Adaptive Sequential Multiple Assignment Randomized Trial Designs

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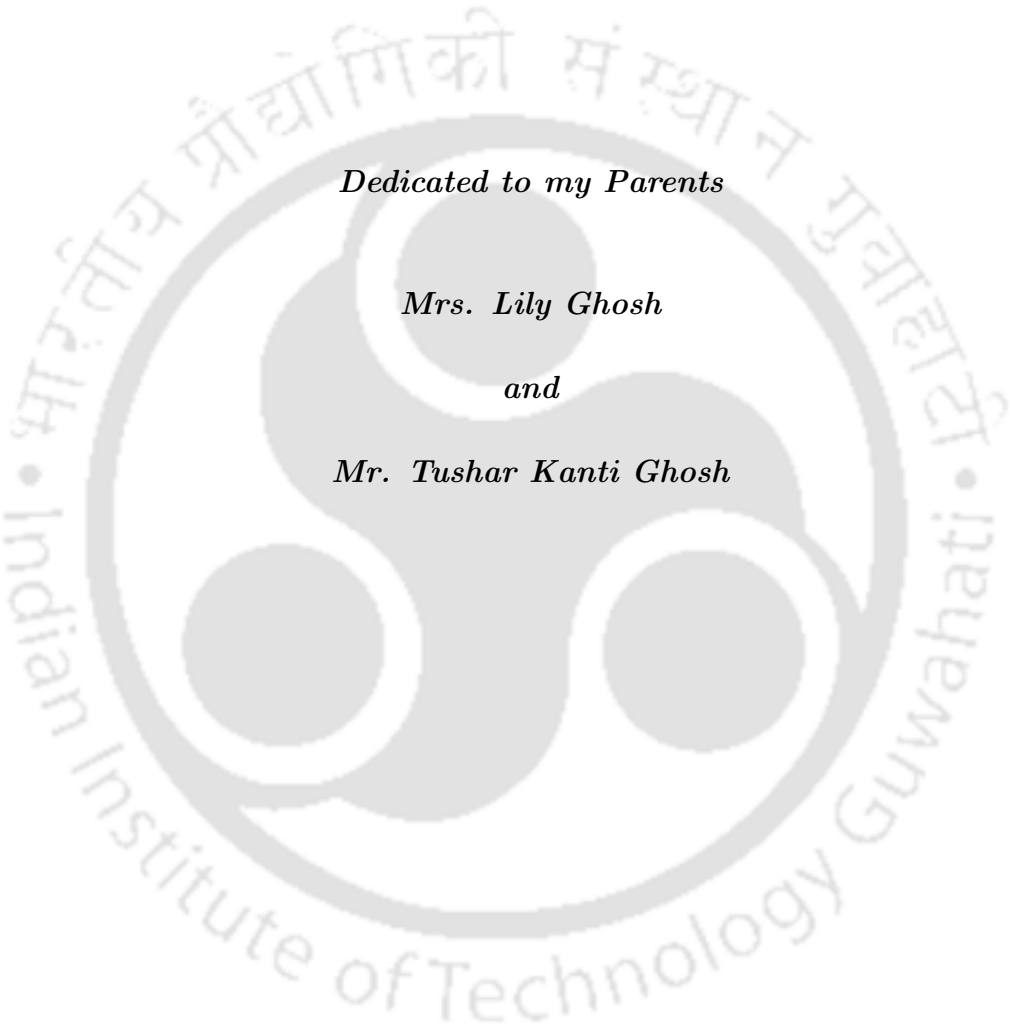

Dedicated to my Parents

Mrs. Lily Ghosh

and

Mr. Tushar Kanti Ghosh

Adaptive Sequential Multiple Assignment Randomized Trial Designs

A Thesis Submitted in Partial Fulfillment
of the Requirements for the Degree of

DOCTOR OF PHILOSOPHY

by

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August, 2025

Declaration

I do hereby declare that the work contained in this thesis entitled ***"Adaptive Sequential Multiple Assignment Randomized Trial Designs"*** has been done by me, under the supervision of **Dr. Palash Ghosh**, Assistant Professor, Department of Mathematics, Indian Institute of Technology Guwahati, for the award of the degree of Doctor of Philosophy, and that this work has not been submitted elsewhere for a degree.

August, 2025

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Certificate

It is to certify that the work contained in this thesis entitled ***"Adaptive Sequential Multiple Assignment Randomized Trial Designs"*** has been carried out by **Rik Ghosh**, a student in the Department of Mathematics, Indian Institute of Technology Guwahati, under my supervision for the award of the degree of Doctor of Philosophy and that this work has not been submitted elsewhere for a degree.

August, 2025

Dr. Palash Ghosh
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The Doctor of Philosophy (PhD) is not merely a degree; it is a transformative journey that shapes an individual both academically and personally. When I first started on this path, I was a bit skeptical. Leaving a well-paying job to follow my passion was an exciting prospect, but making it work was far from easy. Now, as I write this thesis, I can say that with the unwavering support and guidance of my supervisor, I found the determination to see it through. Completing this thesis was not an easy job. Many individuals provided invaluable support and guidance, and their contributions were instrumental throughout my journey. I would like to take this opportunity to acknowledge them. First and foremost, I wish to express my deepest gratitude to God for blessing me with good health and the capacity to pursue my studies.

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Abstract

Sequential Multiple Assignment Randomized Trial (SMART) is an experimental trial framework for evaluating multiple adaptive interventions that tailor treatment sequences to individual responses over time. Traditional SMART designs rely on fixed (non-adaptive) randomization probabilities at each stage and fail to leverage information accumulated during the trial. This may raise ethical concerns by continuing to allocate participants to inferior treatment options. This thesis presents a comprehensive methodology for developing optimal adaptive randomization in SMART designs to enhance both ethical and statistical efficiency. The primary contribution of this work is the derivation of optimal adaptive allocation ratios and procedures for two-stage SMART designs, applicable to both binary and continuous primary outcomes. Building on optimal adaptive randomization theory for two-arm randomized controlled trials, we formulate constrained optimization problems that minimize the total expected number of treatment failures for a binary outcome, subject to fixed asymptotic-variance constraints for prespecified objective functions. For continuous outcomes, the objective function differs. Optimal second-stage allocation ratios are first obtained and are then recursively propagated backward to derive the optimal first-stage allocation.

Theoretical properties of the proposed estimators are established, and extensive simulation studies demonstrate convergence of the estimated allocation ratios to their theoretical optima and improved efficiency. We also demonstrate substantial reductions in the expected number of failures for binary outcomes and in the total expected outcome for continuous outcomes, compared with non-adaptive and existing adaptive SMART designs. The proposed methods also maintain desirable inferential properties, including valid hypothesis testing and competitive power. Applications to real-world studies, including the M-bridge study and a SMART weight-loss management study, illustrate the practical feasibility and advantages of the proposed designs. The thesis further extends the

methodology of optimal adaptive allocation ratio in binary outcome SMART to covariate-adjusted adaptive SMART designs, incorporating baseline covariates into the allocation mechanism to further enhance efficiency and ethical performance. Overall, this work provides a comprehensive framework for optimal adaptive randomization in SMART designs, advancing the methodological foundation for the development of data-driven, ethical, and efficient adaptive interventions in all clinical research.

CHAPTER 1

Introduction

1.1 Preamble

The recent COVID-19 pandemic has introduced nearly all of us to the term "clinical trials" (McIntosh et al., 2020). Clinical trials are primarily clinical evaluations conducted to generate data regarding the dosage, safety, and efficacy of novel drugs, vaccines, or medical procedures (Deleuran et al., 2020; Pocock, 2013). Since prehistoric times, humans have sought ways to alleviate physiological pain in themselves or their loved ones. As medical science has advanced, the development of new drugs, vaccines, and procedures has necessitated rigorous studies to evaluate their effectiveness. The comprehensive data generated from these trials are analyzed using various statistical methods. Typically, a number of individuals who participate voluntarily are enrolled in these studies, exposed to new interventions, and subsequently monitored for changes in clinical measurements.

Clinical trials are most commonly conducted using the conventional Randomized Controlled Trial (RCT) design (Chalmers et al., 1981). In a two-arm RCT, patients are randomly assigned to either a control or treatment group (Lim and In, 2019; Kang et al., 2008), which helps eliminate accidental or selection bias. Treatments are randomly allocated at the start of the trial, without utilizing information that may become available as the trial progresses. This approach overlooks potentially valuable interim data that could be used to assign more participants to a more effective treatment if such evidence emerges. For instance, in a trial with 100 participants, equal allocation would assign 50 individuals to each of the treatment and control groups. However, if it becomes evident during the trial that one treatment is more effective, it would be ethically preferable to assign more participants to the superior treatment. The inability to use accumulating data

to adapt allocations is a significant ethical concern in traditional RCTs (Narita, 2021). Because of these ethical concerns, changes have been suggested to the way clinical trials are conducted to make them more ethical.

In an RCT, randomization assigns subjects to either the treatment or control group according to a predetermined randomization procedure, which generates an unpredictable (random) sequence of allocations. This procedure typically relies on a fixed probability distribution (e.g., 1:1), classifying the RCT as non-adaptive. As argued earlier, non-adaptive RCTs present several drawbacks, including ethical issues related to participant welfare, high costs, and considerable heterogeneity in participant responses to interventions. Since physiological characteristics vary among individuals, responses to the same treatment may differ significantly.

To address these limitations, adaptive methodologies have been developed that utilize accumulating information throughout the trial. In adaptive RCTs, the probability distribution for assigning participants to treatment or control groups is updated as new interim data become available, thereby improving both ethical and scientific outcomes (Atkinson and Biswas, 2013). Moreover, many clinical questions require more than a single-stage treatment approach, especially in fields such as chronic disease or behavioral health, where patient responses to an initial treatment may inform subsequent therapeutic strategies. To address these multi-stage decision processes and the inherent heterogeneity in patient responses, the Sequential Multiple Assignment Randomized Trial (SMART) design was developed (Chakraborty and Moodie, 2013). In a SMART, participants are randomized at multiple stages, with subsequent treatment assignments tailored according to their individual interim responses. This dynamic, multi-stage framework allows researchers to systematically evaluate and refine sequences of treatments, providing a robust methodology for optimizing care pathways (treatment sequences). In this thesis, we aim to optimize the SMART design, further enhancing both the ethical considerations and scientific rigor of clinical trials by integrating adaptive randomization within a multi-stage trial framework.

1.2 Literature Review

1.2.1 Randomized Controlled Trial (RCT)

The Randomized Controlled Trial (RCT) stands as one of the most significant breakthroughs of the twentieth century, fundamentally shaping modern medical practice (Smith, 1998). Recognized as a powerful methodology in clinical research (Stolberg et al., 2004), two-arm RCTs evaluate the impact of interventions by randomly allocating participants from a population to either a treatment or control group (White et al., 2014). This randomization process is crucial for minimizing selection bias and ensuring an equitable

distribution of participant characteristics, such as age, gender, or pre-existing medical conditions, between groups. Through this design, researchers collect and analyze data to determine the efficacy of the intervention under study.

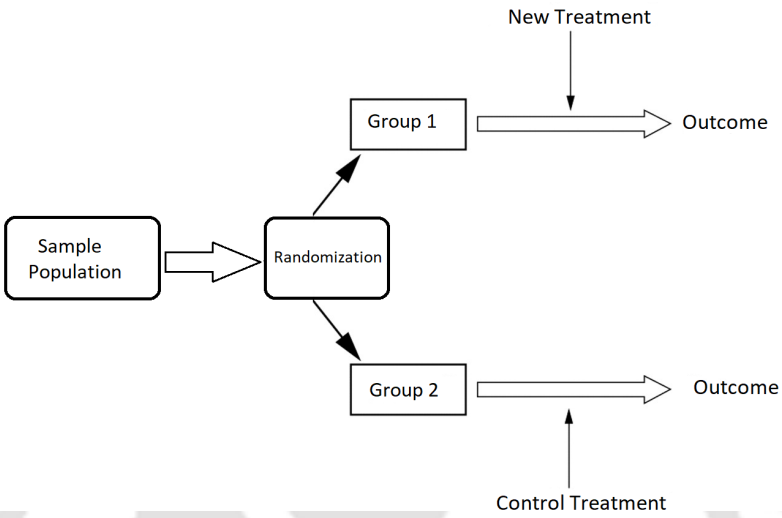


Figure 1.1: A schematic diagram of an Randomized Control Trial.

A typical two-arm RCT, illustrated in Figure 1.1, involves assigning participants to either a treatment group (Group 1) or a control group (Group 2) using a random binary sequence. The treatment group receives the new drug or vaccine, while the control group is administered a existing drug or placebo. The comparison of binary (e.g., blood sugar within the normal range or not) or continuous (e.g., change in blood sugar level) primary outcomes between these groups helps determine the effectiveness of the drug/intervention. A statistically significant difference indicates potential superiority of the drug/intervention. Commonly, RCTs utilize a fixed, pre-specified probability distribution for random participant allocation (Jadad, 1998).

Key stakeholders in an RCT include participants, care providers (such as medical practitioners), and outcome assessors (often statisticians) (Moher et al., 2012). Among these stakeholders, blinding plays an important role. In RCTs, it refers to the practice of keeping one or more of these groups unaware of which treatment or intervention each participant receives. Blinding is essential to minimize various forms of bias, such as placebo effects, observer bias, and differential treatment or assessment that could compromise the validity of the results. The extent of blinding determines the type of trial design: single-blind (only participants are blinded), double-blind (both participants and care providers are blinded), and triple-blind (participants, care providers, and outcome assessors are all blinded).

In a single-blind RCT, participants are unaware of which intervention they receive, helping to eliminate psychological bias. For instance, in a trial evaluating a new antihypertensive drug, participants may receive either the study drug or a placebo, but they remain

blinded to their group assignment. A double-blind RCT extends blinding to both participants and care providers. Here, neither group knows which intervention each participant receives, further reducing the risk of bias. This is typically achieved by coding drugs or using a numbered sequence prepared by an independent statistician, who alone is aware of the actual assignments. In a triple-blind RCT, blinding encompasses participants, care providers, and, to the extent possible, the outcome assessors or statisticians. While it is rarely feasible to blind statisticians completely, partial blinding can be implemented (Misra, 2012). Due to practical challenges, triple-blind designs are seldom used.

One main limitation of conventional RCTs lies in their use of fixed randomization probabilities, which restricts flexibility in adapting to interim data during the trial. This limitation and potential solutions will be discussed in the next section.

1.2.2 Adaptive RCT

In a randomized controlled trial (RCT), the randomization probability is fixed. As discussed in the previous section, an RCT involves assigning participants randomly to either the treatment or the control group. In a non-adaptive RCT, the probability of randomization remains constant throughout the trial. Thus, participants continue to be allocated to treatments according to the same randomization probability until the end of the trial, even if interim analyses suggest that one treatment is performing better than the other. To address the ethical issues posed by this approach, particularly the continued allocation of participants to potentially less effective treatments, regulatory agencies such as the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have strongly recommended the adoption of adaptive designs in clinical trials (Mahajan and Gupta, 2010). The primary aim of adaptive designs is to allow investigators to use interim analysis results to adjust the randomization probabilities, thereby increasing the likelihood that subsequent participants receive the more effective treatment. This adaptation addresses ethical concerns associated with traditional RCTs and helps ensure a more ethical allocation of treatments (Harrington, 2000).

In an adaptive RCT design, the randomization probability may change based on accumulating data. However, this flexibility does not permit arbitrary modifications to the trial procedures. Any changes to the randomization probabilities must be justified by the data collected up to that point in the trial (Atkinson and Biswas, 2013). Specifically, patient outcomes obtained during the course of the trial can be analyzed to assess the relative efficacy of treatments, informing subsequent adjustments to randomization probabilities. Unblinded data collected throughout the course of the trial will inform and guide adjustments to the randomization probabilities as the study progresses.

An adaptive RCT is flexible enough to change the allocation probabilities during the trial based on the information from the interim analysis (Pallmann et al., 2018). In other

words, adaptive RCTs enable the allocation of more patients to better treatment in the long run, (Hulley, 2007). One of the early methods used in adaptive RCTs is the play-the-winner (PW). It was first introduced for dichotomous response in clinical trials with two treatments (Zelen, 1969). In PW, we place a ball marked with 'U' in the urn when success is obtained with treatment U or a failure with treatment V. Similarly, a ball marked with 'V' is placed when success is obtained with treatment V or a failure with treatment U (Wei and Durham, 1978). For a new patient, a ball is drawn at random from the urn without replacement to allocate the corresponding treatment; if the urn is empty, then the allocation is done by tossing an unbiased coin. However, due to delays in getting responses from patients, the PW rule is inconvenient in practical trials as most of the allocation is done by tossing an unbiased coin. Later, a modified PW rule was introduced as the randomized play-the-winner (RPW) (Atkinson and Biswas, 2013). In RPW, an urn consisting of two types (U and V) of balls representing two different treatments (U and V), initially with the same number. For each patient, one ball is drawn (with replacement) at random, and the corresponding treatment is administered. When the outcome of any previous patient is a success (improvement) who obtained treatment U (or V), then α (or β) a number of U-type balls are added to the urn, and β (or α) number of V-type balls are added (Wei and Durham, 1978). The exact opposite scheme is done when the outcome of that patient is a failure (no improvement). This process is repeated till the end of the trial. Note that the RPW rule is not based on any formal optimality criterion. However, in RPW, the limiting allocation is intuitively allocating the treatments using relative-risk. Rosenberger et al. (2001) proposed an adaptive design that allocates treatments based on the formal optimal criterion for RCT with binary outcomes. Adaptive designs may sometimes result in inefficiencies such as higher estimation bias and an imbalance in sample sizes in favor of the inferior treatment (Thall et al., 2015). This problem can be addressed by restricting the adaptive randomization probability away from zero and one, say in $[0.2, 0.8]$ (Wathen and Thall, 2017).

In the optimal adaptive RCT design proposed by Rosenberger et al. (2001), two treatments, A and B, are administered to participants. Each participant exhibits a binary outcome: success or failure. The probability of success for treatment A is denoted by p_A, and the probability of failure by q_A. Similarly, the success and failure probabilities for treatment B are represented by p_B and q_B, respectively. Let n_A and n_B denote the number of participants assigned to treatments A and B, respectively. The primary objective of Rosenberger et al. (2001) was to determine an optimal adaptive allocation that minimizes the total expected number of failures. A participant is classified as a failure if their outcome does not meet a pre-specified improvement criterion (for example, if post-treatment blood sugar remains above 99 mg/dL). Thus, the total expected number of failures can be expressed as $n_A q_A + n_B q_B$. They aimed to identify the optimal adaptive

allocation ratio,

$$M = \frac{n_A}{n_B}. \tag{1.1}$$

Using this optimal adaptive allocation ratio, the total expected number of failures can be reformulated as

$$\frac{M}{M+1} n q_A + \frac{1}{M+1} n q_B, \tag{1.2}$$

where $n = n_A + n_B$. Here, n is a function of (M, p_A, p_B). Let $f(p_A, p_B)$ be a function comparing two binomial probabilities. To express n in terms of these variables, they solved $avar f(\hat{p}_A, \hat{p}_B)$, equating it with a constant. The asymptotic variance ($avar$) for different functions (e.g., difference) of the binomial probabilities p_A, p_B has been studied by Melfi et al. (2001) and Jennison and Turnbull (1999). Melfi et al. (2001) analyzed convergence probabilities in an adaptive setup using martingale properties of the allocation sequence, arriving at the result,

$$As\ k \to \infty,\ \frac{N_{A,k}}{k} \to \pi\ almost\ surely, \tag{1.3}$$

where $N_{A,k}$ denotes the number of the first k observations allocated to population A (who were given treatment A). The two populations are denoted as Population A and Population B, with $\{X_k : k \geq 1\}$ and $\{Y_k : k \geq 1\}$ representing the potential observations from populations A and B, respectively. Suppose the responses from A, X_i, are normally distributed with mean μ_A and standard deviation σ_A, and those from B are normally distributed with mean μ_B and standard deviation σ_B. Using the central limit theorem for adaptive designs (Melfi et al., 2001),

$$\sqrt{k}[(\overline{X}(k) - \overline{Y}(k)) - (\mu_A - \mu_B)] \xrightarrow{d} N(0, (\sigma_A + \sigma_B)^2)\ as\ k \to \infty,$$

where $\overline{X}(k)$ and $\overline{Y}(k)$ denote corresponding sample means; d deontes convergence in distribution. Applying the central limit theorem to the adaptive setup (Melfi et al., 2001), if the asymptotic variance of the difference in binomial probabilities, $avar(\hat{p}_A - \hat{p}_B) = \epsilon$, is constant ($\epsilon > 0$), then

$$\frac{p_A q_A}{n_A} + \frac{p_B q_B}{n_B} = \epsilon. \tag{1.4}$$

Combining (1.1) and (1.4), we obtain $n = \frac{(1+M)(p_A q_A + M p_B q_B)}{\epsilon M}$. The minimization procedure yields the optimal adaptive allocation ratio as

$$M^* = \sqrt{\frac{p_A}{p_B}}. \tag{1.5}$$

This method demonstrates that the optimal adaptive allocation proportion is dependent on the chosen functional form $f(p_A, p_B)$. For example, if the odds ratio is considered

(instead of the difference of binomial probabilities), the expression for the optimal adaptive allocation changes accordingly.

Let $X_1, X_2, ..., X_n$ denote the response indicators (taking value 0 for failure and 1 for success), and $T_1, T_2, ..., T_n$ be the indicators for treatment assignment (1 for A, 0 for B). The conditional expectation of a function $g(\cdot)$ after assigning the treatments to the first i participants and obtaining corresponding responses, is given by

$$E_i(g) = E(g|X_1, X_2, ..., X_i, T_1, T_2, ..., T_i).$$

Let $\hat{p}_{A,i-1}$ be the estimated probability of success for treatment A based on the first $(i-1)$ participants, and analogously for treatment B, $\hat{p}_{B,i-1}$. Thus,

$$\begin{aligned}
N_{A,n} &= \sum_{i=1}^{n} T_i, \\
N_{B,n} &= n - N_{A,n}, \\
\hat{p}_{A,n} &= \sum_{i=1}^{n} \frac{T_i X_i}{N_{A,n}}, \\
\hat{p}_{B,n} &= \sum_{i=1}^{n} \frac{(1-T_i) X_i}{N_{B,n}}, \\
\hat{q}_{A,n} &= 1 - \hat{p}_{A,n}, \\
\hat{q}_{B,n} &= 1 - \hat{p}_{B,n}.
\end{aligned}$$

The optimal adaptive allocation depends on the binomial parameters (p_A, p_B). Since both p_A and p_B are unknown in practice, a sequential design is employed to approximate the optimal adaptive allocation. The allocation method used by Rosenberger et al. (2001) is,

$$E_{i-1}(T_i) = \frac{\sqrt{\hat{p}_{A,i-1}}}{\sqrt{\hat{p}_{A,i-1}} + \sqrt{\hat{p}_{B,i-1}}}.$$

Here, $E_{i-1}(T_i)$ refers to the estimation of the success probability $(\hat{p}_{A,i})$ based on the first $(i-1)$ sequentially enrolled patients to be used for the adaptive randomization of the i^{th} patient. Applying (1.3), and noting $p_A, p_B \in (0,1)$, the following convergence holds,

$$\frac{N_{A,n}}{n} \xrightarrow{a.s} \frac{\sqrt{p_A}}{\sqrt{p_A} + \sqrt{p_B}} \; as \; n \to \infty,$$

where $a.s$ denotes almost sure convergence. Statistical inference is then conducted following completion of the allocation according to the optimal ratio. The hypothesis tested is

$$H_0 : p_A = p_B \text{ vs } H_1 : p_A \neq p_B.$$

The Wald-type test statistic considered by Rosenberger et al. (2001) is

$$Z = \frac{\hat{p}_{A,n} - \hat{p}_{B,n}}{\sqrt{\frac{\hat{p}_{A,n}\hat{q}_{A,n}}{N_{A,n}} + \frac{\hat{p}_{B,n}\hat{q}_{B,n}}{N_{B,n}}}}. \tag{1.6}$$

For Neyman allocation (which minimizes the total sample size when the variance is considered fixed), the adaptive rule is (Melfi and Page, 1998),

$$E_{i-1}(T_i) = \frac{\sqrt{\hat{p}_{A,i-1}\hat{q}_{A,i-1}}}{\sqrt{\hat{p}_{A,i-1}\hat{q}_{A,i-1}} + \sqrt{\hat{p}_{B,i-1}\hat{q}_{B,i-1}}}.$$

For equal allocation, both treatments are assigned randomly with probability 0.5. In the randomized play-the-winner rule, a ball is drawn from an urn containing α_A and α_B balls; the drawn ball determines the assigned treatment, and the number of balls is updated based on observed outcomes before the next draw.

To illustrate, the 6^{th} row of the simulation Table 1 from Rosenberger et al. (2001) shows $p_A = 0.1$ and $p_B = 0.2$, indicating a higher success probability for B. Consequently, more failures are expected among participants assigned to treatment A. The randomization probability for (Rosenberger's) optimal adaptive allocation is 0.42, the lowest among the compared designs, indicating that more participants are allocated to treatment B. Specifically, for 100 participants, on average, 42 would receive A and 58 B; among these, expected successes are 4 for A and 12 for B. For Neyman allocation, 43 are allocated to A (4 expected successes) and 57 to B (11 expected successes). Thus, optimal adaptive allocation results in fewer failures (or higher successes) compared to Neyman allocation (and other procedures) by allocating more participants to the more effective treatment. However, when both treatments have the same success probability (as in the first five rows of the table), all allocation procedures perform similarly.

Using the pooled estimator of the common success probability in the variance, another test statistic proposed by Fleiss et al. (2013) is also considered,

$$Z^* = \frac{\hat{p}_{A,n} - \hat{p}_{B,n}}{\sqrt{\hat{\bar{p}}_n\hat{\bar{q}}_n\left(\frac{1}{N_{A,n}} + \frac{1}{N_{B,n}}\right)}},$$

where $\hat{\bar{p}}_n = \frac{\hat{p}_{A,n}N_{A,n} + \hat{p}_{B,n}N_{B,n}}{n}$ and $\hat{\bar{q}}_n = 1 - \hat{\bar{p}}_n$. This test statistic was also used to evaluate the effectiveness of optimal adaptive allocation compared to other existing methods by comparing the randomization probabilities at the conclusion of the trials.

1.2.3 Adaptive Intervention (AI)

The heterogeneity observed in individuals' responses to different treatment effects has led to the development of adaptive interventions. An adaptive intervention (AI) is defined as a set of prespecified decision rules that guide the sequence of treatments to be administered to individuals (Almirall et al., 2018). AIs are inherently individualized, as they comprise a sequence of treatments tailored according to ongoing information about an individual's progress or response up to that point in time (Ghosh et al., 2020). An AI typically consists of four key components: (i) decision points, (ii) intervention options, (iii) tailoring variables, and (iv) decision rules. (i) Decision points: Specific times when a decision regarding the next treatment in the sequence must be made. These points are often associated with the randomization of treatments. (ii) Intervention options: Various treatments or dosages available to be administered at the decision points. (iii) Tailoring variables: Information (such as vital signs or other relevant metrics) about individuals that assists in determining the appropriate type or dosage of treatment. (iv) Decision rules: Predefined rules that link study variables to intervention options. These rules specify how to modify intervention choices based on the observed values of the tailoring variables (Almirall et al., 2014). An AI can be conceptualized as a multistage sequence of intervention options. At each stage, the treatment to be administered is determined by the observed values of the tailoring variables at that specific decision (time) point.

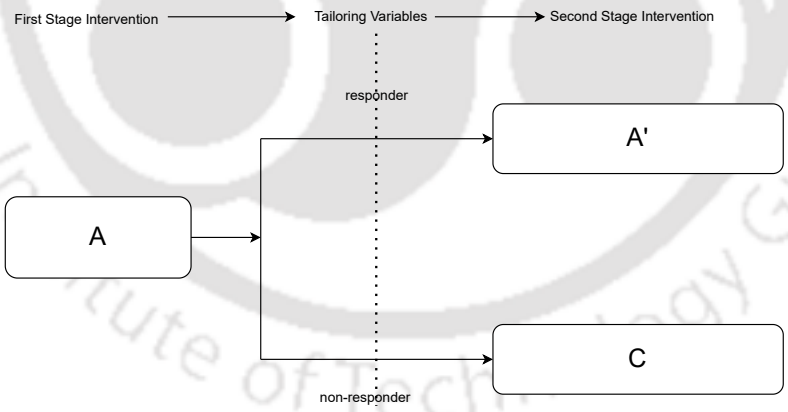


Figure 1.2: A schematic diagram of an adaptive intervention.

In Figure 1.2, a two-stage adaptive intervention scenario is illustrated. In this setup, each individual initially receives treatment A at the first stage. After a predefined duration (here, 2, 4, or 8 weeks), the individual's response to treatment A is evaluated using a tailoring variable. If the individual is classified as a responder (responding well to the given treatment), treatment A' is given; in many cases, $A' = A$. Conversely, if the individual is a non-responder, treatment C is administered at the second stage. Thus, if an individual receives treatment C at stage two, their adaptive intervention sequence is denoted as

(A, C). If additional stages are considered, the AI sequence expands accordingly, based on the treatments randomized and administered after evaluating each response. In general, in a two-stage scenario, an AI can be represented as $(A, A^R C^{1-R})$, where $R \in \{0, 1\}$, reflecting the individual's response at the previous stage: $R = 1$ if responder and $R = 0$ if non-responder.

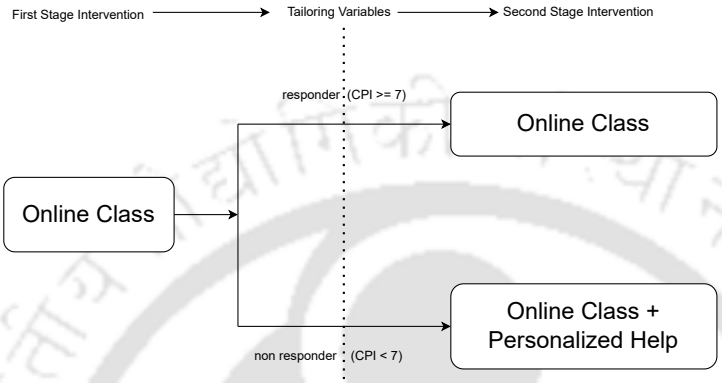


Figure 1.3: Example of an AI in educational field.

AIs have been implemented in diverse fields, including health (Collins et al. (2007); Riley et al. (2011)), academia (Almirall et al., 2014), and clinical practice (Page et al. (2016); Pelham Jr et al. (2016)). In practical applications, the treatments A and C in the above example could be replaced by any specific treatment, vaccine, or intervention under study. For instance, in an academic context, one might investigate the effect of online classes. As depicted in Figure 1.3, all students initially receive online instruction. Students who fail to achieve a Cumulative Performance Index (CPI) of 7 or above out of 10 (non-responders) are subsequently offered personalized doubt-clearing sessions in addition to online classes, while students with a CPI of 7 or above (responders) continue with online classes only.

1.2.4 Sequential Multiple Assignment Randomized Trial

A Sequential Multiple Assignment Randomized Trial (SMART) is an experimental design that uses multi-stage randomization to develop and assess adaptive interventions (Murphy, 2005). In a SMART design, participants are initially randomized to different treatment options (also referred to as interventions). In subsequent stages, participants may be re-randomized to further treatment options based on their response to the earlier intervention (Chakraborty and Murphy, 2014). Each stage in a SMART design corresponds to a decision point where interventions are selected and individualized for participants. In a two-stage SMART, each participant is randomized either once or twice.

Figure 1.4 illustrates a typical two-stage SMART design. At the first stage, participants are randomized between two intervention options, labeled as treatment A and

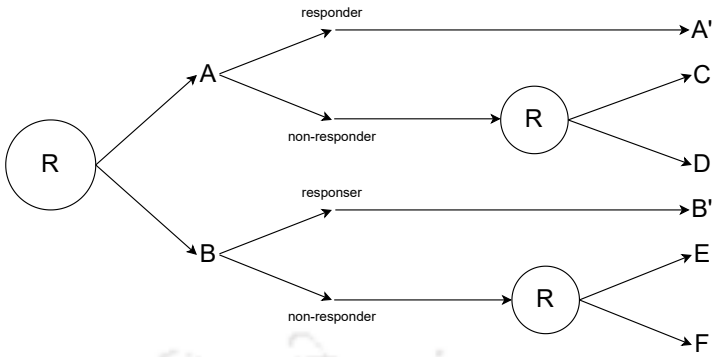


Figure 1.4: A schematic diagram of 2-Stage SMART

treatment B, with predetermined probabilities. After a specified period, participants' responses to these interventions are assessed. Responders are given treatment A' (A' can be the same as the initial treatment A), while non-responders are re-randomized to new intervention options, according to a fixed probability. The "*R in circle*" denotes randomization in Figure 1.4. Specifically, non-responders to treatment A are re-randomized between treatment C and treatment D, while non-responders to treatment B are re-randomized between treatment E and treatment F, again according to predefined probabilities. At the final stage of the SMART design, the primary outcome for each participant is observed. This outcome may be binary (e.g., success or failure) or continuous. In some cases, outcomes are measured at each stage and later combined using a function. For example, in a two-stage SMART, if Y_1 and Y_2 denote the continuous outcomes at the first and second stages, respectively, the primary outcome might be $Y_1 + Y_2$ or $\frac{1}{2}(Y_1 + Y_2)$. In the design shown in Figure 1.4, only non-responders are re-randomized at the second stage, while responders continue with the same (e.g., $A' = A$) or a similar intervention as initially assigned.

