of standard modeling strategies and diagnostic tools; whereas A-learning may be preferred in cases where the form of the decision rules defining the optimal regime is not overly complex.

Other types of learning methods we introduce such as BOWL and SOWL(109) are based on maximizing a nonparametric estimator of the expected long-term outcome over all DTRs. In addition to these learning approaches, Zhang et al.(110) proposed a robust estimation of the optimal DTR based on maximizing a doubly robust augmented inverse probability weighted estimator for the population mean outcome over a restricted class of regimes.

### **1.3.8 Sample size consideration of SMARTs**

Although there are generally several subgroups at the end of a SMART, this trial design does not require prohibitively large sample sizes because we are not comparing the subgroups with covariance analysis. As the basic rule that the minimum sample size for any experimental trial is determined by the primary aim for that trial(111,112), consideration for the sample size of a SMART mainly depends on its two primary aims: the main effect aim and the embedded adaptive intervention aim. When comparing the two main effects of the first-stage interventions in a SMART, data from all the subgroups that start with the same initial

treatment are combined. Therefore, the sample size required for this effect is the same as that for a two-group longitudinal RCT. Similarly, with the primary aim of the second-stage intervention, subgroups with the same second-stage treatment are combined for analysis. When considering the sample size and assuming the embedded adaptive intervention aim as the primary aim, subgroups that constitute an embedded adaptive intervention are compared to subgroups that constitute another embedded adaptive intervention in the SMART.

## **1.4 Motivation and rationale of the studies in this thesis**

### **1.4.1 Time-varying SMART design**

In the modeling analysis of SMART, baseline characteristics and main and interacting effects of the interventions at each stage are included as predictors for the outcomes of interest, which are the dependent variables. Typically, the treatment time of each stage in a SMART is fixed uniformly for all the participants. In some two-stage SMART designs, the response is assessed at several pre-fixed time points during the first stage. Once an assigned criterion is met, randomization is conducted for that individual to the second stage. Examples of such SMART designs are the study of the medication naltrexone for alcohol dependence(80,113,114) and the study of pharmacological and behavioral treatments for children with ADHD(76,80,113). Lu et al.(114) has recently developed an analytic method for such SMARTs by using repeated-measures piecewise marginal models.

However, in such a time-fixed SMART design, subjects are assessed only at fixed time points and thus the time of treatment only takes values along a finite set of time points. Considering the cost and side-effects associated with treatments, there are significant advantages to modifying or changing the current treatment options as soon as an individual achieves an intermediate response. In SMART designs, this strategy corresponds to re-randomization into the next stage, while allowing for a varying duration of treatment among participants in the current stage. Additionally, the time of each treatment is allowed to be a random variable that can take any value on a subset of the positive real line and thus reflects the corresponding treatment effect as an endogenous factor in the SMART. Specifically, for a two-stage SMART, patients can be assigned to the second stage of treatment as soon as his/her response during the first stage reaches a pre-specified goal. The treatment time of the first stage is different among the patients while partially suggesting the effect of the first-stage treatment. Such a time-varying SMART is more efficient compared to the time-fixed SMART designs in terms of cost and side-effects associated with the first-stage intervention. A modeling strategy that can take advantage of the information about the first-stage treatment in addition to the regression of the outcomes of interest is desirable for this type of time-varying SMART. In this thesis, I developed the time-varying SMART design and proposed the joint model for analyzing data obtained from such a design.

#### **1.4.2 Bayesian randomization method for SMART**



Various randomization methods have been proposed and used in experimental designs. With the development of multi-stage trials, allocation strategies that make use of information accumulating during the trials, which fit into the Bayesian framework, are applied. Response-adaptive randomization as developed by Rosenberger and Lachin(115)adjusts the randomization probabilities on the basis of the previous patients' responses, with the goal of assigning more patients to the superior treatment(s) as the trial progresses. Further development of this approach was made by Karrison et al.(116), who proposed a group-sequential response-adaptive design, Thall et al.(117), who developed an adaptive Bayesian design, and Sverdlov et al.(118), who described multiple-objective response-adaptive designs. Rosenberger et al.(119) proposed a covariate-adjusted adaptive allocation design and suggested a covariate-balanced allocation strategy to reduce the bias induced from severe covariate imbalance across treatment arms. This strategy was further developed by Signorini et al.(120), Heritier et al.(121) and others. A combination of the two approaches has been applied by Ning and Huang(122) and Yuan and Huang(123), in which the allocation method was incorporated into a group-sequential randomization design. These methods assign fewer patients to inferior treatment arms while controlling the imbalance of the covariates across treatments when the sample size is moderate or small.

It is not straightforward to apply the above randomization strategies to the SMART designs because participants are re-randomized in multiple stages and embedded interventions are involved in such designs. Randomization in a SMART considers optimizing the interventions for each participant. We can develop the

corresponding allocation probabilities on the basis of certain optimization strategies. The Q-learning algorithm provides parametric regression models that can be fitted within the Bayesian framework and thus implies an allocation probability that favors the optimal treatment options for each patient in a SMART. This probability for optimal treatment assignment can be included with the response-adaptive and covariate-balanced probabilities and then applied to the SMART design. In this thesis, I developed a new allocation strategy for SMART, which extends the existing response-adaptive and covariate-balanced randomization to multiple stages while optimizing the individualized interventions for patients in a SMART.

## **1.5 Organization of the thesis**

This dissertation discusses new designs and randomization methods for SMART designs and shows their advantages in clinical research. The organization of this thesis is as follows. Chapter 2 introduces our novel design of SMART. We first review the design and analytic methods for the standard SMART on which our new SMART design is based. Then we describe in details the proposed time-varying SMART and its corresponding data analysis methods. We show the simulation approaches and results when comparing the proposed modeling methods in chapter 2. We also compare the time-varying SMART with the standard SMART with respect to the power for selecting the optimal intervention and the cost associated with conducting the trials. Other related issues of the proposed design are discussed in the last section of chapter 2.

Chapter 3 describes a new randomization method for SMART. In the first section, we review the existing allocation strategies in a clinical trial and propose the new Bayesian randomization methods for SMART. Then we state the evaluation and simulation approaches for comparing these new methods with other randomization methods. We show the simulation results and discuss the advantage of this proposed randomization method in the last two sections of this chapter.

Chapter 4 provides a conclusion and discussion of future work for the study of SMART designs. The Appendix contains additional information and supplemental tables and figures for Chapters 2 and 3

## **2 Time-varying SMART Design and Data Analysis Methods for Evaluating Adaptive Intervention Effects**

**(Most of the methods and results in this chapter have been published in BMC Medical Research Methodology: Tianjiao Dai and Sanjay Shete, “Time-varying SMART Design and Data Analysis Methods for Evaluating Adaptive Intervention Effects”. The manuscript is currently available online BMC Med Res Methodol. 2016 Aug 30;16(1):112. doi: 10.1186/s12874-016-0202-7. According to the journal policy, the author retains the right to include the published article in full or in part in a dissertation.)**

## **2.1 SMART designs and analysis**

### **2.1.1 SMART designs**

Sequential, multiple assignment, randomized trial (SMART) designs and their analysis are being used to construct high-quality adaptive interventions that can be individualized by repeatedly adjusting the intervention(s) over time on the basis of individual progress(124-127). The SMART design was pioneered by Murphy, building on the work of Lavori and Dawson(65,128). SMART designs involve an initial randomization of individuals to different intervention options, followed by re-randomization of some or all of the individuals to another set of available interventions at the second stage. At subsequent stages, the probability and type of intervention to which individuals are re-randomized may depend on the information collected from the previous stage (e.g., how well the patient responded to the previous treatment; adherence to treatment protocol). Thus, there can be several adaptive interventions embedded within each SMART design. This allows for testing the tailored variables and the efficacy of the interventions in the same trial. There are several practical examples of SMART studies that have been conducted (e.g., the CATIE trial(129) for antipsychotic medications in patients with schizophrenia, STAR\*D for the treatment of depression(125,130), and phase II trials at MD Anderson for treating cancer(126)). The goal of these studies is to optimize the long-term outcomes by incorporating the participant's characteristics and intermediate outcomes(131) evaluated during the intervention.

### **2.1.2 Standard SMART and analytic approaches**

An example of a two-stage SMART design is a study that characterized cognition in nonverbal children with autism(127). To improve verbal capacity, participants were initially randomized to receive either a combination of behavioral interventions (Joint Attention Symbolic Play Engagement and Regulation (JASPER) + Enhanced Milieu Training (EMT)) or an augmented intervention (JASPER+EMT+ speech-generating device [SGD]). Children were assessed for early response versus slow response to the first-stage treatment at the end of 12 weeks. The second-stage interventions, administered for an additional 12 weeks, were chosen on the basis of the response status (only slow responders to JASPER+EMT were re-randomized to intensified JASPER+EMT or received the augmented JASPER+EMT+SGD; slow responders to JASP+EMT+SGD received intensified treatment; all early responders continued on the same intervention). There were three pre-fixed assessment time points: at 12 weeks, 24 weeks and 36 weeks (follow-up), which were the same for all participants in the study. Compared to multiple, one-stage-at-a-time, randomized trials, SMART designs provide better ability to compare the impact of a sequence of treatments, rather than examining each piece individually. For example, a SMART allows us to detect possible delayed effects in which an intervention at a previous stage has an effect that is less likely to occur unless it is followed by a particular subsequent intervention option. The typical modeling approach for the SMART design as described by Nahum-Shani et al. includes the indicators of intervention at each stage as covariates and thus accounts for the delayed effects on the final response. In order to develop a sequence of best decision rules for each individual, various statistical learning

methods of estimating the optimal dynamic treatment regimens have been proposed, among which Q-learning has been developed for assessing the relative quality of the intervention options and estimating the optimal (i.e., most effective) sequence of decision rules with linear regression. For a two-stage SMART, the Q-learning approach controls for the optimal second-stage intervention option when assessing the effect of the first-stage intervention, and reduces the potential bias resulting from unmeasured causes of both the tailored variables and the primary outcome. A similar approach for deriving the optimal decision rules for SMART is A-learning, which is more robust to model misspecification than Q-learning for consistent estimation of the optimal treatment regime(105). Zhao et al. introduced the two learning methods of BOWL and SOWL(109), which are based on directly maximizing over all dynamic treatment regimens (DTRs) a nonparametric estimator of the expected long-term outcome. As an alternative to the above learning approaches, Zhang et al.(110) proposed a robust estimation of the optimal dynamic treatment regimens for sequential treatment decisions, which maximizes a doubly robust augmented inverse probability weighted estimator for the population mean outcome over a restricted class of regimes. All these approaches model the outcomes of interest as dependent variables, and for the predictor variables, they model the main and interacting effects of the intervention options at each stage and the baseline individual characteristics. The amount of time an intervention is administered, however, is not explicitly modeled, although it can be used as a covariate in these regressions.

### **2.1.3 SMART with multiple pre-fixed time point of evaluation**

There are examples of SMART designs in which a participant is assessed at several pre-fixed time points during the first-stage treatment and once he/she meets an assigned criterion for response status, he/she is re-randomized to the second stage of treatment. Such a SMART design has been applied to develop a dynamic treatment regime for individuals with alcohol dependence using the medication naltrexone(80,113,114). At the beginning of the study, patients were randomized to either a stringent or a lenient criterion for early non-response. Initially, all patients received naltrexone. Starting at the end of the second week, patients who showed early response were assessed weekly for eight weeks, and those who met the assigned criterion for non-response were assigned to the second stage randomization in that week; whereas the responders were re-randomized at week eight. Another example of using a SMART design to evaluate multiple, fixed time points is the study of pharmacological and behavioral treatments for children with ADHD, where children were assessed monthly for response or non-response(80,124,132). In addition, Lu et al.(114) developed repeated-measures piecewise marginal models for comparing embedded treatments in such SMART designs with multiple evaluations at fixed time points. In these studies, subjects were assessed at fixed time points; thus, the time of treatment takes values along a finite set of time points.

#### **2.1.4 Time-varying SMART designs**

Although, SMART designs with outcome assessments at fixed time points exist, there are advantages to administering a drug as soon as an individual



achieves an intermediate response. For example, the smoking cessation drugs varenicline and bupropion can increase the risk of psychological side effects such as unusual changes in behavior, hostility, agitation, depressed mood and suicidal thoughts(133-135). In addition, varenicline costs approximately \$300 per month. Therefore, allowing the duration of treatment to vary among participants for one or more stages of the study may reduce the side effects and costs associated with the interventions. For such time-varying SMART designs, the duration of treatment plays an important role in decision making, and including it in the analysis may increase the power of the study and better serve our goal of analysis. To further extend the assignment strategies discussed in the above examples and utilize the information contained in the treatment duration, in this paper, we proposed a novel time-varying SMART design, which enables us to more efficiently assign different intervention options as soon as an individual achieves a set of intermediate response goals. Therefore, the time of treatment is a continuous random variable for each individual that can take any value on a subset of the positive real line, and is treated as an endogenous variable. The existing statistical methods are inappropriate for analyzing data obtained from such a time-varying SMART design. Therefore, to fully utilize the potential of this type of time-varying SMART design in making more efficient decisions, we also proposed two analytic approaches that can be used to analyze data from such a time-varying SMART design. The first approach is a linear mixed model with time-varying fixed effects(136,137), which is in fact a piecewise linear model. The second approach incorporates a joint modeling method in which a survival model is fitted jointly with the linear mixed model(138-

140). We performed simulations to evaluate the statistical properties of both methods. Our simulation results showed that both methods estimated the expected final outcome for each embedded adaptive intervention in the design accurately, but the joint-modeling method provided better estimates for certain parameters in the model.

To compare the power and cost efficiency of the time-varying SMART design to those of an analogous standard SMART design, we simulated two trials with identical sample sizes and intervention effects using (a) the time-varying SMART design and (b) the standard SMART design. These simulations showed that the time-varying SMART design is cost-efficient and has power similar to that of the standard SMART design in selecting the optimal embedded adaptive intervention.

## **2.2 Materials and Methods**

### **2.2.1 Proposed Time-varying SMART Design**

Figures 1 and 2 illustrate the proposed time-varying designs. Both two-stage time-varying SMARTs were designed to provide data regarding how the intensity and combination of two types of interventions might be adapted to a subject's progress in a cost- and time-efficient manner.

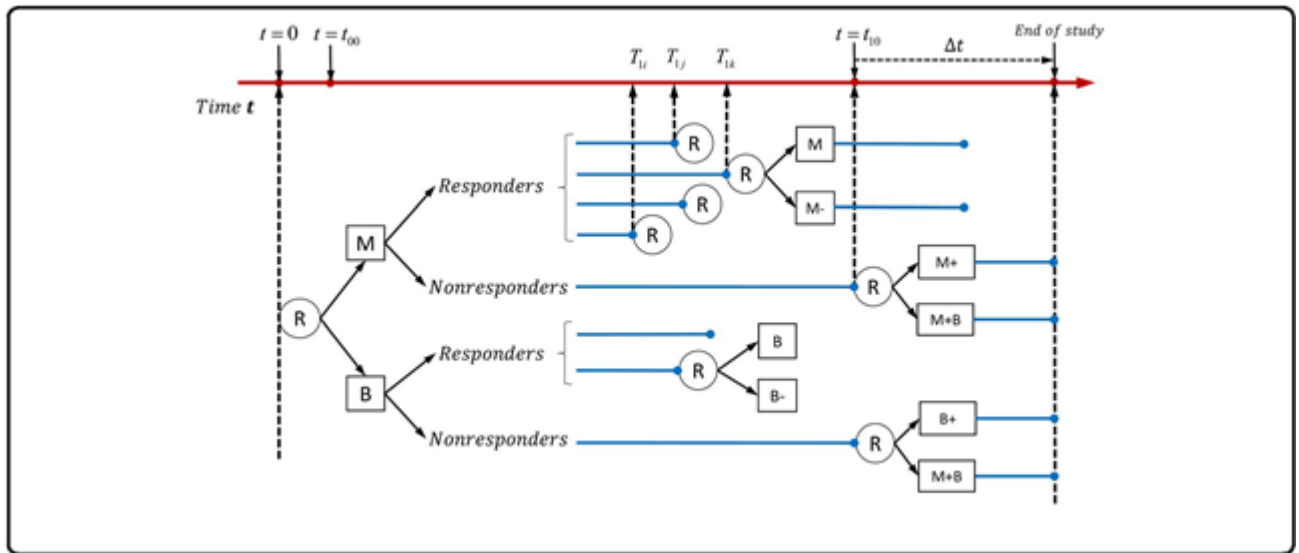


Figure 1. Example of time-varying SMART design with equal probability allocation: each participant is randomized twice

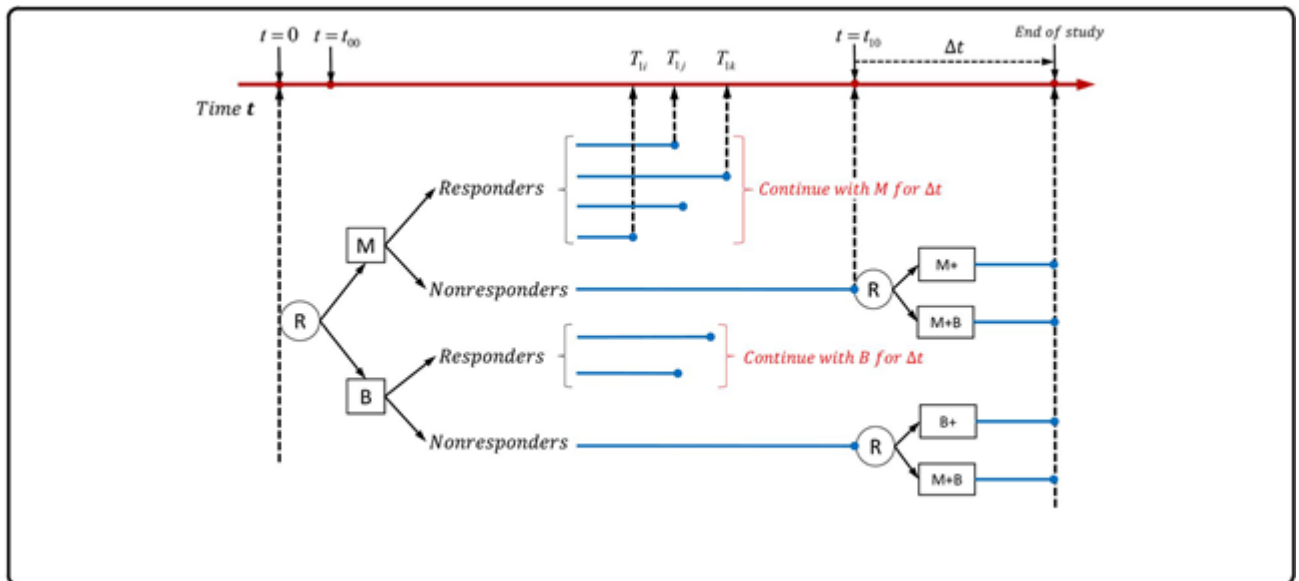


Figure 2. Example of time-varying SMART design with unequal probability allocation: only non-responders are re-randomized in the second stage

In the first example (see Figure 1), suppose medication (M) and behavioral intervention (B) are two initial intervention options for individuals who are heavy smokers (e.g., those who smoke more than or equal to 25 cigarettes per day). The number of cigarettes a subject smokes per day is the outcome of interest and is measured at the beginning of the study, at several intermediate time points and at the end of the study. Let  $Y_0$  denote the number of cigarettes a subject smoked per day at the beginning of the study ( $t=0$ ). Subjects are randomly assigned to the medication or the behavioral interventions at the beginning of the study. Monitoring the outcome of interest begins at a pre-fixed time point (e.g. one week after the initial randomization and is denoted as  $t_{00}$ ) after the initial intervention is implemented, and  $t_{10}$  denotes the time point at which those who did not respond to a first-stage intervention are re-randomized. A subject is considered a responder to the first-stage intervention if there is a significant decrease in the number of cigarettes the person smoked per day (e.g., the decrease in the number of cigarettes smoked per day is above a pre-fixed threshold, C) at an intermediate time point  $T_1$ , before  $t_{10}$ . Thus,  $T_1$  is a random variable of time and varies among responders. A subject is classified as a non-responder if the decrease in the number of cigarettes he or she smoked per day by  $t_{10}$  is below C. Therefore, all the non-responders are given the first-stage intervention for a fixed time period of  $t_{10}$  (e.g., the first month of initial interventions), which can be seen as the right-censored time point. Let  $Y_1$  denote the number of cigarettes smoked per day at the end of the first-stage intervention.