Let T_1 denote the treatment assigned in the first stage, and T_2 the treatment in the second stage. The two-stage adaptive intervention can be represented as $\{T_1, T_2\}$. In this setup, $T_1 \in \{A, B\}$, and T_2 for those initially assigned to A can be A', C, or D. For those initially assigned to B, T_2 can be B', E, or F. The number of participants allocated to each adaptive intervention, $\{T_1, T_2\}$, is denoted by $n_{T_1T_2}$. The primary outcome observed at the end of the trial is denoted by Y. The allocation ratios for the first stage (randomizing to A or B) and the second stage (e.g., randomizing to C or D for initial A non-responders, and to E or F for initial B non-responders) are denoted by τ_A, $\tau_{AC:AD}$, and $\tau_{BE:BF}$, respectively. In a (non-adaptive) SMART design, these ratios are typically held constant (e.g., 1 representing 1:1 allocation) throughout the trial.

Figure 1.5 presents a hypothetical example of incorporating a SMART design into an

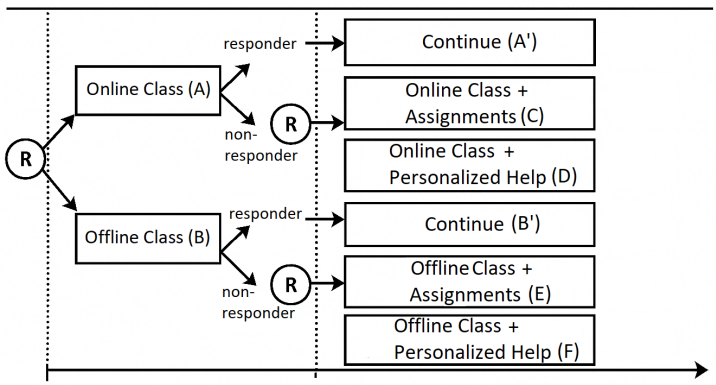


Figure 1.5: A schematic diagram of a SMART in the Educational Field

educational context. The primary question addressed is whether low-cost online classes are more effective than traditional offline (classroom-based) lectures when additional resources (such as assignments or personalized help) are provided at the second stage to students who do not initially respond to their assigned intervention. At the first stage, participants are randomized to receive either online classes only (treatment A) or offline classes (treatment B). Based on a predetermined response criterion, such as achieving a Cumulative Performance Index (CPI) of 7 or higher, subsequent interventions are assigned. Responders continue with their initial intervention, while non-responders are re-randomized: for example, non-responders from the online class group are assigned to either online classes with assignments (treatment C) or online classes with personalized help (treatment D). Similarly, non-responders from the offline class group are assigned to either offline classes with assignments (treatment E) or offline classes with personalized help (treatment F). The primary outcome at the end of the trial may be binary (e.g., whether the student's CPI is 7 or higher, with $Y = 1$ indicating success and $Y = 0$ otherwise) or continuous (e.g., the difference in CPI before and after the trial). In this SMART design, there are four embedded adaptive interventions (AIs), where $R = 1$ denotes a responder and $R = 0$ denotes a non-responder:

- $(A, A^R C^{1-R})$: Start with online classes (A); continue with A for responders or switch to online classes with assignments (C) for non-responders.

- $(A, A^R D^{1-R})$: Start with online classes (A); continue with A for responders or switch to online classes with personalized help (D) for non-responders.

- $(B, B^R E^{1-R})$: Start with offline classes (B); continue with B for responders or switch to offline classes with assignments (E) for non-responders.

- $(B, B^R F^{1-R})$: Start with offline classes (B); continue with B for responders or switch to offline classes with personalized help (F) for non-responders.

Note that the concept of the four embedded adaptive interventions (AIs) is primarily used to guide the study design based on the research question and to inform the analysis once the study is completed. However, these embedded AIs do not influence the enrollment of participants or the randomization process during the trial. Similar to how two treatments are compared in a traditional RCT, a SMART design allows for the comparison of any two embedded adaptive interventions, which represent dynamic sequences of treatments.

A SMART design captures both within-patient and between-patient variability. Within-patient variability is addressed by allowing the treatment strategy for each participant to adapt over time based on individual responses to prior interventions (Chakraborty and Moodie, 2013). Between-patient variability is incorporated through the randomization process, as different participants may receive different sequences of interventions. By accounting for both sources of variability, SMART designs provide a comprehensive framework for evaluating the effectiveness of adaptive interventions across diverse patient populations (Chakraborty and Murphy, 2014).

1.3 Adaptive design in SMART

The SMART design traditionally randomizes treatments to participants using fixed probabilities at each stage, with these probabilities usually predefined before the trial commences (Almirall et al., 2014). However, similar to adaptive randomized controlled trials (RCTs), the randomization probabilities in each stage of a SMART design can also be made adaptive. In adaptive randomization, the allocation of treatments is informed by accumulating, time-varying data from participants who have already completed earlier stages or sequences of adaptive interventions (AIs). This approach not only makes the design more responsive to emerging evidence but also carries an important ethical justification: by dynamically assigning more participants to interventions that appear to be more effective, adaptive randomization can reduce exposure to less effective treatments, thus minimizing potential harm and maximizing the likelihood of benefit for participants.

To date, there have been limited attempts to develop methodologies for adaptive randomization in SMART designs. The main challenge is that adaptive methodologies for two-arm randomized controlled trials (RCTs) cannot be directly implemented in two-stage (or multi-stage) SMART designs. An intuitive approach might consider each stage and randomization point in SMART as independent, applying adaptive randomization procedures from two-arm RCTs directly. However, it has been shown that this approach may lead to sub-optimal solutions Ghosh et al. (2024). Recently, some efforts have been made

to develop adaptive randomization methodologies that specifically skew the randomization probabilities in favor of promising treatments, utilizing information on treatment history and efficacy (Wang et al., 2022; Yang et al., 2024). More work is needed in this area to make adaptive SMARTs feasible and popular among clinicians, thereby benefiting patients.

Adaptive designs may not always be suitable for use within SMART or RCT designs, particularly when there is a considerable delay between patient recruitment and the availability of final outcome data (Atkinson and Biswas, 2013). In adaptive randomization procedures, interim outcome information from earlier participants is used to adjust allocation ratios for those recruited later. However, in many SMART studies, especially those involving long follow-up periods or delayed outcomes, the necessary final outcome data for early-enrolled patients may not be available in time to inform subsequent randomization decisions. This lack of timely outcome information undermines the feasibility and validity of adaptive allocation, as decisions would be based on incomplete or interim data rather than definitive results. Therefore, when outcome ascertainment is significantly lagged or when primary endpoints require extended observation, traditional fixed randomization methods may be more appropriate for SMART designs.

1.4 Thesis Summary

In this thesis, we first derive the optimal adaptive allocation ratios for a two-stage SMART (Figure 1.4), considering both binary and continuous primary outcomes. The central idea is to develop optimal adaptive allocation ratios for the second-stage randomization processes by applying existing methodologies for two-arm adaptive RCTs for binary and continuous outcomes, as proposed by Rosenberger et al. (2001) and Zhang and Rosenberger (2006), respectively. The optimal adaptive allocation ratio for the first-stage randomization is then obtained recursively by passing the optimal adaptive allocation information backward from the second stage to the first stage. The underlying rationale is that the second-stage optimal adaptive allocation ratios are independent of the first-stage allocation ratio, whereas the optimal adaptive allocation ratio for the first stage is determined using information from the second-stage optimal adaptive allocation ratios. Another perspective, when comparing two AIs (not for randomization point of view), is that we aim to optimize the final outcome (binary or continuous) by selecting adaptive interventions (dynamic sequences of treatments). It is possible that the most effective adaptive intervention consists of a less effective first-stage treatment followed by a highly effective second-stage treatment. The effectiveness of the second-stage treatment may be influenced by the application of the first-stage (less effective) treatment, due to the interdependence or interaction effects between the two treatments. Therefore, recursively passing information

from the second stage to the first stage ensures that, given the second-stage allocation ratio is optimized, the optimal first-stage allocation ratio can be determined.

In the *second chapter*, we propose an optimal adaptive allocation procedure for SMART designs with a binary primary outcome. This procedure uses a constrained optimization approach to minimize the total expected number of treatment failures while maintaining a fixed asymptotic variance for a predefined objective function. Theoretical properties of the optimal adaptive allocations are examined. Simulation studies support these results by showing that the estimated allocation ratios converge to the theoretically optimal ratios. The adaptive SMART design also reduces the total expected number of failures compared to a non-adaptive SMART design. Importantly, patient allocation to the embedded dynamic treatment regimes (DTRs) is consistent with the relative performance of these regimes. We illustrate the practical utility of this methodology using data from the M-bridge SMART study, which seeks to develop resource-efficient treatment regimes for first-year college students to address alcohol-related risks.

In the *third chapter*, we introduce an optimal adaptive allocation procedure for SMART designs with a continuous primary outcome. We develop the theoretical framework required to derive optimal adaptive allocation ratios and describe the procedures for implementing adaptive randomization. Specifically, we employ an optimality criterion that aims to minimize the total expected outcome for all participants in a two-stage SMART. Following the approach in the previous chapter, we first derive the optimal adaptive allocation ratio for the second-stage randomization and then recursively use this to determine the first-stage optimal adaptive allocation ratio. Through simulation studies, we empirically examine how well the adaptive allocation procedure estimates the allocation ratios compared to the true optimal ratios. We assess performance using sample standard error, asymptotic standard error, and coverage probability across different model parameters. The practical application of this method is demonstrated using a weight loss management SMART, which evaluates low-cost interventions such as mobile health (mHealth) tools.

In the *fourth chapter*, we extend the adaptive SMART framework for binary outcomes by incorporating covariate information into the allocation ratio using logistic regression. We model the second-stage success probabilities as functions of covariates within a generalized linear model framework, employing the logit link. As in the previous two chapters, we recursively incorporate second-stage allocation information into the first stage to determine the corresponding allocation ratio. This covariate-adjusted approach offers a simpler and more intuitive alternative to methods that rely on the complex structure of the Q-function. Through simulation studies, we demonstrate that the total expected number of failures for the entire SMART is lower with the proposed covariate-adjusted adaptive procedure than with the procedure developed in the second chapter, which does not adjust for covariates. Using data from the M-bridge SMART study, we show that covariates such as gender can be used to adjust the adaptive procedure, thereby improving

intervention allocation to address alcohol-related risks.

In the *fifth and final chapter*, we discuss various future directions based on this thesis. We briefly outline the extension of the adaptive SMART framework to continuous outcomes by incorporating covariate information into the allocation ratio. Other potential directions include multi-stage optimal adaptive SMART design, multi-treatment optimal adaptive SMART design, and optimal adaptive SMART design where responders are also randomized.

CHAPTER 2

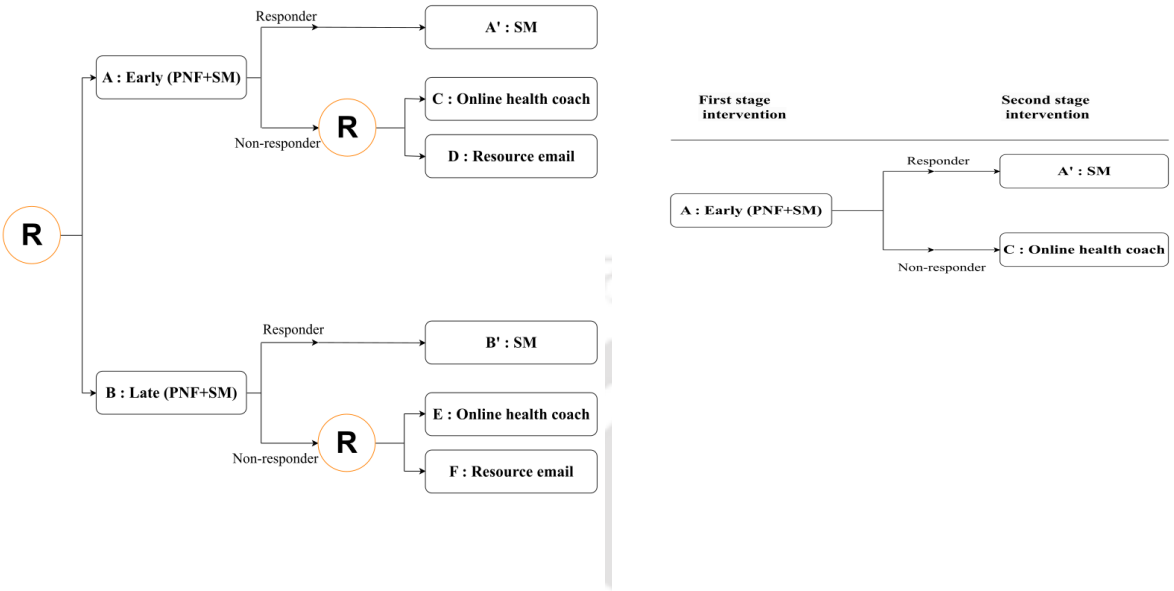
Optimal Adaptive SMART Design with Binary Outcomes

2.1 Introduction

In this chapter, we introduce an optimal adaptive allocation procedure tailored for SMART with a binary primary outcome. Our approach leverages a constrained optimization framework designed to minimize the total expected number of treatment failures, all while ensuring that a predetermined objective function retains a fixed asymptotic variance. This work has been published in Biometrics[1], 2024 (Ghosh et al., 2024).

As a motivating example, consider the M-bridge SMART experimental design to reduce heavy drinking and related risks among college students (Patrick et al., 2020). In this study, there is an assessment only control arm (without any treatment). We do not consider this control arm in the present chapter. The remaining study design of the M-bridge is described in Figure 2.1(a). In the first stage, participants (first-year college students) were randomly assigned (1:1 ratio) to two different timings for delivering a relatively low-cost and low burden initial intervention: (1) early, namely before the start of the Fall semester; or (2) later, namely during the first month of the first semester of college. The initial intervention combined two evidence-based components: personalized normative feedback (PNF) and self-monitoring (SM) of alcohol use (see Patrick et al., 2020, 2021). Participants who self-identify as heavy drinkers based on SM were classified as non-responders and were re-randomized (1:1 ratio) to either an email with alcohol use intervention resources or an invitation to online health coaching (see Figure 2.1(a)).

[1]Ghosh, R., B. Chakraborty, I. Nahum-Shani, M. E. Patrick, and P. Ghosh (2024). Optimal adaptive SMART designs with binary outcomes. Biometrics 80 (4), ujae140.



(a) A schematic diagram of a 2-Stage SMART following M-bridge study. Here R represents randomization.

(b) An example dynamic treatment regime (DTR) to reduce heavy drinking and related risks among college students from M-bridge study.

Figure 2.1: Schematic diagram of a 2-Stage SMART and DTR

Those not identified as heavy drinkers were classified as responders and continued with SM alone. The sequential randomizations in the M-bridge yield four embedded DTRs. One of these DTRs is described in Figure 2.1(b); it recommends delivering PNF+SM before the first semester (i.e., early intervention); once the student is self-identified as a heavy drinker (non-responder), invite them to participate in online health coaching; otherwise (responder) continue with SM.

Typically, SMART participants are randomized with equal probabilities to the available treatments at every stage. Even though this approach maximizes the statistical power to compare different DTRs embedded in a SMART, it raises ethical considerations by ignoring intermediate information that may indicate an advantage to some treatment options (Wang et al., 2022). In other words, despite having interim information about an empirically better treatment, we keep assigning empirically inferior treatment to the same number of patients getting the empirically better treatment. The use of adaptive design in SMART to change the randomization probabilities is limited as opposed to traditional randomized controlled trials (RCTs). Here, 'adaptive design' means adapting treatment decisions between patients instead of within patients in the course of the trial (Cheung et al., 2015). In a non-adaptive SMART, treatments are adapted within patients

rather than between patients. Therefore, an adaptive SMART considers both within- and between-patient adaptation of treatments. A Q-learning-based adaptation of randomization probabilities (SMART-AR) was proposed by Cheung et al. (2015). However, this approach calculates the empirical randomization probabilities simply by maximizing the Q-functions given the interim history, without defining any formal optimality criteria. Recently, Wang et al. (2022) and Yang et al. (2024) developed response adaptive SMART (RA-SMART and GO-SMART, respectively) designs to skew the randomization probabilities in favor of promising treatments, using the information on treatment history and efficacy. Wang et al. (2022) used information about the effectiveness of all treatments used in the first stage to calculate the randomization probabilities in the second stage, whereas Yang et al. (2024) used information from both stages to adjust the randomization probabilities. However, both these works assumed that the same set of treatments is available in all stages. Therefore, those two designs cannot be used when the set of treatments in the second stage differs from that of the first stage, which is highly common in SMART studies.

The development of DTR using SMART design is motivated by the notion that a treatment that is promising in the short term may not be beneficial in the long term (Almirall et al., 2014). Similarly, a treatment that looks not so beneficial at the first stage may be part of the best embedded DTR (Nahum-Shani et al., 2020). Thus, an adaptive SMART that alters randomization probabilities to give better treatments to more patients should be developed by considering the benefits from the entire treatment sequence. In this chapter, we build a novel adaptive randomization procedure that minimizes the total expected number of failures from the entire SMART with a binary primary outcome. To achieve that, we first develop the optimal adaptive allocation ratios for the second-stage randomization processes using the methodology proposed by Rosenberger et al. (2001) for a two-armed RCT with a binary outcome. Then the first-stage optimal adaptive allocation ratio is obtained recursively, passing the optimal adaptive allocation information backward from the second stage to the first stage. Derivation of the first-stage optimal adaptive allocation ratio, the corresponding adaptive allocation process, and the asymptotic distribution of the optimal adaptive allocation ratio are the main contributions of this chapter.

The remainder of this chapter proceeds as follows. In Section 2.2, we develop the general framework required for this work. Section 2.3 describes the optimal adaptive allocation criteria and derives the optimal adaptive allocation ratios. An adaptive allocation process is developed in Section 2.4. Section 2.5 presents the hypothesis testing framework in this context. Sections 2.6 and 2.7 show the simulation study and an application to real data, respectively. The discussion in Section 2.8 wraps up the main arguments presented in the chapter. Section 2.8 ends with a discussion. All detailed derivations and calculations of results used in this chapter are presented in Section 2.9.

2.2 General Framework for binary SMART

Let Y be the binary primary outcome (success or failure) observed at the end of a two-stage SMART. Here, we use generic treatments termed A, A', B, B', C, D, E, and F, as shown in Figure 2.1(a). As in Figure 2.1(a), at the first stage, participants are randomized to the treatments A (early administering of the PNF + SM) or B (late administering of the PNF + SM). Let T_1 denote the first-stage treatment, thus $T_1 \in \{A, B\}$. At the end of the first stage who started with A (or B), based on the intermediate outcome (SM in M-bridge), responders will continue with the SM only denoted as A' (or B'), while non-responders will be randomized to C (online health coach) or D (resource email) if $T_1 = A$, and E (online health coach) or F (resource email) if $T_1 = B$. In this case, C and E (similarly D and F) are the same treatment. However, they may be different in a SMART. Thus, $T_2 \in \{A', C, D\}$ if $T_1 = A$ and $T_2 \in \{B', E, F\}$ if $T_1 = B$. The complete treatment sequence is expressed by $\{T_1, T_2\}$. Define $n_{T_1T_2}$ as the number of participants who obatined $\{T_1, T_2\}$. Let $R_{T_1}, T_1 \in \{A, B\}$ be the response indicator (1: responder, 0: non-responder) who obtained treatment T_1 at the first stage.

The aim of the current chapter is to find optimal values of the three allocation ratios, $\tau_A = \frac{n_A}{n_B}$, $\tau_{AC:AD} = \frac{n_{AC}}{n_{AD}}$ and $\tau_{BE:BF} = \frac{n_{BE}}{n_{BF}}$, corresponding to three randomization processes in the two-stage SMART (see Figure 2.1(a)), where $n_A = n_{AA'} + n_{AC} + n_{AD}$, $n_B = n_{BB'} + n_{BE} + n_{BF}$. The optimal value of each of the three ratios is obtained for a fixed asymptotic variance (reflecting the power of the test) such that it minimizes the total expected number of corresponding treatment failures (Rosenberger et al., 2001). Note that the second-stage optimal adaptive allocation ratios ($\tau_{AC:AD}$ and $\tau_{BE:BF}$) can be viewed as a problem of adaptive allocation in a traditional (single-stage) RCT with two treatment arms. In this chapter, we directly apply the methodology proposed by Rosenberger et al. (2001) to find the second-stage optimal adaptive allocation ratios. Our main contribution is to propose an adaptive sequential design that allocates patients to the first-stage treatments where both the first and the second-stage allocation ratios are optimal. The proposed method ensures the minimization of the total expected number of failures from the entire SMART by recursively passing the optimal adaptive allocation information backward (from the second stage to the first stage). In other words, the second-stage optimal adaptive allocation ratios are not dependent on the first-stage optimal adaptive allocation ratio. However, the first-stage optimal adaptive allocation ratio is obtained using the information from the second-stage optimal adaptive allocation ratios. In Section 2.6.1, we have discussed the concerns to find optimal adaptive allocation ratios simultaneously by minimizing the total expected number of failures from the entire SMART.

Define $p_{T_1T_2}$ ($q_{T_1T_2} = 1 - p_{T_1T_2}$) as the probability of success when the (end of study) binary primary outcome $Y = 1$ (success) corresponding to a patient who obtained the

treatment sequence $\{T_1, T_2\}$. Similarly, p_{T_1} ($q_{T_1} = 1 - p_{T_1}$) is the probability of success for a patient who obtained treatment T_1 at the first stage. It can be shown (see Section 2.9.1) that, $p_{T_1} = \gamma_{T_1} p_{T_1T_1'} + (1-\gamma_{T_1})\frac{\tau_{T_1T_2:T_1T_2^*}}{1+\tau_{T_1T_2:T_1T_2^*}} p_{T_1T_2} + (1-\gamma_{T_1})\frac{1}{1+\tau_{T_1T_2:T_1T_2^*}} p_{T_1T_2^*}$, where $T_2 = C, T_2^* = D$ if $T_1 = A$; $T_2 = E, T_2^* = F$ if $T_1 = B$, and $\gamma_{T_1} = P(R_{T_1} = 1)$ denotes the probability of response among the patients who obtained treatment T_1.

2.3 Optimal Adaptive Allocation Criteria

In this section, we describe the general approach to find the optimal adaptive allocation ratios. The total expected number of failures from the entire SMART is minimized considering an objective function $g(\cdot,\cdot)$ that compares two binomial success probabilities subject to a fixed asymptotic variance ($avar$) of the same objective function. Note that there are multiple randomizations involved in a SMART. With respect to a specific randomization process, the total expected number of failures means the expected number of patients who obtained treatments in that randomization process and then failed (in the future). Among the patients who obtained T_1 at the first stage, the number of failures after a randomization process at the second stage is defined as $F_2(\tau_{T_1T_2:T_1T_2^*}) = n_{T_1T_2}q_{T_1T_2} + n_{T_1T_2^*}q_{T_1T_2^*} = \frac{n_{T_1}(1-\gamma_{T_1})}{1+\tau_{T_1T_2:T_1T_2^*}}\left[\tau_{T_1T_2:T_1T_2^*}q_{T_1T_2} + q_{T_1T_2^*}\right]$. Then the optimum allocation ratio for the second stage is $\tau^*_{T_1T_2:T_1T_2^*} = \arg\min_{\tau_{T_1T_2:T_1T_2^*}} F_2(\tau_{T_1T_2:T_1T_2^*})$ subject to $avar\{g(\hat{p}_{T_1T_2}, \hat{p}_{T_1T_2^*})\} = \epsilon_2$, for some constant $\epsilon_2 > 0$. Similarly, the total number of failures from the entire SMART is

$$\begin{aligned} & F_1(\tau_A, \tau_{AC:AD}, \tau_{BE:BF}) \\ = \; & (n_{AA'}q_{AA'} + n_{AC}q_{AC} + n_{AD}q_{AD}) + (n_{BB'}q_{BB'} + n_{BE}q_{BE} + n_{BF}q_{BF}) \\ = \; & \frac{n}{1+\tau_A}\left[\tau_A\gamma_A q_{AA'} + \tau_A\frac{(1-\gamma_A)}{1+\tau_{AC:AD}}\left(\tau_{AC:AD}q_{AC} + q_{AD}\right)\right. \\ & \left. +\gamma_B q_{BB'} + \frac{(1-\gamma_B)}{1+\tau_{BE:BF}}\left(\tau_{BE:BF}q_{BE} + q_{BF}\right)\right]. \end{aligned}$$

The optimum allocation ratio for the first stage is $\tau^*_A = \arg\min_{\tau_A} F_1(\tau_A, \tau^*_{AC:AD}, \tau^*_{BE:BF})$ subject to $avar\{g(\hat{p}_A, \hat{p}_B)\} = \epsilon_1$, for some constant $\epsilon_1 > 0$. The common choices for the objective function $g(\cdot,\cdot)$ could be the simple difference (e.g. : $p_{AC} - p_{AD}$), the relative-risk (e.g. : q_{AC}/q_{AD}) and the odds-ratio (e.g. : $p_{AC}q_{AD}/p_{AD}q_{AC}$).

2.3.1 Optimal Adaptive Allocation Ratios

Let the objective function be the simple difference between the success probabilities. Thus, for the second-stage randomization to allocate patients to available treatments who started with treatment A at the first stage and became non-responder, the objective function is $g(p_{AC}, p_{AD}) = p_{AC} - p_{AD}$. Similarly, the same is $g(p_{BE}, p_{BF}) = p_{BE} - p_{BF}$ among those who started with treatment B in the first stage and became non-responder. For the

first stage of randomization, $g(p_A, p_B) = p_A - p_B$. Using the optimum allocation criteria stated in Section 2.3, the optimum allocation ratios are $\tau^*_{AC:AD} = \sqrt{\frac{p_{AC}}{p_{AD}}}$, $\tau^*_{BE:BF} = \sqrt{\frac{p_{BE}}{p_{BF}}}$, and

$$\tau^*_A = \sqrt{\frac{(1+\tau^*_{BE:BF})(\gamma_A p_{AA'}(1+\tau^*_{AC:AD}) + (1-\gamma_A)(\tau^*_{AC:AD}p_{AC} + p_{AD}))}{(1+\tau^*_{AC:AD})(\gamma_B p_{BB'}(1+\tau^*_{BE:BF}) + (1-\gamma_B)(\tau^*_{BE:BF}p_{BE} + p_{BF}))}}.$$

See Sections 2.9.2 and 2.9.3 for details. Similarly, considering the objective function as the odds-ratio and relative-risk, the optimum allocation ratios are derived in Sections 2.9.5 and2.9.6, respectively.

2.4 Adaptive Allocation Process

We need to develop an adaptive allocation (randomization) procedure that ensures patients are allocated to available treatments in accordance with the optimal adaptive allocation ratios stated in Section 2.3.1. However, the true optimal adaptive allocation ratios are dependent on unknown parameters. Hence, for implementation in a real SMART, we need to develop a sequential design that will approximate the optimal adaptive allocation ratios. It is also desirable that the proposed sequential design ensures the convergence of sample allocation ratios to the corresponding optimal adaptive allocation ratios. Let Y_i be the binary primary outcome, which can take two values, 1 for success and 0 for failure, corresponding to the i^{th} patient; $i = 1, \cdots, n$. T_{1i} and T_{2i} denote the assigned first- and second-stage treatments to the i^{th} patient, respectively. Thus, we get the total number of patients getting treatment sequence (T_1, T_2) out of k patients, as $n_{T_1T_2,k} = \sum_{i=1}^{k} I(T_{1i} = T_1, T_{2i} = T_2)$, where T_1 and T_2 takes the values as stated in Section 2.2, and $n_{T_1T_2,n} = n_{T_1T_2}$. The corresponding estimates of the success probabilities are obtained as $\hat{p}_{T_1T_2,k} = \left(\sum_{i=1}^{k} I(T_{1i} = T_1, T_{2i} = T_2)Y_i\right) / n_{T_1T_2,k}$. Define $\mathscr{F}_i = \{Y_1, Y_2, ..., Y_i, T_{11}, T_{12}, ..., T_{1i}, T_{21}, T_{22}, ..., T_{2i}\}$ as the history of primary outcomes, as well as, first- and second-stage allocated treatments for the first i patients. Let $E_i(\cdot) = E(\cdot|\mathscr{F}_i)$ denote the conditional expectation.

Now, taking the objective function as the simple difference of the success probabilities, the second-stage allocation process can be explained (Rosenberger et al., 2001) with the help of the above expectation as,

$$E_{i-1}(I(T_{2i} = t_2|T_{1i} = t_1, R_{T_{1i}} = 0)) = \sqrt{\hat{p}_{t_1t_2,i-1}} \Big/ \left(\sqrt{\hat{p}_{t_1t_2,i-1}} + \sqrt{\hat{p}_{t_1t^*_2,i-1}}\right), \qquad (2.1)$$

where, $t_2, t^*_2 \in \{C, D\}$ if $t_1 = A$ or $t_2, t^*_2 \in \{E, F\}$ if $t_1 = B$ and $t^*_2 \neq t_2$ and $R_{T_{1i}}$ is the same as defined in Section 2.2 for the i^{th} patient. In words, (2.1) refers to the estimation of the second-stage success probability $(\hat{p}_{t_1t_2,i})$ based on the first $(i-1)$ sequentially

enrolled patients to be used for the adaptive randomization of the i^{th} patient. Note that $(\hat{p}_{t_1t_2,i})$ being a binomial probability is a consistent estimator of the corresponding true probability. In the same line, in the first-stage randomization, the allocation process can be expressed as,

$$E_{i-1}(T_{1i}) = \sqrt{l_{i-1}} \Big/ \left(\sqrt{l_{i-1}} + \sqrt{m_{i-1}}\right), \tag{2.2}$$

where $l_{i-1} = (1+\hat{\tau}_{BE:BF,i})(\gamma_A \hat{p}_{AA',i-1}(1+\hat{\tau}_{AC:AD,i}) + (1-\gamma_A)(\hat{\tau}_{AC:AD,i}\ \hat{p}_{AC,i-1} + \hat{p}_{AD,i-1}))$ and $m_{i-1} = (1+\hat{\tau}_{AC:AD,i})(\gamma_B \hat{p}_{BB',i-1}(1+\hat{\tau}_{BE:BF,i}) + (1-\gamma_B)(\hat{\tau}_{BE:BF,i}\ \hat{p}_{BE,i-1} + \hat{p}_{BF,i-1}))$. Note that, $\hat{\tau}_{AC:AD,i} = \sqrt{\frac{\hat{p}_{AC,i-1}}{\hat{p}_{AD,i-1}}}$, $\hat{\tau}_{BE:BF,i} = \sqrt{\frac{\hat{p}_{BE,i-1}}{\hat{p}_{BF,i-1}}}$ denote the estimated second-stage allocation ratios for the i^{th} patient (who obtain either A or B at the first stage and is a non-responder) based on the history of $(i-1)$ patients. Similar to the explanation given in Section 2.2, the first-stage allocation process recursively considers the estimated allocations $(\hat{\tau}_{AC:AD,i}, \hat{\tau}_{BE:BF,i})$ at the second stage. It can be seen that the above allocation process replaces the unknown success probabilities in the optimal adaptive allocation ratios obtained in Section 2.3.1 by the current estimates of the success probabilities of each treatment sequence $(\hat{p}_{t_1t_2,i-1})$.

In practice, an investigator allocates patients to available treatments using the allocation process described in (2.1) and (2.2) for the second and the first stages, respectively. Therefore, it is desirable that the limiting allocation (using (2.1) and (2.2)) is optimal. Using results from Rosenberger et al. (2001) and Melfi et al. (2001), for the second-stage randomization with the objective function as the simple difference between the success probabilities, $\hat{\tau}_{AC:AD,n} \xrightarrow{a.s.} \sqrt{\frac{p_{AC}}{p_{AD}}}$, and $\hat{\tau}_{BE:BF,n} \xrightarrow{a.s.} \sqrt{\frac{p_{BE}}{p_{BF}}}$, where $a.s.$ denotes the almost sure convergence for a large value of n. Similarly, as shown in Equation (2.16) of Section 2.9.3,

$$\hat{\tau}_{A,n} \xrightarrow{a.s.} \sqrt{\frac{\left[\sqrt{p_{BE}} + \sqrt{p_{BF}}\right]\left[\gamma_A p_{AA'}(\sqrt{p_{AD}} + \sqrt{p_{AC}}) + (1-\gamma_A)\left((p_{AC})^{\frac{3}{2}} + (p_{AD})^{\frac{3}{2}}\right)\right]}{\left[\sqrt{p_{AC}} + \sqrt{p_{AD}}\right]\left[\gamma_B p_{BB'}(\sqrt{p_{BE}} + \sqrt{p_{BF}}) + (1-\gamma_B)\left((p_{BE})^{\frac{3}{2}} + (p_{BF})^{\frac{3}{2}}\right)\right]}}, \tag{2.3}$$

where $\hat{\tau}_{A,n}$ denotes the estimated first-stage allocation ratio for the n^{th} patient based on the history of $(n-1)$ patients. The asymptotic distributions of the estimated optimum allocation ratios are given by $\sqrt{n}(\hat{\tau}_{AC:AD,n} - \tau^*_{AC:AD}) \xrightarrow{d} N\left(0, \frac{1}{4}\left(\frac{v^{-1}_{AC}}{p_{AC}p_{AD}} + \frac{v^{-1}_{AD}p_{AC}}{p^3_{AD}}\right)\right)$, $\sqrt{n}(\hat{\tau}_{BE:BF,n} - \tau^*_{BE:BF}) \xrightarrow{d} N\left(0, \frac{1}{4}\left(\frac{v^{-1}_{BE}}{p_{BE}p_{BF}} + \frac{v^{-1}_{BF}p_{BE}}{p^3_{BF}}\right)\right)$, and, $\sqrt{n}(\hat{\tau}_{A,n} - \tau^*_A) \xrightarrow{d} N\left(0, \sigma^2_{\tau_A}\right)$, where the expressions of $v^{-1}_{AC}, v^{-1}_{AD}, v^{-1}_{BE}, v^{-1}_{BF}$ and $\sigma^2_{\tau_A}$ are given in Section 2.9.4 along with their derivations in detail. The notation d over the arrow denotes the convergence in distribution. The adaptive allocation processes corresponding to the two other objective functions are derived in Section 2.9.5 (for odds-ratio) and Section 2.9.6 (for relative-risk).