An indicator variable  $\delta$  is defined as  $\delta = I(T_1 < t_{10})$ , where  $I(\cdot)$  is the indicator function that takes the value 1 if  $T_1 < t_{10}$  (i.e., if the subject is a responder) and the value 0 if  $T_1 \geq t_{10}$  (i.e., if the subject is a non-responder). A responder is re-randomized either to continue with the first-stage intervention (M or B) or to receive the first-stage intervention at a reduced intensity (M- or B-); whereas a non-responder is re-randomized to receive the first-stage option at an increased intensity (M+ or B+) or augmented with the other type of intervention (i.e., adding a behavioral intervention for those who started with medication or adding medication for those who started with a behavioral intervention). We let all the subjects in this design stay on their second-stage interventions for a fixed time period,  $\Delta t$  (e.g., one month). Therefore, for a subject whose first-stage intervention time is  $T_1$ , the total study time is  $T_1 + \Delta t$ , which we denote as  $T_2$ . For each participant,  $Y_2$  is the final measurement of the number of cigarettes smoked per day at  $T_2$ ; see Figure 1).

The design illustrated in Figure 2 is similar to that in Figure 1 except that all the responders continue with their first-stage intervention options (i.e., each responder receives the same intervention after the response time point  $T_1$ ) (see Figure 2).

The adaptive interventions that are embedded within the two SMART designs in Figures 1 and 2 are listed in Appendix: Tables S1 and S2.

### 2.2.2 Analytic approaches

Let  $A_1$  and  $A_2$  be the indicators of the first- and second-stage intervention options, respectively. For each individual, we observe the data  $(Y_0, A_1, T_1, Y_1, A_2, Y_2, T_2, \delta)$ . The outcomes of interest are the longitudinal measurements  $Y_0, Y_1$ , and  $Y_2$ , which are fitted with a linear mixed model, assuming they share the same random intercepts at the subject level. Because the intervention options and their durations change over time in this design, we first proposed a straightforward time-varying mixed effects model (TVMEM) to analyze the outcomes. In this approach, the duration of time a treatment is administered is used as a covariate in the model. Such an approach is better than the approaches that ignore the time component of the intervention (i.e., the duration of the intervention influences its effect). However, the time duration is a random variable and one may gain statistical efficiency by treating it as a random variable in the modeling. Therefore, we also proposed a joint-modeling approach that simultaneously postulates a linear mixed effects model for the longitudinal measurements  $Y = (Y_0, Y_1, Y_2)$  and a Cox model for the survival time  $T_1$ . In particular, we fit a survival submodel for  $T_1$  jointly with the previously mentioned TVMEM that will efficiently extract the information contained in  $T_1$ .

### **2.2.2.1 Time-varying mixed effects model of $Y = (Y_0, Y_1, Y_2)$**

A linear TVMEM is fitted to the longitudinal outcomes, with interventions and their interactions and durations included as predictors. For each individual  $i$  in the study, we have

$$\begin{aligned}
Y_i(t) &= m_i(t) + \varepsilon_i(t) = Z_i \eta(t) + X_i(t) \beta(t) + b_i + \varepsilon_i(t) \\
&= Z_i \eta(t) + \beta_0(t) + \beta_1(t) A_{1i}(t) + \beta_2(t) A_{2i}(t) + \beta_3(t) t + \beta_4(t) A_{1i}(t) \cdot A_{2i}(t) + b_i + \varepsilon_i(t) \quad (1),
\end{aligned}$$

where  $m_i(t)$  is the unobserved true value of the longitudinal outcome at time point  $t$ , and  $b_i$  is the subject-level random effects and is assumed to be normally distributed with a mean of zero and variance of  $\sigma_b^2$ ;  $Z_i$  is a vector of the baseline covariates (e.g., age, sex, comorbidities, etc.) with a corresponding vector of the regression coefficients  $\eta(t)$ ;  $X_i(t)$  is the vector of the first-stage and second-stage intervention options, their interactions, and duration of intervention with a corresponding vector of the regression coefficients  $\beta(t)$ . Finally,  $\varepsilon_i(t)$  is the error term at time  $t$  and is assumed to be normally distributed and independent of  $b_i$ .

In our study design, we consider three time points at which the outcomes of interest are measured:  $t = 0$ ,  $T_{1i}$  and  $T_{2i}$ , where  $T_{1i}$  and  $T_{2i}$  are the respective time points at which individual  $i$  completes the first- and second-stage interventions. Therefore,  $A_{1i}(t)$  takes the value of  $A_{1i}$  at times  $T_{1i}$  and  $T_{2i}$  and is equal to 0 at  $t = 0$ , and  $A_{2i}(t)$  takes the value of  $A_{2i}$  at  $T_{2i}$  and is equal to 0 at time points 0, and  $T_{1i}$ . In this way,  $\eta(t)$  and  $\beta(t)$  are piecewise linear fixed coefficients; therefore, model (1) at the three time points is equivalent to the following three linear mixed-effects submodels:

$$\begin{aligned}
Y_{0i} &= Y_i(0) = m_i(0) + \varepsilon_i(0) \\
&= Z_i \eta(0) + X_i^T(0) \beta(0) + b_i + \varepsilon_i(0) \\
&= Z_i \eta_0 + \beta_{00} + b_i + \varepsilon_{0i} \quad (2),
\end{aligned}$$

$$\begin{aligned}
Y_{1i} &= Y_i(T_{1i}) = m_i(T_{1i}) + \varepsilon_i(T_{1i}) \\
&= Z_i \eta(T_{1i}) + X_i^T(T_{1i}) \beta(T_{1i}) + b_i + \varepsilon_i(T_{1i}) \\
&= Z_i \eta_1 + \beta_{01} + \beta_{11} A_{1i} + \beta_{31} T_{1i} + b_i + \varepsilon_{1i} \quad (3)
\end{aligned}$$

and

$$\begin{aligned}
Y_{2i} &= Y_i(T_{2i}) = m_i(T_{2i}) + \varepsilon_i(T_{2i}) \\
&= Z_i \eta(T_{2i}) + X_i^T(T_{2i}) \beta(T_{2i}) + b_i + \varepsilon_i(T_{2i}) \\
&= Z_i \eta_2 + \beta_{02} + \beta_{12} A_{1i} + \beta_2 A_{2i} + \beta_{32} T_{2i} + \beta_4 A_{1i} \cdot A_{2i} + b_i + \varepsilon_{2i} \\
&= Z_i \eta_2 + \beta_{02} + \beta_{12} A_{1i} + \beta_{22} A_{2Ri} + \beta_{23} A_{2NRi} + \beta_{32} T_{2i} + \beta_{41} A_{1i} \cdot A_{2Ri} + \beta_{42} A_{1i} \cdot A_{2NRi} + b_i + \varepsilon_{2i} \quad (4),
\end{aligned}$$

where in equations (2) through (4),  $Y_{0i}$ ,  $Y_{1i}$  and  $Y_{2i}$  are the outcome values at time 0,  $T_{1i}$  and  $T_{2i}$ , respectively;  $A_{1i}$  is the indicator of the first-stage intervention options (-1 for M and +1 for B),  $A_{2i} = (A_{2Ri}, A_{2NRi})$  is the indicator vector for the second-stage intervention options, where  $A_{2Ri}$  is the indicator for the second-stage intervention options for the responders to the first-stage intervention (1=continue the initial intervention; -1= reduce the intensity of the initial intervention) and  $A_{2NRi}$  is the indicator for the second-stage intervention options for the non-responders (1=increase the initial intervention; -1= augment the initial intervention with the other type of intervention), with  $A_{2Ri} = 0$  for non-responders and  $A_{2NRi} = 0$  for responders.  $A_{1i} \cdot A_{2Ri}$  and  $A_{1i} \cdot A_{2NRi}$  are the interaction effects of the first-stage intervention and second-stage intervention among responders and non-responders, respectively, in the submodel of  $Y_{2i}$  (i.e., submodel (4)). Models (1) - (4) can also be written in the form of conditional expectation as shown in supplementary information 1.1 in Appendix.



Parameters  $\eta_0, \eta_1, \eta_2$  and  $\beta_{00}, \beta_{01}, \beta_{02}$  are the coefficients of the baseline covariates and intercepts at time points 0,  $T_{1i}$  and  $T_{2i}$ , respectively; submodel (2) includes only baseline covariates as predictors for the outcomes at the beginning of the study (i.e.,  $Y_{0i}$  at  $t=0$ ); submodel (3) models the outcome of interest at the intermediate time point of the study (i.e.,  $Y_{1i}$  at  $t=T_{1i}$ ) and includes covariates  $A_{1i}$  and  $T_{1i}$ , for which the corresponding coefficients  $\beta_{11}$  and  $\beta_{31}$  account for the direct effect of  $A_{1i}$  and indirect effects through  $T_{1i}$  on  $Y_{1i}$ ; submodel (4) includes all the main and interacting effects of the intervention options at each stage and the duration  $T_{2i}$  ( $T_{2i} = T_{1i} + \Delta t$ ) as predictors, for which the coefficients  $\beta_{12}$  and  $\beta_{32}$  account for the delayed effect of  $A_{1i}$  and delayed indirect effects of  $A_{1i}$  through  $T_{2i}$ . The coefficients  $\beta_2 = (\beta_{22}, \beta_{23})$  and  $\beta_4 = (\beta_{41}, \beta_{42})$  account for the effects of the second-stage interventions and the effects of their interactions with the first-stage interventions on the final outcome  $Y_{2i}$  (measured at the end of the study,  $T_{2i}$ ).

In appendix, we also provided conditional expectations of the final outcomes for each of the 8 embedded adaptive interventions in the SMART design of Figure 1 in supplementary information 1.2 and four embedded adaptive interventions in the SMART design of Figure 2 in supplementary information 1.3.

#### 2.2.2.2 Joint model

In addition to the TVMEM, we postulate a relative risk model for  $T_{1i}$  (time to the event of interest) as

$$h_i(t) = h_0(t) \exp\{\gamma_1 A_{1i} + \gamma_2 W_i + \alpha m_i(0)\}, \quad (5)$$

where  $W_i$  is a vector of the baseline covariates, which could be different from vector  $Z_i$  in model (1), and  $h_0(\cdot)$  is the baseline risk function. The underlying longitudinal measurement  $m_i(0)$  at baseline (i.e., at time point  $t=0$ ), as approximated by the TVMEM, and at the first-stage intervention  $A_{1i}$  are included as predictors in model (5) because the time point at which an individual responds to the first-stage intervention (i.e.,  $T_{1i}$ ) depends only on the type of first-stage intervention the subject received and the baseline covariates.

We jointly estimate the coefficients in models (1) and (5) by using the maximum likelihood estimation method. To define the joint distribution of the time-to-event and longitudinal outcomes, we assume that the random effect  $b_i$  underlies both the longitudinal and survival processes for each subject. This means that the random effect accounts for both the association between the longitudinal and event outcomes and the correlation between the repeated measurements in the longitudinal process. We also assume that the longitudinal outcomes  $\{Y_{0i}, Y_{1i}, Y_{2i}\}$  are independent of the time  $T_{1i}$  conditional on the random effect  $b_i$ . Therefore, the joint likelihood contribution for the  $i$ th subject can be formulated as  $p(T_{1i}, \delta_i, Y_i; \theta) = \int p(T_{1i}, \delta_i | b_i; \beta, \gamma, \alpha, \eta) [\prod_j p\{Y_i(t_{ij}) | b_i; \beta, \eta\}] p(b_i; \sigma_b) db$ , where  $p\{Y_i(t_{ij}) | b_i; \beta, \eta\}$  is the univariate normal density for the longitudinal responses at time point  $t_{ij}$ , which is the element from the vector  $t_i = \{t_{si}\}_{s=0}^2 = \{0, T_{1i}, T_{2i}\}$ ;  $p(b_i; \sigma_b)$  is the normal density with

standard deviation  $\sigma_b$  for the random effects  $b_i$ ; and  $p(T_{1i}, \delta_i | b_i; \beta, \gamma, \alpha, \eta)$  is the likelihood for the time to the intermediate outcome and can be written as

$$p(T_{1i}, \delta_i | b_i; \beta, \gamma, \alpha, \eta) = \{h_i(T_{1i} | m_i(0); \beta, \gamma, \alpha, \eta)\}^{\delta_i} \cdot S_i(T_{1i} | m_i(0), A_{1i}; \beta, \gamma, \alpha, \eta) = \\ \{h_i(T_{1i} | m_i(0); \beta, \gamma, \alpha, \eta)\}^{\delta_i} \cdot \exp\left\{-\int_0^{T_{1i}} h_i(s | m_i(0); \beta, \gamma, \alpha, \eta) ds\right\}, \text{ where } \delta_i = I(T_{1i} < t_{10}).$$

Parameters in the model are estimated by maximizing the corresponding log-likelihood function with respect to  $(\beta, \gamma, \alpha, \eta)$ . We obtained the maximum likelihood estimates using the R package “JM”(141,142).

The parameters  $(\beta_{12}, \beta_{22}, \beta_{23}, \beta_{32}, \beta_{41}, \beta_{42})$  in submodel (4) (i.e., the model of final outcome  $Y_2$ ) are of primary interest and were estimated using the two approaches described above.

The data organization and implementation of these methods are presented in supplementary information 2 and 3 in Appendix.

## 2.3 Simulations

### 2.3.1 Simulation approach 1

For the example illustrated in Figure 1, we considered two simulation scenarios in which  $Y_0$  and  $Y_1$  were simulated using submodels (2) and (3), respectively, and  $Y_2$  was simulated with and without the interaction terms  $(A_{1i} \cdot A_{2Ri}$  and  $A_{1i} \cdot A_{2NRi})$  in submodel (4). In both scenarios, we simulated 500 replicates of  $n=1000$  individuals, and randomly assigned subjects (with probability 0.5) to one of

the two first-stage interventions (i.e.,  $A_1$  to be equal to 1 [behavioral intervention] or -1 [medication]). Responders and non-responders to the initial interventions were then re-randomized (with probability .5) to one of the corresponding second-stage intervention options (i.e.,  $A_{2R}$  and  $A_{2NR}$  were randomly assigned to be 1 or -1 and  $A_{2R}=0$  for non-responders and  $A_{2NR}=0$  for responders; see Figure 1). In both scenarios, the random effects  $\{b_i\}_{i=1}^n$  for subjects  $i = 1, 2, \dots, n$  were generated from the normal distribution with a mean of 0 and a standard deviation of 5, and baseline outcomes  $\{Y_{0i}\}_{i=1}^n$  were simulated using submodel (2) with parameters  $\beta_{00} = 10$  and  $\varepsilon_{2i} \sim N(0, 4^2)$ . The intermediate outcomes  $\{Y_{1i}\}_{i=1}^n$  were simulated using submodel (3) with parameters  $\beta_{01} = 1, \beta_{11} = 0.2$ , and  $\beta_{31} = 0.1$  in the first scenario; whereas outcomes  $\{Y_{1i}\}_{i=1}^n$  in the second scenario were simulated with  $\beta_{01} = 1, \beta_{11} = 0.6$ , and  $\beta_{31} = 0.1$ , with a standard deviation of 5 (i.e.,  $\varepsilon_{1i} \sim N(0, 5^2)$ ) in both scenarios and satisfying the conditions  $Y_{0i} - Y_{1i} \geq 9$  (C=9) if subject  $i$  is a responder and  $Y_{0i} - Y_{1i} < 9$  if subject  $i$  ( $i = 1, 2, \dots, n$ ) is a non-responder.

The time points  $T_{1i}$  were generated from a left-truncated Weibull distribution (truncated from  $t_{00}=0.1$ , the start time for monitoring), with shape=1 and scale= $\exp\{\gamma_0 + \gamma_1 A_{1i} + \alpha m_i(0)\}$ , where  $\gamma_0 = -1.5$ ,  $\gamma_1 = 0.4$ , and  $\alpha = 0.25$ , and those for whom  $T_{1i}$  was greater than 1 (non-responders), were assigned  $T_{1i} = t_{10} = 1$  (the maximum time the first-stage intervention is administered [t10]). The indicator of response status was then defined by  $\delta_i = I(T_{1i} < 1)$ . The final outcomes  $Y_{2i}$  ( $i = 1, \dots, n$ )

were generated using submodel (4), with  $\varepsilon_{2i} \sim N(0, 5^2)$ . The values of the other parameters in submodel (4) are reported in Table 1 (without interactions) and Table 2 (with interactions).

For the intervention strategy depicted in Figure 1, there are eight adaptive interventions imbedded in the design and represented by the three indicators  $A_1, A_{2R}$ , and  $A_{2NR}$ . For example, in adaptive intervention  $(A_1, A_{2R}, A_{2NR}) = (-1, 1, 1)$ , participants are initially randomized to the medication ( $A_1 = -1$ ); those who respond are re-randomized to continue on the medication ( $A_{2R} = 1$ ) and those who do not respond are re-randomized to increased medication ( $A_{2NR} = 1$ ). Another example of an adaptive intervention is  $(A_1, A_{2R}, A_{2NR}) = (1, 1, -1)$ , in which participants are initially randomized to a behavioral intervention ( $A_1 = 1$ ); those who respond are re-randomized to continue on the behavioral intervention ( $A_{2R} = 1$ ), and those who do not respond are re-randomized to an augmented arm (M+B,  $A_{2NR} = -1$ ).

For the design in Figure 2, only the non-responders are re-randomized in the second stage. Therefore, there are four embedded adaptive interventions in this design, which are represented by the vector of two indicators  $(A_1, A_{2NR})$ . For example  $(-1, -1)$  represents the adaptive intervention in which participants are initially randomized to medication ( $A_1 = -1$ ) and those who do not respond are re-randomized to the augmented arm (M+B,  $A_{2NR} = -1$ ), whereas responders continue on the medication arm.