2.5 Hypothesis Testing

The total expected number of failures from the entire SMART can be minimized using the developed adaptive procedure. However, testing (at the end of the trial) whether two given treatment sequences (embedded DTRs) have the same or different efficacy is also essential. This inference can be made by using the Wald-type statistic (Rosenberger et al., 2001). In Figure 2.1(a), there are four embedded DTRs, denoted as $d_1 : (A, A'^R C^{1-R})$, $d_2 : (A, A'^R D^{1-R})$, $d_3 : (B, B'^R E^{1-R})$, and $d_4 : (B, B'^R F^{1-R})$. A patient whose treatment sequence is consistent with d_1 implies that they will start with treatment A at the first stage, then continue with A' if they are doing well (responder) or switch to treatment C otherwise (non-responder). Now, we compare two DTRs. For any pair of DTRs, say (d_i, d_j), the proportion of success is represented by p_{d_i} and p_{d_j}, respectively. Hence, we consider the test,

$$H_0 : p_{d_i} = p_{d_j} \quad vs \quad H_1 : p_{d_i} \neq p_{d_j} \quad \text{where} \quad i, j \in \{1, 2, 3, 4\}, i \neq j.$$

The probability of success of an embedded DTR can be expressed as $p_{d_i} = E(\bar{Y}_{d_i}) = \gamma_{T_1} p_{T_1 T_1'} + (1 - \gamma_{T_1}) p_{T_1 T_2}$ (see 2.9.7). Thus, the Wald-type test statistic is,

$$Z = \frac{\widehat{p}_{d_i} - \widehat{p}_{d_j}}{\sqrt{Var(\widehat{p}_{d_i} - \widehat{p}_{d_j})}}.$$

However, the above test may have an inflated size (Fleiss et al., 2013). To address this, we incorporate an adjustment by Rosenberger et al. (2001), replacing $\hat{p}_{T_1 T_2}$ in $\hat{p}_{d_i}$, by $\hat{p}^*_{T_1 T_2}$, where, $\hat{p}^*_{T_1 T_2} = \left(\sum_{i=1}^{n} I(T_{1i} = T_1, T_{2i} = T_2) Y_i + 1\right) / \left(n_{T_1 T_2} + 2\right)$. In the Simulation Study in Section 2.6, the reported test statistic value is obtained by using the adjusted test statistic,

$$Z_{Adj} = \frac{\widehat{p}^*_{d_3} - \widehat{p}^*_{d_1}}{\sqrt{Var(\widehat{p}^*_{d_3} - \widehat{p}^*_{d_1})}}.$$

2.6 Simulation Study

Simulations are conducted to evaluate the performance of the optimal adaptive allocation process developed in Section 2.4. The main aims of this section are to check (a) empirical convergence of the estimated allocation ratios ($\hat{\tau}$) to the proposed optimal adaptive allocation ratios (τ), (b) empirically showing that the total expected number of failures is lowered using optimal adaptive SMART compared to a non-adaptive SMART, and (c) the number of patients allocated to the dynamic treatment regimes (DTRs) are in synchronization with the performance of the corresponding DTRs.

Here, we consider a two-stage SMART as described in Figure 2.1(a) with a binary

primary outcome having a sample size 500, with simple difference as the objective function. Similar simulations with sample sizes 200, 1000 and 2000 are conducted later in this section. In all the simulations, response probabilities γ_A and γ_B are assumed to be constant at 0.40, and 0.30, respectively. The second column of Table 2.1 shows the considered success probabilities $p_{AA'}, p_{AC}, p_{AD}, p_{BB'}, p_{BE}$ and p_{BF}, corresponding to six feasible combinations of the first- and second-stages treatments $\{T_1, T_2\}$, (see Figure 2.1(a)). However, these success probabilities are unknown to the investigator and must be estimated based on the interim data from the SMART to implement the adaptive allocation (randomization) procedure described in Section 2.4. Therefore, the initial 30 patients (any other number can also be taken) sequentially enrolled in the SMART are randomized with equal probabilities at both stages. The initial estimates of success probabilities ($\hat{p}_{t_1t_2,i}$) are based on the observed $Y_i, i = 1, \cdots, 30$. Using the estimated success probabilities, the allocation ratios corresponding to the first ($\hat{\tau}_{A,i}$) and second stages ($\hat{\tau}_{AC:AD,i}; \hat{\tau}_{BE:BF,i}$) are estimated for the $31^{st}(i = 31)$ patient. Thus, the 31^{st} patient is randomized using $\hat{\tau}_{A,31}$ at the first stage. Now, if the 31st patient is a non-responder, then, depending on the treatment assigned at the first stage, the same patient is randomized using $\hat{\tau}_{AC:AD,31}$ or $\hat{\tau}_{BE:BF,31}$. The same process (re-estimation of success probabilities and then allocation ratios) is repeated for subsequent patients till the end of the trial.

Table 2.1 shows the simulation study results. The success probabilities (in the second column) are chosen in such ways that the true values of the optimum allocation ratios are around 0.5, 1, or 2 in different scenarios. In Table 2.1, in rows 1 to 3, the true values of the optimal adaptive allocation ratio τ_A are 0.521, 1.002, and 2.025, respectively. Similarly, in rows 4 to 6, the true values of the optimal adaptive allocation ratio $\tau_{AC:AD}$ are 0.5, 1, and 2, respectively; and, in rows 7 to 9, the true values of the optimal adaptive allocation ratio $\tau_{BE:BF}$ are 0.5, 1, and 2, respectively. Rows 10 to 16 show the performance of the adaptive allocation procedure when some (or all) of the success probabilities are very high or low, with the true values of the optimal adaptive allocation ratio τ_A close to 1. In row 14, the true values of both $\tau_{AC:AD}$ and $\tau_{BE:BF}$ are high, close to 4.3 and 3, respectively. In row 15, we keep the true value of $\tau_{BE:BF}$ the same as in row 14, but the true value of $\tau_{AC:AD}$ is taken to be small and close to 0.23. In row 16 (last row), we keep the true value of $\tau_{AC:AD}$ the same as in row 14, but the true value of $\tau_{BE:BF}$ is taken to be small and close to 0.33. From Table 2.1, we observe that $\hat{\tau}_A$ and τ_A are close to each other in all the scenarios. The $\hat{\tau}_{AC:AD}$ and $\tau_{AC:AD}$ (similarly, $\hat{\tau}_{BE:BF}$ and $\tau_{BE:BF}$) are close for the value of $\tau_{AC:AD}$ ($\tau_{BE:BF}$) near 0.5 or 1. However, when the value of $\tau_{AC:AD}$ or $\tau_{BE:BF}$ are 2 or more, we observe that the corresponding estimates $\hat{\tau}_{AC:AD}$ and $\hat{\tau}_{BE:BF}$ are overestimating the respective true quantities. Note that a high value of the optimal adaptive allocation ratio is seen when one or more success probabilities are very low or very high (failure probability is low). The overestimation of the optimal adaptive allocation ratio is because of incurred bias in the estimation of low probabilities. We also observe that the sample standard error

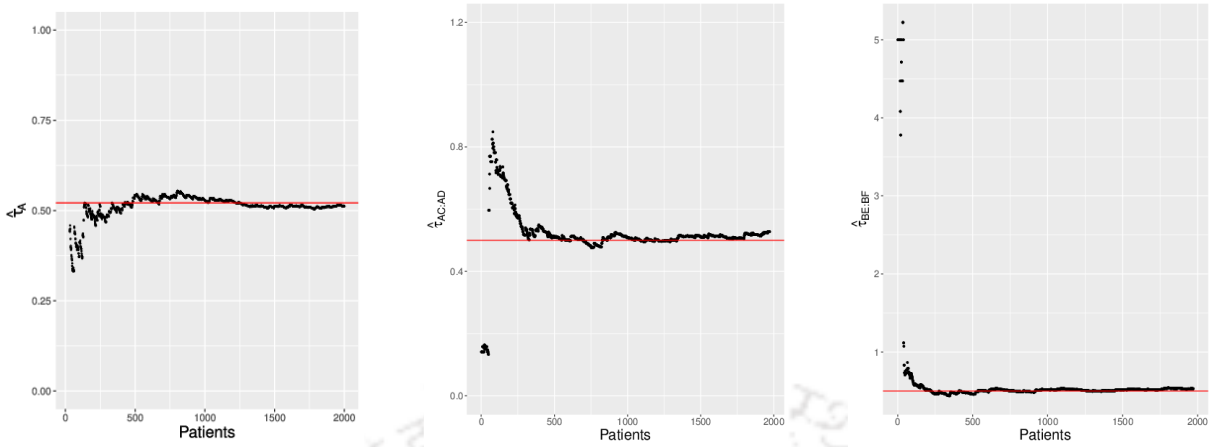
(SSE) and the asymptotic standard error (ASE) are close in most scenarios. The estimated coverage probabilities (CP) corresponding to the three optimal adaptive allocation ratios are mostly near 0.95, except for a few scenarios when at least one success probability is low. The estimated CP improved considerably when the total sample size of the SMART increased from 500 to 1000 and then to 2000 (see Tables 2.3 and 2.4). The last two columns of Table 2.1 show the total expected number of failures from the entire SMART at the end of the trial when the proposed adaptive (randomization) allocation procedure (denoted as "Optimal" in Table 2.1) or non-adaptive randomization (probability is fixed at 0.5 and denoted as "Equal" in Table 2.1) are followed, respectively. It is evident from the results that the proposed adaptive procedure can reduce the total expected number of failures from the entire SMART by a considerable number. The reduced number of failures in rows 3, 14, and 15 are 53 (10.6%), 85 (17%), and 85 (17%) out of 500 patients. From an ethical point of view, we can prefer the adaptive randomization procedure to the non-adaptive one in a SMART, as fewer patients experience failure in the trial. Also note that when all the optimal adaptive allocation ratios are 1 (in row 10 to 13), the total expected number of failures from the entire SMART at the end of the trial are equal for both the "Optimal" and "Equal" randomization processes. In other words, when the optimal adaptive allocation ratio is 1, adaptive and non-adaptive randomizations are the same, as expected.

Figure 2.2 shows the convergence patterns of the estimated (black dots) optimal adaptive allocation ratios to the corresponding true values (red lines) as the sample size increases. In this specific instance (one of 5000 simulations), we observe that $\hat{\tau}_A$ and $\hat{\tau}_{AC:AD}$ both narrow down the gap between their values and corresponding true values after inclusion of 250 or more patients in the SMART. On the other hand, $\hat{\tau}_{BE:BF}$ started to close down the same gap a little earlier. In summary, Figure 2.2 empirically ensures the convergence property of the estimated optimal adaptive allocation ratios following the adaptive procedure described in Section 2.4.

We have seen that the proposed adaptive randomization procedure minimizes the total expected number of failures (compared to a non-adaptive SMART) at the end of the SMART using the last two columns of Table 2.1. Figure 2.3(a) shows the trajectories of the proportion of failures (one of the 5000 simulations) following "Optimal" (dashed brown line) and "Equal" (dotted blue line) allocation processes over the sequential enrollment of 2000 patients. Notice that the proportion of failures is initially higher in the "Optimal" allocation process than in the "Equal" allocation. However, as the number of enrolled patients increases, the proportion of failures in the "Optimal" allocation becomes lower compared to the "Equal" allocation. Thus, by chance, initially, we may observe an increase in the proportion of failures in the "Optimal" allocation compared to the "Equal" allocation. It is interesting to observe that, after 500 patients, the vertical distance between (and the patterns of the two graphs) the two lines is al-

Table 2.1: Estimated first-stage ($\hat{\tau}_A$) and second-stage ($\hat{\tau}_{AC:AD}, \hat{\tau}_{BE:BF}$) allocation ratios along with corresponding SSE, ASE and CP based on 5000 simulations. τ_A, $\tau_{AC:AD}$, and $\tau_{BE:BF}$ denote true values of optimum allocation ratios. Here, $\gamma_A = 0.4$, *and* $\gamma_B = 0.3$, and the sample size is 500 using objective function as Simple Difference. It also shows the total expected number of failures at the end of SMART using optimal adaptive allocation (proposed method) and equal randomization.

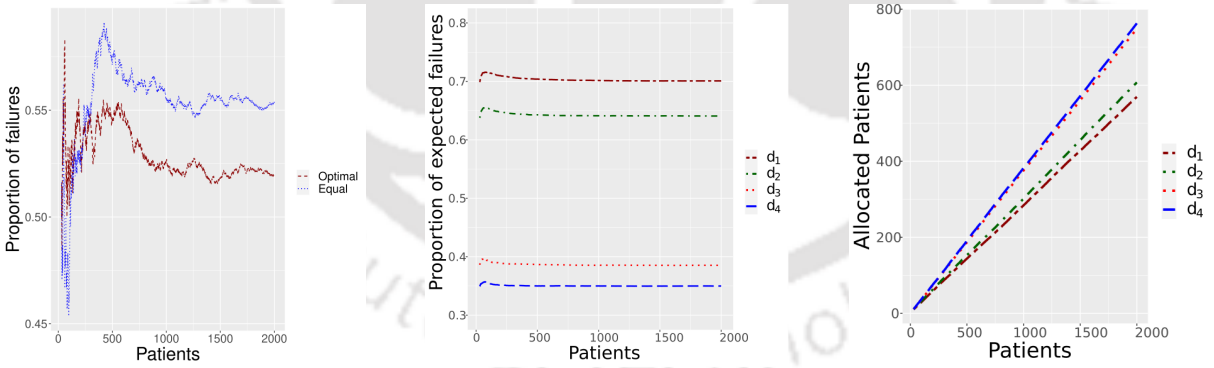
No.	$(p_{AA'}, p_{AC}, p_{AD})$ $(p_{BB'}, p_{BE}, p_{BF})$	τ_A ($\hat{\tau}_A$, SSE, ASE, $\widehat{CP}$)	$\tau_{AC:AD}$ ($\hat{\tau}_{AC:AD}$, SSE, ASE, $\widehat{CP}$)	$\tau_{BE:BF}$ ($\hat{\tau}_{BE:BF}$, SSE, ASE, $\widehat{CP}$)	Total expected number of failures	
					Optimal	Equal
1	(0.20, 0.15, 0.15) (0.45, 0.65, 0.75)	0.521 (0.516, 0.046, 0.046, 0.947)	1.000 (1.099, 0.589, 0.803, 0.929)	0.931 (0.931, 0.043, 0.041, 0.941)	267	302
2	(0.30, 0.80, 0.20) (0.25, 0.60, 0.55)	1.002 (1.008, 0.043, 0.043, 0.953)	2.000 (2.254, 1.057, 1.651, 0.949)	1.044 (1.047, 0.073, 0.070, 0.946)	260	277
3	(0.80, 0.95, 0.85) (0.35, 0.15, 0.15)	2.025 (2.049, 0.160, 0.161, 0.957)	1.057 (1.058, 0.026, 0.026, 0.945)	1.000 (1.078, 0.503, 0.632, 0.925)	179	232
4	(0.30, 0.20, 0.80) (0.25, 0.15, 0.60)	1.109 (1.109, 0.054, 0.053, 0.946)	0.500 (0.481, 0.094, 0.074, 0.914)	0.500 (0.473, 0.112, 0.088, 0.900)	278	311
5	(0.30, 0.20, 0.20) (0.65, 0.15, 0.60)	0.686 (0.681, 0.047, 0.046, 0.948)	1.000 (1.041, 0.376, 0.449, 0.939)	0.500 (0.479, 0.096, 0.077, 0.913)	297	325
6	(0.30, 0.80, 0.20) (0.25, 0.60, 0.60)	0.985 (0.991, 0.042, 0.041, 0.951)	2.000 (2.266, 1.055, 1.651, 0.950)	1.000 (1.002, 0.065, 0.063, 0.949)	256	273
7	(0.30, 0.80, 0.80) (0.65, 0.15, 0.60)	1.085 (1.080, 0.041, 0.041, 0.946)	1.000 (1.002, 0.041, 0.041, 0.954)	0.500 (0.475, 0.108, 0.087, 0.906)	220	235
8	(0.30, 0.80, 0.80) (0.65, 0.15, 0.15)	1.414 (1.420, 0.073, 0.073, 0.951)	1.000 (1.001, 0.038, 0.038, 0.954)	1.000 (1.050, 0.377, 0.409, 0.944)	262	274
9	(0.30, 0.20, 0.20) (0.65, 0.60, 0.15)	0.686 (0.681, 0.047, 0.046, 0.947)	1.000 (1.036, 0.368, 0.433, 0.938)	2.000 (2.227, 0.863, 1.112, 0.953)	297	325
	Very high/low success probability values					
10	(0.10, 0.10, 0.10) (0.10, 0.10, 0.10)	1.000 (1.011, 0.147, 0.144, 0.951)	1.000 (1.061, 0.437, 0.489, 0.927)	1.000 (1.058, 0.402, 0.425, 0.939)	450	450
11	(0.05, 0.05, 0.05) (0.05, 0.05, 0.05)	1.000 (1.026, 0.223, 0.226, 0.963)	1.000 (1.113, 0.539, 0.718, 0.957)	1.000 (1.093, 0.486, 0.609, 0.957)	475	475
12	(0.90, 0.90, 0.90) (0.90, 0.90, 0.90)	1.000 (1.000, 0.015, 0.015, 0.948)	1.000 (1.000, 0.028, 0.028, 0.951)	1.000 (1.001, 0.025, 0.026, 0.956)	50	50
13	(0.95, 0.95, 0.95) (0.95, 0.95, 0.95)	1.000 (1.000, 0.010, 0.010, 0.947)	1.000 (1.000, 0.019, 0.019, 0.967)	1.000 (1.000, 0.018, 0.018, 0.962)	25	25
14	(0.35, 0.95, 0.05) (0.65, 0.90, 0.10)	0.943 (0.946, 0.037, 0.044, 0.974)	4.359 (6.402, 2.901, 8.560, 0.937)	3.000 (4.063, 2.236, 4.198, 0.944)	169	254
15	(0.45, 0.05, 0.95) (0.25, 0.90, 0.10)	1.072 (1.071, 0.046, 0.051, 0.968)	0.229 (0.196, 0.088, 0.110, 0.983)	3.000 (4.114, 2.306, 4.483, 0.950)	190	275
16	(0.95, 0.95, 0.05) (0.90, 0.10, 0.90)	1.057 (1.057, 0.031, 0.036, 0.974)	4.359 (6.362, 2.882, 8.246, 0.934)	0.333 (0.298, 0.102, 0.088, 0.980)	89	174



(a) $\tau_A = 0.521$ (b) $\tau_{AC:AD} = 0.5$ (c) $\tau_{BE:BF} = 0.5$

Figure 2.2: Convergence patterns of estimated (black dots) optimal adaptive allocation ratios ($\hat{\tau}_A$, $\hat{\tau}_{AC:AD}$, and $\hat{\tau}_{BE:BF}$) to corresponding true values ($\tau_A, \tau_{AC:AD}$, and $\tau_{BE:BF}$) indicated by red lines.

most the same till the end. Approximately after 1000 patients' enrollment, the "Optimal" and "Equal" graphs stabilize around 0.52 and 0.56 (with some variations), respectively. The considered values of success probabilities for all three graphs in Figure 2.3 are $p_{AA'} = 0.3$, $p_{AC} = 0.3$, $p_{AD} = 0.4$, $p_{BB'} = 0.65$, $p_{BE} = 0.6$, and $p_{BF} = 0.65$; along with $\gamma_A = 0.4$, $\gamma_B = 0.3$.



(a) Comparison of proportion of failures for Optimal and Equal allocations

(b) Proportions of expected failures along embedded DTRs

(c) Allocated patients along four embedded DTRs

Figure 2.3

Figure 2.3(b) and 2.3(c) compare the embedded DTRs with respect to the proportions of the expected number of failures and the number of allocated patients averaged over 5000 simulations. We observed that the order (from the lowest to the highest proportion of expected failures) of embedded DTRs in Figure 2.3(b) is d_4, d_3, d_2, and d_1, which is the exact same order (highest to lowest number of allocated patients) of the embedded

DTRs in Figure 2.3(c). Thus, from an ethical point of view, we can claim that the proposed methodology assigns more patients to better DTRs (having a lower proportion of failures). At the end of the SMART, we compare two distinct-path DTRs, d_1 and d_3, using the hypothesis testing procedure described in Section 2.5. The test concludes that d_3 is significantly better than d_1 with p-value < 0.01 and the test statistic, $Z_{Adj} = 42.897$. This conclusion is in the same line as we observed from Figures 2.3(b) and 2.3(c).

Earlier in this section, we have shown the simulation studies with the objective function as the simple difference with a sample size of 500. Similar simulations for the same objective function with sample sizes 1000 and 2000 are shown in Tables 2.3 and 2.4, respectively.

In Sections 2.9.5, and 2.9.6, we have obtained the adaptive optimal adaptive allocation ratios and the corresponding adaptive allocation processes with the objective functions as odds-ratio and relative-risk, respectively. We have also established the asymptotic distributions of the developed adaptive optimal adaptive allocation ratios for both the objective functions. Following the same simulation structure as defined earlier in this section, the estimates of the optimal adaptive allocation ratios are obtained. We have considered sample sizes of 500, 1000, and 2000 to estimate the optimal adaptive allocation ratios, and the corresponding SSE, ASE, and CP values in Tables 2.5, 2.6, 2.7 for objective function odds-ratio, and 2.8, 2.9, and 2.10 for relative-risk as the objective function. The success probability setup has been kept exactly same as in Table 2.1,for Tables 2.5, 2.6, 2.7, 2.8, 2.9, and 2.10.

In Tables 2.5, 2.6, and 2.7, we observe when the true values of the optimal adaptive allocation ratios $(\tau^*_A, \tau^*_{AC:AD}, \tau^*_{BE:BF})$ are close to 0.5 or 1, the estimated optimal adaptive allocation ratios $(\hat{\tau}_A, \hat{\tau}_{AC:AD}, \hat{\tau}_{BE:BF})$ are close to their respective true values. However, when the value of τ^*_A, $\tau^*_{AC:AD}$ or $\tau^*_{BE:BF}$ are 2 or more, we observe corresponding estimates $\hat{\tau}_A$, $\hat{\tau}_{AC:AD}$ and $\hat{\tau}_{BE:BF}$ are overestimating the respective optimal adaptive allocation ratios. Such high values of the optimal adaptive allocation ratios are seen when one or more success probabilities are very low or high (failure probability is low). It can be further observed that when the true values of optimal adaptive allocation ratios are close to 0.5 or 1, SSE and ASE are close to each other, and the coverage probability (CP) is close to 0.95. However, when the true values of any of the optimal adaptive allocation ratios are more than 2, we observe the estimated optimal adaptive allocation ratios deviate from the corresponding true values.

In Tables 2.8, 2.9, and 2.10, we observed that for all the values (rows 1 to 9) of the estimated optimal adaptive allocation ratios are close to the corresponding true values of the same. Similarly, in each case, the SSE and the ASE are close, and the coverage probabilities (CP) are close to 0.95. However, for very large (or small) values of some success probabilities (rows 14 to 16), the estimated optimal adaptive allocation ratios deviate from their corresponding true values. In those cases, the values of SSE and ASE

are also far apart.

The simulation study did not yield any one method to be better than the other two, in general. However, we observed that for at least one extreme value of the success probabilities ($p_{T_1T_2}$) that yields high values of optimal adaptive allocation ratios (last 3 rows of Table 2.1 − 2.10), the odds-ratio has been performing better than simple difference, in terms of biases in the respective estimated optimal adaptive allocation ratios. Similarly, the relative-risk approach may not perform well for at least one extreme value of the success probabilities ($p_{T_1T_2}$) that yields high values of optimal adaptive allocation ratios. Thus, we can say the odds-ratio is performing better than the other two approaches in the presence of extreme values of success probabilities.

Table 2.2: Estimated first-stage ($\hat{\tau}_A$) and second-stage ($\hat{\tau}_{AC:AD}, \hat{\tau}_{BE:BF}$) allocation ratios along with corresponding SSE, ASE and CP based on 5000 simulations. τ_A, $\tau_{AC:AD}$, and $\tau_{BE:BF}$ denote true values of optimum allocation ratios. Here, $\gamma_A = 0.4$, *and* $\gamma_B = 0.3$, and the sample size is **200** using objective function as **Simple Difference**. It also shows the total expected number of failures at the end of SMART using optimal adaptive allocation (proposed method) and equal randomization.

No.	$(p_{AA'}, p_{AC}, p_{AD})$ $(p_{BB'}, p_{BE}, p_{BF})$	τ_A ($\hat{\tau}_A$, SSE, ASE, $\widehat{CP}$)	$\tau_{AC:AD}$ ($\hat{\tau}_{AC:AD}$, SSE, ASE, $\widehat{CP}$)	$\tau_{BE:BF}$ ($\hat{\tau}_{BE:BF}$, SSE, ASE, $\widehat{CP}$)	Total expected number of failures	
					Optimal	Equal
1	(0.20, 0.15, 0.15) (0.45, 0.65, 0.75)	0.521 (0.515, 0.077, 0.076, 0.952)	1.000 (1.359, 1.174, 2.798, 0.958)	0.931 (0.932, 0.070, 0.066, 0.949)	109	121
2	(0.30, 0.80, 0.20) (0.25, 0.60, 0.55)	1.002 (1.022, 0.073, 0.075, 0.956)	2.000 (3.121, 2.456, 6.830, 0.936)	1.044 (1.064, 0.275, 0.507, 0.949)	104	111
3	(0.80, 0.95, 0.85) (0.35, 0.15, 0.15)	2.025 (2.079, 0.306, 0.332, 0.958)	1.057 (1.059, 0.044, 0.042, 0.930)	1.000 (1.323, 1.136, 2.521, 0.947)	73	93
4	(0.30, 0.20, 0.80) (0.25, 0.15, 0.60)	1.109 (1.112, 0.092, 0.096, 0.960)	0.500 (0.445, 0.162, 0.133, 0.975)	0.500 (0.435, 0.183, 0.158, 0.981)	112	125
5	(0.30, 0.20, 0.20) (0.65, 0.15, 0.60)	0.686 (0.676, 0.076, 0.076, 0.951)	1.000 (1.261, 1.044, 2.254, 0.927)	0.500 (0.441, 0.179, 0.164, 0.970)	119	130
6	(0.30, 0.80, 0.20) (0.25, 0.60, 0.60)	0.985 (1.002, 0.071, 0.071, 0.955)	2.000 (3.059, 2.397, 6.657, 0.937)	1.000 (1.009, 0.199, 0.348, 0.946)	103	110
7	(0.30, 0.80, 0.80) (0.65, 0.15, 0.60)	1.085 (1.073, 0.067, 0.069, 0.947)	1.000 (1.001, 0.069, 0.066, 0.956)	0.500 (0.433, 0.181, 0.157, 0.981)	88	94
8	(0.30, 0.80, 0.80) (0.65, 0.15, 0.15)	1.414 (1.423, 0.117, 0.120, 0.957)	1.000 (1.001, 0.065, 0.062, 0.953)	1.000 (1.278, 0.999, 1.945, 0.933)	105	109
9	(0.30, 0.20, 0.20) (0.65, 0.60, 0.15)	0.686 (0.677, 0.075, 0.076, 0.951)	1.000 (1.245, 1.027, 2.203, 0.923)	2.000 (2.952, 2.073, 4.836, 0.941)	119	129
	Very high/low success probability values					
10	(0.10, 0.10, 0.10) (0.10, 0.10, 0.10)	1.000 (1.034, 0.288, 0.297, 0.959)	1.000 (1.281, 0.959, 1.873, 0.956)	1.000 (1.243, 0.890, 1.586, 0.939)	180	180
11	(0.05, 0.05, 0.05) (0.05, 0.05, 0.05)	1.000 (1.064, 0.397, 0.475, 0.962)	1.000 (1.237, 0.819, 1.727, 0.988)	1.000 (1.224, 0.779, 1.526, 0.989)	190	190
12	(0.90, 0.90, 0.90) (0.90, 0.90, 0.90)	1.000 (1.000, 0.024, 0.023, 0.950)	1.000 (1.002, 0.046, 0.045, 0.967)	1.000 (1.002, 0.043, 0.041, 0.962)	20	20
13	(0.95, 0.95, 0.95) (0.95, 0.95, 0.95)	1.000 (1.000, 0.016, 0.016, 0.969)	1.000 (1.001, 0.030, 0.031, 0.992)	1.000 (1.000, 0.028, 0.029, 0.988)	10	10
14	(0.35, 0.95, 0.05) (0.65, 0.90, 0.10)	0.943 (0.943, 0.052, 0.079, 0.985)	4.359 (7.467, 3.120, 16.731, 0.931)	3.000 (5.255, 3.202, 10.716, 0.934)	70	101
15	(0.45, 0.05, 0.95) (0.25, 0.90, 0.10)	1.072 (1.067, 0.062, 0.091, 0.989)	0.229 (0.179, 0.108, 0.187, 0.985)	3.000 (5.304, 3.232, 11.179, 0.931)	79	110
16	(0.95, 0.95, 0.05) (0.90, 0.10, 0.90)	1.057 (1.053, 0.042, 0.067, 0.993)	4.359 (7.481, 3.098, 16.295, 0.937)	0.333 (0.268, 0.140, 0.156, 0.981)	37	69

Table 2.3: Estimated first-stage ($\hat{\tau}_A$) and second-stage ($\hat{\tau}_{AC:AD}, \hat{\tau}_{BE:BF}$) allocation ratios along with corresponding SSE, ASE and CP based on 5000 simulations. τ_A, $\tau_{AC:AD}$, and $\tau_{BE:BF}$ denote true values of optimum allocation ratios. Here, $\gamma_A = 0.4$, and $\gamma_B = 0.3$, and the sample size is **1000** using objective function as **Simple Difference**. It also shows the total expected number of failures at the end of SMART using optimal adaptive allocation (proposed method) and equal randomization.