Using this design, we also simulated the treatment of 1000 subjects. However, instead of using equal probability allocations as in Figure 1, we used unequal probability allocations at both stages. Specifically, each of the 1000 subjects were initially assigned to either  $A_1 = -1$  (medication) or  $A_1 = 1$  (behavioral intervention) with probabilities 0.4 and 0.6, respectively. Then, the non-responders were re-allocated into either  $A_{2NR} = -1$  (augmented first-stage intervention, M+B) or  $A_{2NR} = 1$  (intensified first-stage intervention, M+ or B+) with probabilities 0.55 and 0.45, respectively; whereas all responders were continued on their initial interventions (therefore,  $A_{2R} = 0$ ). Random effects ( $b_i$ ), errors ( $\varepsilon_i$ ), and longitudinal outcomes ( $Y_{0i}, Y_{1i} (i = 1, \dots, n)$ ) were generated as described for Figure 1. The final outcomes,  $Y_{2i} (i = 1, \dots, n)$ , were also generated using submodel (4), but without the variable  $A_{2Ri}$ , with the parameter values reported in Tables 3 and 4 for the two scenarios, respectively. In the first scenario, outcomes  $Y_{2i} (i = 1, \dots, n)$  were simulated without interaction terms and with the parameter values shown in Table 3; in the second scenario, outcomes  $Y_{2i} (i = 1, \dots, n)$  were simulated with interaction terms and with the parameter values shown in Table 4.

### 2.3.2 Simulation approach 2

For the design illustrated in Figure 1, we performed an alternate simulation approach that does not simulate values for  $T_{1i}$  from the Weibull distribution. Instead, we considered a situation in which values of  $Y_{1i}$  are monitored and  $T_{1i}$  is the value

for which the  $Y_{1i}$  crosses the pre-specified boundary condition for the first time. In this simulation approach, random effects  $\{b_i\}_{i=1}^n$  and error terms  $\varepsilon_0$ ,  $\varepsilon_1$  and  $\varepsilon_2$  were all simulated the same way as described above. Baseline outcomes  $\{Y_{0i}\}_{i=1}^n = 1$  are simulated using submodel (2) with  $\beta_{00} = 2$  and  $\varepsilon_{0i} \sim N(0, 2^2)$ . Furthermore, we defined an individual  $i$ , as a responder if he/she had a certain percentage reduction in the intermediate outcome value,  $Y_{1i}$ , compared to his/her base-line value  $Y_{0i}$ . This may be a more appropriate definition of responders in some practical scenarios than a simple reduction by a fixed amount (e.g.,  $C = 9$ ) as was used in the previous simulations. In this simulation, those with a 40% reduction from their baseline values were considered responders. The parameter values used for submodel (3) were  $\beta_{01} = -2$ ,  $\beta_{11} = -0.5$ , and  $\beta_{31} = 5$ . For an individual  $i$ , we first simulated  $\varepsilon_{1i} \sim N(0, 2^2)$  and calculated  $T_{1i}^*$  for which the  $\beta_{01} + \beta_{11}A_{1i} + \beta_{31}T_{1i}^* + b_i + \varepsilon_{1i}$  equals the 40% reduction from  $Y_{0i}$ , the baseline value. Therefore, we define  $T_{1i} = t_{00}$ , if  $T_{1i}^* < t_{00}$ ;  $T_{1i} = T_{1i}^*$ , if  $t_{00} \leq T_{1i}^* \leq t_{10}$ ; and  $T_{1i} = t_{10}$ , if  $T_{1i}^* \geq t_{10}$ . Then,  $T_{1i}$  is substituted in the right side of equation (3) to obtain the value of  $Y_{1i}$  for the individual  $i$  ( $i = 1, \dots, n$ ). The final outcomes  $Y_{2i}$  ( $i = 1, \dots, n$ ) were generated using submodel (4), with  $\varepsilon_{2i} \sim N(0, 2^2)$ . As previously, we simulated 500 replicates of  $n = 1000$  individuals in each trial, and randomly assigned subjects (with probability 0.5) to one of the two first-stage interventions (i.e.,  $A_1$  to be equal to 1 [behavioral intervention] or  $-1$  [medication]). Responders and non-responders to the initial interventions were then re-randomized (with probability 0.5) to one of the corresponding second-stage

intervention options (i.e.,  $A_{2R}$  and  $A_{2NR}$  were randomly assigned to be 1 or  $-1$  and  $A_{2R} = 0$  for non-responders and  $A_{2NR} = 0$  for responders; see Figure 1.).

We evaluated the performance of our two proposed analytic approaches in these simulated data sets by measuring the (a) means of the estimates of each of the adaptive interventions embedded in the design, (b) parameter estimates in the model, (c) mean squared error (MSE), (d) estimated coverage probability of the 95% confidence interval, and (e) length of the confidence interval.

Using these simulations parameters, we simulated two trials with identical sample sizes: (a) the time-varying SMART design and (b) the standard SMART design. We evaluated the performance of the time-varying SMART design and an analogous standard SMART design by measuring the (a) power to select the optimal embedded intervention, and (b) associated cost.

## 2.4 Results

Tables 1-4 show the results of the two simulation scenarios based on the design shown in Figure 1. Similarly, Tables 5-8 show the results of the two simulation scenarios for the design in Figure 2.

In Table 1 the true parameters were the coefficient of the first-stage interventions,  $\beta_{12} = 0.4$ ; coefficient of the second-stage intervention for responders,  $\beta_{22} = 0.5$ ; coefficient of the second-stage intervention for non-responders,  $\beta_{23} = 0.5$ ; and coefficient of T2, the total time of the first- and second-stage interventions,  $\beta_{32} = 2$ . The estimates obtained using TVMEM were  $\hat{\beta}_{12} = 0.275$ ,  $\hat{\beta}_{22} = 0.503$ ,  $\hat{\beta}_{23}$



$= 0.501$ , and  $\hat{\beta}_{32} = 4.073$ , while the estimates obtained using the joint model were  $\tilde{\beta}_{12} = 0.407$ ,  $\tilde{\beta}_{22} = 0.503$ ,  $\tilde{\beta}_{23} = 0.502$ , and  $\tilde{\beta}_{32} = 1.790$ . Both approaches estimated coefficients  $\beta_{22}$  and  $\beta_{23}$  accurately. The parameters  $\beta_{12}$  and  $\beta_{32}$  were estimated accurately using the joint model, but poorly using the TVMEM. Similarly, in terms of the MSE, the length of the 95% confidence interval, and the estimated coverage probability of the 95% confidence interval, both approaches performed similarly for estimating  $\beta_{22}$  and  $\beta_{23}$ , but joint modeling performed better for estimating  $\beta_{12}$  and  $\beta_{32}$ . For example, for  $\beta_{12}$ , the estimated coverage probability obtained using the TVMEM was 88%; whereas that obtained from the joint model was 97.8%. For each of the eight embedded adaptive interventions in the design, Table 2 shows that both approaches accurately estimated the means of the final outcome,  $E[Y_2 | (A_1, A_{2R}, A_{2NR})]$ . For example, the simulated means of the adaptive interventions  $(A_1, A_{2R}, A_{2NR}) = (-1, -1, -1)$ ,  $(-1, 1, 1)$ , and  $(1, 1, 1)$  were 4.538, 5.536, and 6.564, respectively, and the estimated means were 4.543, 5.531, and 6.569, respectively, using both the TVMEM and joint model.

**Table 1.** Simulation results for the design in Figure 1.: the estimated means, based on 500 replicates, are reported for coefficients in model (4)

Parameter estimation					
		$\beta_{12}$	$\beta_{22}$	$\beta_{23}$	$\beta_{32}$
		(first-stage interventions $A_1$ )	(second-stage interventions for responders $A_{2R}$ )	(second-stage interventions for non-responders $A_{2NR}$ )	(time of intervention $T_2$ )
True value		0.4	0.5	0.5	2
Joint Model	Estimate	0.407	0.503	0.502	1.790
	MSE	0.011	0.029	0.016	0.147
	CI%	97.8%	95.0%	96.8%	94.2%
	Length of CI	0.478	0.674	0.538	1.447
TVME M	Estimate	0.275	0.503	0.501	4.073
	MSE	0.026	0.030	0.017	4.400
	CI%	88.0%	95.6%	97.0%	0.0%
	Length of CI	0.484	0.695	0.549	1.436

CI%: Coverage probability of the 95 % confidence interval  
MSE mean squared error

**Table 2.** Simulation results for the design in Figure 1.: the estimated means, based on 500 replicates, are reported for the final outcomes of the eight adaptive interventions embedded in the design

Mean of the final outcomes								
	(-1,-1,-1)	(-1,-1,1)	(1,-1,-1)	(1,-1,1)	(-1,1,-1)	(-1,1,1)	(1,1,-1)	(1,1,1)
<b>Simulated means</b>	4.538	5.087	5.554	6.275	4.988	5.536	5.842	6.564
<b>Estimated means by Joint model</b>	4.543	5.093	5.549	6.269	4.982	5.531	5.849	6.569
<b>Estimated means by TVMEM</b>	4.543	5.093	5.549	6.269	4.982	5.531	5.849	6.569

Tables 3 and 4 show results similar to those in Tables 1 and 2, respectively. In Table 3, the coefficient of interaction of the first-stage interventions and second-stage interventions among responders is denoted by  $\beta_{41}$ , and the coefficient of interaction of the first-stage interventions and second-stage interventions among non-responders is denoted by  $\beta_{42}$ . As shown in Table 3, both TVMEM and joint modeling accurately estimated parameters  $\beta_{22}$ ,  $\beta_{23}$ ,  $\beta_{41}$ , and  $\beta_{42}$ , with little difference in the MSE, estimated coverage probability, and length of the 95% confidence interval. However, as in Table 1, the joint modeling approach estimated  $\beta_{12}$  and  $\beta_{32}$  more accurately than the TVMEM approach. For example, the true coefficient of  $T_2$  was  $\beta_{32} = 2.0$ , which was poorly estimated as 4.122 using the TVMEM and estimated as 1.626 using the joint model. Table 4 shows that the estimated means of the eight adaptive interventions obtained from both analytical approaches were identical and close to the simulated means up to the third decimal.

**Table 3.** Simulation results for the design in Figure 1: the estimated means, based on 500 replicates, are reported for coefficients in model (4) with interactions

Parameter estimation		$\beta_{12}$	$\beta_{22}$	$\beta_{23}$	$\beta_{32}$	$\beta_{41}$	$\beta_{42}$
		(first-stage interventions $A_1$ )	(second-stage interventions for responders $A_{2R}$ )	(second-stage interventions for non- responders $A_{2NR}$ )	(time of intervention $T_2$ )	(interaction term $A_1, A_{2R}$ )	(interaction term $A_1, A_{2NR}$ )
<b>True value</b>		-0.4	0.5	0.4	2.0	0.55	-0.40
<b>Joint model</b>	<b>Estimate</b>	-0.381	0.490	0.389	1.626	0.542	-0.397
	<b>MSE</b>	0.014	0.038	0.019	0.305	0.037	0.019
	<b>CI%</b>	97.4%	95.6%	96.8%	87.0%	96.8%	98.0%
	<b>Length of CI</b>	0.521	0.789	0.593	1.671	0.789	0.593
<b>TVME M</b>	<b>Estimate</b>	-0.530	0.489	0.390	4.122	0.542	-0.396
	<b>MSE</b>	0.029	0.039	0.020	4.697	0.037	0.020
	<b>CI%</b>	88.2%	95.8%	96.4%	0.0%	97.0%	97.8%
	<b>Length of CI</b>	0.525	0.809	0.605	1.618	0.809	0.605

CI%: Coverage probability of the 95 % confidence interval  
MSE mean squared error

**Table 4.** Simulation results for the design in Figure 1: the estimated means, based on 500 replicates, are reported for the final outcomes of the eight adaptive interventions embedded in the design with interactions in model (4)

Mean of the final outcomes		(-1,-1,-1)	(-1,-1,1)	(1,-1,-1)	(1,-1,1)	(-1,1,-1)	(-1,1,1)	(1,1,-1)	(1,1,1)
<b>Simulated means</b>		5.456	6.306	5.009	5.000	5.400	6.249	5.577	5.565
<b>Estimated means by Joint model</b>		5.456	6.306	5.009	5.000	5.400	6.249	5.577	5.565
<b>Estimated means by TVMEM</b>		5.456	6.306	5.009	5.000	5.400	6.249	5.577	5.565

Similar trends were observed in Tables 5-8 for the two simulations of Figure 2.  $\beta_{12}$  and  $\beta_{32}$  were better estimated using the joint modeling approach, whereas all the other parameters and the means of the final outcomes of the four adaptive interventions embedded in the design were accurately estimated using both approaches.

In Table 5, the true coefficient values of  $\beta_{12}=0.450$  and  $\beta_{32}=2.0$  were estimated as  $\hat{\beta}_{12}=0.388$  and  $\hat{\beta}_{32}=4.046$  using the TVMEM, and as  $\beta_{12}=0.456$  and  $\tilde{\beta}_{32}=1.767$  using the joint model. Coefficient  $\beta_{23}$  was accurately estimated using both models. As for the four adaptive interventions (i.e.  $(A_1, A_{2NR}) = (-1, 1), (-1, -1), (1, 1)$  and  $(1, -1)$ ) embedded in the design of Figure 2, Table 6 shows that the simulated means were 5.213, 4.802, 6.330, and 5.805, respectively, and the estimated means were 5.228, 4.790, 6.344, and 5.793, respectively, using the TVMEM, and 5.230, 4.788, 6.345, and 5.792, respectively, using the joint model.

**Table 5.** Simulation results for the design in Figure 2: the estimated means, based on 500 replicates, are reported for coefficients in model (4)

Parameter estimation		$\beta_{12}$	$\beta_{23}$	$\beta_{32}$
		(first-stage interventions $A_1$ )	(second-stage interventions for non-responders $A_{2NR}$ )	(time of intervention $T_2$ )
<b>True value</b>		0.450	0.40	2.0
	<b>Estimate</b>	0.456	0.441	1.767
<b>Joint model</b>	<b>MSE</b>	0.013	0.017	0.168
	<b>CI%</b>	95.6%	95.6%	93.6%
	<b>Length of CI</b>	0.482	0.536	1.452
	<b>Estimate</b>	0.388	0.439	4.046
<b>TVMEM</b>	<b>MSE</b>	0.016	0.017	4.297
	<b>CI%</b>	94.0%	96.0%	0.0%
	<b>Length of CI</b>	0.489	0.547	1.442

CI%: Coverage probability of the 95 % confidence interval  
MSE mean squared error

**Table 6.** Simulation results for the design in Figure 2: the estimated means, based on 500 replicates, are reported for the final outcomes of the four adaptive interventions embedded in the design

Mean of the final outcomes		(-1,1)	(-1,-1)	(1,1)	(1,-1)
<b>Simulated means</b>		5.213	4.802	6.330	5.805
<b>Estimated means by joint model</b>		5.230	4.788	6.345	5.792
<b>Estimated means by TVMEM</b>		5.228	4.790	6.344	5.793

Table 7 shows that the true parameters  $\beta_{12}=0.40$  and  $\beta_{32}=2.0$  were respectively estimated as  $\hat{\beta}_{12}=0.298$  and  $\hat{\beta}_{32}=4.308$  using the TVMEM, and as

$\tilde{\beta}_{12}=0.408$  and  $\tilde{\beta}_{32}=1.784$  using the joint model. The other two parameters,  $\beta_{23}$  and  $\beta_{42}$ , were accurately estimated using both approaches. Table 8 shows that the means were accurately estimated using both approaches.

Tables 9 and 10 show the results from the alternative simulation strategy. In Table 9 the true coefficient values of  $\beta_{12} = -0.6$  and  $\beta_{32} = -1.5$  were estimated as  $\hat{\beta}_{12} = -0.534$  and  $\hat{\beta}_{32} = -2.367$  using the TVMEM, and as  $\tilde{\beta}_{12} = -0.608$  and  $\tilde{\beta}_{32} = -1.338$  using the joint model. Coefficients  $\beta_{22}, \beta_{23}$  and the means of the final outcomes of the eight adaptive interventions embedded in the design were accurately estimated using both approaches (Table 10).

**Table 7.** Simulation results for the design in Figure 2: the estimated means, based on 500 replicates, are reported for coefficients in model (4) with interactions

Parameter estimation		$\beta_{12}$	$\beta_{23}$	$\beta_{32}$	$\beta_{42}$
		(first-stage intervention A <sub>1</sub> )	(second-stage interventions for responder A <sub>2NR</sub> )	(time of intervention T <sub>2</sub> )	(interaction term A <sub>1</sub> A <sub>2NR</sub> )
<b>True value</b>		0.4	0.4	2.0	-0.4
<b>Joint model</b>	<b>Estimate</b>	0.408	0.422	1.784	-0.400
	<b>MSE</b>	0.012	0.020	0.157	0.019
	<b>CI%</b>	98.2 %	97.2 %	95.6 %	97.2 %
	<b>Length of CI</b>	0.513	0.594	1.542	0.593
<b>TVMEM</b>	<b>Estimate</b>	0.298	0.419	4.308	-0.399
	<b>MSE</b>	0.021	0.021	5.439	0.020
	<b>CI%</b>	94.8 %	97.4 %	0.0 %	97.4 %
	<b>Length of CI</b>	0.520	0.608	1.532	0.607

CI%: Coverage probability of the 95 % confidence interval;  
MSE: mean squared error

**Table 8.** Simulation results for the design in Figure 2: the estimated means, based on 500 replicates, are reported for the final outcomes of the four adaptive interventions embedded in the design with interactions in model (4)

<b>Mean of the final outcomes</b>				
	(-1,1)	(-1,-1)	(1,1)	(1,-1)
<b>Simulated means</b>	5.487	4.622	6.032	6.059
<b>Estimated means by joint model</b>	5.502	4.610	6.047	6.046
<b>Estimated means by TVMEM</b>	5.500	4.611	6.045	6.048

**Table 9.** Simulation results from the alternative simulation approach: the estimated means, based on 500 replicates, are reported for coefficients in model (4)

<b>Parameter estimation</b>		$\beta_{12}$ (first-stage intervention $A_1$ )	$\beta_{23}$ (second-stage interventions for responder $A_{2NR}$ )	$\beta_{32}$ (time of intervention $T_2$ )	$\beta_{42}$ (interaction term $A_1 \cdot A_{2NR}$ )
<b>True value</b>		-0.6	0.5	0.4	-1.5
	<b>Estimate</b>	-0.608	0.492	0.447	-1.338
<b>Joint model</b>	<b>MSE</b>	0.002	0.003	0.018	0.034
	<b>CI%</b>	97 %	96 %	87 %	70 %
	<b>Length of CI</b>	0.199	0.192	0.376	0.411
	<b>Estimate</b>	-0.534	0.492	0.448	-2.367
<b>TVMEM</b>	<b>MSE</b>	0.007	0.003	0.020	0.763
	<b>CI%</b>	74 %	93 %	84 %	0 %
	<b>Length of CI</b>	0.197	0.191	0.376	0.529

CI%: Coverage probability of the 95 % confidence interval

MSE mean squared error



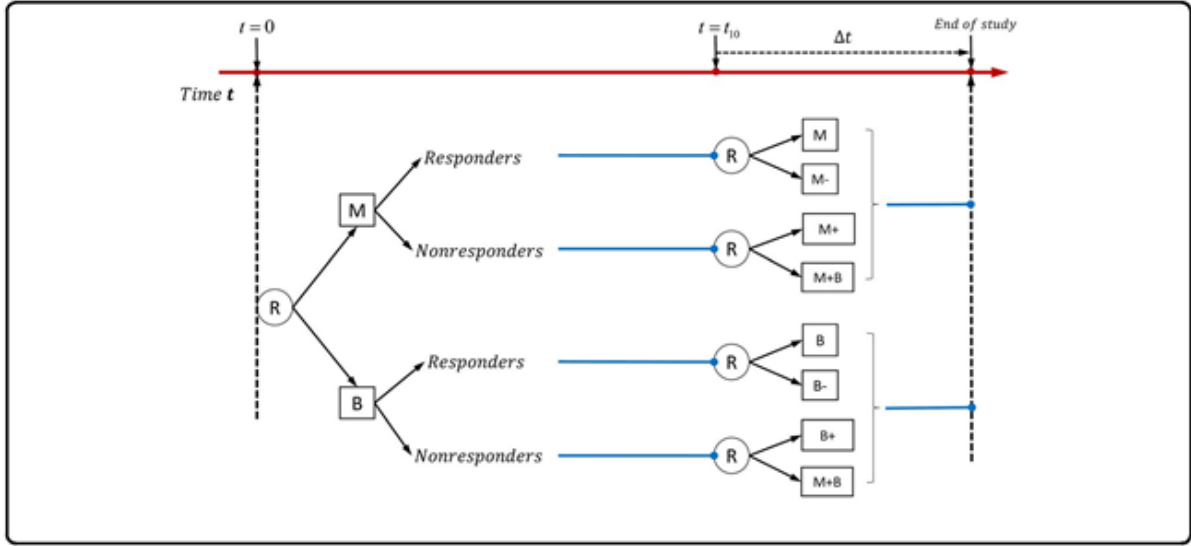
**Table 10.** Simulation results from the alternative simulation approach: the estimated means, based on 500 replicates, are reported for the final outcomes of the eight adaptive interventions embedded in the design

<b>Mean of the final outcomes</b>								
	(-1,-1,-1)	(-1,-1,1)	(1,-1,-1)	(1,-1,1)	(-1,1,-1)	(-1,1,1)	(1,1,-1)	(1,1,1)
<b>Simulated means</b>	-0.208	-0.070	-1.589	-1.356	0.678	0.810	-0.918	-0.689
<b>Estimated means by Joint model</b>	-0.203	-0.066	-1.595	-1.359	0.675	0.804	-0.915	-0.683
<b>Estimated means by TVMEM</b>	-0.203	-0.063	-1.594	-1.363	0.672	0.804	-0.912	-0.684

## 2.5 Comparison of power between the time-varying SMART design and the standard SMART design

We analyzed the time-varying SMART design's ability to select the most optimal embedded intervention and compared the associated power to that of the standard SMART design. We performed the comparison by conducting two trials with identical sample sizes and intervention effects using (a) the time-varying SMART design and (b) the standard SMART design. Figure 3 represents the standard SMART design that is analogous to the time-varying SMART design depicted in Figure 1. The major difference between the two designs is that in the time-varying SMART design, a responder is re-randomized to the second-stage intervention at a random response time  $T_1 (< t_{10})$ ; whereas in the standard SMART design, everyone is re-randomized at a fixed time point  $t_{10}$ . Responders are defined similarly in both designs. In our example, a subject is considered a responder to the first-stage intervention if there is a significant decrease in the number of cigarettes

the person smoked per day. The second-stage intervention is identical for both designs.



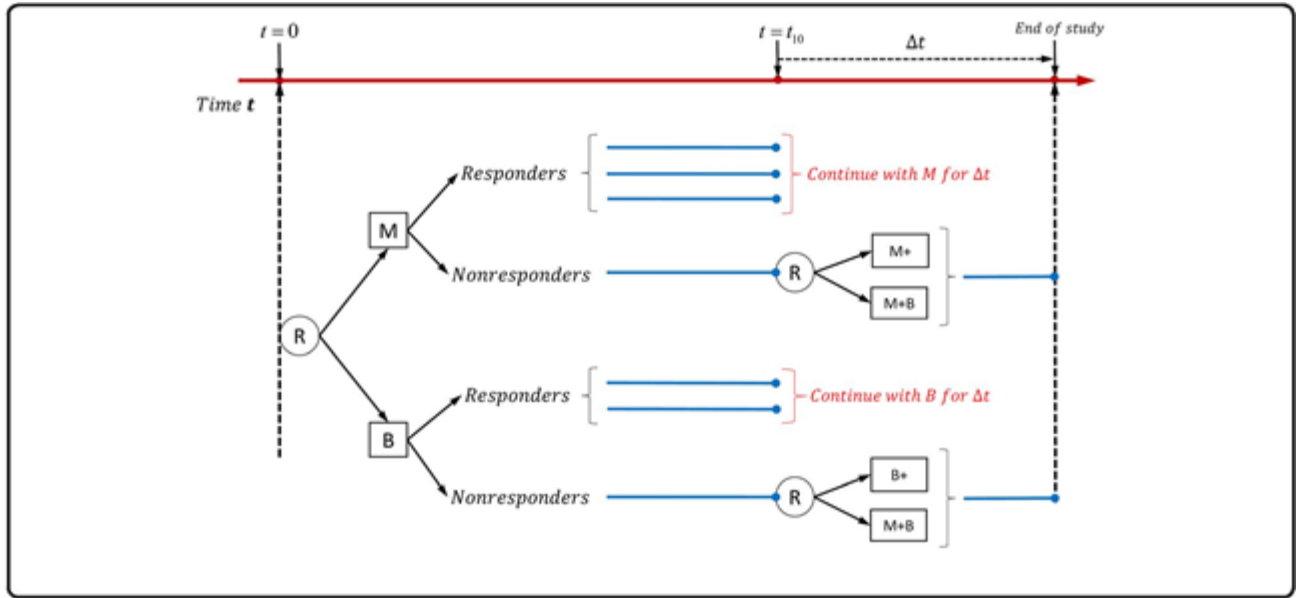
**Figure 3. Example of standard SMART design with equal probability allocation: each participant is randomized twice**

For both designs, we calculated the percentage of times the best embedded intervention is selected (i.e., the power of the design). We simulated six parameter scenarios: the true parameters for the coefficient of the first-stage interventions,  $\beta_{21}$ ; coefficient of the second-stage intervention for responders,  $\beta_{22}$ ; coefficient of the second-stage intervention for non-responders,  $\beta_{23}$ ; coefficient of  $T_2$ , the total time of the first- and second-stage interventions,  $\beta_{32}$ ; coefficient of interaction of the first-stage interventions and second-stage interventions among responders  $\beta_{41}$ ; and the coefficient of interaction of the first-stage interventions and second-stage interventions among non-responders  $\beta_{42}$ . The simulated values of each of these parameters are reported in Tables 11 and 12. The simulation results are based on

500 replicates and are shown in Table 11 for comparing the two designs in Figure 1 (time-varying SMART) and Figure 3 (analogous standard SMART). Overall, both designs were equally effective in selecting the optimal embedded adaptive intervention. For example, when  $\beta_{21} = 0.4$ ,  $\beta_{22} = 0.5$ ,  $\beta_{23} = 0.5$  and  $\beta_{32} = 2$ , using the joint model and implementing the time-varying SMART design showed 82.8% power to select the optimal embedded adaptive intervention; whereas the power associated with the standard SMART design was 83.0%. Similar results were obtained when comparing the time-varying SMART design in Figure 2 and the standard SMART design in Figure 4 (see Table 12).

**Table 11.** Power to select the optimal embedded adaptive intervention strategy for designs in Figures 1 and 3.

Comparison of designs in Figures 1 and 3.	$\beta_{12}$	$\beta_{22}$	$\beta_{23}$	$\beta_{32}$	$\beta_{41}$	$\beta_{42}$	Power to select optimal embedded adaptive strategy	
							Time-Varying SMART	Standard SMART
Without interaction	0.4	0.5	0.5	2			82.8%	83.0%
	0.3	-0.2	0.4	2			60.2%	59.2%
	0.3	-0.5	0.4	2			76.2%	75.0%
With interaction	0.4	0.5	0.5	2	0.5	-0.3	99.2%	97.0%
	0.6	0.5	0.4	2	0.2	0.2	63.0%	62.8%
	0.6	-0.5	-0.5	2	0.2	-0.3	72.2%	73.4%



**Figure 4. Example of standard SMART design: only non-responders are re-randomized in the second stage**

**Table 12.** Power to select the optimal embedded adaptive intervention strategy for designs in Figures 2 and 4

Comparison of designs in Figures 2 and 4.	$\beta_{12}$	$\beta_{23}$	$\beta_{32}$	$\beta_{42}$	Power to select optimal embedded adaptive strategy	
					Time-Varying SMART	Standard SMART
Without interaction	0.5	0.5	2		92.8%	90.6%
	0.45	0.4	2		86.6%	83.6%
	-0.2	0.2	2		68.4%	66.2%
With interaction	0.4	0.4	2	-0.4	98.2%	97.4%
	0.2	0.2	2	-0.4	88.4%	87.6%
	0.4	0.1	2	-0.25	77.4%	78.6%

## 2.6 Comparison of the cost associated with conducting the time-varying SMART design versus that associated with conducting the standard SMART design

To assess the cost associated with the conducting trials using these two competing designs, we considered a linear cost function for both SMART designs. Let  $c_1$  and  $c_2$  be the cost of the medication (M) and behavioral intervention (B), respectively. Additionally, we assumed that the reduced and increased intensity of the first-stage intervention are at half and twice the cost of the first-stage intervention, respectively, and that augmentation of the first-stage intervention in the second stage (M+B) has the cost  $c_1 + c_2$ . Using these parameters, the cost for the time-varying SMART design in Figure 1 is

$$\begin{aligned} \text{cost} = & c_1 \left( \sum_{A_{1i}=M} T_{1i} \right) + c_1 \left( \sum_{A_{2i}=M} \Delta t \right) + \left( \frac{c_1}{2} \right) \left( \sum_{A_{2i}=M-} \Delta t \right) + (2c_1) \left( \sum_{A_{2i}=M+} \Delta t \right) + \\ & c_2 \left( \sum_{A_{1i}=B} T_{1i} \right) + c_2 \left( \sum_{A_{2i}=B} \Delta t \right) + \left( \frac{c_2}{2} \right) \left( \sum_{A_{2i}=B-} \Delta t \right) + (2c_2) \left( \sum_{A_{2i}=B+} \Delta t \right) + (c_1 + c_2) \left( \sum_{A_{2i}=M+B} \Delta t \right), \end{aligned}$$

and the cost for the corresponding standard SMART in Figure 3 is

$$\begin{aligned} \text{cost} = & c_1 \left( \sum_{A_{1i}=M} t_{10} \right) + c_1 \left( \sum_{A_{2i}=M} \Delta t \right) + \left( \frac{c_1}{2} \right) \left( \sum_{A_{2i}=M-} \Delta t \right) + (2c_1) \left( \sum_{A_{2i}=M+} \Delta t \right) + \\ & c_2 \left( \sum_{A_{1i}=B} t_{10} \right) + c_2 \left( \sum_{A_{2i}=B} \Delta t \right) + \left( \frac{c_2}{2} \right) \left( \sum_{A_{2i}=B-} \Delta t \right) + (2c_2) \left( \sum_{A_{2i}=B+} \Delta t \right) + (c_1 + c_2) \left( \sum_{A_{2i}=M+B} \Delta t \right). \end{aligned}$$

Similarly, the cost for the time-varying SMART in Figure 2 is

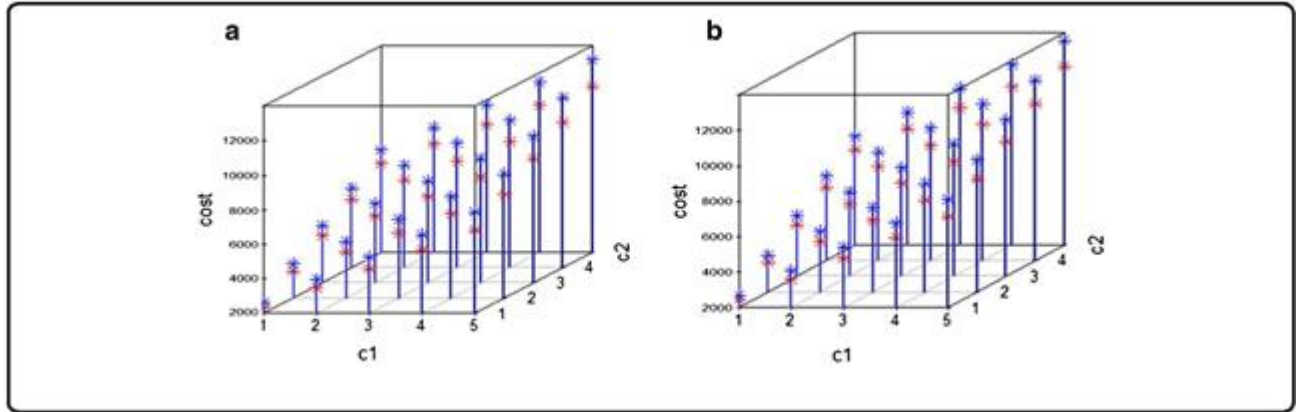
$$\begin{aligned} \text{cost} = & c_1 \left( \sum_{A_{1i}=M} T_{1i} \right) + c_1 \left( \sum_{A_{2i}=M} \Delta t \right) + (2c_1) \left( \sum_{A_{2i}=M+} \Delta t \right) + \\ & c_2 \left( \sum_{A_{1i}=B} T_{1i} \right) + c_2 \left( \sum_{A_{2i}=B} \Delta t \right) + (2c_2) \left( \sum_{A_{2i}=B+} \Delta t \right) + (c_1 + c_2) \left( \sum_{A_{2i}=M+B} \Delta t \right), \end{aligned}$$

and the cost for the corresponding standard SMART in Figure 4 is

$$\begin{aligned} \text{cost} = & c_1 \left( \sum_{A_{1i}=M} t_{10} \right) + c_1 \left( \sum_{A_{2i}=M} \Delta t \right) + (2c_1) \left( \sum_{A_{2i}=M+} \Delta t \right) + \\ & c_2 \left( \sum_{A_{1i}=B} t_{10} \right) + c_2 \left( \sum_{A_{2i}=B} \Delta t \right) + (2c_2) \left( \sum_{A_{2i}=B+} \Delta t \right) + (c_1 + c_2) \left( \sum_{A_{2i}=M+B} \Delta t \right). \end{aligned}$$

Note that in the above equations,  $T_{1i}=t_{10}$  for non-responders, and  $(c_1 + c_2) \left( \sum_{A_{2i}=M+B} \Delta t \right)$  is the cost of the second stage for all the subjects assigned to the intervention M+B.

Figure 5 shows the cost as a function of  $c_1$  and  $c_2$ , where red represents the cost of the time-varying SMART design and blue represents the cost of the standard SMART design. We can see that the cost of the time-varying SMART is less than the cost of the standard SMART in all scenarios. Table 13 shows the average costs and standard deviations calculated at select values of  $c_1$  and  $c_2$  based on 1000 replicates. For example, when the unit costs are  $c_1=2$  and  $c_2=1$  for medication and behavioral intervention, the average cost of the time-varying SMART in Figure 1 is 3446.5, with standard deviation 49.87, while the average cost of the corresponding standard SMART is 3935.8, with standard deviation 41.47. Thus, the cost of the standard SMART is about 12% higher than that of the time-varying SMART in this scenario.



**Figure 5.** The cost associated with implementing a standard SMART (blue) and equivalent time-varying SMART (red)

**Table 13.** Examples of the average cost for time-varying SMART and the standard SMART.

	$c_1$	$c_2$	Average Cost(SD)	
			Time-varying SMART	Standard SMART
Design in Figures 1 and 3: All the subjects are re-randomized	2	1	3446.5(49.87)	3935.8(41.47)
	1	1	2325.7(29.82)	2631.4(19.15)
	1	2	3526.5(57.00)	3953.2(46.63)
Design in Figures 2 and 4: Only non-responders are re-randomized	2	1	3593.4(45.40)	4056.9(36.52)
	1	1	2416.1(24.12)	2704.9(14.59)
	1	2	3655.5(53.53)	4056.7(42.77)

## 2.7 Discussion

The proposed time-varying two-stage SMART design can take into account the time associated with the first-stage interventions and thus could result in clinical

trials with fewer side effects and lower expected cost. Additionally, the two modeling approaches we proposed are able to provide good estimations of the means of the final outcomes of all the embedded interventions. The joint modeling approach resulted in more accurate estimates and higher estimated coverage probabilities; therefore, we recommend using joint modeling to analyze data generated from the time-varying designs proposed in this manuscript.

In the standard SMART design, the timing of the intervention is generally ignored, which leads to a model of regression without the predictor of a time variable. Therefore, in this article, we proposed a time-varying SMART design that allows the re-randomization to the second-stage interventions to occur at different times for different individuals. The two modeling approaches we proposed for analyzing data using such time-varying designs provided good estimations of the means of the final outcomes of all the embedded interventions. However, the joint modeling approach provided more accurate parameter estimates and higher estimated coverage probability than the TVMEM, and we recommend the joint model for analyzing data generated from time-varying designs.

In the examples illustrated in Figures 1 and 2, a participant was defined as a responder if there was a significant decrease in the number of cigarettes the participant smoked per day. One may question the validity of re-randomizing individuals who have a quick response to the first-stage intervention because such a response indicates the effectiveness of the intervention. However, if significant adverse effects are associated with the intervention (e.g., radiation therapy for many types of cancer is commonly associated with skin damage(143), fatigue(144),



diarrhea(145,146), and rectal bleeding(147)), it is reasonable to shorten the duration of the intervention to avoid side effects. Therefore, the allocation strategy for the responders in the examples of the time-varying SMART design makes it more efficient than the standard SMART design.