No.	$(p_{AA'}, p_{AC}, p_{AD})$ $(p_{BB'}, p_{BE}, p_{BF})$	τ_A ($\hat{\tau}_A$, SSE, ASE, $\widehat{CP}$)	$\tau_{AC:AD}$ ($\hat{\tau}_{AC:AD}$, SSE, ASE, $\widehat{CP}$)	$\tau_{BE:BF}$ ($\hat{\tau}_{BE:BF}$, SSE, ASE, $\widehat{CP}$)	Total expected number of failures	
					Optimal	Equal
1	(0.20, 0.15, 0.15) (0.45, 0.65, 0.75)	0.521 (0.518, 0.033, 0.032, 0.946)	1.000 (1.025, 0.242, 0.218, 0.949)	0.931 (0.931, 0.029, 0.029, 0.953)	532	603
2	(0.30, 0.80, 0.20) (0.25, 0.60, 0.55)	1.002 (1.004, 0.030, 0.030, 0.949)	2.000 (2.073, 0.402, 0.410, 0.955)	1.044 (1.046, 0.049, 0.049, 0.952)	520	553
3	(0.80, 0.95, 0.85) (0.35, 0.15, 0.15)	2.025 (2.039, 0.111, 0.110, 0.954)	1.057 (1.058, 0.018, 0.018, 0.947)	1.000 (1.018, 0.207, 0.191, 0.951)	356	464
4	(0.30, 0.20, 0.80) (0.25, 0.15, 0.60)	1.109 (1.109, 0.036, 0.036, 0.954)	0.500 (0.492, 0.058, 0.050, 0.926)	0.500 (0.490, 0.069, 0.059, 0.926)	558	622
5	(0.30, 0.20, 0.20) (0.65, 0.15, 0.60)	0.686 (0.683, 0.033, 0.033, 0.947)	1.000 (1.011, 0.154, 0.146, 0.948)	0.500 (0.493, 0.059, 0.053, 0.934)	596	651
6	(0.30, 0.80, 0.20) (0.25, 0.60, 0.60)	0.985 (0.987, 0.028, 0.028, 0.949)	2.000 (2.077, 0.416, 0.428, 0.956)	1.000 (1.001, 0.045, 0.044, 0.951)	511	544
7	(0.30, 0.80, 0.80) (0.65, 0.15, 0.60)	1.085 (1.083, 0.028, 0.028, 0.954)	1.000 (1.000, 0.028, 0.029, 0.955)	0.500 (0.491, 0.067, 0.059, 0.934)	440	471
8	(0.30, 0.80, 0.80) (0.65, 0.15, 0.15)	1.414 (1.417, 0.051, 0.051, 0.953)	1.000 (1.001, 0.027, 0.027, 0.958)	1.000 (1.017, 0.176, 0.161, 0.954)	524	549
9	(0.30, 0.20, 0.20) (0.65, 0.60, 0.15)	0.686 (0.683, 0.033, 0.033, 0.949)	1.000 (1.009, 0.147, 0.138, 0.949)	2.000 (2.061, 0.324, 0.290, 0.952)	596	651
Very high/low success probability values						
10	(0.10, 0.10, 0.10) (0.10, 0.10, 0.10)	1.000 (1.005, 0.099, 0.098, 0.953)	1.000 (1.020, 0.241, 0.218, 0.952)	1.000 (1.012, 0.210, 0.187, 0.941)	900	900
11	(0.05, 0.05, 0.05) (0.05, 0.05, 0.05)	1.000 (1.011, 0.149, 0.147, 0.956)	1.000 (1.060, 0.383, 0.391, 0.942)	1.000 (1.050, 0.342, 0.340, 0.944)	950	950
12	(0.90, 0.90, 0.90) (0.90, 0.90, 0.90)	1.000 (1.000, 0.010, 0.011, 0.953)	1.000 (1.001, 0.019, 0.019, 0.952)	1.000 (1.000, 0.018, 0.012, 0.950)	100	100
13	(0.95, 0.95, 0.95) (0.95, 0.95, 0.95)	1.000 (1.000, 0.007, 0.007, 0.948)	1.000 (1.000, 0.013, 0.013, 0.953)	1.000 (1.000, 0.013, 0.012, 0.949)	50	50
14	(0.35, 0.95, 0.05) (0.65, 0.90, 0.10)	0.943 (0.947, 0.028, 0.029, 0.962)	4.359 (5.670, 2.363, 4.608, 0.937)	3.000 (3.371, 1.174, 1.380, 0.950)	340	508
15	(0.45, 0.05, 0.95) (0.25, 0.90, 0.10)	1.072 (1.074, 0.033, 0.033, 0.957)	0.229 (0.206, 0.071, 0.073, 0.980)	3.000 (3.430, 1.277, 1.578, 0.949)	190	275
16	(0.95, 0.95, 0.05) (0.90, 0.10, 0.90)	1.057 (1.059, 0.022, 0.023, 0.960)	4.359 (5.605, 2.308, 4.358, 0.940)	0.333 (0.316, 0.070, 0.058, 0.904)	89	174

Table 2.4: Estimated first-stage ($\hat{\tau}_A$) and second-stage ($\hat{\tau}_{AC:AD}, \hat{\tau}_{BE:BF}$) allocation ratios along with corresponding SSE, ASE and CP based on 5000 simulations. τ_A, $\tau_{AC:AD}$, and $\tau_{BE:BF}$ denote true values of optimum allocation ratios. Here, $\gamma_A = 0.4$, and $\gamma_B = 0.3$, and the sample size is **2000** using objective function as **Simple Difference**. It also shows the total expected number of failures at the end of SMART using optimal adaptive allocation (proposed method) and equal randomization.

No.	$(p_{AA'}, p_{AC}, p_{AD})$ $(p_{BB'}, p_{BE}, p_{BF})$	τ_A ($\hat{\tau}_A$, SSE, ASE, $\widehat{CP}$)	$\tau_{AC:AD}$ ($\hat{\tau}_{AC:AD}$, SSE, ASE, $\widehat{CP}$)	$\tau_{BE:BF}$ ($\hat{\tau}_{BE:BF}$, SSE, ASE, $\widehat{CP}$)	Total expected number of failures	
					Optimal	Equal
1	(0.20, 0.15, 0.15) (0.45, 0.65, 0.75)	0.521 (0.519, 0.023, 0.023, 0.950)	1.000 (1.009, 0.132, 0.125, 0.948)	0.931 (0.931, 0.020, 0.020, 0.952)	1061	1205
2	(0.30, 0.80, 0.20) (0.25, 0.60, 0.55)	1.002 (1.003, 0.021, 0.021, 0.945)	2.000 (2.022, 0.158, 0.152, 0.952)	1.044 (1.045, 0.034, 0.034, 0.950)	1040	1103
3	(0.80, 0.95, 0.85) (0.35, 0.15, 0.15)	2.025 (2.032, 0.077, 0.076, 0.951)	1.057 (1.058, 0.013, 0.013, 0.947)	1.000 (1.003, 0.119, 0.116, 0.949)	710	929
4	(0.30, 0.20, 0.80) (0.25, 0.15, 0.60)	1.109 (1.110, 0.025, 0.025, 0.952)	0.500 (0.497, 0.037, 0.035, 0.942)	0.500 (0.497, 0.044, 0.041, 0.940)	1120	1243
5	(0.30, 0.20, 0.20) (0.65, 0.15, 0.60)	0.686 (0.684, 0.023, 0.023, 0.952)	1.000 (1.003, 0.096, 0.093, 0.947)	0.500 (0.497, 0.039, 0.037, 0.943)	1196	1302
6	(0.30, 0.80, 0.20) (0.25, 0.60, 0.60)	0.985 (0.985, 0.020, 0.020, 0.948)	2.000 (2.021, 0.161, 0.153, 0.951)	1.000 (1.001, 0.031, 0.031, 0.954)	1023	1086
7	(0.30, 0.80, 0.80) (0.65, 0.15, 0.60)	1.085 (1.084, 0.020, 0.020, 0.950)	1.000 (1.001, 0.020, 0.020, 0.954)	0.500 (0.497, 0.044, 0.041, 0.937)	883	942
8	(0.30, 0.80, 0.80) (0.65, 0.15, 0.15)	1.414 (1.416, 0.036, 0.036, 0.947)	1.000 (1.000, 0.019, 0.019, 0.952)	1.000 (1.005, 0.102, 0.102, 0.956)	1049	1099
9	(0.30, 0.20, 0.20) (0.65, 0.60, 0.15)	0.686 (0.684, 0.023, 0.023, 0.953)	1.000 (1.003, 0.095, 0.093, 0.949)	2.000 (2.025, 0.163, 0.156, 0.951)	1195	1302
	Very high/low success probability values					
10	(0.10, 0.10, 0.10) (0.10, 0.10, 0.10)	1.000 (1.001, 0.068, 0.068, 0.954)	1.000 (1.009, 0.135, 0.130, 0.947)	1.000 (1.009, 0.126, 0.120, 0.950)	1800	1800
11	(0.05, 0.05, 0.05) (0.05, 0.05, 0.05)	1.000 (1.005, 0.103, 0.100, 0.950)	1.000 (1.031, 0.225, 0.212, 0.955)	1.000 (1.016, 0.201, 0.189, 0.949)	1900	1900
12	(0.90, 0.90, 0.90) (0.90, 0.90, 0.90)	1.000 (1.000, 0.007, 0.007, 0.952)	1.000 (1.000, 0.014, 0.014, 0.955)	1.000 (1.000, 0.013, 0.013, 0.951)	200	200
13	(0.95, 0.95, 0.95) (0.95, 0.95, 0.95)	1.000 (1.000, 0.005, 0.005, 0.953)	1.000 (1.000, 0.010, 0.009, 0.944)	1.000 (1.000, 0.009, 0.009, 0.953)	100	100
14	(0.35, 0.95, 0.05) (0.65, 0.90, 0.10)	0.943 (0.947, 0.020, 0.019, 0.952)	4.359 (5.123, 1.716, 2.262, 0.949)	3.000 (3.133, 0.531, 0.464, 0.954)	685	1015
15	(0.45, 0.05, 0.95) (0.25, 0.90, 0.10)	1.072 (1.074, 0.022, 0.021, 0.951)	0.229 (0.216, 0.053, 0.049, 0.980)	3.000 (3.140, 0.559, 0.504, 0.956)	764	1096
16	(0.95, 0.95, 0.05) (0.90, 0.10, 0.90)	1.057 (1.059, 0.016, 0.015, 0.949)	4.359 (5.041, 1.640, 2.089, 0.939)	0.333 (0.326, 0.045, 0.039, 0.927)	368	699

Table 2.5: Estimated first-stage ($\hat{\tau}_A$) and second-stage ($\hat{\tau}_{AC:AD}, \hat{\tau}_{BE:BF}$) allocation ratios along with corresponding SSE, ASE and CP based on 5000 simulations. τ_A, $\tau_{AC:AD}$, and $\tau_{BE:BF}$ denote true values of optimum allocation ratios. Here, $\gamma_A = 0.4$, and $\gamma_B = 0.3$, and the sample size is **500** using objective function as **Odds-Ratio**. It also shows the total expected number of failures at the end of SMART using optimal adaptive allocation (proposed method) and equal randomization.

No.	$(p_{AA'}, p_{AC}, p_{AD})$ $(p_{BB'}, p_{BE}, p_{BF})$	τ_A ($\hat{\tau}_A$, SSE, ASE, $\widehat{CP}$)	$\tau_{AC:AD}$ ($\hat{\tau}_{AC:AD}$, SSE, ASE, $\widehat{CP}$)	$\tau_{BE:BF}$ ($\hat{\tau}_{BE:BF}$, SSE, ASE, $\widehat{CP}$)	Total expected number of failures	
					Optimal	Equal
1	(0.20, 0.15, 0.15) (0.45, 0.65, 0.75)	0.864 (0.866, 0.060, 0.060, 0.950)	1.000 (1.013, 0.143, 0.146, 0.971)	0.767 (0.780, 0.140, 0.141, 0.944)	293	302
2	(0.30, 0.80, 0.20) (0.25, 0.60, 0.55)	1.002 (1.003, 0.035, 0.035, 0.954)	2.000 (2.025, 0.409, 0.419, 0.938)	1.082 (1.077, 0.124, 0.125, 0.945	263	277
3	(0.80, 0.95, 0.85) (0.35, 0.15, 0.15)	2.804 (2.785, 0.389, 0.393, 0.932)	2.838 (3.385, 2.062, 2.146, 0.923)	1.000 (1.014, 0.182, 0.191, 0.974)	158	232
4	(0.30, 0.20, 0.80) (0.25, 0.15, 0.60)	1.057 (1.058, 0.028, 0.028, 0.954)	0.500 (0.512, 0.099, 0.098, 0.942)	0.941 (0.958, 0.123, 0.125, 0.966)	296	311
5	(0.30, 0.20, 0.20) (0.65, 0.15, 0.60)	0.940 (0.939, 0.037, 0.038, 0.952)	1.000 (1.004, 0.094, 0.095, 0.977)	0.941 (0.954, 0.116, 0.120, 0.963)	322	325
6	(0.30, 0.80, 0.20) (0.25, 0.60, 0.60)	0.986 (0.988, 0.037, 0.037, 0.955)	2.000 (2.024, 0.411, 0.420, 0.934)	1.000 (1.008, 0.127, 0.127, 0.948)	259	272
7	(0.30, 0.80, 0.80) (0.65, 0.15, 0.60)	1.129 (1.124, 0.064, 0.063, 0.944)	1.000 (1.048, 0.303, 0.308, 0.941)	0.941 (0.958, 0.127, 0.127, 0.962)	233	235
8	(0.30, 0.80, 0.80) (0.65, 0.15, 0.15)	1.237 (1.234, 0.053, 0.054, 0.934)	1.000 (1.035, 0.295, 0.298, 0.936)	1.000 (1.007, 0.133, 0.137, 0.964)	267	274
9	(0.30, 0.20, 0.20) (0.65, 0.60, 0.15)	0.940 (0.938, 0.037, 0.038, 0.954)	1.000 (1.006, 0.093, 0.095, 0.982)	1.063 (1.064, 0.129, 0.131, 0.955)	322	325
Very high/low success probability values						
10	(0.10, 0.10, 0.10) (0.10, 0.10, 0.10)	1.000 (1.007, 0.107, 0.109, 0.953)	1.000 (1.022, 0.218, 0.219, 0.956)	1.000 (1.021, 0.199, 0.197, 0.954)	450	450
11	(0.05, 0.05, 0.05) (0.05, 0.05, 0.05)	1.000 (1.021, 0.190, 0.198, 0.956)	1.000 (1.064, 0.407, 0.433, 0.936)	1.000 (1.058, 0.367, 0.383, 0.933)	475	475
12	(0.90, 0.90, 0.90) (0.90, 0.90, 0.90)	1.000 (1.041, 0.285, 0.278, 0.931)	1.000 (1.152, 0.718, 0.694, 0.904)	1.000 (1.118, 0.568, 0.558, 0.908)	50	50
13	(0.95, 0.95, 0.95) (0.95, 0.95, 0.95)	1.000 (1.107, 0.513, 0.506, 0.913)	1.000 (1.509, 1.892, 2.408, 0.870)	1.000 (1.377, 1.562, 1.876, 0.866)	25	25
14	(0.35, 0.95, 0.05) (0.65, 0.90, 0.10)	0.855 (0.858, 0.079, 0.086, 0.967)	4.359 (5.216, 3.940, 5.206, 0.914)	3.000 (3.122, 1.041, 1.048, 0.930)	186	254
15	(0.45, 0.05, 0.95) (0.25, 0.90, 0.10)	1.157 (1.162, 0.096, 0.107, 0.956)	0.229 (0.262, 0.141, 0.173, 0.914)	3.000 (3.143, 1.114, 1.176, 0.927)	207	274
16	(0.95, 0.95, 0.05) (0.90, 0.10, 0.90)	1.506 (1.549, 0.326, 0.397, 0.938)	4.359 (4.979, 3.182, 3.761, 0.921)	0.333 (0.359, 0.134, 0.139, 0.943)	103	173

Table 2.6: Estimated first-stage ($\hat{\tau}_A$) and second-stage ($\hat{\tau}_{AC:AD}, \hat{\tau}_{BE:BF}$) allocation ratios along with corresponding SSE, ASE and CP based on 5000 simulations. τ_A, $\tau_{AC:AD}$, and $\tau_{BE:BF}$ denote true values of optimum allocation ratios. Here, $\gamma_A = 0.4$, and $\gamma_B = 0.3$, and the sample size is **1000** using objective function as **Odds-Ratio**. It also shows the total expected number of failures at the end of SMART using optimal adaptive allocation (proposed method) and equal randomization.

No.	$(p_{AA'}, p_{AC}, p_{AD})$ $(p_{BB'}, p_{BE}, p_{BF})$	τ_A ($\hat{\tau}_A$, SSE, ASE, $\widehat{CP}$)	$\tau_{AC:AD}$ ($\hat{\tau}_{AC:AD}$, SSE, ASE, $\widehat{CP}$)	$\tau_{BE:BF}$ ($\hat{\tau}_{BE:BF}$, SSE, ASE, $\widehat{CP}$)	Total expected number of failures	
					Optimal	Equal
1	(0.20, 0.15, 0.15) (0.45, 0.65, 0.75)	0.864 (0.865, 0.042, 0.042, 0.946)	1.000 (1.004, 0.098, 0.097, 0.957)	0.767 (0.774, 0.099, 0.098, 0.947)	585	603
2	(0.30, 0.80, 0.20) (0.25, 0.60, 0.55)	1.003 (1.002, 0.025, 0.025, 0.954)	2.000 (2.010, 0.274, 0.280, 0.947)	1.082 (1.080, 0.087, 0.086, 0.946	524	553
3	(0.80, 0.95, 0.85) (0.35, 0.15, 0.15)	2.804 (2.795, 0.275, 0.272, 0.937)	2.838 (3.071, 1.095, 1.071, 0.938)	1.000 (1.006, 0.121, 0.123, 0.971)	308	464
4	(0.30, 0.20, 0.80) (0.25, 0.15, 0.60)	1.057 (1.058, 0.019, 0.019, 0.957)	0.500 (0.505, 0.067, 0.067, 0.952)	0.941 (0.949, 0.083, 0.084, 0.960)	590	622
5	(0.30, 0.20, 0.20) (0.65, 0.15, 0.60)	0.940 (0.940, 0.027, 0.026, 0.950)	1.000 (1.002, 0.063, 0.062, 0.966)	0.941 (0.948, 0.081, 0.081, 0.957)	645	650
6	(0.30, 0.80, 0.20) (0.25, 0.60, 0.60)	0.986 (0.987, 0.026, 0.026, 0.952)	2.000 (2.007, 0.278, 0.280, 0.938)	1.000 (1.002, 0.087, 0.088, 0.956)	515	544
7	(0.30, 0.80, 0.80) (0.65, 0.15, 0.60)	1.129 (1.128, 0.045, 0.045, 0.947)	1.000 (1.019, 0.203, 0.206, 0.943)	0.941 (0.951, 0.087, 0.086, 0.954)	466	471
8	(0.30, 0.80, 0.80) (0.65, 0.15, 0.15)	1.237 (1.236, 0.037, 0.038, 0.941)	1.000 (1.017, 0.202, 0.201, 0.942)	1.000 (1.004, 0.091, 0.091, 0.957)	534	549
9	(0.30, 0.20, 0.20) (0.65, 0.60, 0.15)	0.940 (0.940, 0.026, 0.026, 0.951)	1.000 (1.001, 0.063, 0.062, 0.964)	1.063 (1.062, 0.091, 0.090, 0.948)	645	651
	Very high/low success probability values					
10	(0.10, 0.10, 0.10) (0.10, 0.10, 0.10)	1.000 (1.003, 0.075, 0.076, 0.953)	1.000 (1.008, 0.143, 0.142, 0.955)	1.000 (1.010, 0.132, 0.131, 0.947)	900	900
11	(0.05, 0.05, 0.05) (0.05, 0.05, 0.05)	1.000 (1.009, 0.128, 0.131, 0.956)	1.000 (1.027, 0.251, 0.253, 0.945)	1.000 (1.025, 0.233, 0.231, 0.945)	950	950
12	(0.90, 0.90, 0.90) (0.90, 0.90, 0.90)	1.000 (1.020, 0.190, 0.187, 0.943)	1.000 (1.060, 0.384, 0.376, 0.926)	1.000 (1.048, 0.346, 0.339, 0.922)	100	100
13	(0.95, 0.95, 0.95) (0.95, 0.95, 0.95)	1.000 (1.050, 0.321, 0.304, 0.927)	1.000 (1.173, 0.904, 0.901, 0.893)	1.000 (1.143, 0.784, 0.731, 0.906)	50	50
14	(0.35, 0.95, 0.05) (0.65, 0.90, 0.10)	0.855 (0.857, 0.056, 0.058, 0.960)	4.359 (4.724, 2.135, 2.285, 0.927)	3.000 (3.058, 0.669, 0.669, 0.938)	362	508
15	(0.45, 0.05, 0.95) (0.25, 0.90, 0.10)	1.157 (1.161, 0.071, 0.072, 0.952)	0.229 (0.248, 0.097, 0.106, 0.927)	3.000 (3.074, 0.728, 0.734, 0.941)	403	548
16	(0.95, 0.95, 0.05) (0.90, 0.10, 0.90)	1.506 (1.527, 0.233, 0.246, 0.938)	4.359 (4.639, 1.788, 1.817, 0.936)	0.333 (0.345, 0.083, 0.088, 0.944)	198	349

Table 2.7: Estimated first-stage ($\hat{\tau}_A$) and second-stage ($\hat{\tau}_{AC:AD}, \hat{\tau}_{BE:BF}$) allocation ratios along with corresponding SSE, ASE and CP based on 5000 simulations. τ_A, $\tau_{AC:AD}$, and $\tau_{BE:BF}$ denote true values of optimum allocation ratios. Here, $\gamma_A = 0.4$, and $\gamma_B = 0.3$, and the sample size is **2000** using objective function as **Odds-Ratio**. It also shows the total expected number of failures at the end of SMART using optimal adaptive allocation (proposed method) and equal randomization.

No.	$(p_{AA'}, p_{AC}, p_{AD})$ $(p_{BB'}, p_{BE}, p_{BF})$	τ_A ($\hat{\tau}_A$, SSE, ASE, $\widehat{CP}$)	$\tau_{AC:AD}$ ($\hat{\tau}_{AC:AD}$, SSE, ASE, $\widehat{CP}$)	$\tau_{BE:BF}$ ($\hat{\tau}_{BE:BF}$, SSE, ASE, $\widehat{CP}$)	Total expected number of failures	
					Optimal	Equal
1	(0.20, 0.15, 0.15) (0.45, 0.65, 0.75)	0.864 (0.865, 0.030, 0.030, 0.953)	1.000 (1.003, 0.067, 0.067, 0.955)	0.767 (0.770, 0.069, 0.069, 0.947)	1169	1205
2	(0.30, 0.80, 0.20) (0.25, 0.60, 0.55)	1.002 (1.002, 0.018, 0.017, 0.949)	2.000 (2.002, 0.196, 0.193, 0.939)	1.082 (1.080, 0.061, 0.061, 0.948	1045	1103
3	(0.80, 0.95, 0.85) (0.35, 0.15, 0.15)	2.804 (2.801, 0.192, 0.190, 0.942)	2.838 (2.928, 0.693, 0.677, 0.938)	1.000 (1.003, 0.083, 0.084, 0.960)	610	929
4	(0.30, 0.20, 0.80) (0.25, 0.15, 0.60)	1.057 (1.057, 0.013, 0.013, 0.949)	0.500 (0.504, 0.047, 0.047, 0.949)	0.941 (0.947, 0.059, 0.059, 0.951)	1178	1243
5	(0.30, 0.20, 0.20) (0.65, 0.15, 0.60)	0.940 (0.940, 0.019, 0.019, 0.951)	1.000 (1.001, 0.043, 0.043, 0.958)	0.941 (0.945, 0.056, 0.057, 0.951)	1291	1302
6	(0.30, 0.80, 0.20) (0.25, 0.60, 0.60)	0.986 (0.986, 0.018, 0.018, 0.947)	2.000 (2.006, 0.192, 0.194, 0.946)	1.000 (1.004, 0.063, 0.062, 0.945)	1028	1086
7	(0.30, 0.80, 0.80) (0.65, 0.15, 0.60)	1.129 (1.128, 0.031, 0.031, 0.950)	1.000 (1.014, 0.140, 0.143, 0.951)	0.941 (0.946, 0.060, 0.060, 0.949)	931	942
8	(0.30, 0.80, 0.80) (0.65, 0.15, 0.15)	1.237 (1.237, 0.026, 0.027, 0.953)	1.000 (1.009, 0.135, 0.139, 0.956)	1.000 (1.001, 0.063, 0.063, 0.955)	1068	1099
9	(0.30, 0.20, 0.20) (0.65, 0.60, 0.15)	0.940 (0.940, 0.019, 0.019, 0.951)	1.000 (1.001, 0.043, 0.043, 0.955)	1.063 (1.062, 0.063, 0.063, 0.953)	1291	1302
Very high/low success probability values						
10	(0.10, 0.10, 0.10) (0.10, 0.10, 0.10)	1.000 (1.002, 0.052, 0.053, 0.951)	1.000 (1.006, 0.098, 0.098, 0.953)	1.000 (1.004, 0.091, 0.090, 0.948)	1800	1800
11	(0.05, 0.05, 0.05) (0.05, 0.05, 0.05)	1.000 (1.005, 0.088, 0.090, 0.954)	1.000 (1.012, 0.168, 0.168, 0.949)	1.000 (1.012, 0.155, 0.154, 0.948)	1900	1900
12	(0.90, 0.90, 0.90) (0.90, 0.90, 0.90)	1.000 (1.008, 0.127, 0.129, 0.952)	1.000 (1.026, 0.248, 0.246, 0.942)	1.000 (1.028, 0.229, 0.227, 0.937)	200	200
13	(0.95, 0.95, 0.95) (0.95, 0.95, 0.95)	1.000 (1.021, 0.321, 0.207, 0.936)	1.000 (1.077, 0.427, 0.409, 0.923)	1.000 (1.068, 0.392, 0.370, 0.924)	100	100
14	(0.35, 0.95, 0.05) (0.65, 0.90, 0.10)	0.855 (0.856, 0.040, 0.040, 0.955)	4.359 (4.499, 1.303, 1.346, 0.936)	3.000 (3.027, 0.458, 0.455, 0.942)	715	1015
15	(0.45, 0.05, 0.95) (0.25, 0.90, 0.10)	1.157 (1.158, 0.050, 0.050, 0.947)	0.229 (0.237, 0.064, 0.066, 0.938)	3.000 (3.036, 0.491, 0.495, 0.950)	795	1096
16	(0.95, 0.95, 0.05) (0.90, 0.10, 0.90)	1.506 (1.514, 0.159, 0.162, 0.945)	4.359 (4.484, 1.115, 1.149, 0.949)	0.333 (0.339, 0.058, 0.059, 0.949)	387	699

Table 2.8: Estimated first-stage ($\hat{\tau}_A$) and second-stage ($\hat{\tau}_{AC:AD}, \hat{\tau}_{BE:BF}$) allocation ratios along with corresponding SSE, ASE and CP based on 5000 simulations. τ_A, $\tau_{AC:AD}$, and $\tau_{BE:BF}$ denote true values of optimum allocation ratios. Here, $\gamma_A = 0.4$, and $\gamma_B = 0.3$, and the sample size is **500** using objective function as **Relative-Risk**. It also shows the total expected number of failures at the end of SMART using optimal adaptive allocation (proposed method) and equal randomization.

No.	$(p_{AA'}, p_{AC}, p_{AD})$ $(p_{BB'}, p_{BE}, p_{BF})$	τ_A ($\hat{\tau}_A$, SSE, ASE, $\widehat{CP}$)	$\tau_{AC:AD}$ ($\hat{\tau}_{AC:AD}$, SSE, ASE, $\widehat{CP}$)	$\tau_{BE:BF}$ ($\hat{\tau}_{BE:BF}$, SSE, ASE, $\widehat{CP}$)	Total expected number of failures	
					Optimal	Equal
1	(0.20, 0.15, 0.15) (0.45, 0.65, 0.75)	0.235 (0.233, 0.042, 0.043, 0.954)	1.000 (1.366, 1.264, 2.672, 0.897)	0.665 (0.675, 0.160, 0.155, 0.931)	233	302
2	(0.30, 0.80, 0.20) (0.25, 0.60, 0.55)	1.006 (1.089, 0.170, 0.248, 0.961)	8.000 (16.450, 15.869, 58.974, 0.953)	1.175 (1.234, 0.518, 0.774, 0.926	241	277
3	(0.80, 0.40, 0.60) (0.35, 0.65, 0.45)	1.512 (1.539, 0.214, 0.214, 0.948)	0.544 (0.545, 0.144, 0.132, 0.918)	1.889 (2.191, 1.926, 4.281, 0.936)	207	223
4	(0.30, 0.20, 0.80) (0.25, 0.15, 0.60)	1.301 (1.340, 0.209, 0.301, 0.972)	0.125 (0.108, 0.058, 0.053, 0.934)	0.235 (0.209, 0.118, 0.124, 0.902)	296	311
5	(0.30, 0.20, 0.20) (0.65, 0.15, 0.60)	0.442 (0.427, 0.063, 0.064, 0.932)	1.000 (1.195, 0.962, 1.598, 0.898)	0.235 (0.217, 0.080, 0.065, 0.862)	322	325
6	(0.30, 0.60, 0.45) (0.25, 0.60, 0.60)	0.846 (0.850, 0.112, 0.108, 0.937)	1.588 (1.769, 1.191, 2.355, 0.939)	1.000 (1.034, 0.279, 0.256, 0.923)	265	269
7	(0.30, 0.80, 0.80) (0.65, 0.15, 0.60)	1.329 (1.280, 0.178, 0.193, 0.939)	1.000 (1.072, 0.791, 1.999, 0.916)	0.235 (0.208, 0.097, 0.084, 0.895)	209	235
8	(0.30, 0.80, 0.80) (0.65, 0.15, 0.15)	2.475 (2.499, 0.325, 0.326, 0.949)	1.000 (1.055, 0.358, 0.347, 0.927)	1.000 (1.176, 0.825, 1.223, 0.907)	245	274
9	(0.30, 0.20, 0.20) (0.65, 0.55, 0.40)	0.414 (0.413, 0.061, 0.060, 0.944)	1.000 (1.206, 0.986, 1.649, 0.905)	1.563 (1.636, 0.542, 0.702, 0.937)	268	325
	Very high/low success probability values					
10	(0.10, 0.10, 0.10) (0.10, 0.10, 0.10)	1.000 (1.017, 0.185, 0.178, 0.948)	1.000 (1.114, 0.594, 0.707, 0.920)	1.000 (1.089, 0.533, 0.579, 0.913)	450	450
11	(0.05, 0.05, 0.05) (0.05, 0.05, 0.05)	1.000 (1.026, 0.249, 0.250, 0.952)	1.000 (1.146, 0.601, 0.816, 0.951)	1.000 (1.110, 0.531, 0.674, 0.944)	475	475
12	(0.90, 0.90, 0.90) (0.90, 0.90, 0.90)	1.000 (1.065, 0.355, 0.328, 0.930)	1.000 (1.196, 0.917, 0.980, 0.892)	1.000 (1.200, 1.418, 4.662, 0.894)	50	50
13	(0.95, 0.95, 0.95) (0.95, 0.95, 0.95)	1.000 (1.135, 0.602, 0.590, 0.905)	1.000 (1.642, 2.898, 4.726, 0.855)	1.000 (1.585, 2.842, 4.491, 0.858)	25	25
14	(0.35, 0.95, 0.05) (0.65, 0.90, 0.10)	0.760 (0.735, 0.186, 0.931, 0.997)	82.819 (200.255, 157.539, 2617.842, 0.949)	27.000 (63.353, 42.085, 269.637, 0.953)	125	254
15	(0.45, 0.05, 0.95) (0.25, 0.90, 0.10)	1.329 (1.334, 0.300, 1.539, 0.996)	0.010 (0.012, 0.010, 0.027, 0.999)	27.000 (65.787, 45.008, 339.797, 0.956)	148	274
16	(0.95, 0.95, 0.05) (0.90, 0.10, 0.90)	1.683 (1.875, 0.724, 5.531, 0.993)	82.819 (179.597, 113.899, 1462.250, 0.951)	0.037 (0.029, 0.026, 0.044, 0.999)	45	173

Table 2.9: Estimated first-stage ($\hat{\tau}_A$) and second-stage ($\hat{\tau}_{AC:AD}, \hat{\tau}_{BE:BF}$) allocation ratios along with corresponding SSE, ASE and CP based on 5000 simulations. τ_A, $\tau_{AC:AD}$, and $\tau_{BE:BF}$ denote true values of optimum allocation ratios. Here, $\gamma_A = 0.4$, and $\gamma_B = 0.3$, and the sample size is **1000** using objective function as **Relative-Risk**. It also shows the total expected number of failures at the end of SMART using optimal adaptive allocation (proposed method) and equal randomization.

No.	$(p_{AA'}, p_{AC}, p_{AD})$ $(p_{BB'}, p_{BE}, p_{BF})$	τ_A ($\hat{\tau}_A$, SSE, ASE, $\widehat{CP}$)	$\tau_{AC:AD}$ ($\hat{\tau}_{AC:AD}$, SSE, ASE, $\widehat{CP}$)	$\tau_{BE:BF}$ ($\hat{\tau}_{BE:BF}$, SSE, ASE, $\widehat{CP}$)	Total expected number of failures	
					Optimal	Equal
1	(0.20, 0.15, 0.15) (0.45, 0.65, 0.75)	0.235 (0.232, 0.030, 0.030, 0.943)	1.000 (1.139, 0.725, 1.007, 0.912)	0.665 (0.668, 0.109, 0.107, 0.940)	460	603
2	(0.30, 0.80, 0.20) (0.25, 0.60, 0.55)	1.006 (1.050, 0.116, 0.135, 0.960)	8.000 (12.591, 11.660, 28.489, 0.951)	1.175 (1.199, 0.218, 0.212, 0.943	479	553
3	(0.80, 0.40, 0.60) (0.35, 0.15, 0.15)	1.512 (1.527, 0.151, 0.147, 0.943)	0.544 (0.546, 0.095, 0.092, 0.933)	1.889 (1.969, 0.557, 0.660, 0.945)	413	445
4	(0.30, 0.20, 0.80) (0.25, 0.15, 0.60)	1.301 (1.326, 0.148, 0.163, 0.961)	0.125 (0.114, 0.044, 0.036, 0.860)	0.235 (0.220, 0.070, 0.057, 0.882)	492	622
5	(0.30, 0.20, 0.20) (0.65, 0.15, 0.60)	0.442 (0.435, 0.044, 0.043, 0.937)	1.000 (1.051, 0.391, 0.407, 0.931)	0.235 (0.228, 0.052, 0.044, 0.909)	537	651
6	(0.30, 0.60, 0.45) (0.25, 0.60, 0.60)	0.846 (0.847, 0.077, 0.076, 0.944)	1.588 (1.635, 0.339, 0.323, 0.946)	1.000 (1.016, 0.178, 0.174, 0.941)	529	536
7	(0.30, 0.80, 0.80) (0.65, 0.15, 0.60)	1.329 (1.305, 0.126, 0.123, 0.936)	1.000 (1.035, 0.272, 0.263, 0.934)	0.235 (0.220, 0.068, 0.057, 0.887)	418	471
8	(0.30, 0.80, 0.80) (0.65, 0.15, 0.15)	2.475 (2.494, 0.228, 0.226, 0.950)	1.000 (1.028, 0.234, 0.231, 0.939)	1.000 (1.146, 0.343, 0.319, 0.932)	489	549
9	(0.30, 0.20, 0.20) (0.65, 0.55, 0.40)	0.414 (0.411, 0.042, 0.042, 0.945)	1.000 (1.044, 0.353, 0.355, 0.935)	1.563 (1.586, 0.230, 0.220, 0.941)	549	616
Very high/low success probability values						
10	(0.10, 0.10, 0.10) (0.10, 0.10, 0.10)	1.000 (1.007, 0.122, 0.119, 0.944)	1.000 (1.037, 0.295, 0.267, 0.938)	1.000 (1.030, 0.266, 0.240, 0.941)	900	900
11	(0.05, 0.05, 0.05) (0.05, 0.05, 0.05)	1.000 (1.017, 0.167, 0.163, 0.956)	1.000 (1.062, 0.398, 0.413, 0.938)	1.000 (1.062, 0.383, 0.382, 0.936)	950	950
12	(0.90, 0.90, 0.90) (0.90, 0.90, 0.90)	1.000 (1.023, 0.221, 0.212, 0.935)	1.000 (1.078, 0.480, 0.446, 0.914)	1.000 (1.064, 0.422, 0.395, 0.921)	100	100
13	(0.95, 0.95, 0.95) (0.95, 0.95, 0.95)	1.000 (1.061, 0.379, 0.334, 0.920)	1.000 (1.256, 2.392, 3.991, 0.887)	1.000 (1.188, 1.180, 1.168, 0.899)	50	50
14	(0.35, 0.95, 0.05) (0.65, 0.90, 0.10)	0.760 (0.755, 0.166, 0.599, 0.995)	82.819 (172.191, 89.869, 976.680, 0.956)	27.000 (54.425, 36.587, 153.248, 0.955)	242	508
15	(0.45, 0.05, 0.95) (0.25, 0.90, 0.10)	1.329 (1.343, 0.274, 1.005, 0.996)	0.010 (0.009, 0.008, 0.019, 0.999)	27.000 (59.231, 39.071, 197.466, 0.949)	288	548
16	(0.95, 0.95, 0.05) (0.90, 0.10, 0.90)	1.683 (1.900, 0.675, 3.536, 0.990)	82.819 (163.388, 80.285, 695.320, 0.958)	0.037 (0.030, 0.021, 0.030, 0.999)	83	348

Table 2.10: Estimated first-stage ($\hat{\tau}_A$) and second-stage ($\hat{\tau}_{AC:AD}, \hat{\tau}_{BE:BF}$) allocation ratios along with corresponding SSE, ASE and CP based on 5000 simulations. τ_A, $\tau_{AC:AD}$, and $\tau_{BE:BF}$ denote true values of optimum allocation ratios. Here, $\gamma_A = 0.4$, and $\gamma_B = 0.3$, and the sample size is **2000** using objective function as **Relative-Risk**. It also shows the total expected number of failures at the end of SMART using optimal adaptive allocation (proposed method) and equal randomization.