We proposed two approaches for analyzing the longitudinal outcomes obtained from the time-varying SMART design: the TVMEM and the joint model. According to the simulation results, the joint modeling approach better estimated the effects of the timing of the intervention (i.e.,  $T_2$ ) and the first-stage interventions (i.e.,  $A_1$ ) in model (4). More specifically, the joint modeling approach had more accurate estimates, smaller MSEs, higher estimated coverage probabilities, and smaller 95% confidence intervals (i.e., smaller estimated standard deviations) for the coefficients of the effects of the first-stage intervention and the time of intervention. Because we wanted to illustrate the cost efficiency of the proposed time-varying SMART design and its ability to select the optimal embedded adaptive intervention, we implemented a rather simplified linear mixed-effects submodels (2)-(4) of the more general TVMEM in model (1). We showed that the joint model performs better than the TVMEM in analyzing the data collected from such time-varying SMART designs. The joint modeling approach extracts part of the information contained in the time of the response, which is a function of the first-stage treatment assignment. Also, the association between the longitudinal and event outcomes is accounted for by the random effect that underlies both the longitudinal and survival processes for each subject. Therefore, although complex, time-varying SMART designs may require more complicated models for time and an extra layer of joint modeling, and as such

one would expect a better performance from joint modeling in general. Nevertheless, both modeling approaches performed well in estimating the other parameters and the mean of the final outcomes for each adaptive intervention embedded in the corresponding designs. Furthermore, equation (1) is a general form of TVMEM, and in our study is equivalent to equations (2) ~ (4) at time points  $t = 0, T_{1i}, T_{2i}$  for each subject  $i$ .  $T_{1i}$  is a subject-specific random variable, and coefficients in equation (3) can also be subject-specific. However, in practice, modeling coefficients to be subject-specific may lead to the estimation of too many parameters which, in some scenarios, may not be identifiable, particularly with small sample sizes. Therefore, as an initial attempt, we modeled  $T_{1i}$  as a subject-specific random variable and the coefficients as fixed parameters. For example, coefficients  $\beta_0(t), \beta_1(t), \beta_3(t)$  in equation (1) are fixed coefficients  $\beta_{01}, \beta_{11}, \beta_{31}$  in equation (3), as model (1) is equivalent to submodel (3) at time point  $T_{1i}$ . More complicated models such as subject-specific and time-varying coefficients in submodels (2)-(4) can be considered, if the sample sizes are large.

We also illustrated the effectiveness of the joint modeling approach in accurately estimating the parameters even when no specific model was assumed for the duration of the first-stage intervention,  $T_{1i}$ . The conclusions were qualitatively similar as that in the simulation where Weibull model was assumed for the duration of the first-stage intervention.

In the scenarios we considered here, the time at which individuals were re-randomized was assessed only for responders to the first-stage intervention.

However, one may also consider varying times for the non-responders and for the second-stage interventions. For example, a non-responder showing severe side effects or no trend towards achieving intermediate goals may be re-randomized sooner than  $t_{10}$ . The analytic approaches for such designs would be similar to the joint or time-varying mixed effects models proposed in this manuscript, for example, with an extra submodel for the duration of the second-stage interventions. Instead of randomization with certain pre-defined probabilities (e.g., in the first two simulation scenarios, randomization with probability 0.5 was used for both stages; in the last two scenarios, unequal randomization with probabilities 0.4(0.6) and 0.55(0.45) was used for the two stages, respectively), information concerning potential moderators could be used to tailor and assign the interventions. For example, the choice of the first-stage intervention options could depend on the severity of the subject's smoking habit at the beginning of the study; whereas the choice of the second-stage intervention option could depend on the subject's adherence to the first-stage intervention. The analysis of such a randomization scheme would require assigning weights each subject(148).

We also compared the cost and power associated with selecting the optimal embedded adaptive intervention for the proposed time-varying SMART design versus that for the analogous standard SMART design. Our simulation results showed similar power for the two designs. We used a linear cost function to assess the cost efficiency of the proposed design and found that it can have substantially lower expected cost than the standard design. Several other forms of cost functions can be used to assess cost efficiency. However, as long as the cost is an increasing

function of time, the proposed time-varying SMART design will have lower expected cost than the standard SMART design. Therefore, the time-varying SMART design can be used to study how the intensity and combination of two types of interventions might be adapted to a subject's progress in a cost- and time-efficient manner.

In our study, we assume that there is no unmeasured confounder. As suggested by Chakraborty and Murphy(63), the assumption of “no unmeasured confounders” holds in a SMART design if the randomization probabilities of  $A_1$  at most depend on the baseline covariates, and the randomization probabilities of  $A_2$  at most depend on the baseline covariates, the intermediate outcome, and  $A_1$ . We performed additional simulations to investigate the role of unmeasured confounders on the parameter estimations. From these simulations, we see that when the unmeasured confounders affect only  $T_1$  and  $Y_1$ , the parameter estimation is still accurate (see Appendix: Table S4). However, when these unmeasured confounders affect  $Y_2$ , there is bias in the estimation of  $T_2$  (see Appendix: Tables S5-S6).

In the ADHD SMART study discussed by Nahum-Shani et al.(76), a weighted average was applied to the final outcomes when their primary goal of analysis was to compare the imbedded adaptive intervention options in the design. In our Time-Varying SMART study, we used regression-based methods to identify more efficient adaptive decision rules for each subject along with their longitudinal outcomes. Similar to the analytic process of the standard SMART design by Q-learning<sup>5</sup> in which a regression model for the outcome is postulated at each decision as a function of the patient's information to that point, our TVMEM in equation (1) is

equivalent to submodels (2)-(4) at three time points of longitudinal outcomes for each individual. Therefore, we did not include weights in this study of the time-varying SMART design. However, for increased complexity of time-varying SMART designs, weights may be incorporated into the analysis in a future study to develop more robust estimations and results.

### **3 A Bayesian response-adaptive, covariate-balanced and optimal-decision-consistent randomization method for SMART designs**

### **3.1 Materials and methods**

#### **3.1.1 Existing randomization strategies for SMART**

In sequential multiple assignment randomized trial (i.e., SMART) designs(76), various randomization strategies have been developed to allocate subjects into the embedded interventions. Besides the standard total randomization in which subjects are randomized into different interventions with equal probability, subjects can also be assigned to the interventions according to their baseline characteristics, intermediate covariates or intermediate outcomes, or historical information. The goals of such allocation schemes are to assign subjects to the superior interventions with higher probabilities. Different kinds of allocation methods can be found in the clinical trial literature. Response-adaptive randomization, in which allocation probabilities are adjusted based on the previous patients' responses in the study, allow more patients to be assigned to the superior treatment as the trial progresses. For example, Efron(149) proposed a biased coin design to balance the numbers of individuals in the experimental treatment and control arms while avoiding various experimental biases; Berry and Eick(150) compared a balanced randomization strategy to adaptive randomization in clinical research; Rosenberger et al.(151) developed an optimal allocation between two treatments in a clinical trial; Thall, Inoue and Martin(152) proposed an adaptive Bayesian design for patients with hematologic malignancies; Zhang and Rosenberger(153) evaluated the performance of different response-adaptive randomization procedures in clinical

trials with continuous outcomes; and Sverdlov et al.(118) proposed a multiple-objective response-adaptive design.

However such response-adaptive designs lead to covariate imbalance, which results in bias when comparing treatment efficacy. Several methods have been proposed to balance covariate distributions across intervention arms during randomization. For example, Signorini et.al.(120) proposed a randomization method for balancing treatment allocations both within strata and across the trial. This approach was further improved by Heritier, Gebski and Pillai(154) to maintain a marginal balance over important strata. Thall and Wathen(86) proposed a Bayesian design for a multi-center, randomized clinical trial using covariate-adjusted adaptive randomization. Shao and Yu(155) established asymptotic results for covariate-adaptive biased coin randomization under generalized linear models. Recent research efforts have combined these two approaches. For example, Ning and Huang(122) developed a patient allocation scheme for trials with binary outcomes to adjust the covariate imbalance during response-adaptive randomization. In particular, Yuan et al.(123) proposed a randomization procedure and incorporated this method into a group sequential response-adaptive randomization design with a goal of achieving the benefits of the response-adaptive design while balancing the covariates. These methods have the advantage of assigning fewer patients to inferior treatments or controlling the imbalance of covariates across treatments when the sample size is moderate or small. Scott et al.(156) and Green(157) provided comprehensive reviews on the allocation method of minimization for balancing treatment groups.

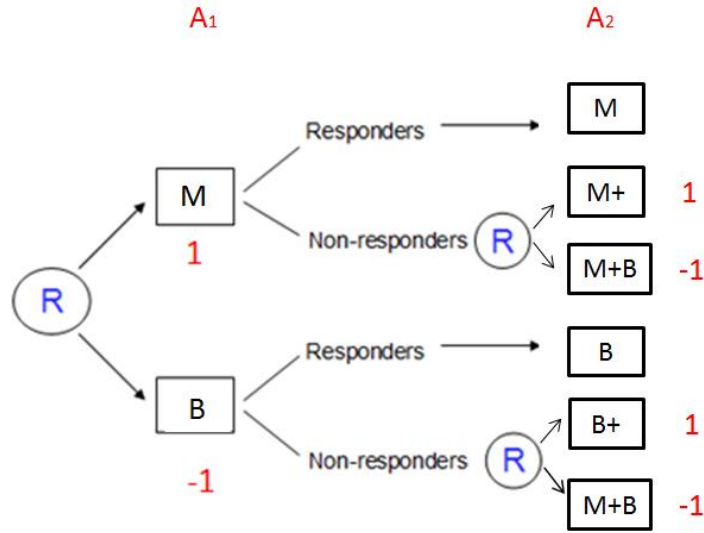


However, these randomization strategies are not straightforward to apply for SMART designs because participants are re-randomized in multiple stages and embedded interventions are involved in such a design. There are several optimization strategies for choosing the interventions for subjects in the SMART design. One of the most recently developed methods is Q-learning(103,131), which selects the optimal intervention for each subject according to the Q-learning regression model at each stage. The Q-learning algorithm estimates both the direct and indirect effects of the first-stage intervention options while controlling for the optimal second-stage intervention option when assessing the effect of the first-stage intervention. It also reduces the potential bias resulting from unmeasured causes associated with both the tailoring variables and primary outcomes.

In this article, we propose a randomization method that takes into account the Q-learning optimization while also being response-adaptive and balancing covariates between competing interventions at each stage of SMART. This approach, instead of randomizing the subjects all at one time, uses a more practical approach, assigning the subjects to treatments in sequential groups with a response-adaptive, covariate-balanced and decision-consistent probability based on the information obtained from previously enrolled groups. We performed simulation studies to compare the proposed allocation strategy to other possible allocation strategies.

### **3.1.2 Methods**

The proposed allocation procedure for SMART is response-adaptive and also optimizes each individual's intervention based on the Q-learning algorithm while balancing the covariates(123,158) across all available interventions at each stage of the SMART design. This strategy is applied to SMART in a group sequential manner such that the resulting design skews the allocation probability to the better interventions to optimize the final outcomes and lowers the covariate imbalance based on the information from previous participants. Specifically, subjects enroll into a SMART in sequential groups of sizes  $\{N_k\}, k=1, \dots, K$ , where  $N_k$  is the sample size of the  $k^{\text{th}}$  group. The subjects enter the trial sequentially and the allocation probabilities are updated using the observed data from previous participants enrolled in the study. If little information regarding the superiority of the interventions is known before conducting the trial, subjects in the 1<sup>st</sup> ( $k=1$ ) group are allocated randomly to the interventions at both stages of SMART, i.e., the allocation probability is 0.5. Other randomization probabilities can be applied to the first group if historical information regarding the embedded interventions is known before the trial, or based on the baseline characteristics, intermediate covariates or intermediate outcomes of the subjects. For subsequent groups ( $k=2, \dots, K$ ), calculations of the allocation probability are described below. We motivate our methodology with a standard two-stage SMART design (depicted in Figure 7) in which subjects in the first stage are randomized into one of two interventions: medication ( $A_1=+1$ ) or behavioral intervention ( $A_1=-1$ ). At the second stage, only non-responders from the first stage are re-randomized to either increase the dose of the initial intervention ( $A_2=+1$ ) or add the alternative intervention ( $A_2=-1$ ).



**Figure 6. SMARTs in which re-randomization to different second-stage intervention options depends on an intermediate outcome (only non-responders are re-randomized in the second stage)**

Let  $O_1$  be the baseline covariates assessed before the first-stage intervention (e.g., level of depression, sex, age, etc.) and  $O_2$  be the intermediate covariates assessed prior to the second-stage intervention (e.g., adherence to the first-stage intervention). Let  $Y$  be the final outcome value at the end of the trial.

### 3.1.2.1 Decision-consistent randomization probability by Q-learning optimization

First, we briefly introduce the Q-learning approach, which can be used to develop adaptive interventions from the data(103,131). In Q-learning, optimal decisions are derived by maximizing the Q-functions if a higher value of outcome is desired (minimizing the Q-functions if a lower value of the final outcome is desired). The Q-function of the second stage is

$Q_2(O_1, A_1, O_2, A_2, \gamma_2, \alpha_2) = \gamma_{20} + \gamma_{21}O_1 + \gamma_{22}O_2 + \gamma_{23}A_1 + \gamma_{24}A_1 \cdot O_1 + (\alpha_{20} + \alpha_{21}A_1 + \alpha_{22}O_2) \cdot A_2$   
 where  $O_1 = (O_{11}, O_{12}, \dots)$  and  $O_2 = (O_{21}, O_{22}, \dots)$  are the respective vectors of the

baseline and intermediate covariates. The parameters  $\alpha_2 = (\alpha_{20}, \alpha_{21}, \alpha_{22})$  reflect how the second-stage intervention ( $A_2$ ) varies as a function of the candidate tailoring variables (here,  $A_1$  and  $O_2$ ). Based on this equation, the second-stage intervention option ( $A_2$ ) that maximizes  $Q_2$  is the one that maximizes the term

$(\alpha_{20} + \alpha_{21}A_{1i} + \alpha_{22}O_{2i})A_{2i}$ . If  $(\alpha_{20} + \alpha_{21}A_{1i} + \alpha_{22}O_{2i}) > 0$ , the term

$(\alpha_{20} + \alpha_{21}A_{1i} + \alpha_{22}O_{2i})A_{2i}$  attains its maximal value for  $A_{2i} = 1$ ; and if

$(\alpha_{20} + \alpha_{21}A_{1i} + \alpha_{22}O_{2i}) < 0$ , the term  $(\alpha_{20} + \alpha_{21}A_{1i} + \alpha_{22}O_{2i})A_{2i}$  attains its maximal value for  $A_{2i} = -1$ . Therefore, the optimal second-stage decision for subject  $i$  is

$$d_{2i}^* = \text{sign}(\alpha_{20} + \alpha_{21}A_{1i} + \alpha_{22}O_{2i}).$$

In our proposed approach, the allocation probability utilizes the optimal decisions derived from the Q-learning algorithm(103,131) for SMART designs. We estimated the parameters in the model

$$Y_i \sim \gamma_{20} + \gamma_{21}O_{1i} + \gamma_{22}O_{2i} + \gamma_{23}A_{1i} + \gamma_{24}A_{1i} \cdot O_{1i} + (\alpha_{20} + \alpha_{21}A_{1i} + \alpha_{22}O_{2i}) \cdot A_{2i}$$

using a Bayesian linear regression model with the data from the previous  $k-1$  groups, i.e.,  $D_k$ . In this

Bayesian approach, we assume a vague normally distributed prior  $N(0, 10^6)$  for all model parameters, which is a commonly used type of priors when little information is known about the parameters.

The estimated posterior means of the parameters are denoted by

$(\gamma_{20}, \gamma_{21}, \gamma_{22}, \gamma_{23}, \gamma_{24}, \alpha_{20}, \alpha_{21}, \alpha_{22})$ . Therefore, the decision-consistent probability

according to Q-learning optimization for assigning subject  $i$  to the second-stage intervention  $A_{2=1}$  is

$$p_{ki}^{D(2)} = \Pr(\alpha_{20} + \alpha_{21}A_{1i} + \alpha_{22}O_{2i} > 0 \mid D_k) \quad (1).$$

Then, we move backwards in time to construct the first-stage decision-consistent probability by maximizing the first stage

Q-function:  $Q_1(O_1, A_1; \gamma_1, \alpha_1) = \gamma_{10} + \gamma_{11}O_1 + (\alpha_{10} + \alpha_{11}O_1) \cdot A_1$ , which leads to the optimal

first-stage decision  $d_{1i}^* = \text{sign}(\alpha_{10} + \alpha_{11}O_{1i})$  (103,131). We then estimate  $\gamma_1, \alpha_1$  in

model  $Y_i \sim \gamma_{10} + \gamma_{11}O_{1i} + (\alpha_{10} + \alpha_{11}O_{1i}) \cdot A_{1i}$  using a Bayesian linear regression. Here  $Y_i$

is the maximal value of the Q<sub>2</sub>-function calculated with

$(\gamma_{20}, \gamma_{21}, \gamma_{22}, \gamma_{23}, \gamma_{24}, \alpha_{20}, \alpha_{21}, \alpha_{22})$  if subject  $i$  is a non-responder to the first-stage intervention; it is equal to  $Y_i$  if subject  $i$  is a responder to the first-stage intervention.

In this regression, we also assume that the coefficients in the above model have a prior distribution  $N(0, 10^6)$ . Finally, the first-stage decision-consistent probability for subject  $i$  to  $A_{1=+1}$  is

$$p_{ki}^{D(1)} = \Pr(\alpha_{10} + \alpha_{11}O_{1i} > 0 \mid D_k) \quad (2).$$

### 3.1.2.2 Covariate-balanced randomization probability according to the prognostic score

The part of covariate-balanced probability  $p_{ki}^{C(2)}$  for each subject  $i$

$(i = N \cdot (k-1) + 1, \dots, N \cdot k)$  in the  $k^{th}$  ( $k = 1, \dots, K$ ) group is derived from the Bayesian

marginal model of the second stage  $Y \sim \beta_{20} + \beta_{21}O_1 + \beta_{22}O_2 + \beta_{23}A_1 + \beta_{24}A_2 + \beta_{25}A_1 \cdot A_2$ ,

where the coefficients  $\beta_{21} = (\beta_{21}^1, \beta_{21}^2, \dots)$  and  $\beta_{22} = (\beta_{22}^1, \beta_{22}^2, \dots)$  reflect the importance

of the baseline covariates  $O_1 = (O_{11}, O_{12}, \dots)$  and intermediate covariates

$O_2 = (O_{21}, O_{22}, \dots)$  in predicting the final outcomes. All the coefficients in this model are assumed to have normal distributions with vague prior  $N(0, 10^6)$ , and their posterior means are estimated as  $\beta_2 = (\beta_{20}, \beta_{21}, \beta_{22}, \beta_{23}, \beta_{24}, \beta_{25})$  by MCMC regression with  $data_k$ . The prognostic score for subject  $i$  in group  $k$  is defined as

$w_{2i} = \beta_{21}O_{1i} + \beta_{22}O_{2i}, i = N \cdot (k-1) + 1, \dots, N \cdot k$  (100, 123). This definition allows us to balance the covariates through the single variable  $w_{1i}$  while accommodating both categorical and continuous covariates in  $O_{1i}$  and  $O_{2i}$ . Let  $w_{A_1, A_2}$  be the vector of the current prognostic score for the non-responders who received interventions  $(A_1, A_2)$ , which is calculated with the estimated posterior means  $\beta_2$ . Then  $KS_{A_1, A_2, i}$ ,  $A_1 = 1$  or  $-1$  are the two Kolmogorov-Smirnov (KS) statistics (159, 160) for subject  $i$  who received intervention  $A_{1i}$  at the first stage and was then assigned to the second-stage intervention  $A_2$  ( $A_2 = 1$  or  $-1$ ) based on  $w_{A_{1i}, A_2=1}$  and  $w_{A_{1i}, A_2=-1}$ . Because higher values of the KS statistics indicate more severe imbalance, the covariate-balanced probability of assigning subject  $i$  to intervention  $A_2=1$  at the second stage is defined as

$$p_{ki}^{C(2)} = \frac{KS_{A_{1i}, A_2=-1, i}}{KS_{A_{1i}, A_2=1, i} + KS_{A_{1i}, A_2=-1, i}} \quad (3).$$

To avoid extreme values (i.e., values close to 1 or 0) in certain circumstances, a root transformation such as that suggested by Yuan et al. (123, 158) can be

applied to stabilize the probability in (8) as  $p_{ki, \text{stabilized}}^{C(2)} = \frac{\sqrt{p_{ki}^{C(2)}}}{\sqrt{p_{ki}^{C(2)}} + \sqrt{1 - p_{ki}^{C(2)}}}$ . We still use

$p_{ki}^{C(2)}$  to denote  $p_{ki, \text{stabilized}}^{C(2)}$  for simplicity.

At the first stage, the probability of randomizing subject  $i$  to the intervention

$$A_1=1 \text{ is } p_{ki}^{C(1)} = \frac{KS_{A_1=-1,i}}{KS_{A_1=1,i} + KS_{A_1=-1,i}} \quad (4)$$

where  $KS_{A_1=1,i}$  and  $KS_{A_1=-1,i}$  are the two KS statistics calculated for subject  $i$  when assigned to the first-stage intervention  $A_1=1$  and  $A_1=-1$ , respectively. The probability in (4) may also be stabilized by the aforementioned root transformation.

### 3.1.2.3 Response-adaptive randomization probability based on outcomes of previous groups

The final outcomes ( $Y$ ) of the intervention  $(A_1, A_2)$  at the second stage are assumed to follow a normal distribution with mean  $\mu_{A_1, A_2}$  which are further assumed to be normally distributed with vague priors  $N(0, 10^6)$ . The posterior distribution of  $\mu_{A_1, A_2}$  follows a normal distribution,  $N(\mu_{A_1, A_2}^{(k)}, \nu_{A_1, A_2}^{(k)})$ . Therefore, the posterior distribution of the difference  $\mu_{a_1, A_2=1} - \mu_{a_1, A_2=-1}$  is normal with mean  $\mu_{a_1, A_2=1}^{(k)} - \mu_{a_1, A_2=-1}^{(k)}$  and variance  $(\nu_{a_1, A_2=1}^{(k)})^2 + (\nu_{a_1, A_2=-1}^{(k)})^2$ . If higher values of the final outcomes are desired, the response-adaptive randomization probability for intervention  $A_2=1$  at the second stage is calculated as:  $p_k^{R(2)} = \Pr(\mu_{a_1, A_2=1} - \mu_{a_1, A_2=-1} > 0 \mid D_k)$  (5)

for a subject who received  $A_1=a_1$  as the first-stage intervention. This probability is common for all the subjects in the  $k^{\text{th}}$  group and may also be stabilized with a root

transformation: 
$$p_{k,\text{stabilized}}^{R(2)} = \frac{\sqrt{p_k^{R(2)}}}{\sqrt{p_k^{R(2)}} + \sqrt{1-p_k^{R(2)}}}.$$

Similarly, the probability of randomizing subjects to interventions  $A_1=1$  at the first stage is calculated by MCMC regression as

$$p_k^{R(1)} = \Pr(\mu_{A_1=1} - \mu_{A_1=-1} > 0 \mid D_k), k = 2, \dots, K \quad (6),$$

where  $\mu_{A_1=1}$  and  $\mu_{A_1=-1}$  are the means of the final outcomes for subjects who received first-stage interventions  $A_1=1$  and  $A_1=-1$ , respectively.

With different combinations of the three types of allocation probabilities above, we developed different randomization methods, which we describe in the next section.

#### **3.1.2.4 Response-adaptive, covariate-balanced and decision-consistent (RCD) randomization method**

The response- adaptive, covariate-balanced and decision-consistent allocation probability of assigning each individual  $i$  in the  $k^{\text{th}}$  group to intervention  $A_s=1$  at the

$$s \ (s=1,2) \text{ stage is } p_{ki}^{(s)} = p_k^{R(s)} \cdot p_{ki}^{C(s)} \cdot p_{ki}^{D(s)}, \ s=1,2; \ k=1,\dots,K; \ i=1,\dots,n \quad (7),$$

where  $p_k^{R(s)}$ ,  $p_{ki}^{C(s)}$  and  $p_{ki}^{D(s)}$  are the response-adaptive, covariate-balanced and decision-consistent probabilities, respectively. Data from the first  $k$  groups, i.e.,  $data_k$ , are used for calculating the allocation probability for the subjects in the



(k+1)<sup>th</sup> group. Therefore, the allocation probabilities are updated with data from the ongoing trial.

### 3.1.2.5 Response-adaptive and decision-consistent (RD) randomization method

Because the SMART design is adaptive to each individual's characteristics, in cases in which balancing the covariates between two competing interventions is not as important as optimizing the final outcomes and decisions during randomization, the allocation probability can be further simplified to be only response-adaptive and decision-consistent. This is the RD randomization method in which the allocation probability to  $A_s=1$ ,  $s=1,2$  for each subject  $i$  in the  $k^{\text{th}}$  group is defined as

$$p_{ki}^{(s)} = p_k^{R(s)} \cdot p_{ki}^{D(s)}, \quad s=1,2; \quad k=1,\dots,K; \quad i=1,\dots,n \quad (8) ,$$

where  $p_k^{R(s)}$  and  $p_{ki}^{D(s)}$  are the respective response-adaptive and decision-consistent probabilities.

### 3.1.2.6 Other randomization methods

There are other existing randomization strategies or straightforward extensions of randomization strategies based on the allocation probabilities defined above that can be applied to SMART designs. Using the definitions in equations (1) ~ (6) above, we define the following randomization strategies. The response adaptive randomization (R) is similar to the Bayesian response-adaptive randomization design(153,161) for which the randomization probability is

$$p_{k_i}^{(s)} = p_k^{R(s)} \quad (9) ;$$

the covariate-balanced randomization (C) is similar to the Pocock and Simon strategy(162) for which the randomization probability is  $p_i^{(s)} = p_k^{C(s)}$  (10);

the combination of the response-adaptive and covariate-balanced randomization (RC) is similar to that proposed by Yuan et al.(123) for which the randomization probability is  $p_{k_i}^{(s)} = p_k^{R(s)} \cdot p_{ki}^{C(s)}$  (11);

the decision-consistent randomization (D) according to the Q-learning optimization for which the randomization probability is  $p_{ki}^{(s)} = p_k^{D(s)}$  (12);

the covariate-balanced and decision-consistent randomization (CD) for which the randomization probability is  $p_{k_i}^{(s)} = p_k^{C(s)} \cdot p_{ki}^{D(s)}$  (13);

and the total randomization at both stages (T), the probability for which is

$$p_{ki}^{(s)} = 0.5 \quad (14).$$

### 3.2 Simulation models and assessment methods

We applied the proposed and existing randomization methods to the SMART design (see Figure 6). We used simulation studies to evaluate the proposed response-adaptive, covariate-balanced and decision-consistent randomization (RCD) method and the response-adaptive and decision-consistent randomization (RD) method, and compared them with covariate-balanced and decision-consistent randomization (CD), decision-consistent randomization (D) and other existing randomization methods used in standard clinical trials such as response-adaptive and covariate-balanced randomization (RC), total randomization (Total), response-

adaptive randomization (R), and covariate-balanced randomization (C), for which the corresponding probabilities are defined in (8)~(14).

We generated data for subject  $i$  using the following model

$$Y_i = \gamma_{20} + \gamma_{21}O_{1i} + \gamma_{22}O_{2i} + \gamma_{23}A_{1i} + \alpha_{20} \cdot A_{2i} + \alpha_{21}A_{1i} \cdot A_{2i} + \gamma_{24}A_{1i} \cdot O_{1i} + \alpha_{22}A_{2i} \cdot O_{1i} + \varepsilon_i, \varepsilon_i \sim N(0,1) \quad (15)$$

where  $A_1$  and  $A_2$  are intervention indicators of the two stages of SMART;  $O_1$  is the baseline covariate vector and  $O_2$  is the intermediate covariate vector. The results reported in tables are based on 1000 replicates. For each comparison, we carried out simulations with complete (probability equal to 0.5) and unequal randomization (i.e., the probability of randomizing a non-responder in the first group depends on the value of his/her intermediate covariates,  $O_2$ ). The model parameters were estimated using the “MCMCpack”(163,164) package in R.

We considered three summary measures to compare the proposed and existing randomization strategies. We used the percentage of the inferior treatment number (ITN%), which is the percentage of subjects who were assigned to the inferior intervention arms (i.e., interventions for which the expected final outcomes are lower than those expected for the competing interventions). We also calculated the KS statistic for the prognostic score. We report the percentage of the occurrence of significant covariate imbalance, i.e., for each of the two first-stage interventions:  $A_1=1$  and  $A_1=-1$ , we report the percentage of the p-values of the KS statistic that is less than 0.05. In addition, we report the percentage of subjects

assigned to their optimal adaptive strategies according to the Q-learning algorithm (ODQ%).

### 3.3 Simulation results

Tables 14–17 show the simulation results based on the SMART in Figure 6. Data for the simulations were generated using model (15) with the following parameter choices:  $\gamma_{20}=1$ ,  $\gamma_{21}=1$ ,  $\gamma_{22}=-1$ ,  $\gamma_{23}=-0.3$ ,  $\gamma_{24}=0.1$ ,  $\alpha_{20}=0.1$ ,  $\alpha_{21}=-0.2$  and  $\alpha_{22}=-0.2$ . The values of  $O_1$  and  $O_2$ , which are univariate covariates, were generated from the normal distributions  $N(3,1^2)$  and  $N(0.1,0.3^2)$ , respectively.

In Table 14, the total study sample size is 200 individuals and the group size is 40, i.e., the allocation probability is updated for each sequential group of 40 subjects.

The non-responders in the first group were assigned to the second stage intervention based on their intermediate covariate  $O_2$  (i.e., unequal randomization). Specifically, a non-responder was assigned to the intervention  $A_2=1$  with probability equal to the cumulative normal distribution at his/her observed  $O_2$  value. As shown in the table, the percentages of the subjects who were assigned to the inferior intervention arms were 22.73% and 21.96% for the RCD and RD methods, respectively, which were lower than those for the other methods. These two methods also had the highest percentage of subjects assigned to the most optimal adaptive strategy: 67.21% and 67.99% compared to RC (59.91%), CD (62.09%), D (62.60%) and R (60.51%). As expected, the ODQ% was 50.13% and 50.24% for

the TR and C methods, respectively. Importantly, the proposed RCD method had an acceptable percentage of significant covariate imbalance (2%, 2%) compared with that of the RD (8.5%, 7%), D (7.5%, 6%), and R (8.5%, 9%) methods for each of the two first-stage interventions:  $A_1=1$  and  $A_1=-1$ . The level of imbalance for the RC, CD, TR and C methods was also acceptable.

**Table 14.** Simulation results based on 1000 replicates for SMART in Figure 6 with parameter values  $\gamma_{20}=1$ ,  $\gamma_{21}=1$ ,  $\gamma_{22}=-1$ ,  $\gamma_{23}=-0.3$ ,  $\gamma_{24}=0.1$ ,  $\alpha_{20}=0.1$ ,  $\alpha_{21}=-0.2$  and  $\alpha_{22}=-0.2$ ; the sample size was 200 with group sizes of 40 and the non-responders in the first group were assigned to the second-stage intervention based on their intermediate outcome  $O_2$  (i.e., unequal randomization).

	ITN%	Percentage of significant		ODQ%
		covariate imbalance		
		A1=1	A1=-1	
RCD	22.73%	2.0%	2.0%	67.21%
RD	21.96%	8.5%	7.0%	67.99%
RC	27.91%	3.5%	2.5%	59.91%
CD	26.39%	1.0%	1.0%	62.09%
Total	34.94%	5.0%	6.5%	50.13%
D	26.12%	7.5%	6.0%	62.60%
R	27.46%	8.5%	9.0%	60.51%
C	35.20%	1.5%	1.5%	50.24%

In Table 15, we present results for the same sample sizes and the same parameter configurations as in Table 1 except instead of unequal randomization, we applied complete randomization to the first group in the trial (i.e., subjects were randomized into the two interventions with probability 0.5). Overall, the results are similar to those shown in Table 1. The RCD method had the lowest ITN% (21.97%)

and the highest ODQ% (68.35%), which is similar to those respective values for the RD method: 22.86% and 67.30%. The TR and C methods showed the highest ITN% (34.64% and 34.66%, respectively) and lowest ODQ% (50.60% and 50.49%) among all the methods. The RCD method had an acceptable level (2.5%) of significant covariate imbalance for each of the two first-stage interventions:  $A_1=1$  and  $A_1=-1$ . The percentage of significant covariate imbalance for the various methods was RC (3% and 1%), CD (3.5% and 2.5%), C (2.5% and 1%), RD (6.5% and 4%), D (6.5% and 5%), TR (6% and 4.5%) and R (8% and 5.5%).

**Table 15.** Simulation results based on 1000 replicates for SMART in Figure 6 with parameter values  $\gamma_{20}=1$ ,  $\gamma_{21}=1$ ,  $\gamma_{22}=-1$ ,  $\gamma_{23}=-0.3$ ,  $\gamma_{24}=0.1$ ,  $\alpha_{20}=0.1$ ,  $\alpha_{21}=-0.2$  and  $\alpha_{22}=-0.2$ ; the sample size was 200 with group sizes of 40 and the non-responders in the first group were assigned to the second-stage intervention completely at random (i.e., equal randomization)

		Percentage of significant		
	ITN%	covariate imbalance		ODQ%
		A1=1	A1=-1	
RCD	21.97%	2.5%	2.5%	68.35%
RD	22.86%	6.5%	4.0%	67.30%
RC	27.16%	3.0%	1.0%	61.05%
CD	25.70%	3.5%	2.5%	63.36%
Total	34.64%	6.0%	4.5%	50.60%
D	25.87%	6.5%	5.0%	63.02%
R	27.87%	8.0%	5.5%	60.04%
C	34.66%	2.5%	1.0%	50.49%

Table 16 shows the results for the same simulation parameters as shown in Table 1, except that the group size is 100, with a total sample size of 500. Similar to

the results in Table 1, the RCD and RD methods had lower ITN% (17.49% and 17.15%, respectively) and higher ODQ% (74.41% and 74.80%, respectively) than the other methods. The percentage of significant covariate imbalance for the RCD method was (7.5%, 9%); whereas that for the RD method was (11.5%, 13%). Although the percentage of significant covariate imbalance was acceptable for the TR and C methods, 4%, 7% and 3.5%, 3% respectively, these methods had higher ITN% (35.03% and 34.84%, respectively) and lower ODQ% (49.74% and 49.96%, respectively) when compared to the other methods.

**Table 16.** Simulation results based on 1000 replicates for SMART in Figure 6 with parameter values  $\gamma_{20}=1$ ,  $\gamma_{21}=1$ ,  $\gamma_{22}=-1$ ,  $\gamma_{23}=-0.3$ ,  $\gamma_{24}=0.1$ ,  $\alpha_{20}=0.1$ ,  $\alpha_{21}=-0.2$  and  $\alpha_{22}=-0.2$ ; the sample size was 500 with group sizes of 100; and the non-responders in the first group were assigned to the second-stage intervention based on their intermediate outcome  $O_2$  (i.e., unequal randomization).

	ITN%	Percentage of significant		ODQ%
		covariate imbalance		
		A1=1	A1=-1	
RCD	17.49%	7.5%	9.0%	74.41%
RD	17.15%	11.5%	13.0%	74.80%
RC	22.66%	3.0%	2.5%	66.98%
CD	21.93%	7.0%	6.5%	69.05%
Total	35.03%	4.0%	7.0%	49.74%
D	21.79%	10.5%	11.0%	68.95%
R	22.38%	4.5%	5.5%	67.32%
C	34.84%	3.5%	3.0%	49.96%

Table 17 shows the results of the same simulation parameters as shown in Table 2, except that the group size is 100 and the total sample size is 500. The

RCD method again showed the best performance with respect to all three statistics, i.e., lowest ITN% (18.44%) and highest ODQ% (73.39%) among all the methods with acceptable percentages of significant covariate imbalance (4%, for both first stages). Meanwhile, the RD method had ITN% (19.85%) and ODQ% (71.52%) close to those from the RCD method, but had higher covariate imbalance (11%, 9%). Both the CD and D methods had higher ITN% (21.25% and 21.47%, respectively) and lower ODQ% (69.63% and 69.3%, respectively) than the RCD and RD methods.

**Table 17.** Simulation results based on 1000 replicates for SMART in Figure 6 with parameter values  $\gamma_{20}=1$ ,  $\gamma_{21}=1$ ,  $\gamma_{22}=-1$ ,  $\gamma_{23}=-0.3$ ,  $\gamma_{24}=0.1$ ,  $\alpha_{20}=0.1$ ,  $\alpha_{21}=-0.2$  and  $\alpha_{22}=-0.2$ ; the sample size was 500 with group sizes of 100; and the non-responders in the first group were assigned to the second-stage intervention completely at random (i.e., equal randomization).

	ITN%	Percentage of significant		ODQ%
		covariate imbalance		
		A1=1	A1=-1	
RCD	18.44%	4.0%	4.0%	73.39%
RD	19.85%	11.0%	9.0%	71.52%
RC	23.07%	2.0%	1.5%	66.47%
CD	21.25%	5.5%	4.5%	69.63%
Total	35.02%	3.0%	5.0%	49.97%
D	21.47%	9.5%	6.0%	69.30%
R	23.85%	4.5%	5.5%	65.75%
C	35.17%	2.5%	2.5%	49.75%

### 3.4 Discussion



We have proposed a Bayesian response-adaptive, covariate-balanced and optimal Q-learning decision-consistent randomization strategy (RCD) for SMART that successfully combines the advantages of the response-adaptive randomization strategy and the covariate-balanced randomization strategy while having the highest consistency for the optimal interventions derived by the Q-learning algorithm. In this approach, the assignment probability for a new subject who enters the SMART depends on his/her covariates and the previous subjects' treatment assignments and responses. In this method, more subjects are assigned to the better interventions because the randomization probability uses the individual's optimal decisions under the Q-learning algorithm, which leads to higher ODQ%.

The second approach (RD) that we suggested combines the decision-consistent probability (i.e., randomization according to the individuals' optimal decisions derived by Q-learning) with the response-adaptive probability (i.e., randomization according to the final outcomes). This method has the advantages of the two strategies: response-adaptive and decision-consistent randomization, i.e., low ITN% and high ODQ%, however, the method leads to higher imbalance than the RCD method, especially when the first group in the trial was randomized according to the intermediate covariates, as demonstrated in the simulation studies. Both the CD and D methods showed higher ITN% and lower ODQ%, while the D method also had less controlled covariate balance than the RCD and RD methods.