No.	$(p_{AA'}, p_{AC}, p_{AD})$ $(p_{BB'}, p_{BE}, p_{BF})$	τ_A ($\hat{\tau}_A$, SSE, ASE, $\widehat{CP}$)	$\tau_{AC:AD}$ ($\hat{\tau}_{AC:AD}$, SSE, ASE, $\widehat{CP}$)	$\tau_{BE:BF}$ ($\hat{\tau}_{BE:BF}$, SSE, ASE, $\widehat{CP}$)	Total expected number of failures	
					Optimal	Equal
1	(0.20, 0.15, 0.15) (0.45, 0.65, 0.75)	0.235 (0.233, 0.021, 0.021, 0.945)	1.000 (1.039, 0.318, 0.298, 0.931)	0.665 (0.668, 0.076, 0.075, 0.947)	916	1205
2	(0.30, 0.80, 0.20) (0.25, 0.60, 0.55)	1.006 (1.023, 0.070, 0.069, 0.955)	8.000 (9.580, 5.909, 9.278, 0.958)	1.175 (1.185, 0.146, 0.145, 0.949	958	1104
3	(0.80, 0.40, 0.60) (0.35, 0.65, 0.45)	1.512 (1.518, 0.105, 0.103, 0.945)	0.544 (0.544, 0.785, 0.769, 0.945)	1.889 (1.927, 0.686, 0.965, 0.910)	365	930
4	(0.30, 0.20, 0.80) (0.25, 0.15, 0.60)	1.301 (1.309, 0.083, 0.081, 0.956)	0.125 (0.120, 0.029, 0.025, 0.900)	0.235 (0.228, 0.046, 0.040, 0.908)	983	1243
5	(0.30, 0.20, 0.20) (0.65, 0.15, 0.60)	0.442 (0.439, 0.030, 0.030, 0.943)	1.000 (1.016, 0.178, 0.166, 0.941)	0.235 (0.233, 0.034, 0.031, 0.927)	1077	1302
6	(0.30, 0.60, 0.45) (0.25, 0.60, 0.60)	0.846 (0.846, 0.053, 0.053, 0.951)	1.588 (1.609, 0.223, 0.219, 0.947)	1.000 (1.004, 0.120, 0.120, 0.945)	1056	1071
7	(0.30, 0.80, 0.80) (0.65, 0.15, 0.60)	1.329 (1.321, 0.083, 0.083, 0.946)	1.000 (1.012, 0.178, 0.178, 0.944)	0.235 (0.230, 0.044, 0.040, 0.922)	836	941
8	(0.30, 0.80, 0.80) (0.65, 0.15, 0.15)	2.475 (2.489, 0.161, 0.159, 0.946)	1.000 (1.011, 0.157, 0.158, 0.947)	1.000 (1.018, 0.182, 0.171, 0.941)	975	1099
9	(0.30, 0.20, 0.20) (0.65, 0.55, 0.40)	0.414 (0.413, 0.030, 0.030, 0.942)	1.000 (1.017, 0.179, 0.169, 0.942)	1.563 (1.576, 0.157, 0.153, 0.946)	1098	1232
	Very high/low success probability values					
10	(0.10, 0.10, 0.10) (0.10, 0.10, 0.10)	1.000 (1.004, 0.085, 0.083, 0.943)	1.000 (1.013, 0.165, 0.159, 0.945)	1.000 (1.009, 0.152, 0.145, 0.947)	1800	1800
11	(0.05, 0.05, 0.05) (0.05, 0.05, 0.05)	1.000 (1.006, 0.113, 0.111, 0.948)	1.000 (1.031, 0.250, 0.234, 0.949)	1.000 (1.020, 0.223, 0.209, 0.944)	1900	1900
12	(0.90, 0.90, 0.90) (0.90, 0.90, 0.90)	1.000 (1.008, 0.146, 0.145, 0.940)	1.000 (1.036, 0.294, 0.281, 0.928)	1.000 (1.033, 0.266, 257, 0.940)	200	200
13	(0.95, 0.95, 0.95) (0.95, 0.95, 0.95)	1.000 (1.019, 0.219, 0.211, 0.936)	1.000 (1.087, 0.489, 0.448, 0.924)	1.000 (1.073, 0.420, 0.396, 0.922)	100	100
14	(0.35, 0.95, 0.05) (0.65, 0.90, 0.10)	0.760 (0.774, 0.149, 0.399, 0.992)	82.819 (158.768, 76.379, 568.527, 0.950)	27.000 (45.587, 30.845, 84.325, 0.954)	477	1015
15	(0.45, 0.05, 0.95) (0.25, 0.90, 0.10)	1.329 (1.362, 0.246, 0.667, 0.989)	0.010 (0.009, 0.007, 0.013, 0.999)	27.000 (50.493, 33.603, 111.278, 0.958)	566	1096
16	(0.95, 0.95, 0.05) (0.90, 0.10, 0.90)	1.683 (1.910, 0.622, 2.322, 0.980)	82.819 (152.549, 70.758, 425.214, 0.949)	0.037 (0.030, 0.018, 0.020, 0.998)	160	699

2.6.1 Demerits of Simultaneous Optimization

In the proposed approach, the first-stage optimal adaptive allocation ratio is obtained recursively, passing the optimal adaptive allocation information backward from the second stage to the first stage. However, it is natural to consider simultaneous optimization to find the values of all three allocation ratios. To illustrate the importance of moving through stages instead of simultaneous optimization, we have done simulation studies to find the optimal adaptive allocation ratios $(\tau_A, \tau_{AC:AD}, \tau_{BE:BF})$ simultaneously by minimizing $F_1(\tau_A, \tau_{AC:AD}, \tau_{BE:BF})$ under the asymptotic variance constraint $avar\{g(\hat{p}_A, \hat{p}_B)\} = \epsilon_1$, where,

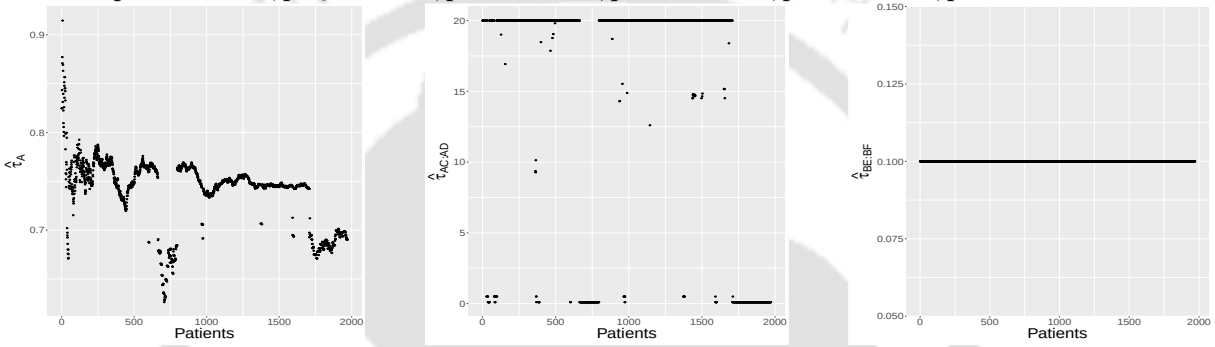
$$F_1(\tau_A, \tau_{AC:AD}, \tau_{BE:BF}) = \frac{\tau_A}{1+\tau_A} n\gamma_A q_{AA'} + \frac{1}{1+\tau_A} n\gamma_B q_{BB'} + F_2(\tau_{AC:AD}) + F_2(\tau_{BE:BF}), \tag{2.4}$$

where, $F_2(\tau_{AC:AD}) = \frac{n\tau_A(1-\gamma_A)}{(1+\tau_A)(1+\tau_{AC:AD})}\left(\tau_{AC:AD} q_{AC} + q_{AD}\right)$ and $F_2(\tau_{BE:BF}) = \frac{n(1-\gamma_B)}{(1+\tau_A)(1+\tau_{BE:BF})}\left(\tau_{BE:BF} q_{BE} + q_{BF}\right)$. First, we have done the constraint optimization of (2.4), with no upper bounds on the values of allocation ratios, namely τ_A, $\tau_{AC:AD}$, and $\tau_{BE:BF}$ (lower bounds are taken as zero). We have used the built-in optimization function, *optim* in the R software for this simulation. Here, we observe that the estimated values of optimal adaptive allocation ratios may be very high or very low, which may not be realistic in most practical scenarios. For example, we have found scenarios where one of the optimal adaptive allocation ratios (using constraint optimization of (2.4)) is greater than 50 or less than 0.01, which makes the corresponding adaptive randomization probabilities to be close to 1 or 0, respectively. Therefore, we have also done the constraint optimization of (2.4), with upper and lower bounds of the values of allocation ratios.

Now, we consider the constraint optimization of (2.4), with lower and upper bounds of the values of allocation ratios as 0.1 and 20, respectively. In this approach, we have seen scenarios where the optimal adaptive allocation ratio has not converged to a specific value. Figures 2.4 and 2.5 demonstrate four scenarios (in each row) with different combinations of success probabilities. We observe that $\hat{\tau}_A$ and $\hat{\tau}_{AC:AD}$ have not converged to a specific value(s) in each of the four scenarios. In Figures, 2.4(b), 2.4(e), 2.5(b) and 2.5(e) the difference between the estimated lowest and highest values of the allocation ratio $(\tau_{AC:AD})$ is large, even after 1000 samples. These four scenarios (each row of Figures 2.4 and 2.5) are one of the 5000 simulations. There are many such scenarios among the 5000 simulations. Therefore, we can say that finding optimal adaptive allocation ratios $(\tau_A, \tau_{AC:AD}, \tau_{BE:BF})$ simultaneously by minimizing (2.4) (with lower and upper bounds) may not ensure the convergence of the estimated optimal adaptive allocation ratios.

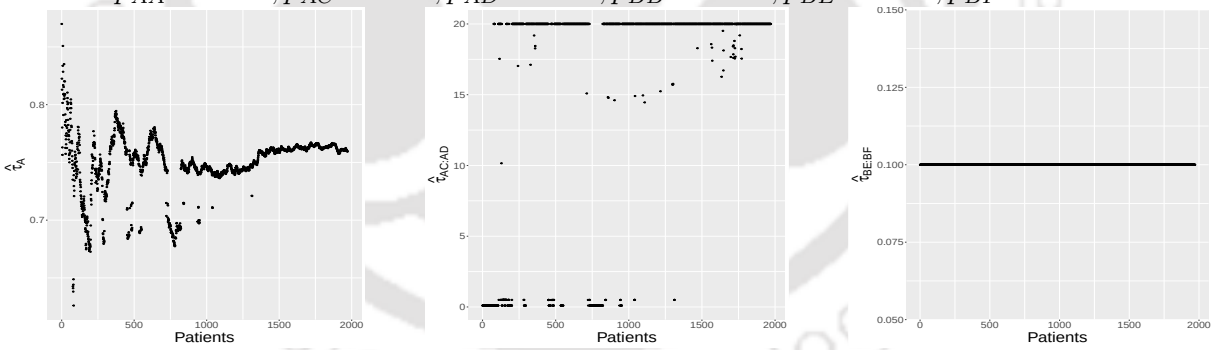
$\gamma_A = 0.4, \gamma_B = 0.3$

$p_{AA'} = 0.20, p_{AC} = 0.65, p_{AD} = 0.35, p_{BB'} = 0.45, p_{BE} = 0.35, p_{BF} = 0.65$



(a) $\hat{\tau}_A$ (b) $\hat{\tau}_{AC:AD}$ (c) $\hat{\tau}_{BE:BF}$

$p_{AA'} = 0.30, p_{AC} = 0.65, p_{AD} = 0.35, p_{BB'} = 0.45, p_{BE} = 0.45, p_{BF} = 0.65$

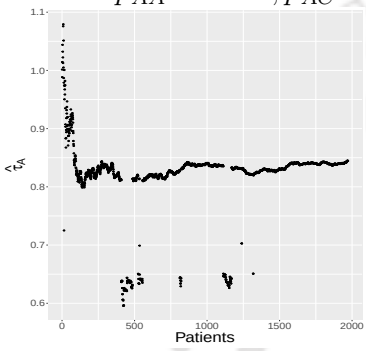


(d) $\hat{\tau}_A$ (e) $\hat{\tau}_{AC:AD}$ (f) $\hat{\tau}_{BE:BF}$

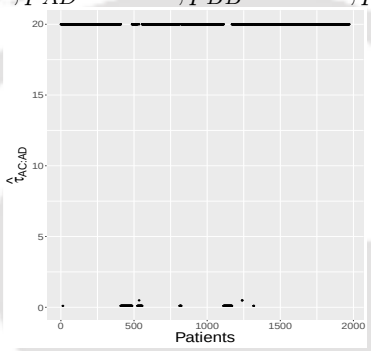
Figure 2.4: Convergence of allocation proportions using numerical optimization techniques

$$\gamma_A = 0.4, \gamma_B = 0.3$$

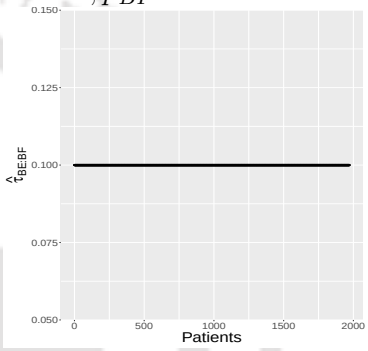
$$p_{AA'} = 0.30, p_{AC} = 0.65, p_{AD} = 0.35, p_{BB'} = 0.65, p_{BE} = 0.25, p_{BF} = 0.75$$



(a) $\hat{\tau}_A$

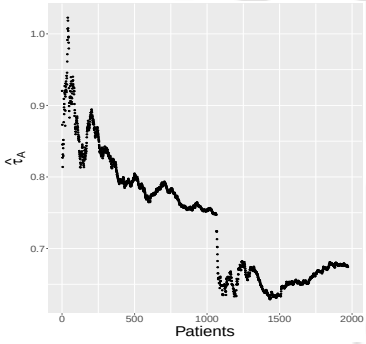


(b) $\hat{\tau}_{AC:AD}$

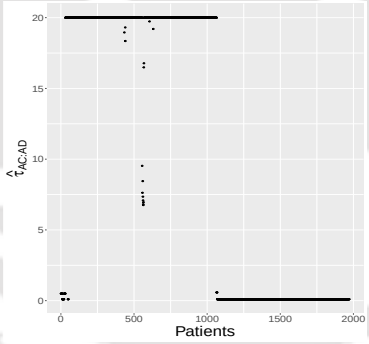


(c) $\hat{\tau}_{BE:BF}$

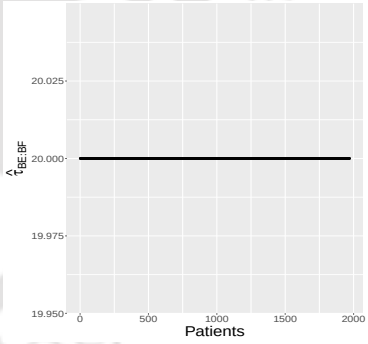
$$p_{AA'} = 0.20, p_{AC} = 0.65, p_{AD} = 0.35, p_{BB'} = 0.45, p_{BE} = 0.65, p_{BF} = 0.25$$



(d) $\hat{\tau}_A$



(e) $\hat{\tau}_{AC:AD}$

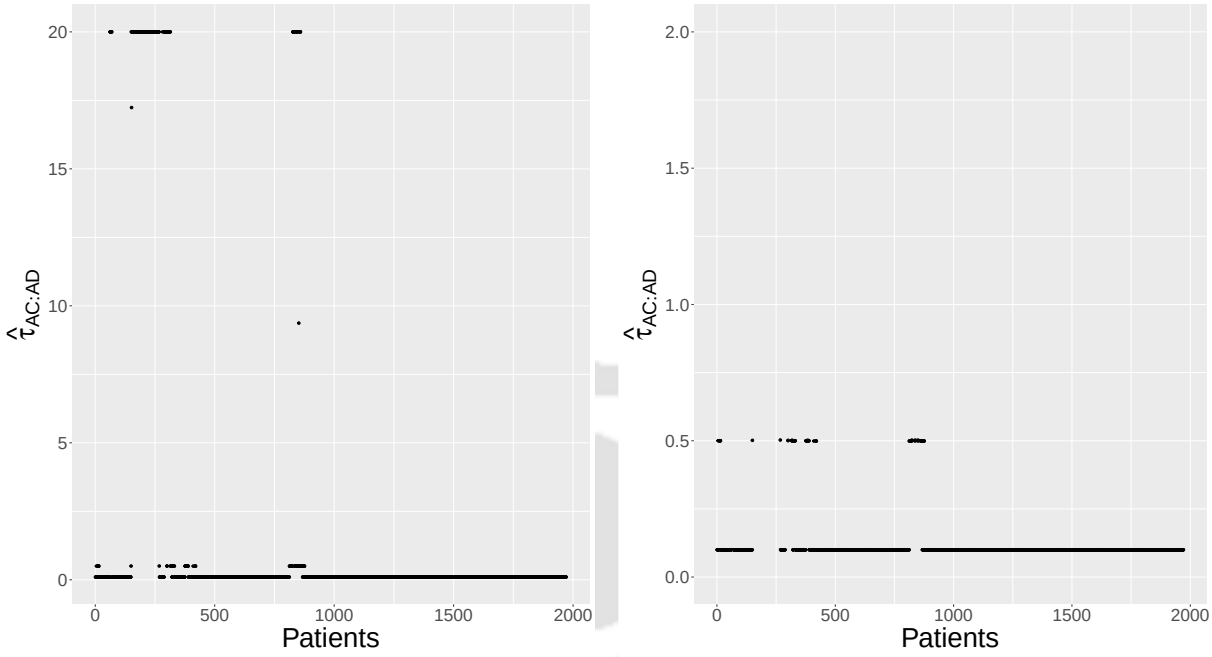


(f) $\hat{\tau}_{BE:BF}$

Figure 2.5: Convergence of allocation proportions using numerical optimization techniques (Contd.)

$$\gamma_A = 0.4, \gamma_B = 0.3$$

$$p_{AA'} = 0.20, p_{AC} = 0.65, p_{AD} = 0.35, p_{BB'} = 0.45, p_{BE} = 0.35, p_{BF} = 0.65$$



(a) $\hat{\tau}_{AC:AD}$

(b) Magnified version of the y-axis from Figure 2.6(a)

Figure 2.6: Convergence of $\hat{\tau}_{AC:AD}$, in a scenario, when it is expected $\tau_{AC:AD} > 1$.

In addition to the issues of convergence discussed above, we also observed scenarios where more patients are getting treatment having less success probability compared to the treatment having higher success probability using the estimated optimal adaptive allocation ratios by minimizing (2.4). It contradicts the objective of adaptive randomization to provide better treatment to more patients during the trial period (Robertson et al., 2023). In Figure 2.6, we consider a scenario (one of the 5000 simulations) where $p_{AC} = 0.65$ and $p_{AD} = 0.35$. Because $p_{AC} > p_{AD}$, at the second stage, we expect more patients to be allocated to treatment C compared to treatment D among the patients who obtained treatment A at the first stage and became non-responders. Therefore, in this scenario, we also expect the estimated optimal adaptive allocation ratio to be more than 1. However, in Figure 2.6(b), we observe that the estimated value of the optimal adaptive allocation ratio, $\hat{\tau}_{AC:AD}$ is close to 0.1. Hence, the second-stage random allocation process allocates more patients to treatment D compared to treatment C, among the patients who obtained treatment A at the first stage and became non-responders.

In the proposed approach, we have shown both theoretically and empirically (using simulation studies) that the estimated optimal adaptive allocation ratios converge to their respective true values. Also, in the simulation studies, we noticed that the proposed random allocation process allocates more patients to the treatment with a higher success

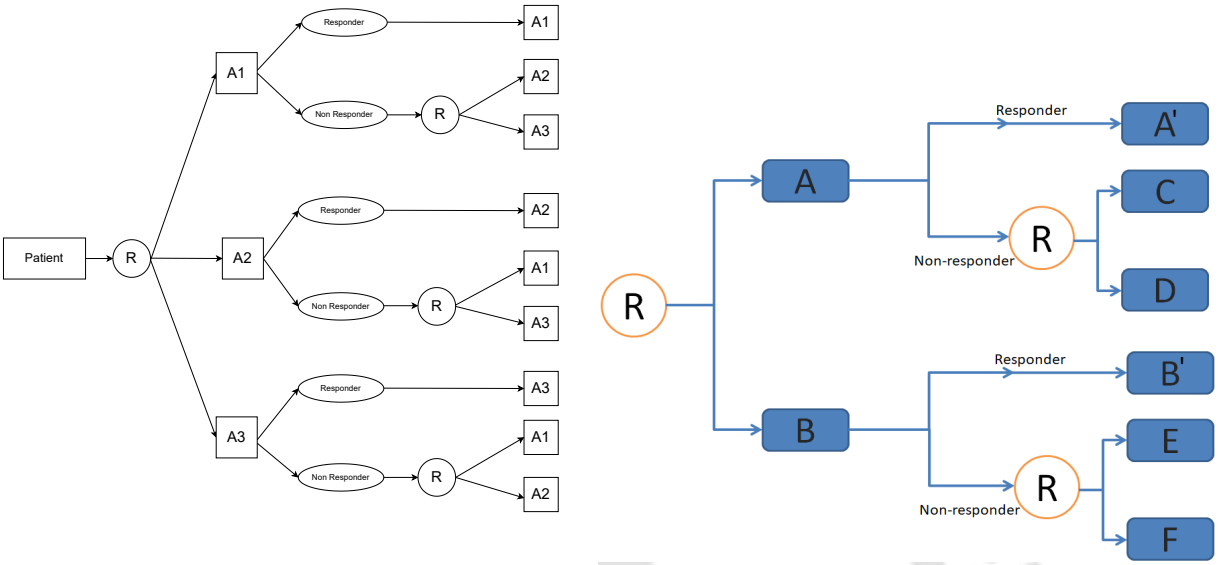
probability compared to the treatment having a lower success probability.

Note that the two constraints $avar\{g(\hat{p}_{T_1T_2}, \hat{p}_{T_1T_2^*})\} = \epsilon_2$ and $avar\{g(\hat{p}_A, \hat{p}_B)\} = \epsilon_1$ are dependent. However, it can be seen the dependency is one way only, by design. Specifically, the first-stage constraint, $avar\{g(\hat{p}_A, \hat{p}_B)\} = \epsilon_1$, is dependent on the second-stage constraint, $avar\{g(\hat{p}_{T_1T_2}, \hat{p}_{T_1T_2^*})\} = \epsilon_2$; but not the other way round. Therefore to minimize the total expected number of failures from the entire SMART, we first develop the optimal adaptive allocation ratios for the second-stage randomization processes using the methodology proposed by Rosenberger et al. (2001) for two-arms RCT with binary outcome. Then the first-stage optimal adaptive allocation ratio is obtained recursively, passing the optimal adaptive allocation information backward from the second stage to the first stage. This process incorporates the dependency of the first-stage constraint, $avar\{g(\hat{p}_A, \hat{p}_B)\} = \epsilon_1$, on the second-stage constraint, $avar\{g(\hat{p}_{T_1T_2}, \hat{p}_{T_1T_2^*})\} = \epsilon_2$. Note that the idea of recursively passing "optimal" information from the second stage to the first stage is also used in the Q-learning approach that is widely used to find the stage-specific optimal dynamic treatment regimes (or adaptive interventions (AIs) or adaptive treatment strategies) in SMART design (Murphy, 2003; Chakraborty and Moodie, 2013; Chakraborty et al., 2016). In section 3.4.2 of Chakraborty and Moodie (2013), they have discussed "Why Move Through Stages" instead of simultaneous optimization at once in the context of Q-learning, as there is a possibility of bias in the estimation of stage 1 treatment effect; they argued this arises as a consequence of collider-stratification bias or Berkson's paradox.

2.6.2 Comparison with Existing Adaptive SMART techniques

In Section 2.6 we have compared the proposed optimal adaptive allocation scheme with equal randomization to show that it is performing better than the latter. Here, we have compared the proposed methodology with the Response Adaptive SMART (RA-SMART) from Wang et al. (2022).

Figure 2.7 shows the schematic diagrams of RA-SMART (Figure 2.7(a)) and the proposed adaptive SMART (Figure 2.7(b)). It is evident from Figure 2.7 that two adaptive designs are substantially different from each other with respect to the number of arms in the first stage (three versus two). Also, RA-SMART (Wang et al., 2022) assumed that the same set of treatments (A_1, A_2, A_3) are available in the first and second stages. Whereas, in the proposed adaptive SMART, the second-stage treatments (C/D or E/F) for non-responders may be different from their first-stage treatment (A or B). Hence, to make both designs comparable, we have considered certain specific combinations of success probabilities. Let in the RA-SMART design (Figure 2.7(a)), the success probability of treatments, A_1 and A_2 be equal to each other, so that both the arms with first-stage intervention A_1, and A_2 emulate each other. We also assume that the response rates (γ_A, γ_B) of treatments



(a) Schematic diagram of RA-SMART design (Wang et al., 2022).

(b) Schematic diagram of proposed Optimal Adaptive SMART design.

Figure 2.7: Schematic Diagrams

A, and B (Figure 2.7(b)) are equal to the success probabilities ($\pi_1^{A_1} = \pi_1^{A_2}, \pi_1^{A_3}$) of the first-stage treatments (Figure 2.7(a)) A_1 (also A_2) and A_3, respectively. Note that in the RA-SMART, the user (clinician/statistician) has to provide the second-stage randomization probabilities Q'_{jl} (as used in Wang et al. (2022)) in favor of better treatment (decided from the estimated first-stage success probabilities of (A_1, A_2, A_3)), where $j, l \in \{1, 2, 3\}$. To make the two schemes (Figure 2.7(a) and Figure 2.7(b)) comparable, we have taken $Q'_{12} = Q'_{21} = \frac{\sqrt{p_{AC}}}{\sqrt{p_{AC}}+\sqrt{p_{AD}}}$, which is the optimal adaptive allocation probability in favor of treatment sequence (A, C) obtained using the proposed adaptive SMART design. Note that $Q'_{31} = \frac{1}{2}$ as A_1 and A_2 are equivalent with respect to the success probabilities. We also assume $p_{AA'} = p_{BB'} = 1$, $\gamma_A = p_{AC} = p_{BE} = p_{BF} = \pi_1^{A_1} = \pi_1^{A_2}$, $\gamma_B = p_{AD} = \pi_1^{A_3}$. Also, for RA-SMART (Wang et al., 2022), a pre-decided number of patients, n_0, (which is less than the total sample size) is considered to evaluate the effectiveness of the initial treatments. It is equivalent to what we have also defined as the initial period of equal randomization (non-adaptive), termed the "burn-in" (or "warm-up" or "warm-start") period. We have taken $n_0 = 120$ (one of the values considered in Wang et al. (2022)) in all the scenarios for both SMART designs. To compare the said two SMART designs with respect to the corresponding equal randomization schemes, we define

$$\text{Gain (\%)} = 100 \times \frac{\text{Total expected number of failures in equal randomization} - \text{Total expected number of failures in adaptive SMART design}}{\text{Total expected number of failures in equal randomization}}.$$

Table 2.11: The total expected number of failures at the end of SMART using optimal adaptive allocation (proposed method), equal randomization (using both designs), and RA-SMART (Wang et al., 2022). The sample size (n) is 600, and $n_0 = 120$ for both methods. The objective function used for the proposed method is simple difference.

No.	(γ_A, γ_B)	$(p_{AA'}, p_{AC}, p_{AD})$ $(p_{BB'}, p_{BE}, p_{BF})$	$(\pi_1^{A_1}, \pi_1^{A_2}, \pi_1^{A_3})$	Total expected number of failures				Gain (%)	
				Proposed	Equal (Proposed)	RA-SMART	Equal (RA-SMART)	Proposed	RA-SMART
1	(0.30, 0.40)	(1.00, 0.30, 0.40) (1.00, 0.30, 0.30)	(0.30, 0.30, 0.40)	250	251	266	266	0.40	0
2	(0.30, 0.50)	(1.00, 0.30, 0.50) (1.00, 0.30, 0.30)	(0.30, 0.30, 0.50)	221	224	237	238	1.34	0.42
3	(0.30, 0.15)	(1.00, 0.30, 0.15) (1.00, 0.30, 0.30)	(0.30, 0.30, 0.15)	314	318	333	336	1.26	0.89
4	(0.45, 0.15)	(1.00, 0.45, 0.15) (1.00, 0.45, 0.45)	(0.45, 0.45, 0.15)	235	242	240	248	2.89	3.23

Table 2.11 shows a notable gain (%) for the proposed Optimal Adaptive Allocation procedure over RA-SMART, except in row 4. In row 4 of Table 2.11, the gain (%) with respect to corresponding equal randomization is better for the RA-SMART (3.23%) compared to the proposed Optimal Adaptive method (2.89%). However, the total expected number of failures is lower for the proposed Optimal Adaptive method compared to the RA-SMART. Note that, in this simulation for RA-SMART, we have considered $Q'_{12} = Q'_{21} = \frac{\sqrt{p_{AC}}}{\sqrt{p_{AC}}+\sqrt{p_{AD}}}$, which is the optimal adaptive allocation probability in favor of treatment sequence (A, C), derived using the proposed method. However, in practice, it will be unknown. Therefore, the RA-SMART uses the optimal adaptive allocation probability (obtained from our proposed method) for each allocation after $n_0 = 120$. However, in the proposed method, the optimal adaptive allocation probability is unknown, and an optimal adaptive allocation procedure is developed so that corresponding probability estimates converge to the respective true values. The convergence may not happen immediately after $n_0 = 120$ in the proposed case, which explains the higher gain(%) in row 4. Note that, in row 4, the difference between p_{AC} and p_{AD} is large (0.30), which is unlikely in practice. In rows 1-3, when the difference between p_{AC} and p_{AD} is comparatively small, we observe that the proposed method is doing better than RA-SMART both in terms of the total expected number of failures and gain (%).

In RA-SMART, consider a scenario where two success probabilities (say $\pi_1^{A_1} = \pi_1^{A_2} = 0.40$ and $\pi_1^{A_3} = 0.38$) are close to each other. In this case, the choice of $Q'_{12} = Q'_{21}$, which is subjective (and fixed) and based on the estimated success probabilities obtained from the first n_0 samples only, may result in allocating more patient to the inferior treatment. However, the proposed method will converge to the true optimal adaptive allocation

probability over time, even if the initial estimates based on the first n_0 samples are biased. Therefore, the proposed method does not depend on any subjective choice of the allocation probability while conducting the trial.