For all the methods, when the group sizes were larger, the observed imbalance was higher, as seen by comparing Tables 16 and 17 to Tables 13 and 14.

The parameters can be better estimated using the larger group sizes, however, because each subject was allocated based on only the covariate imbalance of the previous groups, the assignment of the current group of subjects was “over-skewed,” which resulted in higher covariate imbalance.

This trade-off needs to be taken into account when randomizing subjects into a SMART. We can use simulations to determine the appropriate group size. In many behavioral interventions, relatively smaller group sizes (e.g., 10 or 20) are used, therefore, the proposed methods are appropriate in such scenarios.

We illustrated the proposed methods and compared them to other randomization strategies by applying them to the two-stage SMART in Figure 6. They can also be applied to multi-stage SMART (i.e., SMART with more than two stages) and the allocation probabilities of the  $s^{\text{th}}$  stage are defined similarly to those in equation (7) for the RCD method and equation (8) for the RD method.

The proposed RCD method combines the three parts of adaptive probabilities in a multiplicative manner; however other combinations can also be used. For example, one may define the allocation probability for subject  $i$  as

$$p_i^{(s)} = \varphi_1(p_k^{R(s)}) \cdot \varphi_2(p_{ki}^{C(s)}) \cdot \varphi_3(p_{ki}^{D(s)}) \text{ where } \varphi_1, \varphi_2 \text{ and } \varphi_3 \text{ can be any monotonic}$$

increasing function. In addition, one can also weight the three probabilities unequally in order of their importance in the treatment assignment strategy.

Furthermore, the randomization probabilities can be updated as frequently as one wishes and the group size can be adjusted to serve this purpose.

In our simulations, we updated the randomization probabilities after each group using vague priors for the model parameters in MCMC regression, which allows for independent estimation of the parameters. One can also estimate the model parameters using other priors such as distributions of historical data from similar trials or the posteriors obtained based on previous groups. However, such an approach may lead to an exclusive assignment to one of the interventions (i.e., subjects may all be assigned to one intervention) after several sequential updates, which may lead to difficulty in parameter estimation and comparison of embedded interventions in SMART. As a remedy, a mixture of this strategy and a randomization strategy that has higher uncertainty can be applied.

Similar results were obtained for another type of SMART design (Figure S1), where individuals were re-randomized irrespective of the intermediate covariates (i.e., all the subjects were re-randomized at the second stage). See Supplementary Information 4 and the results in Tables S7 and S8 in the Appendix.

In conclusion, among all the randomization methods we compared, the proposed RCD randomization method showed the best performance in assigning fewer subjects to the inferior interventions and more subjects to the optimal Q-learning interventions than the other methods while controlling the covariate balance at an acceptable level when an appropriate group size was used.

## **4 Conclusions and future directions**

## 4.1 Conclusions

In this dissertation study, I focused on investigating and utilizing the ability of SMART to develop adaptive interventions for subjects involved in a multiple-stage trial. To achieve this essential goal, we performed the study using the following two-part process. 1) We proposed a novel SMART design to reduce the side-effects and cost associated with treatments, and the corresponding data analysis approaches for such a design to estimate the effect of the treatment and the treatment time. 2) We proposed a new randomization strategy for SMART to assign more subjects to the optimal treatment while taking into account the overall performance of each embedded intervention and the covariate balance among subjects.

We first proposed the time-varying SMART, which is a novel design that takes into account the treatment time as an endogenous variable. Rather than a fixed period of treatment as that in the standard SMART design, each subject involved in the proposed design moves to the next stage of treatment as soon as he/she achieves certain pre-defined criteria (e.g., a pre-fixed threshold for the outcome of interest), which potentially shortens the treatment time for the current stage. With the simulation study, we show that such SMART designs can reduce the cost and/or side effects associated with treatments while maintaining the same power as the standard SMART design for selecting the optimal embedded intervention(s). We also proposed the corresponding two modeling approaches, TVMEM and the joint model for such a SMART design. We recommended joint modeling for data analysis

after comparing the two modeling approaches with simulations. Joint modeling provides better parameter estimation, while both methods show a good estimation of the means of the final outcomes for all the embedded interventions.

Compared to the standard SMART design, the proposed time-varying SMART design can accommodate more realistic situations and is more easily applied in a clinical trial as it allows the treatment time to adapt to the subject's response with monitoring. The information regarding the treatment effects embedded in the treatment time is utilized by the survival submodel in the joint modelling approach. Therefore, the time-varying SMART design enables a more efficient study of adaptive interventions and optimal intervention strategies with the ability to reduce the associated cost and side effects.

In addition, we proposed a Bayesian response-adaptive, covariate-balanced and optimal decision-consistent randomization method for SMART designs with the goal to assign subjects in a way that is consistent with the scientific aims of SMART. Based on existing randomization strategies developed for clinical trials, this new method we proposed also takes into account the consistency of the optimal intervention for each subject involved in a SMART with the use of the Q-learning optimization algorithm. It balances the randomization considerations among the three following parts: the average performance of each embedded intervention, the covariate balance among all the subjects, and the optimal intervention for each individual. The Bayesian framework is adopted into the proposed method and the randomization probability is updated sequentially with divided groups. Based on our

simulation study, we concluded that our proposed allocation strategy is more appropriate for SMART than the existing methods for clinical trials because it takes into account the individual optimization of the adaptive interventions while allowing for ongoing updating based on the information accumulating during the trial.

## **4.2 Future directions**

The time-varying SMART design we proposed can be extended to frameworks with more flexibility. 1) We can vary the treatment time for both non-responders and responders, which can be accommodated by defining another criterion for non-responders and applying a strategy similar to that for responders and assigning the subjects to the next stage of treatment. The treatment times for the two types of treatment may need to be treated differently in the analysis. 2) We can vary the treatment time of the second stage, which will introduce the variable of time for the second-stage treatment and increase the complexity of the joint modeling if another survival model is posted as well as the analysis of the combined effects of the first-stage and second-stage treatments. 3) We can apply a multi-stage SMART design with a varying treatment time for some or all of the stages, which may not be a straightforward extension of the two-stage SMART design and will require advanced modeling and computing strategies. (4) Similarly to the study of standard SMART, we can also conduct sample size calculations or apply Bayesian framework on TVSMART, Future studies can be conducted to assess these research topics.

The optimization of the treatment time can be included in the study of time-varying SMART designs and the treatment time can be adapted to the individual's characteristics, needs and responses. This may also be done conditionally, i.e., finding the treatment time for the current stage based on the optimal treatment time that has been used for the other stage for each individual. Therefore, the treatment can be optimized regarding the type as well as its time of allocation. Furthermore, the commonly used “early stopping rule” in clinical trials can be applied to SMART designs.

In addition to the treatment time, other types of endogenous variables or intermediate measurements on the causal pathway to the outcome of interest can be embedded into SMART designs, with the corresponding analytic methods properly accounting for them. Instead of approaches similar to joint modeling, we may also consider strategies like principal stratification(165,166).

Because SMART designs have similarities to standard trial designs while featuring unique characteristics, existing randomization methods can be applied with some modifications such as forward or backward conditional computation for multi-stage designs and cross-comparison among embedded interventions or interventions at the same stage. Moreover, randomization methods for SMART designs can be developed with respect to the goal of the study. For example, different weights can be assigned to each part of the randomization probabilities proposed in Chapter 3 to construct the overall allocation strategy based on different priorities in the trial design and different research aims. In addition, choosing



adaptive interventions for each individual can make use of optimization algorithms other than Q-learning.

According to the simulation study in Chapter 3, an optimal group size for each sequential update can be further investigated by taking into account the trade-off between parameter estimation and covariate balance, as well as the power of choosing the optimal intervention for each subject.

Although the new randomization method in Chapter 3 is developed for standard SMART designs, it can be modified to accommodate the time-varying SMART, for which the time of treatment is also taken into account during randomization and a more adaptive SMART is constructed. Following this line of thinking, each design part of SMART can be potentially more adaptive to the subjects while targeting the scientific aims of the SMART design.

The application of SMART designs can also be combined with traditional methods and clinical trial designs, for which the SMART can be embedded into certain parts of the trial and used to indicate intervention options. Strategies developed for other types of clinical trial designs can also be used in certain stages or parts of a SMART to achieve multiple analytic goals within one SMART.

## APPENDIX

### Supplemental information:

#### 1. Conditional expectation of TVMEM:

**1.1 Models (1) - (4) can also be written in the form of conditional expectation as**

$$E[Y_i | A_{1i}(t), A_{2i}(t), t] = Z_i \eta(t) + \beta_0(t) + \beta_1(t)A_{1i}(t) + \beta_2(t)A_{2i}(t) + \beta_3(t)t + \beta_4(t)A_{1i}(t) \cdot A_{2i}(t) \quad (1),$$

$$E[Y_i | t = 0] = Z_i \eta_0 + \beta_{00} \quad (2),$$

$$E[Y_i | A_{1i}, t = T_{1i}] = Z_i \eta_1 + \beta_{01} + \beta_{11}A_{1i} + \beta_{31}T_{1i}(A_{1i}) \quad (3),$$

and

$$E[Y_i | A_{1i}, A_{2Ri}, A_{2NRi}, t = T_{2i}] = Z_i \eta_2 + \beta_{02} + \beta_{12}A_{1i} + \beta_{22}A_{2Ri} + \beta_{23}A_{2NRi} + \beta_{32}T_{2i}(A_{1i}, A_{2Ri}, A_{2NRi}) + \beta_{41}A_{1i} \cdot A_{2Ri} + \beta_{42}A_{1i} \cdot A_{2NRi} \quad (4).$$

**1.2 Accordingly, the conditional expectation of the final outcomes for each of the 8 embedded adaptive interventions in the SMART design of Figure 1 is**

$$E[Y_i | 1, 1, 1, t = T_{2i}] = Z_i \eta_2 + \beta_{02} + \beta_{12} + \beta_{22} + \beta_{23} + \beta_{32}T_{2i}(1, 1, 1) + \beta_{41} + \beta_{42} \text{ for subjects}$$

following adaptive intervention ( $A_1=1, A_{2R}=1, A_{2NR}=1$ );

$E[Y_i | 1, 1, -1, t = T_{2i}] = Z_i \eta_2 + \beta_{02} + \beta_{12} + \beta_{22} - \beta_{23} + \beta_{32} T_{2i}(1, 1, -1) + \beta_{41} - \beta_{42}$  for subjects

following adaptive intervention ( $A_1=1, A_{2R}=1, A_{2NR}=-1$ );

$E[Y_i | 1, -1, 1, t = T_{2i}] = Z_i \eta_2 + \beta_{02} + \beta_{12} - \beta_{22} + \beta_{23} + \beta_{32} T_{2i}(1, -1, 1) - \beta_{41} + \beta_{42}$  for subjects

following adaptive intervention ( $A_1=1, A_{2R}=-1, A_{2NR}=1$ );

$E[Y_i | 1, -1, -1, t = T_{2i}] = Z_i \eta_2 + \beta_{02} + \beta_{12} - \beta_{22} - \beta_{23} + \beta_{32} T_{2i}(1, -1, -1) - \beta_{41} - \beta_{42}$  for subjects

following adaptive intervention ( $A_1=1, A_{2R}=-1, A_{2NR}=-1$ );

$E[Y_i | -1, 1, 1, t = T_{2i}] = Z_i \eta_2 + \beta_{02} - \beta_{12} + \beta_{22} + \beta_{23} + \beta_{32} T_{2i}(-1, 1, 1) - \beta_{41} - \beta_{42}$  for subjects

following adaptive intervention ( $A_1=-1, A_{2R}=1, A_{2NR}=1$ );

$E[Y_i | -1, 1, -1, t = T_{2i}] = Z_i \eta_2 + \beta_{02} - \beta_{12} + \beta_{22} - \beta_{23} + \beta_{32} T_{2i}(-1, 1, -1) - \beta_{41} + \beta_{42}$  for subjects

following adaptive intervention ( $A_1=-1, A_{2R}=1, A_{2NR}=-1$ );

$E[Y_i | -1, -1, 1, t = T_{2i}] = Z_i \eta_2 + \beta_{02} - \beta_{12} - \beta_{22} + \beta_{23} + \beta_{32} T_{2i}(-1, -1, 1) + \beta_{41} - \beta_{42}$  for subjects

following adaptive intervention ( $A_1=-1, A_{2R}=-1, A_{2NR}=1$ );

$E[Y_i | -1, -1, -1, t = T_{2i}] = Z_i \eta_2 + \beta_{02} - \beta_{12} - \beta_{22} - \beta_{23} + \beta_{32} T_{2i}(-1, -1, -1) + \beta_{41} + \beta_{42}$  for

subjects following adaptive intervention ( $A_1=-1, A_{2R}=-1, A_{2NR}=-1$ ).

### 1.3 The conditional expectation of the final outcomes for each of the 4 embedded adaptive interventions in the SMART design of Figure 2 is

$E[Y_i | 1, 1, t = T_{2i}] = Z_i \eta_2 + \beta_{02} + \beta_{12} + \beta_{23} + \beta_{32} T_{2i}(1, 1) + \beta_{42}$  for subjects following adaptive intervention ( $A_1=1, A_{2NR}=1$ );

$E[Y_i | 1, -1, t = T_{2i}] = Z_i \eta_2 + \beta_{02} + \beta_{12} - \beta_{23} + \beta_{32} T_{2i}(1, -1) - \beta_{42}$  for subjects following adaptive intervention ( $A_1=1, A_{2NR}=-1$ );

$E[Y_i | -1, 1, t = T_{2i}] = Z_i \eta_2 + \beta_{02} - \beta_{12} + \beta_{23} + \beta_{32} T_{2i}(-1, 1) - \beta_{42}$  for subjects following adaptive intervention ( $A_1=-1, A_{2NR}=1$ );

$E[Y_i | -1, -1, t = T_{2i}] = Z_i \eta_2 + \beta_{02} - \beta_{12} - \beta_{23} + \beta_{32} T_{2i}(-1, -1) + \beta_{42}$  for subjects following adaptive intervention ( $A_1=-1, A_{2NR}=-1$ ).

## 2 Data organization for Chapter 2

As discussed in the Methods, both analytic approaches required a linear mixed model fitted in R by function “*lme()*” in package “*nlme*”(167). Data obtained from the design had to be organized longitudinally to apply this function. Therefore, we stacked the observed data at three time points  $\{0, T_1, T_2\}$  and formed a new data set, as shown in Table A1. For each variable, the three parts of data in that column represent the corresponding measurements for all the subjects at time points  $\{0, T_1, T_2\}$ , respectively. The first column is the subject’s “**id**”, which is numbered from 1 to n (number of subjects), and thus the vector (1,2,...,n) is repeated for the three parts in that column. The variable “**Y**” in the second column is the longitudinal outcome of interest. Columns 3 to 14 represent the design matrix in models (2)–(4),

and the corresponding coefficients are  $(\beta_0^{Y_0}, \beta_0^{Y_1}, \beta_0^{Y_2}, \eta, \beta_1, \beta_{21}, \beta_{22}, \beta_{23}, \beta_{31}, \beta_{32}, \dots, \beta_{41}, \beta_{42})$ .

Data analyses were conducted with the data organized in Table S3 using the two proposed modeling approaches.

### 3 Implementation for Chapter 2

Data analysis using the joint model was implemented in R with package “JM”(141). A linear mixed model was fitted for the longitudinal outcomes  $Y = (0, Y_1, Y_2)$  using function “*lme()*”, and a Cox model was fitted for the time to the event of interest,  $T_1$ . Then the outputs from these two models were supplied as the main arguments in function “*jointModel()*” for fitting the joint model, using the data in Table A1. (More specifically, the joint model fitted using “*jointModel()*” had exactly the same structure for the linear mixed effects and survival submodels as these two separately fitted models, with the addition that in the survival model the effect of the estimated “true” baseline longitudinal outcome  $m_i(0)$  was included in the linear predictor.) This function approximates the integral

$$\int p(T1_i, \delta_i | b_i; \beta, \gamma, \alpha, \eta) \left[ \prod_j p\{Y_i(t_{ij}) | b_i; \beta, \eta\} \right] p(b_i; \sigma_b) db$$
 using either the Gauss-

Hermite rule or the fully exponential Laplace approximation and the integral

$$\int_0^{T1_i} h_i(s | m_i(0); \beta, \gamma, \alpha, \eta) ds$$
 in the likelihood model of  $T1_i$  using the Gauss-Kronrod

rule. The maximization of the log-likelihood is based on a hybrid optimization procedure, which starts with the expectation-maximization algorithm for a fixed number of iterations, and if convergence is not achieved, switches to a quasi-

Newton algorithm(168) (method “BFGS” in R function “optim()”(169-171)) until convergence is attained.

For all these options, the linear predictors in model (5) were written as  $\eta_i = \gamma_0 + \gamma_1 A1_i + \gamma_2 W_i + \alpha m_i\{\max(t-k, 0)\}$  where we let “*parameterization* = “*value*” in the function of “*jointModel()*”. Because in our example only the underlying baseline measurement  $m_i(0)$  was included in model (5), the linear predictor above should satisfy  $m_i\{\max(t-k, 0)\} = m_i(0)$ , which indicates that  $\max(t-k, 0) = 0$  and  $(t-k) \leq 0$ . In this expression, “*t*” is specified by the “*timeVar*” argument, which refers to the time variable and “*k*” is specified by the “*lag*” argument, denoting a lag effect in the time-dependent covariate represented by the TVMEM in the function “*jointmodel()*”. Therefore, we set “*timeVar*” equal to “ $T_1$ ” and “*lag*” equal to any value larger than  $t_{10}$  (e.g., in the simulations, we set “*lag*=2” as  $t_{10}=1$ ). In this way, we had  $\max(t-k, 0)=0$  for all the subjects and thus only the baseline longitudinal measurement was included in the survival submodel. Moreover, we set **method = “weibull-PH-GH”** in the function to apply the Weibull relative risk model in the regression of  $T_1$ .

#### 4 Supplementary simulations for Chapter 3

In this supplementary information, we showed simulation results for the simple SMART design in Figure S1, where all the subjects were randomized to two interventions at both stages. Results are shown in Tables S7 and S8, which are similar to Tables 14–17 for Figure 6. The results suggested that the proposed RCD

method showed overall good performance, i.e., the RCD method effectively allocated the subjects with respect to the final outcome values, covariate balance and consistency of optimal Q-learning decisions. RD performed as well as RCD with respect to the final outcomes and consistency of optimal Q-learning decisions, but had higher percentage of significant imbalance of covariates, especially when unequal randomization was applied to the first group in the trial.

Table S7 shows the simulation results for the SMART in Figure S1 with complete randomization (with probability 0.5) applied to the first group of subjects in the trial.