2.6.3 Power Comparison

In this section, we have made a power comparison study considering the sample size the same as that of the corresponding non-adaptive SMART design. Here, in Table 2.12, we have shown empirically that there is no loss of statistical power while testing, $H_0 : p_{d_1} = p_{d_3}$ vs $H_1 : p_{d_1} \neq p_{d_3}$, where $d_1 = (A, A'^R C^{1-R})$, and $d_3 = (B, B'^R E^{1-R})$ based on 5000 simulations, compared to a corresponding non-adaptive SMART design. For the above testing of the hypothesis, we have considered the estimated sample size of a similar non-adaptive SMART design with binary outcome (Ghosh et al., 2015). Here, for calculating the non-adaptive sample size, we have considered the nominal power to be 80% and the type-I error rate as 0.05. We have conducted the simulation study applying the proposed adaptive allocation procedure till the calculated sample size for the corresponding non-adaptive SMART. Table 2.12 shows that there is no loss in empirical power when considering the same sample size as of non-adaptive SMART design.

Table 2.12: Estimated Power of test for testing $H_0 : p_{d_1} = p_{d_3}$ vs $H_1 : p_{d_1} \neq p_{d_3}$, where $d_1 = (A, A'^R C^{1-R})$, and $d_3 = (B, B'^R E^{1-R})$ based on 5000 simulations. Here, $\gamma_A = 0.4$, *and* $\gamma_B = 0.3$.

No.	$(p_{AA'}, p_{AC}, p_{AD})$ $(p_{BB'}, p_{BE}, p_{BF})$	$(p_{d_1} = p_{(A,A'^R C^{1-R})})$ $(p_{d_3} = p_{(B,B'^R E^{1-R})})$	Sample Size (N): using non-adaptive SMART design	Empirical Power
1	(0.45, 0.80, 0.65) (0.50, 0.40, 0.45)	(0.66) (0.43)	232	0.998
2	(0.35, 0.85, 0.65) (0.65, 0.35, 0.45)	(0.65) (0.44)	278	0.999
3	(0.35, 0.20, 0.35) (0.55, 0.35, 0.45)	(0.26) (0.41)	501	0.998
4	(0.35, 0.20, 0.35) (0.75, 0.45, 0.45)	(0.26) (0.54)	146	0.995

2.6.4 Normality Assumption Analysis

In this section, we try to understand the sample size (n), for which the normality assumptions hold for all the optimal adaptive allocation ratios. Figure 2.8, 2.9, and 2.10 show

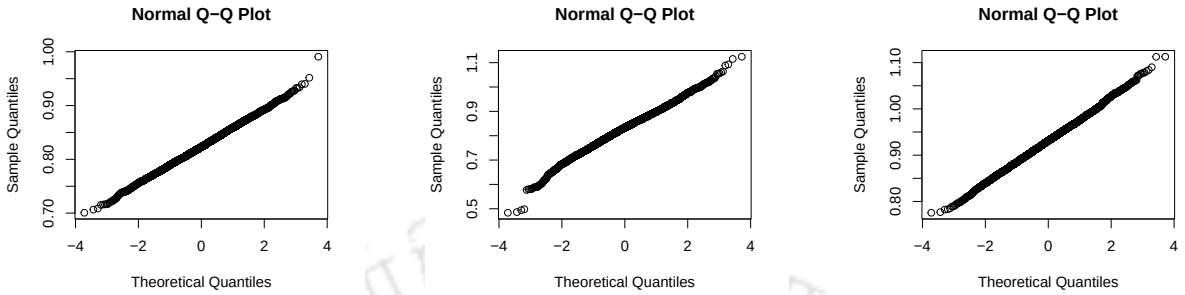
(with $\gamma_A = 0.4$ and $\gamma_B = 0.3$ in all three Figures) the quantile-quantile (Q-Q) plots for each of the optimal adaptive allocation ratios ($\tau_A, \tau_{AC:AD}$, and $\tau_{BE:BF}$) with different sets of success probabilities along with different sample size. In each of the three Figures, it can be observed that for a sample size of around 500, the normal approximation can be assumed. However, even for a sample size less than 500, the Q-Q plot of τ_A indicates good normal approximations, while the same is not noticed for optimal adaptive allocation ratios, $\tau_{AC:AD}$ and $\tau_{BE:BF}$. This is due to less number of participants allocated to the treatment sequence of (A, C) and (A, D) compared to the number of participants allocated to the first-stage treatment A, by design. The same is also true for the treatment sequences (B, E) and (B, F) with respect to the first-stage treatment B.

The set of success probabilities in Figure 2.10 and Figure 2.11 are exactly the same. However, the response rates (γ_A, γ_B) in Figure 2.10 and Figure 2.11 are (0.4, 0.3) and (0.2, 0.1), respectively. Note that, a lower response rate helps to have more participants in the non-responder arms (e.g., (A, C) and (A, D)). For example, in Figure 2.11(e) with a total sample size of 400, the normal approximation (from Q-Q plot) looks similar to that of in Figure 2.10(e) with a total sample size of 500. This is because more participants (proportionally) have been allocated to the non-responder arms, (A, C) and (A, D) in Figure 2.11 compared to Figure 2.10. Intuitively, the normal approximations will hold (reasonably) if each treatment arm (T_1, T_2) has a sufficiently high number of participants.

2.7 Application to the M-bridge Data

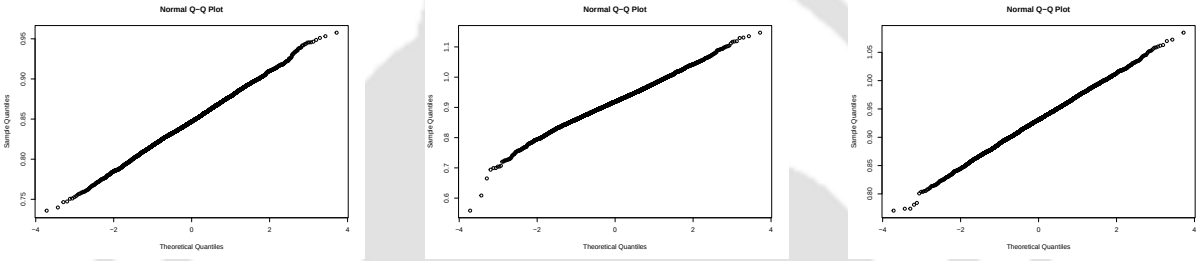
In this section, we demonstrate an application of the developed adaptive allocation (randomization) procedure using M-bridge data (Patrick et al., 2021). The binary primary outcome is based on the frequency of consuming 4/5+ drinks by the participants within a two-hour period in the past 30 days in any of the three follow-ups at the end of the study. If the frequency is one or more, then the binary outcome is 0 (failure); otherwise, it is 1 (success). Note that the M-bridge study used equal randomizations both at the first- and the second-stage randomization processes. Here, the objective is to show what benefit would have happened if the adaptive allocation procedure had been used instead of equal randomization during the allotment of the participants to different treatments in the M-bridge study. Specifically, we show that the developed procedure would have resulted in fewer failures, and more participants would have gotten better DTRs (having a higher chance of success). To retrospectively apply the developed adaptive allocation procedure in the M-bridge study, first, we arrange (in increasing order) all the 521 intervention group participants according to their entry date and time in the study. Note that 70 participants who did not appear in any follow-up studies or were administered both treatment options, namely online health coach and resource email at the second stage, were removed from the current analysis. For illustration purposes, let us consider

$$\gamma_A = 0.4, \gamma_B = 0.3$$
$$p_{AA'} = 0.25, p_{AC} = 0.55, p_{AD} = 0.65, p_{BB'} = 0.50, p_{BE} = 0.65, p_{BF} = 0.75$$
$$n = 500$$



(a) $\hat{\tau}_A$ (b) $\hat{\tau}_{AC:AD}$ (c) $\hat{\tau}_{BE:BF}$

$$n = 600$$



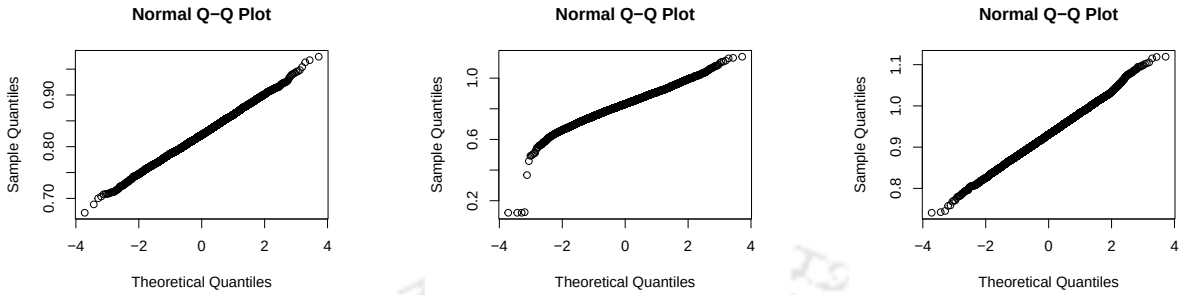
(d) $\hat{\tau}_A$ (e) $\hat{\tau}_{AC:AD}$ (f) $\hat{\tau}_{BE:BF}$

Figure 2.8: Quantile Quantile graph of the optimal adaptive allocation ratios

a version of the M-bridge study where the recruitment of participants can be done on a rolling basis as opposed to one-time recruitment. We also assume that the binary primary outcome for a participant is available before the entry of the next participant. Here, we consider the first 60 participants without adaptive randomization (randomization using the M-bridge protocol with a 1:1 ratio) to obtain the initial estimates of the success probabilities. After that, each participant is allocated to a treatment following the developed adaptive allocation procedure (see Section 2.4) using the simple difference of the success probabilities as the objective function $g(\cdot, \cdot)$ (for odds-ratio and relative-risk, see Sections 2.9.5 and 2.9.6). During the retrospective adaptive randomization (say 60 participants are already allocated), if the allocated treatments at the first stage and the second stage for the 61^{st} participant are A and C, respectively, then we will pick that participant who was first given the treatment sequence $\{A, C\}$ from the remaining arranged participants using their time stamp. The selected participant may be higher ranked than 61 in the arranged list of participants.

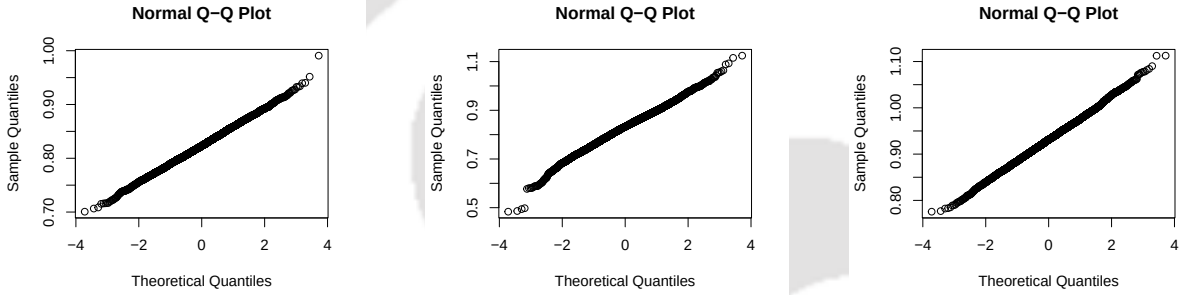
Figure 2.12 presents the convergence patterns of the estimated optimal adaptive allocation ratios $\hat{\tau}_A$, $\hat{\tau}_{AC:AD}$, and $\hat{\tau}_{BE:BF}$ in the M-bridge study. From Figure 2.12(a), we observe that $\hat{\tau}_A$ converges around 1, with the last estimated value of $\hat{\tau}_A$ is 1.00 with ASE

$$\gamma_A = 0.4, \gamma_B = 0.3$$
$$p_{AA'} = 0.25, p_{AC} = 0.45, p_{AD} = 0.65, p_{BB'} = 0.50, p_{BE} = 0.65, p_{BF} = 0.75$$
$$n = 400$$



(a) $\hat{\tau}_A$ (b) $\hat{\tau}_{AC:AD}$ (c) $\hat{\tau}_{BE:BF}$

$$n = 500$$



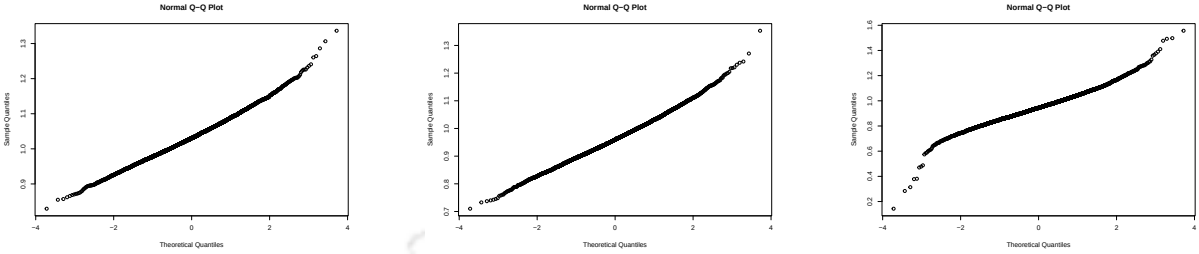
(d) $\hat{\tau}_A$ (e) $\hat{\tau}_{AC:AD}$ (f) $\hat{\tau}_{BE:BF}$

Figure 2.9: Quantile Quantile graph of the optimal adaptive allocation ratios (Contd.)

0.001. On the other hand, $\hat{\tau}_{AC:AD}$ converges to a value just below 1.2, with the last estimated value of $\hat{\tau}_{AC:AD}$ being 1.16 with ASE 0.029 (see Figure 2.12(b)), and $\hat{\tau}_{BE:BF}$ takes the values between 0.8 and 1 at the end of the study, with the last estimated value of $\hat{\tau}_{BE:BF}$ is 0.94 with ASE 0.018 (see Figure 2.12(c)). Notice that the convergence pattern of $\hat{\tau}_A$ is more convincing than the other two optimal adaptive allocation ratios at the second stage of M-bridge. This is because $\hat{\tau}_A$ is based on all the samples (470, see Table 2.13) of M-bridge, but $\hat{\tau}_{AC:AD}$ and $\hat{\tau}_{BE:BF}$ are based on much fewer samples which are consistent with the corresponding treatment sequences.

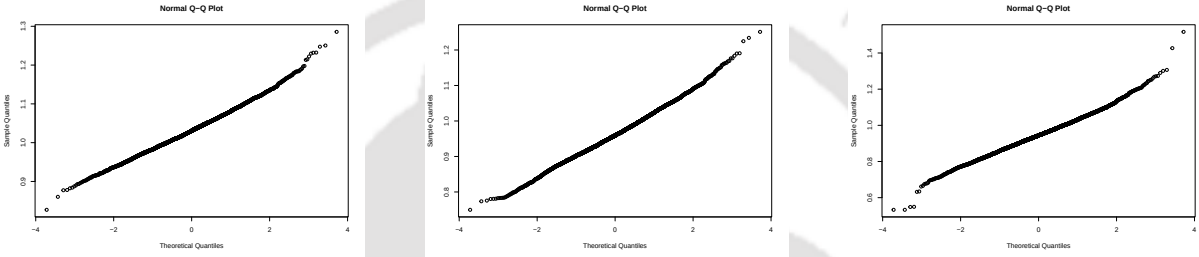
Table 2.13 compares optimal adaptive allocation (OAA) with the original (1:1) randomized allocation with respect to allocated participants and the proportion of failures. The comparison is made among the four embedded DTRs d_1, d_2, d_3, d_4 using the total number of participants and the proportion of failures in those four embedded DTRs. Note that the proportion of failures for d_i is $q_{d_i} = 1 - p_{d_i}, i = 1, \cdots, 4$, whereas the proportion of failure (in the last row of Table 2.13) is the ratio of the total number of failures to the total number of participants. In OAA, we have used 470 participants as the treatment sequence $\{A, C\}$ of M-bridge SMART has no further available participants.

$$\gamma_A = 0.4, \gamma_B = 0.3$$
$$p_{AA'} = 0.25, p_{AC} = 0.60, p_{AD} = 0.65, p_{BB'} = 0.50, p_{BE} = 0.40, p_{BF} = 0.45$$
$$n = 400$$



(a) $\hat{\tau}_A$ (b) $\hat{\tau}_{AC:AD}$ (c) $\hat{\tau}_{BE:BF}$

$$n = 500$$



(d) $\hat{\tau}_A$ (e) $\hat{\tau}_{AC:AD}$ (f) $\hat{\tau}_{BE:BF}$

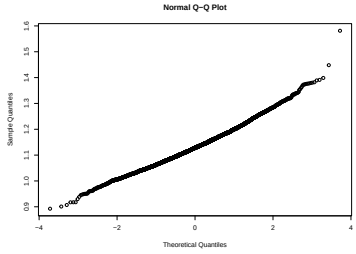
Figure 2.10: Quantile Quantile graph of the optimal adaptive allocation ratios (Contd.)

Table 2.13: Allocated participants and proportion of failures (in parentheses) following optimal adaptive allocation (OAA) and 1:1 allocation in M-bridge study. The simple difference of the success probabilities is used as the objective function $g(\cdot, \cdot)$. The OAA has to stop after 470 participants as treatment sequence $\{A, C\}$ of the M-bridge SMART has no available participants. The proportion of failures for d_i is q_{d_i}, whereas the proportion of failure (in the last row) is the ratio of the total number of failures to total participants.

DTR	Responder (R) + Non-Responder (NR) = Total (Proportion of failures)				
	Optimal Adaptive Allocation (OAA)		M-bridge Allocation		M-bridge Study allocation (end of study)
	Participants with OAA	Remaining participants	Till 470 participants	Remaining 51 participants	All participants
d_1	174 + 37 = 211 (0.233)	13 + 0 = 13 (0.795)	167 + 34 = 201 (0.237)	20 + 3 = 23 (0.798)	187 + 37 = 224 (0.235)
d_2	174 + 22 = 196 (0.268)	13 + 16 = 29 (0.676)	167 + 35 = 202 (0.274)	20 + 3 = 23 (0.607)	187 + 38 = 225 (0.284)
d_3	166 + 35 = 201 (0.259)	10 + 1 = 11 (0.544)	160 + 30 = 190 (0.284)	16 + 6 = 22 (0.808)	176 + 36 = 212 (0.266)
d_4	166 + 36 = 202 (0.244)	10 + 11 = 21 (0.660)	160 + 44 = 204 (0.249)	16 + 3 = 19 (0.702)	176 + 47 = 223 (0.252)
Total	470 (0.236)	51 (0.471)	470 (0.260)	51 (0.255)	521 (0.259)

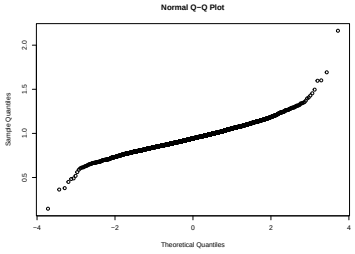
The last row of Table 2.13 confirms that the proportion of failure using OAA is 0.236, which is lower than the proportion of failure of 0.260 in the original M-bridge study considering the same number of 470 participants. It supports our claim that the developed procedure OAA would have resulted in fewer failures. In the original M-bridge study,

$$\gamma_A = 0.2, \gamma_B = 0.1$$
$$p_{AA'} = 0.25, p_{AC} = 0.60, p_{AD} = 0.65, p_{BB'} = 0.50, p_{BE} = 0.40, p_{BF} = 0.45$$
$$n = 300$$



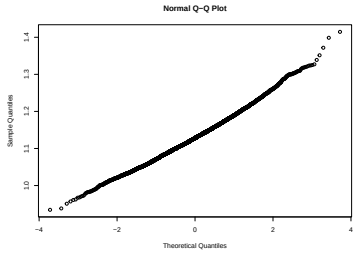
(a) $\hat{\tau}_A$

(b) $\hat{\tau}_{AC:AD}$

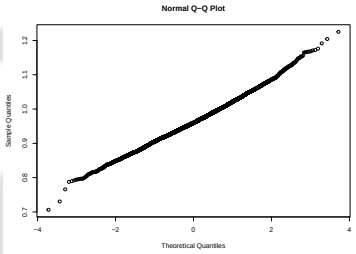


(c) $\hat{\tau}_{BE:BF}$

$$n = 400$$



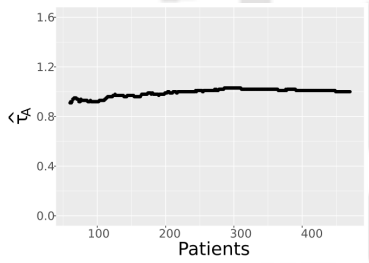
(d) $\hat{\tau}_A$



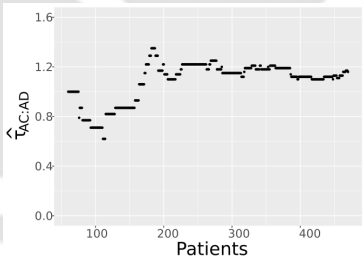
(e) $\hat{\tau}_{AC:AD}$

(f) $\hat{\tau}_{BE:BF}$

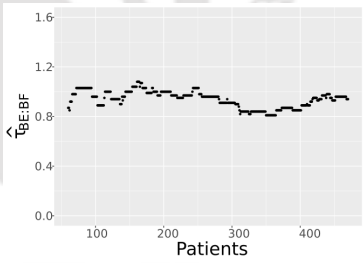
Figure 2.11: Quantile Quantile graph of the optimal adaptive allocation ratios (Contd.)



(a) $\hat{\tau}_A$: The estimated first stage optimal adaptive allocation ratio.



(b) $\hat{\tau}_{AC:AD}$: The estimated second-stage optimal adaptive allocation ratio for non-responders who obtained A at the first stage.



(c) $\hat{\tau}_{BE:BF}$: The estimated second-stage optimal adaptive allocation ratio for non-responders who obtained B at the first stage.

Figure 2.12: Convergence patterns of estimated (black dots) optimal adaptive allocation ratios $\hat{\tau}_A$, $\hat{\tau}_{AC:AD}$, and $\hat{\tau}_{BE:BF}$ in the M-bridge study.

the DTR d_2 had the highest proportion of failures (0.284), but has the highest (225) participants allocated to it using a 1:1 randomization scheme at both stages. However, the developed OAA procedure rightfully allocated a maximum number of participants (211) to the best performing DTR d_1 having the lowest failure proportion of 0.233. Similarly, OAA allocates the lowest number of participants (196) to the DTR d_2 having the highest proportion of failures (0.268). Therefore, from the second column of Table 2.13, we

observe that the allocated number of participants is decreasing in DTRs d_1, d_4, d_3 and d_2, respectively, which is consistent with the increasing order of proportion of failures in DTRs d_1, d_4, d_3 and d_2, respectively. However, we found no statistically significant evidence in the pairwise comparison of embedded DTRs $\{d_i, d_j\}, i = 1, 2; j = 3, 4$, following the hypothesis testing procedure described in Section 2.5. This result is consistent with the findings reported in Patrick et al. (2021).

Until now, we have demonstrated an application of the developed adaptive allocation (randomization) procedure using M-bridge data (Patrick et al., 2021) with the simple difference of the success probabilities (separately for the first and second stages) as the objective function. Here, we show the application of the developed procedure using the M-bridge data for the two other objective functions, namely odds-ratio and relative-risk.

Figures 2.13 and 2.14 report the convergence patterns of each of the three allocation ratios for the objective function of odds-ratio, and relative-risk, respectively. On the other hand, Tables 2.14 and 2.15 report the allocated patients to the different dynamic treatment regimes and compare the result with equal (M-bridge) allocation procedure. Following the optimal adaptive allocation process using both objective functions, Tables 2.14 and 2.15 show there is an improvement over the M-bridge (equal) allocation.

Table 2.14: Allocated participants and proportion of failures (in parentheses) following optimal adaptive allocation (OAA) and 1:1 allocation in M-bridge study. The **odds-ratio** of the success probabilities is used as the objective function $g(\cdot, \cdot)$. The OAA has to stop after 482 participants as treatment sequence $\{B, B'\}$ of the M-bridge SMART has no available participants. The proportion of failures for d_i is q_{d_i}, whereas the proportion of failure (in the last row) is the ratio of the total number of failures to total participants.

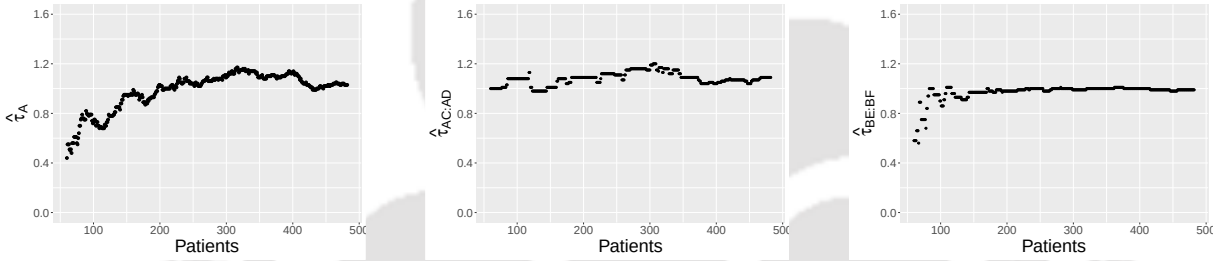
DTR	Responder (R) + Non-Responder (NR) = Total (Proportion of failures)				
	Optimal Adaptive Allocation (OAA)		M-bridge Allocation		M-bridge Study allocation (end of study)
	Participants with OAA	Remaining participants	Till 482 participants	Remaining 39 participants	All participants
d_1	178 + 36 = 214 (0.231)	9 + 1 = 10 (0.635)	171 + 36 = 207 (0.227)	16 + 1 = 17 (0.580)	187 + 37 = 224 (0.235)
d_2	178 + 22 = 200 (0.270)	9 + 16 = 25 (0.706)	171 + 35 = 206 (0.271)	16 + 3 = 19 (0.580)	187 + 38 = 225 (0.284)
d_3	176 + 33 = 209 (0.266)	0 + 3 = 3 (0.107)	165 + 30 = 195 (0.282)	11 + 6 = 17 (0.770)	176 + 36 = 212 (0.266)
d_4	176 + 37 = 213 (0.252)	0 + 10 = 10 (0.128)	165 + 45 = 210 (0.250)	11 + 2 = 13 (0.716)	176 + 47 = 223 (0.252)
Total	482 (0.234)	39 (0.564)	482 (0.256)	39 (0.308)	521 (0.259)

2.8 Discussion

In this chapter, we have developed an optimal adaptive allocation (randomization) procedure that minimizes the total expected number of failures in a SMART and gives better DTRs to more participants. Using simulation and artificially infusing adaptive randomization in the M-bridge study, we have shown how a SMART design can incorporate adaptive

Table 2.15: Allocated participants and proportion of failures (in parentheses) following optimal adaptive allocation (OAA) and 1:1 allocation in M-bridge study. The **relative-risk** of the success probabilities is used as the objective function $g(\cdot, \cdot)$. The OAA has to stop after 493 participants as treatment sequence $\{B, B'\}$ of the M-bridge SMART has no available participants. The proportion of failures for d_i is q_{d_i}, whereas the proportion of failure (in the last row) is the ratio of the total number of failures to total participants.

DTR	Responder (R) + Non-Responder (NR) = Total (Proportion of failures)				
	Optimal Adaptive Allocation (OAA)		M-bridge Allocation		M-bridge Study allocation (end of study)
	Participants with OAA	Remaining participants	Till 493 participants	Remaining 28 participants	All participants
d_1	183 + 35 = 218 (0.237)	4 + 2 = 10 (0.857)	177 + 36 = 213 (0.232)	10 + 1 = 11 (0.643)	187 + 37 = 224 (0.235)
d_2	183 + 26 = 209 (0.267)	4 + 12 = 25 (0.762)	177 + 36 = 213 (0.279)	10 + 2 = 12 (0.643)	187 + 38 = 225 (0.284)
d_3	176 + 34 = 210 (0.260)	0 + 2 = 2 (0.000)	168 + 31 = 199 (0.278)	8 + 5 = 13 (0.787)	176 + 36 = 212 (0.266)
d_4	176 + 39 = 215 (0.251)	0 + 8 = 8 (0.120)	168 + 45 = 213 (0.253)	8 + 2 = 10 (0.755)	176 + 47 = 223 (0.252)
Total	493 (0.237)	28 (0.643)	493 (0.258)	28 (0.286)	521 (0.259)



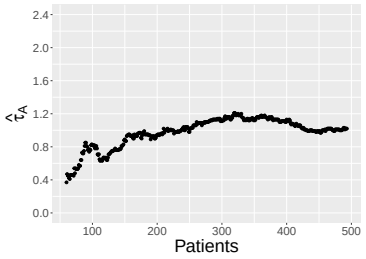
(a) $\hat{\tau}_A$: The estimated first-stage optimal adaptive allocation ratio.

(b) $\hat{\tau}_{AC:AD}$: The estimated second-stage optimal adaptive allocation ratio for non-responders who obtained A at the first stage.

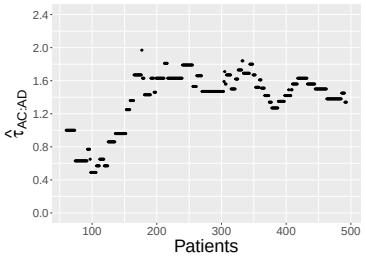
(c) $\hat{\tau}_{BE:BF}$: The estimated second-stage optimal adaptive allocation ratio for non-responders who obtained B at the first stage.

Figure 2.13: Convergence patterns of estimated (black dots) optimal adaptive allocation ratios $\hat{\tau}_A$, $\hat{\tau}_{AC:AD}$, and $\hat{\tau}_{BE:BF}$ in the M-bridge study with the objective function as odds-ratio.

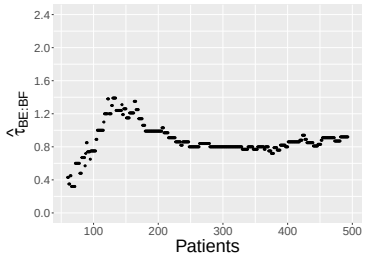
randomization to make it potentially more popular among both clinicians and patients by better addressing ethical concerns. The developed procedure needs only the response rates (as constants) and the estimation of success probabilities for the implementation. Retrospective implementation in the M-bridge study endorses the feasibility of adaptive randomization in a SMART with a sample size of less than 500. Due to the unavailability of participants in the treatment sequence $\{A, C\}$ of the M-bridge study, the adaptive procedure had to stop after including 470 participants. If we were able to use all the 521 participants of M-bridge, the convergence of the second-stage optimal adaptive allocation ratios would have been better. Notice that, in Figures 2.12(b) and 2.12(c), the graphs for $\hat{\tau}_{AC:AD}$ and $\hat{\tau}_{BE:BF}$ are more like step functions whereas the graph for $\hat{\tau}_A$ in Figure



(a) $\hat{\tau}_A$: The estimated first-stage optimal adaptive allocation ratio.



(b) $\hat{\tau}_{AC:AD}$: The estimated second-stage optimal adaptive allocation ratio for non-responders who obtained A at the first stage.



(c) $\hat{\tau}_{BE:BF}$: The estimated second-stage optimal adaptive allocation ratio for non-responders who obtained B at the first stage.

Figure 2.14: Convergence patterns of estimated (black dots) optimal adaptive allocation ratios $\hat{\tau}_A$, $\hat{\tau}_{AC:AD}$, and $\hat{\tau}_{BE:BF}$ in the M-bridge study with the objective function as relative-risk.

2.12(a) is more like a continuous function. This is because the value of $\hat{\tau}_A$ is updated for each new participant, but $\hat{\tau}_{AC:AD}$ or $\hat{\tau}_{BE:BF}$ are updated for a new participant only if the earlier participant had a treatment sequence that is consistent with those second-stage optimal ratios. Thus, it is possible that $\hat{\tau}_{AC:AD}$ or $\hat{\tau}_{BE:BF}$ may remain constant for few consecutive participants. It is to be noted that, if an estimated optimum allocation ratio ($\tau_A, \tau_{AC:AD}$ or $\tau_{BE:BF}$), with the simple difference as the objective function, is not in [0.25, 4] (corresponding to adaptive randomization probabilities [0.2, 0.8]), it is recommended to restrict the optimum allocation ratio value to be 0.25 or 4, depending on the estimated value of the same, to avoid estimation biases. However, based on our simulation studies, we have seen that the estimated optimum allocation ratio(s) is expected to be higher than 4.35 (say $\tau_{AC:AD}$) when the corresponding success probabilities (p_{AC} and p_{AD}) are at the extremes (above 0.95 and less than 0.05, respectively). Similarly, the estimated optimum allocation ratio(s) is expected to be lower than 0.23 (say $\tau_{AC:AD}$) when the corresponding success probabilities (p_{AC} and p_{AD}) are at the extremes (less than 0.05 and above 0.95, respectively).

Note that, to our knowledge, SMARTs have yet to integrate an adaptive allocation (randomization) procedure. The original M-bridge study was specifically designed around the timing of the academic year. All study participants were randomized to the initial options (intervention timing) at the same time (in accordance with the timing of the academic school year). Therefore, to highlight the importance and advantages of the adaptive SMART, we retrospectively applied the developed adaptive allocation procedure in the M-bridge study assuming the recruitment of participants could be done on a rolling basis as opposed to one-time recruitment. In other words, using the application to M-bridge data in Section 2.7, we have shown that the developed adaptive allocation (randomiza-

tion) procedure could maximize the benefit of treatments by providing better treatment sequences to a greater number of participants compared to the 1:1 randomization used in the original study. In the future, an adaptive version of the M-bridge study can be developed where participants can be recruited over a few semesters or academic years. In that scenario, the optimal adaptive allocation ratios can be updated (to be used for the upcoming semester) at the end of each semester by observing the performances of the participants.

In simulation studies and in the application to the M-bridge study, we have used an initial period of equal randomization, which is referred to as the "burn-in" or "warm-up" or "warm-start" period (Du et al., 2018). In the adaptive randomization procedure, the burn-in period is necessary to get the initial estimates of the unknown success probabilities that are required to calculate the optimal adaptive allocation ratios. How much of such initial exploration (equal randomization) is necessary? In this chapter, we have decided on the length of the burn-in period on an ad-hoc basis. There is no optimality claim associated with the initial period of equal randomization we are employing in our simulations and in the application to the M-bridge study. However, one can decide on a sample size for the burn-in period such that each treatment sequence (T_1, T_2) arm gets enough participants (say 5) having at least one success and one failure, before the start of the optimal adaptive allocation procedure. This issue also arises in online reinforcement learning / contextual bandit algorithms literature in computer science, where they call it the "exploration-exploitation dilemma" (Sutton and Barto, 2018). Future work that decides the length of the burn-in period based on some optimality criteria will be useful in the context of SMART.

The optimal adaptive allocation ratios ($\tau^*_{AC:AD}$ and $\tau^*_{BE:BF}$) corresponding to the second-stage randomizations are functions of related success probabilities ($\{p_{AC}, p_{AD}\}$ or $\{p_{BE}, p_{BF}\}$) only. However, the first-stage optimal adaptive allocation ratio, τ^*_A, is a function of all the success probabilities in the entire SMART, the second-stage optimal adaptive allocation ratios, and the response probabilities (γ_A and γ_B). In other words, τ^*_A takes into account optimal adaptive allocations at the second stage. For high values of γ_A and γ_B (close to 1), the expression for τ^*_A approximately becomes

$$\sqrt{\frac{p_{AA'}}{p_{BB'}}}, \left(\sqrt{\frac{p_{BB'}}{p_{AA'}}}\right)\left(\frac{q_{BB'}}{q_{AA'}}\right) \text{ and } \left(\sqrt{\frac{p_{AA'}}{p_{BB'}}}\right)\left(\frac{q_{BB'}}{q_{AA'}}\right),$$

corresponding to the choice of the objective function as, simple difference, odds-ratio and relative-risk, respectively.

2.9 Detailed Derivations

2.9.1 Derivation of the First-Stage Success Probability (p_{T_1})

p_{T_1}, $q_{T_1}(=1-p_{T_1})$ is the probability of success and failure for a patient receiving treatment T_1 ($T_1 \in (A, B)$) at the first stage, respectively. The $p_{T_1T_2}$ is the success probability (observed at the end of study) for the patient who obtained the treatment sequence $\{T_1, T_2\}$, where $T_2 \in \{A', C, D\}$ when $T_1 = A$ and $T_2 \in \{B', E, F\}$ for $T_1 = B$. Then, the first-stage probability can be expressed as,

$$
\begin{aligned}
p_{T_1} &= \frac{Number\ of\ successes\ for\ participants\ started\ with\ T_1}{n_{T_1}} \\
&= \frac{n_{T_1T_1'}p_{T_1T_1'} + n_{T_1T_2}p_{T_1T_2} + n_{T_1T_2^*}p_{T_1T_2^*}}{n_{T_1}}, \text{ where } T_2 = C, T_2^* = D \text{ if } T_1 = A; \qquad (2.5) \\
&\quad T_2 = E, T_2^* = F \text{ if } T_1 = B \\
&= \frac{n_{T_1}\gamma_{T_1}p_{T_1T_1'} + n_{T_1}(1-\gamma_{T_1})\frac{\tau_{T_1T_2:T_1T_2^*}}{1+\tau_{T_1T_2:T_1T_2^*}}p_{T_1T_2} + n_{T_1}(1-\gamma_{T_1})\frac{1}{1+\tau_{T_1T_2:T_1T_2^*}}p_{T_1T_2^*}}{n_{T_1}} \\
&= \gamma_{T_1}p_{T_1T_1'} + (1-\gamma_{T_1})\frac{\tau_{T_1T_2:T_1T_2^*}}{1+\tau_{T_1T_2:T_1T_2^*}}p_{T_1T_2} + (1-\gamma_{T_1})\frac{1}{1+\tau_{T_1T_2:T_1T_2^*}}p_{T_1T_2^*}. \qquad (2.6)
\end{aligned}
$$

Note that the sum of the coefficients in (2.6) of above expression is,

$$
\begin{aligned}
&\gamma_{T_1} + (1-\gamma_{T_1})\frac{\tau_{T_1T_2:T_1T_2^*}}{1+\tau_{T_1T_2:T_1T_2^*}} + (1-\gamma_{T_1})\frac{1}{1+\tau_{T_1T_2:T_1T_2^*}} \\
&= \gamma_{T_1} + (1-\gamma_{T_1})\left(\frac{\tau_{T_1T_2:T_1T_2^*}}{1+\tau_{T_1T_2:T_1T_2^*}} + \frac{1}{1+\tau_{T_1T_2:T_1T_2^*}}\right) \\
&= \gamma_{T_1} + (1-\gamma_{T_1}) \\
&= 1. \qquad (2.7)
\end{aligned}
$$

Thus, using (2.6) and (2.7), we have

$$
\begin{aligned}
q_{T_1} &= 1 - p_{T_1} \\
&= 1 - \gamma_{T_1}p_{T_1T_1'} - (1-\gamma_{T_1})\frac{\tau_{T_1T_2:T_1T_2^*}}{1+\tau_{T_1T_2:T_1T_2^*}}p_{T_1T_2} - (1-\gamma_{T_1})\frac{1}{1+\tau_{T_1T_2:T_1T_2^*}}p_{T_1T_2^*} \\
&= \gamma_{T_1} + (1-\gamma_{T_1})\frac{\tau_{T_1T_2:T_1T_2^*}}{1+\tau_{T_1T_2:T_1T_2^*}} + (1-\gamma_{T_1})\frac{1}{1+\tau_{T_1T_2:T_1T_2^*}} - \gamma_{T_1}p_{T_1T_1'} \\
&\quad - (1-\gamma_{T_1})\frac{\tau_{T_1T_2:T_1T_2^*}}{1+\tau_{T_1T_2:T_1T_2^*}}p_{T_1T_2} - (1-\gamma_{T_1})\frac{1}{1+\tau_{T_1T_2:T_1T_2^*}}p_{T_1T_2^*} \\
&= \gamma_{T_1}q_{T_1T_1'} + (1-\gamma_{T_1})\frac{\tau_{T_1T_2:T_1T_2^*}}{1+\tau_{T_1T_2:T_1T_2^*}}q_{T_1T_2} + (1-\gamma_{T_1})\frac{1}{1+\tau_{T_1T_2:T_1T_2^*}}q_{T_1T_2^*}.
\end{aligned}
$$

2.9.2 Derivation of Second-Stage Optimal Adaptive Allocation Ratio for Simple Difference

We consider the objective function $g(\cdot,\cdot)$ as introduced in Section 2.3.1 to be the simple difference. The objective function of simple difference for comparing the two second-stage probabilities ($p_{T_1T_2}$, and $p_{T_1T_2^*}$) is given by $p_{T_1T_2} - p_{T_1T_2^*}$, where $T_2 = C, T_2^* = D$ if $T_1 = A$; $T_2 = E, T_2^* = F$ if $T_1 = B$. The optimality criterion (as defined in Section 2.3.1), using the asymptotic variance of the objective function $avar(g(\cdot,\cdot))$ can be expressed as,

$$\frac{p_{T_1T_2}q_{T_1T_2}}{n_{T_1T_2}} + \frac{p_{T_1T_2^*}q_{T_1T_2^*}}{n_{T_1T_2^*}} = \epsilon_2, \text{ for some constant } \epsilon_2 > 0.$$

Note that, $\tau_{T_1T_2:T_1T_2^*} = \frac{n_{T_1T_2}}{n_{T_1T_2^*}}$. The $n_{T_1T_2}$ and $n_{T_1T_2^*}$ can be written as,

$$n_{T_1T_2} = n_{T_1}^{NR}\left(\frac{\tau_{T_1T_2:T_1T_2^*}}{1+\tau_{T_1T_2:T_1T_2^*}}\right), n_{T_1T_2^*} = \frac{n_{T_1}^{NR}}{1+\tau_{T_1T_2:T_1T_2^*}},$$

where $n_{T_1}^{NR} = n_{T_1T_2} + n_{T_1T_2^*}$, is the total number of patients who obtained treatment T_1 at the first stage and become non-responders at the end of the first stage. Substituting the expressions of $n_{T_1T_2}$ and $n_{T_1T_2^*}$ in asymptotic variance expression obtained earlier,

$$\frac{p_{T_1T_2}q_{T_1T_2}}{\frac{n_{T_1}^{NR}\tau_{T_1T_2:T_1T_2^*}}{1+\tau_{T_1T_2:T_1T_2^*}}} + \frac{p_{T_1T_2^*}q_{T_1T_2^*}}{\frac{n_{T_1}^{NR}}{1+\tau_{T_1T_2:T_1T_2^*}}} = \epsilon_2.$$

$$\implies n_{T_1}^{NR} = \frac{\left(1+\tau_{T_1T_2:T_1T_2^*}\right)\left(p_{T_1T_2}q_{T_1T_2} + \tau_{T_1T_2:T_1T_2^*}p_{T_1T_2^*}q_{T_1T_2^*}\right)}{\epsilon_2\tau_{T_1T_2:T_1T_2^*}}. \tag{2.8}$$

From Section 2.3.1, the second-stage optimal adaptive allocation ratio is obtained as,

$$\tau^*_{T_1T_2:T_1T_2^*} = \arg\min_{\tau_{T_1T_2:T_1T_2^*}} F_2(\tau_{T_1T_2:T_1T_2^*}) \text{ subject to } \frac{p_{T_1T_2}q_{T_1T_2}}{n_{T_1T_2}} + \frac{p_{T_1T_2^*}q_{T_1T_2^*}}{n_{T_1T_2^*}} = \epsilon_2.$$

Among the patients who obtained T_1 at the first stage, the number of failures after a randomization process at the second stage is (see Section 2.3.1)

$$\begin{aligned}
F_2(\tau_{T_1T_2:T_1T_2^*}) &= n_{T_1T_2}q_{T_1T_2} + n_{T_1T_2^*}q_{T_1T_2^*} \\
&= n_{T_1}^{NR}\left(\frac{\tau_{T_1T_2:T_1T_2^*}}{1+\tau_{T_1T_2:T_1T_2^*}}\right)q_{T_1T_2} + \frac{n_{T_1}^{NR}}{1+\tau_{T_1T_2:T_1T_2^*}}q_{T_1T_2^*} \\
&= \left(p_{T_1T_2}q_{T_1T_2} + \tau_{T_1T_2:T_1T_2^*}p_{T_1T_2^*}q_{T_1T_2^*}\right)\frac{q_{T_1T_2}}{\epsilon_2} \\
&+ \frac{\left(p_{T_1T_2}q_{T_1T_2} + \tau_{T_1T_2:T_1T_2^*}p_{T_1T_2^*}q_{T_1T_2^*}\right)q_{T_1T_2^*}}{\epsilon_2\tau_{T_1T_2:T_1T_2^*}}.
\end{aligned}$$

Now, we have

$$\frac{\partial F_2(\tau_{T_1T_2:T_1T_2^*})}{\partial \tau_{T_1T_2:T_1T_2^*}} = p_{T_1T_2^*} q_{T_1T_2^*} \frac{q_{T_1T_2}}{\epsilon_2} - \frac{p_{T_1T_2} q_{T_1T_2} q_{T_1T_2^*}}{\epsilon_2 \tau^2_{T_1T_2:T_1T_2^*}}.$$

Equating the above expression with 0 gives the optimal value of $\tau_{T_1T_2:T_1T_2^*}$ as,

$$\tau^*_{T_1T_2:T_1T_2^*} = \sqrt{\frac{p_{T_1T_2}}{p_{T_1T_2^*}}}. \tag{2.9}$$

Now, we show that the estimated second-stage allocation ratio for the n^{th} patient (see Section 2.4)

$$\hat{\tau}_{T_1T_2:T_1T_2^*,n} \xrightarrow{a.s} \tau^*_{T_1T_2:T_1T_2^*}.$$

Define **Lemma 1** (same as **Lemma 1.2.6** in Sokol and Rønn-Nielsen (2013)) : $\{X_n\}$ be a sequence of random variables, and let X be some other random variable. Let $f : R \to R$ be a continuous function. If X_n converges almost surely $(a.s)$ to X, then $f(X_n)$ converges almost surely to $f(X)$. If X_n converges in probability to X, then $f(X_n)$ converges in probability to $f(X)$.

Note that $\hat{p}_{T_1T_2,n} \xrightarrow{a.s} p_{T_1T_2}$; and $(\hat{p}_{AA'}, \hat{p}_{AC}, \hat{p}_{AD}, \hat{p}_{BB'}, \hat{p}_{BE}, \hat{p}_{BF}) \in (0,1)$. Now consider $f(x) = \frac{1}{x}$, $x \in (0,1)$. Then the $f(x)$ is a continuous function in the support space. Thus, using Lemma 1,

$$\hat{\tau}_{T_1T_2:T_1T_2^*,n} \xrightarrow{a.s} \sqrt{\frac{p_{T_1T_2}}{p_{T_1T_2^*}}} \implies \hat{\tau}_{T_1T_2:T_1T_2^*,n} \xrightarrow{a.s} \tau^*_{T_1T_2:T_1T_2^*}. \tag{2.10}$$

2.9.3 Derivation of First-Stage Optimal Adaptive Allocation Ratio for Simple Difference

We consider the objective function $g(\cdot,\cdot)$ as introduced in Section 2.3.1 to be a simple difference. The objective function of simple difference for comparing the two first-stage probabilities (p_A, and p_B) is given by $p_A - p_B$. The optimality criterion (as defined in Section 2.3.1) for the first-stage allocation ratio using the asymptotic variance of the objective function $avar(g(\cdot,\cdot))$ can be expressed as

$$\frac{p_A q_A}{n_A} + \frac{p_B q_B}{n_B} = \epsilon_1.$$

Using the expression for first-stage success probability (p_{T_1}) and failure probability (q_{T_1}) as obtained in 2.9.1, in above equation, we get,

$$\frac{\left(\gamma_A p_{AA'} + (1-\gamma_A)\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}} p_{AC} + (1-\gamma_A)\frac{1}{1+\tau_{AC:AD}} p_{AD}\right)\left(\gamma_A q_{AA'} + (1-\gamma_A)\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}} q_{AC} + (1-\gamma_A)\frac{1}{1+\tau_{AC:AD}} q_{AD}\right)}{n_A}$$
$$+\frac{\left(\gamma_B p_{BB'} + (1-\gamma_B)\frac{\tau_{BE:BF}}{1+\tau_{BE:BF}} p_{BE} + (1-\gamma_B)\frac{1}{1+\tau_{BE:BF}} p_{BF}\right)\left(\gamma_B q_{BB'} + (1-\gamma_B)\frac{\tau_{BE:BF}}{1+\tau_{BE:BF}} q_{BE} + (1-\gamma_B)\frac{1}{1+\tau_{BE:BF}} q_{BF}\right)}{n_B}$$
$$= \epsilon_1.$$

Since, $\tau_A = \frac{n_A}{n_B}$, n_A, and n_B can be written as,

$$n_A = n\left(\frac{\tau_A}{1+\tau_A}\right),\ n_B = \frac{n}{1+\tau_A}.$$

Substituting the expression of n_A and n_B in asymptotic variance expression obtained earlier,

$$\frac{\left(\gamma_A p_{AA'} + (1-\gamma_A)\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}} p_{AC} + (1-\gamma_A)\frac{1}{1+\tau_{AC:AD}} p_{AD}\right)\left(\gamma_A q_{AA'} + (1-\gamma_A)\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}} q_{AC} + (1-\gamma_A)\frac{1}{1+\tau_{AC:AD}} q_{AD}\right)}{\frac{n\tau_A}{1+\tau_A}}$$
$$+\frac{\left(\gamma_B p_{BB'} + (1-\gamma_B)\frac{\tau_{BE:BF}}{1+\tau_{BE:BF}} p_{BE} + (1-\gamma_B)\frac{1}{1+\tau_{BE:BF}} p_{BF}\right)\left(\gamma_B q_{BB'} + (1-\gamma_B)\frac{\tau_{BE:BF}}{1+\tau_{BE:BF}} q_{BE} + (1-\gamma_B)\frac{1}{1+\tau_{BE:BF}} q_{BF}\right)}{\frac{n}{1+\tau_A}}$$
$$= \epsilon_1.$$

Let,

$$\gamma_A p_{AA'} + \frac{(1-\gamma_A)\tau_{AC:AD}}{1+\tau_{AC:AD}} p_{AC} + \frac{(1-\gamma_A)}{1+\tau_{AC:AD}} p_{AD} = t_1,$$
$$\gamma_A q_{AA'} + \frac{(1-\gamma_A)\tau_{AC:AD}}{1+\tau_{AC:AD}} q_{AC} + \frac{(1-\gamma_A)}{1+\tau_{AC:AD}} q_{AD} = t_2,$$
$$\gamma_B p_{BB'} + \frac{(1-\gamma_B)\tau_{BE:BF}}{1+\tau_{BE:BF}} p_{BE} + \frac{(1-\gamma_B)}{1+\tau_{BE:BF}} p_{BF} = l_1,$$
$$\gamma_B q_{BB'} + \frac{(1-\gamma_B)\tau_{BE:BF}}{1+\tau_{BE:BF}} q_{BE} + \frac{(1-\gamma_B)}{1+\tau_{BE:BF}} q_{BF} = l_2.$$

Further using the expressions of t_1, t_2, l_1 and l_2 in the asymptotic variance expression we get,

$$\frac{t_1 t_2}{\frac{n\tau_A}{1+\tau_A}} + \frac{l_1 l_2}{\frac{n}{1+\tau_A}} = \epsilon_1. \tag{2.11}$$

The total number of failures after the completion of SMART can be expressed as,

$$\begin{aligned}
F_1(\tau_A, \tau_{AC:AD}, \tau_{BE:BF}) &= n_{AA'}q_{AA'} + n_{AC}q_{AC} + n_{AD}q_{AD} + n_{BB'}q_{BB'} + n_{BE}q_{BE} + n_{BF}q_{BF} \\
&= \frac{n\tau_A}{1+\tau_A}\gamma_A q_{AA'} + \frac{n\tau_A(1-\gamma_A)}{1+\tau_A}\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}} q_{AC} + \frac{n\tau_A}{1+\tau_A}(1-\gamma_A)\frac{1}{1+\tau_{AC:AD}} q_{AD} \\
&\quad + \frac{n}{1+\tau_A}\gamma_B q_{BB'} + \frac{n(1-\gamma_B)}{1+\tau_A}\frac{\tau_{BE:BF}}{1+\tau_{BE:BF}} q_{BE} + \frac{n(1-\gamma_B)}{1+\tau_A}\frac{1}{1+\tau_{BE:BF}} q_{BF} \\
&= \frac{t_1 t_2 + \tau_A l_1 l_2}{\epsilon_1}\gamma_A q_{AA'} + \frac{t_1 t_2 + \tau_A l_1 l_2}{\epsilon_1}\frac{1-\gamma_A}{1+\tau_{AC:AD}}\left(\tau_{AC:AD} q_{AC} + q_{AD}\right) \\
&\quad + \frac{t_1 t_2 + \tau_A l_1 l_2}{\tau_A \epsilon_1}\gamma_B q_{BB'} + \frac{t_1 t_2 + \tau_A l_1 l_2}{\tau_A \epsilon_1}\frac{1-\gamma_B}{1+\tau_{BE:BF}}\left(\tau_{BE:BF} q_{BE} + q_{BF}\right).
\end{aligned}$$

To obtain the first-stage optimal adaptive allocation ratio, the above expression is

differentiated with respect to the allocation ratio (τ_A) and is to be equated with 0. Note that the two second-stage allocation ratios are replaced by corresponding optimal adaptive allocation ratios from (2.10) (see Section 2.3) Hence,

$$\begin{aligned}\frac{\partial F_1(\tau_A, \tau^*_{AC:AD}, \tau^*_{BE:BF})}{\partial \tau_A} &= \frac{l_1 l_2}{\epsilon_1}\gamma_A q_{AA'} + \frac{l_1 l_2}{\epsilon_1}\frac{1-\gamma_A}{1+\tau^*_{AC:AD}}(\tau^*_{AC:AD} q_{AC} + q_{AD}) \\ &\quad - \frac{t_1 t_2}{\epsilon_1 \tau_A^2}\gamma_B q_{BB'} - \frac{t_1 t_2}{\epsilon_1 \tau_A^2}\frac{1-\gamma_B}{1+\tau^*_{BE:BF}}(\tau^*_{BE:BF} q_{BE} + q_{BF}). \end{aligned} \tag{2.12}$$

Equating (2.12) with 0 gives us the value of τ_A to be,

$$\begin{aligned}\tau^*_A &= \sqrt{\frac{t_1 t_2 \gamma_B q_{BB'} + t_1 t_2 \frac{1-\gamma_B}{1+\tau^*_{BE:BF}}(\tau^*_{BE:BF} q_{BE} + q_{BF})}{l_1 l_2 \gamma_A q_{AA'} + l_1 l_2 \frac{1-\gamma_A}{1+\tau^*_{AC:AD}}(\tau^*_{AC:AD} q_{AC} + q_{AD})}} \\ &= \sqrt{\frac{(1+\tau^*_{AC:AD}) t_1 t_2 (\gamma_B q_{BB'}(1+\tau^*_{BE:BF}) + (1-\gamma_B)(\tau^*_{BE:BF} q_{BE} + q_{BF}))}{(1+\tau^*_{BE:BF}) l_1 l_2 (\gamma_A q_{AA'}(1+\tau^*_{AC:AD}) + (1-\gamma_A)(\tau^*_{AC:AD} q_{AC} + q_{AD}))}} \\ &= \sqrt{\frac{(1+\tau^*_{BE:BF})(\gamma_A p_{AA'}(1+\tau^*_{AC:AD}) + (1-\gamma_A)(\tau^*_{AC:AD} p_{AC} + p_{AD}))}{(1+\tau^*_{AC:AD})(\gamma_B p_{BB'}(1+\tau^*_{BE:BF}) + (1-\gamma_B)(\tau^*_{BE:BF} p_{BE} + p_{BF}))}}. \end{aligned} \tag{2.13}$$

Lemma 2 (same as **Lemma 1.2.10** in Sokol and Rønn-Nielsen (2013)) states that, let $\{X_n\}$ and $\{Y_n\}$ be sequences of random variables, and let X and Y be two other random variables. If X_n converges in probability to X and Y_n converges in probability to Y, then $X_n + Y_n$ converges in probability to $X + Y$, and $X_n Y_n$ converges in probability to XY. Also, if X_n converges almost surely to X and Y_n converges almost surely to Y, then $X_n + Y_n$ converges almost surely to $X + Y$, and $X_n Y_n$ converges almost surely to XY. Thus, using Lemma 2, we have (see (2.10)),

$$\gamma_A \hat{p}_{AA',n}(1 + \hat{\tau}_{AC:AD,n}) \xrightarrow{a.s} \gamma_A p_{AA'} \left(\frac{\sqrt{p_{AC}} + \sqrt{p_{AD}}}{\sqrt{p_{AD}}} \right)$$

$$(1-\gamma_A)(\hat{\tau}_{AC:AD,n}\hat{p}_{AC,n} + \hat{p}_{AD,n}) \xrightarrow{a.s} (1-\gamma_A) \left(\frac{(p_{AC})^{\frac{3}{2}} + (p_{AD})^{\frac{3}{2}}}{\sqrt{p_{AD}}} \right).$$

Using Lemma 2 on equation (2.10) and the above two asymptotic expressions, we obtain that,

$$\begin{aligned}&(1 + \hat{\tau}_{BE:BF,n})(\gamma_A \hat{p}_{AA',n}(1 + \hat{\tau}_{AC:AD,n}) + (1-\gamma_A)(\hat{\tau}_{AC:AD,n}\hat{p}_{AC,n} + \hat{p}_{AD,n})) \\ &\xrightarrow{a.s} \left(\frac{\sqrt{p_{BF}} + \sqrt{p_{BE}}}{\sqrt{p_{BF}}} \right) \left(\gamma_A p_{AA'} \left(\frac{\sqrt{p_{AC}} + \sqrt{p_{AD}}}{\sqrt{p_{AD}}} \right) + (1-\gamma_A) \left(\frac{(p_{AC})^{\frac{3}{2}} + (p_{AD})^{\frac{3}{2}}}{\sqrt{p_{AD}}} \right) \right). \end{aligned} \tag{2.14}$$

Similarly, using Lemma 2, we have,

$$\gamma_B \hat{p}_{BB',n}(1+\hat{\tau}_{BE:BF,n}) \xrightarrow{a.s} \gamma_B p_{BB'} \left(\frac{\sqrt{p_{BE}}+\sqrt{p_{BF}}}{\sqrt{p_{BF}}} \right)$$

$$(1-\gamma_B)(\hat{\tau}_{BE:BF,n}\hat{p}_{BE,n}+\hat{p}_{BF,n}) \xrightarrow{a.s} (1-\gamma_B) \left(\frac{(p_{BE})^{\frac{3}{2}}+(p_{BF})^{\frac{3}{2}}}{\sqrt{p_{BF}}} \right).$$

Again using Lemma 2, on the above two obtained expressions, we get,

$$\begin{aligned}&(1+\hat{\tau}_{AC:AD,n})(\gamma_B \hat{p}_{BB',n}(1+\hat{\tau}_{BE:BF,n})+(1-\gamma_B)(\hat{\tau}_{BE:BF,n}\hat{p}_{BE,n}+\hat{p}_{BF,n})) \\ &\xrightarrow{a.s} \left(\frac{\sqrt{p_{AC}}+\sqrt{p_{AD}}}{\sqrt{p_{AD}}}\right)\left(\gamma_B p_{BB'}\left(\frac{\sqrt{p_{BE}}+\sqrt{p_{BF}}}{\sqrt{p_{BF}}}\right)+(1-\gamma_B)\left(\frac{(p_{BE})^{\frac{3}{2}}+(p_{BF})^{\frac{3}{2}}}{\sqrt{p_{BF}}}\right)\right). \quad (2.15)\end{aligned}$$

Thus, using Lemma 1, Lemma 2, and equations (2.13), (2.14) and (2.15), we have

$$\begin{aligned}\hat{\tau}_{A,n} \xrightarrow{a.s} &\sqrt{\frac{\left[\sqrt{p_{BE}}+\sqrt{p_{BF}}\right]\left[\gamma_A p_{AA'}(\sqrt{p_{AD}}+\sqrt{p_{AC}})+(1-\gamma_A)\left((p_{AC})^{\frac{3}{2}}+(p_{AD})^{\frac{3}{2}}\right)\right]}{\left[\sqrt{p_{AC}}+\sqrt{p_{AD}}\right]\left[\gamma_B p_{BB'}(\sqrt{p_{BE}}+\sqrt{p_{BF}})+(1-\gamma_B)\left((p_{BE})^{\frac{3}{2}}+(p_{BF})^{\frac{3}{2}}\right)\right]}} \\ = &\sqrt{\frac{(1+\tau^*_{BE:BF})(\gamma_A p_{AA'}(1+\tau^*_{AC:AD})+(1-\gamma_A)(\tau^*_{AC:AD}p_{AC}+p_{AD}))}{(1+\tau^*_{AC:AD})(\gamma_B p_{BB'}(1+\tau^*_{BE:BF})+(1-\gamma_B)(\tau^*_{BE:BF}p_{BE}+p_{BF}))}}. \quad (2.16)\end{aligned}$$

2.9.4 Derivation of Asymptotic Variance of Success Probabilities: $\hat{p}_{T_1T_2}$

Let us consider $\{Y_1, Y_2, ..., Y_n\}$ be the binary primary outcome variables, where,

$$Y_i = \begin{cases} 1, & \text{if } i^{th} \text{ patient observes success at the end of study,} \\ 0, & \text{otherwise.} \end{cases}$$

T_{1i} and T_{2i} denote the assigned first- and second-stage treatments to the i^{th} patient, respectively. T_{1i} can take values A and B; $T_{2i} \in \{A', C, D\}$ where $T_{1i} = A$ and $T_{2i} \in \{B', E, F\}$ where $T_{1i} = B$. As defined in Section 2.4,$\mathscr{F}_i = \{Y_1, Y_2, ..., Y_i, T_{11}, T_{12}, ..., T_{1i}, T_{21}, T_{22}, ..., T_{2i}\}$ as the history of primary outcome variables, first and second-stage allocated treatments for the first i patients. Also, the conditional expectation as, $E_{i-1}(\cdot) = E(\cdot|\mathscr{F}_{i-1})$. Let, $T_1^n = (T_{11}, T_{12}, ..., T_{1n})$, and $T_2^n = (T_{21}, T_{22}, ..., T_{2n})$ be the history of treatment assignment of the first and second-stage allocated treatments, respectively; and $Y^n = (Y_1, Y_2, ..., Y_n)$ be the history of primary outcome variables. The likelihood function from the data is

(Rosenberger et al., 1997),

$$\begin{aligned}\mathscr{L}_n &\equiv \{Y^n, T_1^n, T_2^n\} \\ &\equiv \mathscr{L}(Y_n, T_{1n}, T_{2n}|\mathscr{F}_{n-1})\mathscr{L}_{n-1},\end{aligned}$$

where $\mathscr{L}(Y_n, T_{1n}, T_{2n}|\mathscr{F}_{n-1})$ is the likelihood contribution from the n^{th} patient given the history of earlier patients. Now,

$$\mathscr{L}_n = \prod_{i=1}^{n} \mathscr{L}(Y_i, T_{1i}, T_{2i}|\mathscr{F}_{i-1}), \tag{2.17}$$

with $\mathscr{L}_0 = 1$, where,

$$\begin{aligned}
&\mathscr{L}(Y_i, T_{1i}, T_{2i}|\mathscr{F}_{i-1}) \\
&= \mathscr{L}(Y_i|T_{1i}, T_{2i}, \mathscr{F}_{i-1})\mathscr{L}(T_{1i}, T_{2i}|\mathscr{F}_{i-1}) = \mathscr{L}(Y_i|T_{1i}, T_{2i}, \mathscr{F}_{i-1})\mathscr{L}(T_{2i}|T_{1i}, \mathscr{F}_{i-1})\mathscr{L}(T_{1i}|\mathscr{F}_{i-1}) \\
&= p_{AC}^{Y_i I(T_{1i}=A,T_{2i}=C)}(1-p_{AC})^{(1-Y_i)I(T_{1i}=A,T_{2i}=C)}\times \\
&p_{AD}^{Y_i I(T_{1i}=A,T_{2i}=D)}(1-p_{AD})^{(1-Y_i)I(T_{1i}=A,T_{2i}=D)}\times \\
&p_{AA'}^{Y_i I(T_{1i}=A,T_{2i}=A')}(1-p_{AA'})^{(1-Y_i)I(T_{1i}=A,T_{2i}=A')}\times \\
&p_{BE}^{Y_i I(T_{1i}=B,T_{2i}=E)}(1-p_{BE})^{(1-Y_i)I(T_{1i}=B,T_{2i}=E)}\times \\
&p_{BF}^{Y_i I(T_{1i}=B,T_{2i}=F)}(1-p_{BF})^{(1-Y_i)I(T_{1i}=B,T_{2i}=F)}\times \\
&p_{BB'}^{Y_i I(T_{1i}=B,T_{2i}=B')}(1-p_{BB'})^{(1-Y_i)I(T_{1i}=B,T_{2i}=B')}\times \\
&\{E_{i-1}(I(T_{2i}=A'|T_{1i}=A))\}^{I(T_{1i}=A,T_{2i}=A')}\times \\
&\left[\{E_{i-1}(I(T_{2i}=C|T_{1i}=A))\}^{I(T_{1i}=A,T_{2i}=C)}\right]^{1-I(T_{1i}=A,T_{2i}=A')}\times \\
&\left[\{E_{i-1}(1-I(T_{2i}=C|T_{1i}=A))\}^{I(T_{1i}=A,T_{2i}=D)}\right]^{1-I(T_{1i}=A,T_{2i}=A')}\times \\
&\{E_{i-1}(I(T_{2i}=B'|T_{1i}=B))\}^{I(T_{1i}=B,T_{2i}=B')}\times \\
&\left[\{E_{i-1}(I(T_{2i}=E|T_{1i}=B))\}^{I(T_{1i}=B,T_{2i}=E)}\right]^{1-I(T_{1i}=B,T_{2i}=B')}\times \\
&\left[\{E_{i-1}(1-I(T_{2i}=E|T_{1i}=B))\}^{I(T_{1i}=B,T_{2i}=F)}\right]^{1-I(T_{1i}=B,T_{2i}=B')}\times \\
&\{E_{i-1}(I(T_{1i}=A))\}^{I(T_{1i}=A)}\{E_{i-1}(1-I(T_{1i}=A))\}^{I(T_{1i}=B)}.
\end{aligned} \tag{2.18}$$