Data were simulated by model (7) with parameter values:  $\gamma_{20}=0.5$ ,

$\gamma_{21}=0.5$ ,  $\gamma_{22}=-1$ ,  $\gamma_{23}=0.6$ ,  $\gamma_{24}=0.2$ ,  $\alpha_{20}=0.1$ ,  $\alpha_{21}=-0.1$  and  $\alpha_{22}=0.35$ .  $O_1$  and  $O_2$  are single covariates generated from normal distributions  $N(3,1^2)$  and  $N(0.1,0.3^2)$ ,

respectively. The group size is 40 and the total sample size is 200. In this table, the RCD and RD methods showed better performance than the other methods with respect to the final outcome values and consistency of optimal Q-learning decisions, i.e., ITN% was 31.79% and 33.22% under the RCD and RD methods, respectively; both were lower than those values from the other methods; ODQ% was 69.54% and 68.41% under the RCD and RD methods, respectively; both were higher than those values from the other methods. Meanwhile, RCD had lower percentage of significant imbalance (i.e., 14.3%, 16.3%) than the RD and D methods, for which the percentages of significant imbalance were 21.7%, 24.0% and 27.5%, 23.3%, respectively.

Table S8 shows the simulation results for Figure S1 with the same group size, parameter values and distributions of  $O_1$  and  $O_2$  as that for Table S1, but the first group of subjects were completely randomized (with probability 0.5). The results were similar to those in Table S1, but RD and RCD both showed well controlled covariate balance (i.e., RCD had 8.5% significant imbalance and RD had 10%). The ITN% was 27.48% and 27.27% for the RCD and RD methods, respectively, which was lower than the percentages obtained under the other methods. In addition, ODQ% for RCD and RD was 71.92% and 71.88%, respectively, which was higher than the percentages obtained under the other methods. In both Tables S7 and S8, RC showed higher ITN% and ODQ% than the RCD and RD methods, but had much lower percentage of significant covariate imbalance.

Tables S9 and S10 (S3 & S4) show the simulation results for the group size of 100 subjects (the total sample size is 500 subjects), with the first group randomized according to their intermediate covariate (S9 and S3) and completely randomized (S10 and S4). Although better performance with respect to ITN% and ODQ% (lower ITN% and higher ODQ%) was obtained, we had much more severe imbalance of covariates, especially for the methods (RCD, RD, CD, and D) we proposed. This is because of the “over-skewed” allocation of subjects in the current group when the group size is too large. In Table S9, the RCD and RD methods showed 27.8% and 28.89% for the ITN% and 73.61% and 73.56% for the ODQ%, respectively. They both showed severe imbalance of covariates (i.e., 45.5%, 57.5% for RCD; 48.0% and 63.0% for RD). All the other methods also showed higher percentage of covariate imbalance than that in Table S7 because of the unequal randomization of

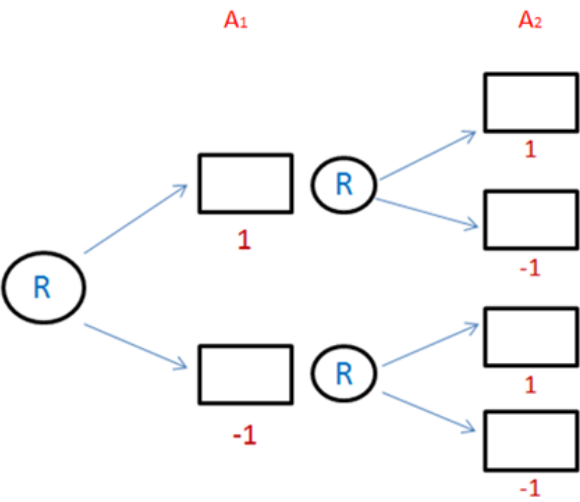


the first group in the trial; whereas they all (except the method of total randomization) had better ITN% and ODQ% estimations than that in Table S7. Similar results are shown in Table S10, with lower ITN% and higher ODQ%; whereas higher percentages of significant imbalance were obtained compared to those values in Table S8.

In order to show the effect of the group size, we obtained the results of the simulations with a group size of 20 (total sample size is 100) in Table S11 and S12. (s5 and s6). The simulation setting for Table S11 was the same as that of Table S7 except for a smaller group size. All the methods showed much lower percentage of significant imbalance than that in Table S7, except for the covariate-balance and total randomization methods. RCD had 9.5% and 6% significant covariate imbalance, while RD had 13% for both first-stage interventions. They had 35.8% and 36.66% of ITN% and 65.28% and 64.57% of ODQ%, respectively, which were both better than the percentages obtained from the other methods. In Table S12, where the first group of subjects was completely randomized, all the methods showed acceptable percentage of significant covariate imbalance; whereas RCD and RD had better performance with respect to ITN% (34.46% and 35.11%, respectively) and ODQ% (65.32% and 64.74%, respectively) than the other methods. However, all the methods (except covariate-balance and total randomization) showed higher ITN% and lower ODQ% than that in Table S8.

So, we can see that a smaller group size does ensure a better covariate balance, but relatively more subjects are assigned to inferior intervention arms and fewer subjects are assigned to the optimal Q-learning interventions in general.

Supplemental Figures:



**Figure S1.** SMARTs in which the decision of whether to re-randomize or not depends on an intermediate covariate and prior intervention

## Supplemental Tables:

**Table S1.** Eight embedded adaptive interventions in the SMART design of Figure 1.

	$(A_1, A_{2R}, A_{2NR})$	Adaptive interventions
(B,B,B+)	(1,1,1)	First, offer behavioral intervention; then continue behavioral intervention for responders and increase the intensity of behavioral intervention for non-responders.
(B,B,B+M)	(1,1,-1)	First, offer behavioral intervention; then continue behavioral intervention for responders and add medication for non-responders.
(B,B-,B+)	(1,-1,1)	First, offer behavioral intervention; then decrease the intensity of behavioral intervention for responders and increase the intensity of behavioral intervention for non-responders.
(B,B-,B+M)	(1,-1,-1)	First, offer behavioral intervention; then decrease the intensity of behavioral intervention for responders and add medication for non-responders.
(M,M,M+)	(-1,1,1)	First, offer medication; then continue medication for responders and increase the intensity of medication for non-responders.
(M,M,B+M)	(-1,1,-1)	First, offer medication; then continue medication for responders and add behavioral intervention for non-responders.
(M,M-,M+)	(-1,-1,1)	First, offer medication; then decrease the intensity of medication for responders and increase the intensity of medication for non-responders.
(M,M-,B+M)	(-1,-1,-1)	First, offer medication; then decrease the intensity of medication for responders and add behavioral intervention for non-responders.

*M: medication; B: behavioral intervention; M+: intensified medication; B+: intensified behavioral intervention; B+M: combined treatment of behavioral intervention and medication*

**Table S2.** Four embedded adaptive interventions in the SMART of Figure 2.

$(A_1, A_{2NR})$		Adaptive interventions
(B,B+)	(1, 1)	First, offer behavioral intervention; then continue behavioral intervention for responders and increase the intensity of behavioral intervention for non-responders.
(B,B+M)	(1, 1)	First, offer behavioral intervention; then continue behavioral intervention for responders and add medication for non-responders.
(M,M+)	(-1,1)	First, offer medication; then continue medication for responders and increase the intensity of medication for non-responders.
(M,B+M)	(-1,-1)	First, offer medication; then continue medication for responders and add behavioral intervention for non-responders.

**Table S3.** Longitudinal data organization

id	Y	int <sub>0</sub>	int <sub>1</sub>	int <sub>2</sub>	Z	$A_1(Y_1)$	$A_1(Y_2)$	$A_{2R}(Y_2)$	$A_{2NR}(Y_2)$	$T_1$	$T_2$	$A_{2R} \cdot A_1(Y_2)$	$A_{2NR} \cdot A_1(Y_2)$
1:n	$Y_0$	1	0	0	Z	0	0	0	0	0	0	0	0
1:n	$Y_1$	0	1	0	Z	$Y_2$	0	0	0	$T_1$	0	0	0
1:n	$Y_2$	0	0	1	Z	0	$A_1$	$A_{2R}$	$A_{2NR}$	0	$T_2$	$A_1 \cdot A_{2R}$	$A_1 \cdot A_{2NR}$

**Table S4.** The effect sizes associated with  $U_1$  and  $U_2$  (simulated two unmeasured variables,  $U_1$  and  $U_2$  that affect the outcomes but were not included in the analyses) influencing  $T_1$  and  $Y_1$  but not  $Y_2$

**Panel A: The coefficients of unobserved confounders in the simulation model**

	$U_1$	$U_2$
$T_1$	0.2	-0.3
$Y_1$	-0.4	0.3
$Y_2$	0	0

**Panel B: Parameter estimation**

		$\beta_{12}$ (first-stage interventions $A_1$ )	$\beta_{22}$ (second-stage interventions for responders $A_{2R}$ )	$\beta_{23}$ (second-stage interventions for non- responders $A_{2NR}$ )	$\beta_{32}$ (time of intervention $T_2$ )
<b>True value</b>		<b>- 0.4</b>	<b>0.5</b>	<b>0.4</b>	<b>2.0</b>
Joint Model	Estimate	-0.391	0.515	0.389	1.909
	MSE	0.011	0.033	0.016	0.134
	CI%	98%	94%	96%	97%
	Length of CI	0.476	0.688	0.530	1.464
TVMEM	Estimate	-0.508	0.513	0.389	4.010
	MSE	0.023	0.033	0.017	4.165
	CI%	89.5%	94%	96%	0%
	Length of CI	0.482	0.706	0.541	1.446

**Table S5.** The effect sizes associated with  $U_1$  and  $U_2$  influencing  $T_1$ ,  $Y_1$  and  $Y_2$

**Panel A: coefficients of unobserved confounders in the simulation model**

	$U_1$	$U_2$
$T_1$	0.2	-0.3
$Y_1$	-0.4	0.3
$Y_2$	-0.2	-0.3

**Panel B: coefficients of unobserved confounders**

		$\beta_{12}$	$\beta_{22}$	$\beta_{23}$	$\beta_{32}$
		(first-stage interventions $A_1$ )	(second-stage interventions for responders $A_{2R}$ )	(second-stage interventions for non- responders $A_{2NR}$ )	(time of intervention $T_2$ )
<b>True value</b>		<b>- 0.4</b>	<b>0.5</b>	<b>0.4</b>	<b>2.0</b>
Joint Model	Estimate	-0.391	0.513	0.396	1.638
	MSE	0.010	0.037	0.015	0.218
	CI%	98%	96%	97%	92%
	Length of CI	0.476	0.689	0.529	1.458
TVMEM	Estimate	-0.505	0.515	0.395	3.731
	MSE	0.021	0.037	0.015	3.090
	CI%	90%	95%	97%	1%
	Length of CI	0.482	0.707	0.539	1.441

**Table S6.** The effect sizes associated with  $U_1$  and  $U_2$  influencing  $T_1$  and  $Y_2$  but not  $Y_1$

**Panel A: coefficients of unobserved confounders in the simulation model**

	$U_1$	$U_2$
$T_1$	0.3	-0.4
$Y_1$	0	0
$Y_2$	0.2	-0.3

**Panel B: coefficients of unobserved confounders**

		$\beta_{12}$ (first-stage interventions $A_1$ )	$\beta_{22}$ (second-stage interventions for responders $A_{2R}$ )	$\beta_{23}$ (second-stage interventions for non- responders $A_{2NR}$ )	$\beta_{32}$ (time of intervention $T_2$ )
<b>True value</b>		<b>- 0.4</b>	<b>0.5</b>	<b>0.4</b>	<b>2.0</b>
Joint Model	Estimate	-0.420	0.490	0.408	2.210
	MSE	0.012	0.035	0.015	0.163
	CI%	99%	91%	96%	94%
	Length of CI	0.477	0.696	0.529	1.463
TVMEM	Estimate	-0.531	0.491	0.410	4.263
	MSE	0.028	0.037	0.016	5.232
	CI%	83%	91%	96%	0%
	Length of CI	0.483	0.714	0.539	1.439

**Table S7.** Simulation results based on 1000 replicates for SMART in Figure S1 with parameter values  $\gamma_{20}=0.5$  ,  $\gamma_{21}=0.5$ ,  $\gamma_{22}=-1$ ,  $\gamma_{23}=0.6$ ,  $\gamma_{24}=0.2$ ,  $\alpha_{20}=0.1$ ,  $\alpha_{21}=-0.1$  and  $\alpha_{22}=0.35$ ; The sample size was 200 with group sizes of 40; subjects in the first group were assigned to the second-stage intervention based on their intermediate covariate  $O_2$  (i.e., unequal randomization).

	ITN%	Percentage of significant covariate imbalance		ODQ%
		A1=1	A1=-1	
<b>RCD</b>	31.79%	14.3%	16.3%	69.54%
<b>RD</b>	33.22%	21.7%	24.0%	68.41%
<b>RC</b>	37.71%	5.4%	3.8%	63.04%
<b>CD</b>	36.91%	13.7%	15.7%	64.78%
<b>Total</b>	49.93%	6.5%	5.0%	51.37%
<b>D</b>	37.16%	27.5%	23.0%	64.70%
<b>R</b>	37.63%	7.5%	7.0%	63.35%
<b>C</b>	50.11%	2.0%	3.7%	50.96%



**Table S8.** Simulation results based on 1000 replicates for SMART in Figure S1 with parameter values  $\gamma_{20}=0.5$ ,  $\gamma_{21}=0.5$ ,  $\gamma_{22}=-1$ ,  $\gamma_{23}=0.6$ ,  $\gamma_{24}=0.2$ ,  $\alpha_{20}=0.1$ ,  $\alpha_{21}=-0.1$  and  $\alpha_{22}=0.35$ ; the sample size was 200 with group sizes of 40; subjects in the first group were assigned to the second-stage intervention completely at random (i.e., equal randomization).

	ITN%	Percentage of significant		ODQ%
		covariate imbalance		
		A1=1	A1=-1	
RCD	27.48%	8.5%	8.5%	71.92%
RD	27.27%	10.0%	10.0%	71.88%
RC	32.55%	2.5%	3.5%	66.57%
CD	35.68%	6.0%	7.5%	64.69%
Total	49.79%	4.5%	7.0%	50.15%
D	35.34%	15.0%	13.5%	64.95%
R	32.15%	3.5%	3.5%	66.88%
C	49.88%	2.5%	1.0%	49.96%

**Table S9.** Simulation results based on 1000 replicates for SMART in Figure S1 with parameter values  $\gamma_{20}=0.5$  ,  $\gamma_{21}=0.5$ ,  $\gamma_{22}=-1$ ,  $\gamma_{23}=0.6$ ,  $\gamma_{24}=0.2$ ,  $\alpha_{20}=0.1$ ,  $\alpha_{21}=-0.1$  and  $\alpha_{22}=0.35$  ; The sample size was 500 with group sizes of 100; subjects were assigned to the second-stage intervention based on their intermediate outcome  $O_2$  (i.e. unequal randomization).

	ITN%	Percentage of significant covariate imbalance		ODQ%
		A1=1	A1=-1	
<b>RCD</b>	27.80%	45.5%	57.5%	73.61%
<b>RD</b>	27.89%	48.0%	63.0%	73.56%
<b>RC</b>	31.72%	6.5%	7.0%	68.83%
<b>CD</b>	29.47%	38.5%	46.5%	72.17%
<b>Total</b>	50.05%	11.0%	10.5%	51.36%
<b>D</b>	29.60%	42.0%	50.5%	72.24%
<b>R</b>	32.41%	15.5%	13.0%	68.45%
<b>C</b>	49.88%	4.5%	7.0%	51.88%

**Table S10.** Simulation results based on 1000 replicates for SMART in Figure S1 with parameters  $\gamma_{20}=0.5$ ,  $\gamma_{21}=0.5$ ,  $\gamma_{22}=-1$ ,  $\gamma_{23}=0.6$ ,  $\gamma_{24}=0.2$ ,  $\alpha_{20}=0.1$ ,  $\alpha_{21}=-0.1$  and  $\alpha_{22}=0.35$ ; the sample size was 500 with group sizes of 100; subjects were assigned to the second-stage intervention completely at random (i.e., equal randomization).

	ITN%	Percentage of significant covariate imbalance		ODQ%
		A1=1	A1=-1	
<b>RCD</b>	21.80%	32.0%	40.5%	77.22%
<b>RD</b>	22.13%	35.2%	40.5%	76.92%
<b>RC</b>	24.14%	3.5%	3.5%	74.22%
<b>CD</b>	29.17%	19.4%	23.2%	71.53%
<b>Total</b>	50.09%	4.5%	7.0%	50.0%
<b>D</b>	29.16%	26.5%	29.1%	71.66%
<b>R</b>	24.13%	4.0%	3.0%	74.34%
<b>C</b>	50.02%	0.5%	0.1%	49.88%

**Table S11.** Simulation results based 1000 replicates for SMART in Figure S1 with parameter values  $\gamma_{20}=0.5$  ,  $\gamma_{21}=0.5$ ,  $\gamma_{22}=-1$ ,  $\gamma_{23}=0.6$ ,  $\gamma_{24}=0.2$ ,  $\alpha_{20}=0.1$ ,  $\alpha_{21}=-0.1$  and  $\alpha_{22}=0.35$  ; the sample size was 100 with group sizes of 20; subjects were assigned to the second-stage intervention based on their intermediate outcome  $O_2$  (i.e., unequal randomization).

	ITN%	Percentage of significant		ODQ%
		covariate imbalance		
		A1=1	A1=-1	
RCD	35.80%	9.5%	6.1%	65.28%
RD	36.66%	13.1%	13.2%	64.57%
RC	42.17%	2.4%	1.1%	48.65%
CD	40.75%	5.1%	5.2%	60.54%
Total	50.33%	5.3%	7.5%	50.99%
D	40.20%	15.0%	15.5%	61.33%
R	41.46%	6.2%	4.3%	59.76%
C	49.88%	4.5%	7.3%	51.45%

**Table S12.** Simulation results based on 1000 replicates for SMART Figure S1 with parameters  $\gamma_{20}=0.5$ ,  $\gamma_{21}=0.5$ ,  $\gamma_{22}=-1$ ,  $\gamma_{23}=0.6$ ,  $\gamma_{24}=0.2$ ,  $\alpha_{20}=0.1$ ,  $\alpha_{21}=-0.1$  and  $\alpha_{22}=0.35$ ; the sample size was 100 with group sizes of 20; subjects were assigned to the second-stage intervention completely at random (i.e., equal randomization).

	ITN%	Percentage of significant covariate imbalance		ODQ%
		A1=1	A1=-1	
<b>RCD</b>	34.46%	5.0%	5.3%	65.32%
<b>RD</b>	35.11 %	6.1%	5.3%	64.74%
<b>RC</b>	38.28%	3.1%	3.6%	61.11%
<b>CD</b>	40.63%	4.2%	4.3%	59.70%
<b>Total</b>	49.79%	5.3%	4.7%	50.10%
<b>D</b>	40.79%	5.4%	7.4%	59.51%
<b>R</b>	39.25%	2.4%	5.4%	60.23%
<b>C</b>	49.73%	2.0%	2.2%	50.25%

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