Thus, using (2.18), the equation (2.17) can be expressed as,

$$\begin{aligned}
&\mathscr{L}_n \\
&= \left(p_{AC}^{\sum_i Y_i I(T_{1i}=A,T_{2i}=C)}(1-p_{AC})^{\sum_i (1-Y_i)I(T_{1i}=A,T_{2i}=C)}\right) \\
&\left(p_{AD}^{\sum_i Y_i I(T_{1i}=A,T_{2i}=D)}(1-p_{AD})^{\sum_i (1-Y_i)I(T_{1i}=A,T_{2i}=D)}\right)\times \\
&\left(p_{AA'}^{\sum_i Y_i I(T_{1i}=A,T_{2i}=A')}(1-p_{AA'})^{\sum_i (1-Y_i)I(T_{1i}=A,T_{2i}=A')}\right)\times
\end{aligned}$$

$$\left(\prod_{i=1}^{n}\{E_{i-1}(I(T_{2i}=A'|T_{1i}=A))\}^{I(T_{1i}=A,T_{2i}=A')}\right)\times$$
$$\left(\prod_{i=1}^{n}\left[\{E_{i-1}(I(T_{2i}=C|T_{1i}=A))\}^{I(T_{1i}=A,T_{2i}=C)}\right]^{1-I(T_{1i}=A,T_{2i}=A')}\right)\times$$
$$\left(\prod_{i=1}^{n}\left[\{E_{i-1}(1-I(T_{2i}=C|T_{1i}=A))\}^{I(T_{1i}=A,T_{2i}=D)}\right]^{1-I(T_{1i}=A,T_{2i}=A')}\right)\times$$
$$\left(p_{BE}^{\sum_i Y_i I(T_{1i}=B,T_{2i}=E)}(1-p_{BE})^{\sum_i (1-Y_i)I(T_{1i}=B,T_{2i}=E)}\right)\times$$
$$\left(p_{BF}^{\sum_i Y_i I(T_{1i}=B,T_{2i}=F)}(1-p_{BF})^{\sum_i (1-Y_i)I(T_{1i}=B,T_{2i}=F)}\right)\times$$
$$\left(p_{BB'}^{\sum_i Y_i I(T_{1i}=B,T_{2i}=B')}(1-p_{BB'})^{\sum_i (1-Y_i)I(T_{1i}=B,T_{2i}=B')}\right)\times$$
$$\left(\prod_{i=1}^{n}\{E_{i-1}(I(T_{2i}=B'|T_{1i}=B))\}^{I(T_{1i}=B,T_{2i}=B')}\right)\times$$
$$\left(\prod_{i=1}^{n}\left[\{E_{i-1}(I(T_{2i}=E|T_{1i}=B))\}^{I(T_{1i}=B,T_{2i}=E)}\right]^{1-I(T_{1i}=B,T_{2i}=B')}\right)\times$$
$$\left(\prod_{i=1}^{n}\left[\{E_{i-1}(1-I(T_{2i}=E|T_{1i}=B))\}^{I(T_{1i}=B,T_{2i}=F)}\right]^{1-I(T_{1i}=B,T_{2i}=B')}\right)\times$$
$$\left(\prod_{i=1}^{n}(E_{i-1}(I(T_{1i}=A))^{I(T_{1i}=A)}(1-E_{i-1}(I(T_{1i}=A)))^{I(T_{1i}=B)}\right). \tag{2.19}$$

Now, using the equation $(A3)$ of Rosenberger et al. (1997), $-n^{-1}\sum_{i=1}^{n} E_{i-1}\{\frac{\partial^2 log\mathscr{L}_i}{\partial p_{AC}^2}\}$ from (2.18) becomes

$$n^{-1}\sum_{i=1}^{n}\left[p_{AC}^{-2}E_{i-1}(Y_i I(T_{1i}=A,T_{2i}=C))+(1-p_{AC})^{-2}E_{i-1}((1-Y_i)I(T_{1i}=A,T_{2i}=C))\right]$$
$$=n^{-1}\sum_{i=1}^{n}\left(p_{AC}^{-1}+(1-p_{AC})^{-1}\right)E_{i-1}(I(T_{1i}=A,T_{2i}=C))$$
$$\xrightarrow{a.s}(1-\gamma_A)(p_{AC}^{-1}+(1-p_{AC})^{-1})\left(\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}}\right)\left(\frac{\tau_A}{1+\tau_A}\right)\equiv v_{AC}. \tag{2.20}$$

The last step of the above is done using the results from the Appendix of Rosenberger et al. (2001). Thus, the variance of $\hat{p}_{AC}(\equiv \hat{p}_{AC,n})$ is $\frac{1}{n}v_{AC}^{-1}$. Similarly,

$$n^{-1}\sum_{i=1}^{n}\left[p_{AD}^{-2}E_{i-1}(Y_i I(T_{1i}=A,T_{2i}=D))+(1-p_{AD})^{-2}E_{i-1}((1-Y_i)I(T_{1i}=A,T_{2i}=D))\right]$$
$$=n^{-1}\sum_{i=1}^{n}\left(p_{AD}^{-1}+(1-p_{AD})^{-1}\right)E_{i-1}(I(T_{1i}=A,T_{2i}=D))$$

$$\xrightarrow{a.s} (1-\gamma_A)(p_{AD}^{-1}+(1-p_{AD})^{-1})\left(\frac{1}{1+\tau_{AC:AD}}\right)\left(\frac{\tau_A}{1+\tau_A}\right) \equiv v_{AD}. \tag{2.21}$$

Thus, the variance of $\hat{p}_{AD}(\equiv \hat{p}_{AD,n})$ is $\frac{1}{n}v_{AD}^{-1}$. Now,

$$\begin{aligned}
&n^{-1}\sum_{i=1}^{n}\left[p_{AA'}^{-2}E_{i-1}(Y_iI(T_{1i}=A,T_{2i}=A'))+(1-p_{AA'})^{-2}E_{i-1}((1-Y_i)I(T_{1i}=A,T_{2i}=A'))\right]\\
&=n^{-1}\sum_{i=1}^{n}\left(p_{AA'}^{-1}+(1-p_{AA'})^{-1}\right)E_{i-1}(I(T_{1i}=A,T_{2i}=A'))\\
&\xrightarrow{a.s}\gamma_A(p_{AA'}^{-1}+(1-p_{AA'})^{-1})\left(\frac{\tau_A}{1+\tau_A}\right)\equiv v_{AA'}.
\end{aligned} \tag{2.22}$$

So, the variance of $\hat{p}_{AA'}(\equiv \hat{p}_{AA',n})$ is $\frac{1}{n}v_{AA'}^{-1}$. Similarly,

$$\begin{aligned}
&n^{-1}\sum_{i=1}^{n}\left[p_{BE}^{-2}E_{i-1}(Y_iI(T_{1i}=B,T_{2i}=E))+(1-p_{BE})^{-2}E_{i-1}((1-Y_i)I(T_{1i}=B,T_{2i}=E))\right]\\
&=n^{-1}\sum_{i=1}^{n}\left(p_{BE}^{-1}+(1-p_{BE})^{-1}\right)E_{i-1}(I(T_{1i}=B,T_{2i}=E))\\
&\xrightarrow{a.s}(1-\gamma_B)(p_{BE}^{-1}+(1-p_{BE})^{-1})\left(\frac{\tau_{BE:BF}}{1+\tau_{BE:BF}}\right)\left(\frac{1}{1+\tau_A}\right)\equiv v_{BE}.
\end{aligned} \tag{2.23}$$

Thus, the variance of $\hat{p}_{BE}(\equiv \hat{p}_{BE,n})$ is $\frac{1}{n}v_{BE}^{-1}$. Similarly,

$$\begin{aligned}
&n^{-1}\sum_{i=1}^{n}\left[p_{BF}^{-2}E_{i-1}(Y_iI(T_{1i}=B,T_{2i}=F))+(1-p_{BF})^{-2}E_{i-1}((1-Y_i)I(T_{1i}=B,T_{2i}=F))\right]\\
&=n^{-1}\sum_{i=1}^{n}\left(p_{BF}^{-1}+(1-p_{BF})^{-1}\right)E_{i-1}(I(T_{1i}=B,T_{2i}=F))\\
&\xrightarrow{a.s}(1-\gamma_B)(p_{BF}^{-1}+(1-p_{BF})^{-1})\left(\frac{1}{1+\tau_{BE:BF}}\right)\left(\frac{1}{1+\tau_A}\right)\equiv v_{BF}.
\end{aligned} \tag{2.24}$$

So, the variance of $\hat{p}_{BF}(\equiv \hat{p}_{BF,n})$ is $\frac{1}{n}v_{BF}^{-1}$. Similarly,

$$\begin{aligned}
&n^{-1}\sum_{i=1}^{n}\left[p_{BB'}^{-2}E_{i-1}(Y_iI(T_{1i}=B,T_{2i}=B'))+(1-p_{BB'})^{-2}E_{i-1}((1-Y_i)I(T_{1i}=B,T_{2i}=B'))\right]\\
&=n^{-1}\sum_{i=1}^{n}\left(p_{BB'}^{-1}+(1-p_{BB'})^{-1}\right)E_{i-1}(I(T_{1i}=B,T_{2i}=B'))\\
&\xrightarrow{a.s}\gamma_B(p_{BB'}^{-1}+(1-p_{BB'})^{-1})\left(\frac{1}{1+\tau_A}\right)\equiv v_{BB'}.
\end{aligned} \tag{2.25}$$

Thus, the variance of $\hat{p}_{BB'}(\equiv \hat{p}_{BB',n})$ is $\frac{1}{n}v_{BB'}^{-1}$.

Derivation of Asymptotic Variance of Second-Stage Allocation Ratio

Using equations (2.20), (2.21), (2.23), and (2.24) from 2.9.4, we have (See Rosenberger et al. (1997), Rosenberger et al. (2001)),

$$\begin{aligned}
\sqrt{n}(\hat{p}_{AC,n} - p_{AC}) &\xrightarrow{d} N(0, v_{AC}^{-1}),\\
\sqrt{n}(\hat{p}_{AD,n} - p_{AD}) &\xrightarrow{d} N(0, v_{AD}^{-1}),\\
\sqrt{n}(\hat{p}_{BE,n} - p_{BE}) &\xrightarrow{d} N(0, v_{BE}^{-1}),\\
\sqrt{n}(\hat{p}_{BF,n} - p_{BF}) &\xrightarrow{d} N(0, v_{BF}^{-1}),
\end{aligned}$$

and are asymptotically independent. Using Slutsky's theorem,

$$\begin{aligned}
\sqrt{n}\left(\begin{bmatrix}\hat{p}_{AC,n} - p_{AC}\\ \hat{p}_{AD,n} - p_{AD}\end{bmatrix}\right) &\xrightarrow{d} N\left(\begin{bmatrix}0\\0\end{bmatrix}, \begin{bmatrix}v_{AC}^{-1} & 0\\ 0 & v_{AD}^{-1}\end{bmatrix}\right),\\
\sqrt{n}\left(\begin{bmatrix}\hat{p}_{BE,n} - p_{BE}\\ \hat{p}_{BF,n} - p_{BF}\end{bmatrix}\right) &\xrightarrow{d} N\left(\begin{bmatrix}0\\0\end{bmatrix}, \begin{bmatrix}v_{BE}^{-1} & 0\\ 0 & v_{BF}^{-1}\end{bmatrix}\right).
\end{aligned}$$

Note that, $\hat{\tau}_{AC:AD,n} = \sqrt{\frac{\hat{p}_{AC,n}}{\hat{p}_{AD,n}}}$, and $\hat{\tau}_{BE:BF,n} = \sqrt{\frac{\hat{p}_{BE,n}}{\hat{p}_{BF,n}}}$. Now using Delta Method (with function, $h(x,y) = \sqrt{\frac{x}{y}}$), we have,

$$\begin{aligned}
\sqrt{n}(\hat{\tau}_{AC:AD,n} - \tau^*_{AC:AD}) &\xrightarrow{d} N\left(0, \frac{1}{4}\left(\frac{v_{AC}^{-1}}{p_{AC}p_{AD}} + \frac{v_{AD}^{-1}p_{AC}}{p_{AD}^3}\right)\right),\\
\sqrt{n}(\hat{\tau}_{BE:BF,n} - \tau^*_{BE:BF}) &\xrightarrow{d} N\left(0, \frac{1}{4}\left(\frac{v_{BE}^{-1}}{p_{BE}p_{BF}} + \frac{v_{BF}^{-1}p_{BE}}{p_{BF}^3}\right)\right).
\end{aligned}$$

Finally, the asymptotic variances of the second-stage optimal adaptive allocation ratios are obtained as,

$$\begin{aligned}
Var(\hat{\tau}_{AC:AD,n}) &= \frac{1}{4n}\left(\frac{v_{AC}^{-1}}{p_{AC}p_{AD}} + \frac{v_{AD}^{-1}p_{AC}}{p_{AD}^3}\right),\\
Var(\hat{\tau}_{BE:BF,n}) &= \frac{1}{4n}\left(\frac{v_{BE}^{-1}}{p_{BE}p_{BF}} + \frac{v_{BF}^{-1}p_{BE}}{p_{BF}^3}\right).
\end{aligned}$$

Derivation of Asymptotic Variance of First-Stage Allocation Ratio

Using equations (2.20), (2.21), (2.22), (2.23), (2.24), and (2.25) from 2.9.4, we have,

$$\begin{aligned}
\sqrt{n}(\hat{p}_{AA',n} - p_{AA'}) &\xrightarrow{d} N(0, v_{AA'}^{-1}),\\
\sqrt{n}(\hat{p}_{AC,n} - p_{AC}) &\xrightarrow{d} N(0, v_{AC}^{-1}),\\
\sqrt{n}(\hat{p}_{AD,n} - p_{AD}) &\xrightarrow{d} N(0, v_{AD}^{-1}),
\end{aligned}$$

$$\begin{aligned}\sqrt{n}(\hat{p}_{BB',n} - p_{BB'}) &\xrightarrow{d} N(0, v_{BB'}^{-1}),\\ \sqrt{n}(\hat{p}_{BE,n} - p_{BE}) &\xrightarrow{d} N(0, v_{BE}^{-1}),\\ \sqrt{n}(\hat{p}_{BF,n} - p_{BF}) &\xrightarrow{d} N(0, v_{BF}^{-1}),\end{aligned}$$

and are asymptotically independent. Using Slutsky's theorem,

$$\sqrt{n}\left(\begin{bmatrix}\hat{p}_{AA',n} - p_{AA'}\\ \hat{p}_{AC,n} - p_{AC}\\ \hat{p}_{AD,n} - p_{AD}\end{bmatrix}\right) \xrightarrow{d} N\left(\begin{bmatrix}0\\0\\0\end{bmatrix}, \begin{bmatrix}v_{AA'}^{-1} & 0 & 0\\ 0 & v_{AC}^{-1} & 0\\ 0 & 0 & v_{AD}^{-1}\end{bmatrix}\right).$$

Similarly,

$$\sqrt{n}\left(\begin{bmatrix}\hat{p}_{BB',n} - p_{BB'}\\ \hat{p}_{BE,n} - p_{BE}\\ \hat{p}_{BF,n} - p_{BF}\end{bmatrix}\right) \xrightarrow{d} N\left(\begin{bmatrix}0\\0\\0\end{bmatrix}, \begin{bmatrix}v_{BB'}^{-1} & 0 & 0\\ 0 & v_{BE}^{-1} & 0\\ 0 & 0 & v_{BF}^{-1}\end{bmatrix}\right).$$

Now, we use the Delta method to derive the asymptotic distribution of the estimated first-stage success probability from 2.9.1. The chosen functional form for the Delta method is $h_1(x, y, z) = \gamma_{T_1} x + (1 - \gamma_{T_1}) \begin{bmatrix}\frac{y^{\frac{3}{2}} + z^{\frac{3}{2}}}{y^{\frac{1}{2}} + z^{\frac{1}{2}}}\end{bmatrix}$. Now, we have,

$$\begin{aligned}Var(\sqrt{n}\hat{p}_{T_1,n}) &= \gamma_{T_1}^2 \times v_{T_1T_1'}^{-1}\\ &+ \left(\frac{(1-\gamma_{T_1})\left(2\left(p_{T_1T_2}\right)^{\frac{3}{2}} + 3p_{T_1T_2}(p_{T_1T_2^*})^{\frac{1}{2}} - \left(p_{T_1T_2^*}\right)^{\frac{3}{2}}\right)}{2\left(p_{T_1T_2}\right)^{\frac{1}{2}}\left(p_{T_1T_2}^{\frac{1}{2}} + p_{T_1T_2^*}^{\frac{1}{2}}\right)^2}\right)^2 \times v_{T_1T_2}^{-1}\\ &+ \left(\frac{(1-\gamma_{T_1})\left(2\left(p_{T_1T_2^*}\right)^{\frac{3}{2}} + 3p_{T_1T_2^*}(p_{T_1T_2})^{\frac{1}{2}} - \left(p_{T_1T_2}\right)^{\frac{3}{2}}\right)}{2\left(p_{T_1T_2^*}\right)^{\frac{1}{2}}\left(p_{T_1T_2}^{\frac{1}{2}} + p_{T_1T_2^*}^{\frac{1}{2}}\right)^2}\right)^2 \times v_{T_1T_2^*}^{-1}\\ &\equiv v_{T_1}.\end{aligned}$$

Thus,

$$\sqrt{n}\left(\hat{p}_{T_1,n} - p_{T_1}\right) \xrightarrow{d} N(0, v_{T_1}).$$

Using the above equation, we have,

$$\sqrt{n}\left(\begin{bmatrix}\hat{p}_A - p_A\\ \hat{p}_B - p_B\end{bmatrix}\right) \xrightarrow{d} N\left(\begin{bmatrix}0\\0\end{bmatrix}, \begin{bmatrix}v_A & 0\\ 0 & v_B\end{bmatrix}\right).$$

Now, using the same approach as in 2.9.4, the variance of the first-stage optimal adaptive allocation ratio is obtained as,

$$\sigma^2_{\tau_A} = Var(\hat{\tau}_{A,n}) = \left(\frac{1}{4n}\right)\left(\frac{v_A}{\left(\gamma_A p_{AA'} + (1-\gamma_A)\left(\frac{p_{AC}^{3/2}+p_{AD}^{3/2}}{p_{AC}^{1/2}+p_{AD}^{1/2}}\right)\right)\left(\gamma_B p_{BB'} + (1-\gamma_B)\left(\frac{p_{BE}^{3/2}+p_{BF}^{3/2}}{p_{BE}^{1/2}+p_{BF}^{1/2}}\right)\right)}\right) + \left(\frac{1}{4n}\right)\left(\frac{v_B\left(\gamma_A p_{AA'} + (1-\gamma_A)\left(\frac{p_{AC}^{3/2}+p_{AD}^{3/2}}{p_{AC}^{1/2}+p_{AD}^{1/2}}\right)\right)}{\left(\gamma_B p_{BB'} + (1-\gamma_B)\left(\frac{p_{BE}^{3/2}+p_{BF}^{3/2}}{p_{BE}^{1/2}+p_{BF}^{1/2}}\right)\right)^3}\right).$$

2.9.5 Optimal Adaptive Allocation Ratio for Odds-Ratio

In this section, we consider the objective function as the odds-ratio. The corresponding optimum allocation ratios for the same objective function are,

$$\tau^*_{AC:AD} = \left(\sqrt{\frac{p_{AD}}{p_{AC}}}\right)\left(\frac{q_{AD}}{q_{AC}}\right), \quad \tau^*_{BE:BF} = \left(\sqrt{\frac{p_{BF}}{p_{BE}}}\right)\left(\frac{q_{BF}}{q_{BE}}\right) \quad \text{and}$$

$$\tau^*_A = \left(\frac{1+\tau^*_{AC:AD}}{1+\tau^*_{BE:BF}}\right)^{\frac{3}{2}}\left(\frac{(\gamma_B p_{BB'}(1+\tau^*_{BE:BF}) + (1-\gamma_B)(\tau^*_{BE:BF}p_{BE} + p_{BF}))}{(\gamma_A p_{AA'}(1+\tau^*_{AC:AD}) + (1-\gamma_A)(\tau^*_{AC:AD}p_{AC} + p_{AD}))}\right)^{\frac{1}{2}} \times \left(\frac{(\gamma_B q_{BB'}(1+\tau^*_{BE:BF}) + (1-\gamma_B)(\tau^*_{BE:BF}q_{BE} + q_{BF}))}{(\gamma_A q_{AA'}(1+\tau^*_{AC:AD}) + (1-\gamma_A)(\tau^*_{AC:AD}q_{AC} + q_{AD}))}\right).$$

Derivation of Second-Stage Optimal Adaptive Allocation Ratio for Odds-Ratio

Let us consider the objective function $g(\cdot,\cdot)$ as introduced in Section 2.3 to be odds-ratio. We consider the same setup as in 2.9.2. The odds-ratio of corresponding to treatment sequences $\{T_1, T_2\}$ and $\{T_1, T_2^*\}$ is defined as, $\frac{p_{T_1T_2}(1-p_{T_1T_2^*})}{p_{T_1T_2^*}(1-p_{T_1T_2})}$. The optimality criterion (as defined in Section 2.3)using the asymptotic variance of the objective function $avar(g(\hat{p}_{T_1T_2}, \hat{p}_{T_1T_2^*}))$ can be expressed,

$$\left(\frac{p_{T_1T_2}q_{T_1T_2^*}}{p_{T_1T_2^*}q_{T_1T_2}}\right)^2\left(\frac{1}{n_{T_1T_2}p_{T_1T_2}} + \frac{1}{n_{T_1T_2}q_{T_1T_2}} + \frac{1}{n_{T_1T_2^*}p_{T_1T_2^*}} + \frac{1}{n_{T_1T_2^*}q_{T_1T_2^*}}\right) = \epsilon_2, \quad \text{for some constant } \epsilon_2 > 0.$$

Note that, $\tau_{T_1T_2:T_1T_2^*} = \frac{n_{T_1T_2}}{n_{T_1T_2^*}}$. The $n_{T_1T_2}$, and $n_{T_1T_2^*}$ can be written as,

$$n_{T_1T_2} = n^{NR}_{T_1}\left(\frac{\tau_{T_1T_2:T_1T_2^*}}{1+\tau_{T_1T_2:T_1T_2^*}}\right), n_{T_1T_2^*} = \frac{n^{NR}_{T_1}}{1+\tau_{T_1T_2:T_1T_2^*}},$$

where $n_{T_1}^{NR} = n_{T_1T_2} + n_{T_1T_2^*}$, is the total number of patients who obtained treatment T_1 at the first stage and become non-responders at the end of the first stage. Substituting the expressions of $n_{T_1T_2}$ and $n_{T_1T_2^*}$ in asymptotic variance expression obtained earlier,

$$\frac{1}{\frac{n_{T_1}^{NR}\tau_{T_1T_2:T_1T_2^*}}{1+\tau_{T_1T_2:T_1T_2^*}}p_{T_1T_2}q_{T_1T_2}} + \frac{1}{\frac{n_{T_1}^{NR}}{1+\tau_{T_1T_2:T_1T_2^*}}p_{T_1T_2^*}q_{T_1T_2^*}} = \epsilon_2\left(\frac{p_{T_1T_2^*}q_{T_1T_2}}{p_{T_1T_2}q_{T_1T_2^*}}\right)^2.$$

Solving for $n_{T_1}^{NR}$, gives,

$$n_{T_1}^{NR} = \frac{\left(1+\tau_{T_1T_2:T_1T_2^*}\right)\left(p_{T_1T_2^*}q_{T_1T_2^*} + \tau_{T_1T_2:T_1T_2^*}p_{T_1T_2}q_{T_1T_2}\right)}{\epsilon_2\tau_{T_1T_2:T_1T_2^*}p_{T_1T_2}q_{T_1T_2}p_{T_1T_2^*}q_{T_1T_2^*}}\left(\frac{p_{T_1T_2}q_{T_1T_2^*}}{p_{T_1T_2^*}q_{T_1T_2}}\right)^2. \tag{2.26}$$

From Section 2.3, the second-stage optimal adaptive allocation ratio is obtained as,

$$\tau^*_{T_1T_2:T_1T_2^*} = \arg\min_{\tau_{T_1T_2:T_1T_2^*}} F_2(\tau_{T_1T_2:T_1T_2^*}) \quad \text{subject to}$$
$$\left(\frac{p_{T_1T_2}q_{T_1T_2^*}}{p_{T_1T_2^*}q_{T_1T_2}}\right)^2\left(\frac{1}{n_{T_1T_2}p_{T_1T_2}} + \frac{1}{n_{T_1T_2}q_{T_1T_2}} + \frac{1}{n_{T_1T_2^*}p_{T_1T_2^*}} + \frac{1}{n_{T_1T_2^*}q_{T_1T_2^*}}\right) = \epsilon_2.$$

Thus using the above optimality criterion, the optimal value of $\tau_{T_1T_2:T_1T_2^*}$ is,

$$\tau^*_{T_1T_2:T_1T_2^*} = \left(\sqrt{\frac{p_{T_1T_2^*}}{p_{T_1T_2}}}\right)\left(\frac{q_{T_1T_2^*}}{q_{T_1T_2}}\right). \tag{2.27}$$

As derived in 2.9.2 using Lemma 1, on equation (2.27) we have,

$$\hat{\tau}_{T_1T_2:T_1T_2^*,n} \xrightarrow{a.s} \left(\sqrt{\frac{p_{T_1T_2^*}}{p_{T_1T_2}}}\right)\left(\frac{q_{T_1T_2^*}}{q_{T_1T_2}}\right). \tag{2.28}$$

Allocation Procedure

Similar to the procedure of Section 2.4 (as given by Equation (2.1) for simple difference), the adaptive allocation process for the second-stage optimal adaptive allocation ratio using odds-ratio as the objective function is,

$$E_{i-1}(I(T_{2i} = t_2|T_{1i} = t_1, R_{T_{1i}} = 0)) = \frac{\sqrt{\hat{p}_{t_1t_2^*,i-1}}\hat{q}_{t_1t_2^*,i-1}}{\sqrt{\hat{p}_{t_1t_2,i-1}}\hat{q}_{t_1t_2,i-1} + \sqrt{\hat{p}_{t_1t_2^*,i-1}}\hat{q}_{t_1t_2^*,i-1}}. \tag{2.29}$$

Asymptotic Variance

Following the same procedure, as mentioned in 2.9.4, using Delta method with the function $h(x,y)$ as $\sqrt{\frac{y}{x}}\frac{1-y}{1-x}$, the variance of the two second-stage optimal adaptive allocation ratios

$\hat{\tau}_{AC:AD,n}$, and $\hat{\tau}_{BE:BF,n}$ are,

$$Var(\hat{\tau}_{AC:AD,n}) = \frac{1}{4n}\left(\frac{v_{AC}^{-1}\left(1-3p_{AC}\right)^2\left(1-p_{AD}\right)^2 p_{AD}}{p_{AC}^3\left(1-p_{AC}\right)^4} + \frac{v_{AD}^{-1}\left(1-3p_{AD}\right)^2}{p_{AC}\left(1-p_{AC}\right)^2 p_{AD}}\right),$$

$$Var(\hat{\tau}_{BE:BF,n}) = \frac{1}{4n}\left(\frac{v_{BE}^{-1}\left(1-3p_{BE}\right)^2\left(1-p_{BF}\right)^2 p_{BF}}{p_{BE}^3\left(1-p_{BE}\right)^4} + \frac{v_{BF}^{-1}\left(1-3p_{BF}\right)^2}{p_{BE}\left(1-p_{BE}\right)^2 p_{BF}}\right),$$

where v_{AC}, v_{AD}, v_{BE}, and v_{BF} are from 2.9.4. Thus, the asymptotic distributions of the estimated second-stage optimum allocation ratios are,

$$\sqrt{n}(\hat{\tau}_{AC:AD,n} - \tau^*_{AC:AD}) \xrightarrow{d} N\left(0, \frac{1}{4}\left(\frac{v_{AC}^{-1}\left(1-3p_{AC}\right)^2\left(1-p_{AD}\right)^2 p_{AD}}{p_{AC}^3\left(1-p_{AC}\right)^4} + \frac{v_{AD}^{-1}\left(1-3p_{AD}\right)^2}{p_{AC}\left(1-p_{AC}\right)^2 p_{AD}}\right)\right),$$

$$\sqrt{n}(\hat{\tau}_{BE:BF,n} - \tau^*_{BE:BF}) \xrightarrow{d} N\left(0, \frac{1}{4}\left(\frac{v_{BE}^{-1}\left(1-3p_{BE}\right)^2\left(1-p_{BF}\right)^2 p_{BF}}{p_{BE}^3\left(1-p_{BE}\right)^4} + \frac{v_{BF}^{-1}\left(1-3p_{BF}\right)^2}{p_{BE}\left(1-p_{BE}\right)^2 p_{BF}}\right)\right).$$

Derivation of First-Stage Optimal Adaptive Allocation Ratio for Odds-Ratio

We consider the objective function $g(\cdot,\cdot)$ as introduced in Section 2.3 to be the odds-ratio. The objective function of odds-ratio for comparing the two first-stage probabilities (p_A, and p_B) is given by $\frac{p_A(1-p_B)}{p_B(1-p_A)}$. The optimality criterion (as defined in Section 2.3) for the first-stage allocation ratio using the asymptotic variance of the objective function $avar(g(\hat{p}_A, \hat{p}_B))$ can be expressed as

$$\left(\frac{p_A q_B}{p_B q_A}\right)^2\left(\frac{1}{n_A p_A} + \frac{1}{n_A q_A} + \frac{1}{n_B p_B} + \frac{1}{n_B q_B}\right) = \epsilon_1.$$

Using the expression for first-stage success probability (p_{T_1}) and failure probability (q_{T_1}) as obtained in 2.9.1, in above equation, we get,

$$\left(\frac{\left(\gamma_A p_{AA'} + (1-\gamma_A)\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}}p_{AC} + (1-\gamma_A)\frac{1}{1+\tau_{AC:AD}}p_{AD}\right)\left(\gamma_B q_{BB'} + (1-\gamma_B)\frac{\tau_{BE:BF}}{1+\tau_{BE:BF}}q_{BE} + (1-\gamma_B)\frac{1}{1+\tau_{BE:BF}}q_{BF}\right)}{\left(\gamma_B p_{BB'} + (1-\gamma_B)\frac{\tau_{BE:BF}}{1+\tau_{BE:BF}}p_{BE} + (1-\gamma_B)\frac{1}{1+\tau_{BE:BF}}p_{BF}\right)\left(\gamma_A q_{AA'} + (1-\gamma_A)\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}}q_{AC} + (1-\gamma_A)\frac{1}{1+\tau_{AC:AD}}q_{AD}\right)}\right)^2 \left[\frac{1}{n_A p_A q_A} + \frac{1}{n_B p_B q_B}\right] = \epsilon_1.$$

Since, $\tau_A = \frac{n_A}{n_B}$, n_A, and n_B can be written as,

$$n_A = n\left(\frac{\tau_A}{1+\tau_A}\right), n_B = \frac{n}{1+\tau_A}.$$

The total number of failures that is obtained after completion of SMART can be

expressed as,

$$F_1(\tau_A, \tau_{AC:AD}, \tau_{BE:BF}) = n_{AA'}q_{AA'} + n_{AC}q_{AC} + n_{AD}q_{AD} + n_{BB'}q_{BB'} + n_{BE}q_{BE} + n_{BF}q_{BF}$$

Now, from Section 2.3, we have,

$$\tau_A^* = \arg\min_{\tau_A} F_1(\tau_A, \tau_{AC:AD}^*, \tau_{BE:BF}^*) \text{ subject to}$$
$$\left(\frac{\left(\gamma_A p_{AA'}+(1-\gamma_A)\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}}p_{AC}+(1-\gamma_A)\frac{1}{1+\tau_{AC:AD}}p_{AD}\right)\left(\gamma_B q_{BB'}+(1-\gamma_B)\frac{\tau_{BE:BF}}{1+\tau_{BE:BF}}q_{BE}+(1-\gamma_B)\frac{1}{1+\tau_{BE:BF}}q_{BF}\right)}{\left(\gamma_B p_{BB'}+(1-\gamma_B)\frac{\tau_{BE:BF}}{1+\tau_{BE:BF}}p_{BE}+(1-\gamma_B)\frac{1}{1+\tau_{BE:BF}}p_{BF}\right)\left(\gamma_A q_{AA'}+(1-\gamma_A)\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}}q_{AC}+(1-\gamma_A)\frac{1}{1+\tau_{AC:AD}}q_{AD}\right)}\right)^2$$
$$\left[\frac{1}{n_A p_A q_A} + \frac{1}{n_B p_B q_B}\right] = \epsilon_1.$$

Using the above optimality criterion and the expression of n_A, n_B, we get the first-stage optimal adaptive allocation ratio as,

$$\tau_A^* = \left(\frac{1+\tau_{AC:AD}^*}{1+\tau_{BE:BF}^*}\right)^{\frac{3}{2}} \left(\frac{(\gamma_B p_{BB'}(1+\tau_{BE:BF}^*) + (1-\gamma_B)(\tau_{BE:BF}^* p_{BE} + p_{BF}))}{(\gamma_A p_{AA'}(1+\tau_{AC:AD}^*) + (1-\gamma_A)(\tau_{AC:AD}^* p_{AC} + p_{AD}))}\right)^{\frac{1}{2}}$$
$$\times \left(\frac{(\gamma_B q_{BB'}(1+\tau_{BE:BF}^*) + (1-\gamma_B)(\tau_{BE:BF}^* q_{BE} + q_{BF}))}{(\gamma_A q_{AA'}(1+\tau_{AC:AD}^*) + (1-\gamma_A)(\tau_{AC:AD}^* q_{AC} + q_{AD}))}\right). \quad (2.30)$$

Similar to the 2.9.3, using Lemma 1, and Lemma 2 on equation (2.30), we get,

$$\hat{\tau}_{A,n} \xrightarrow{a.s} \left(\frac{\left(\sqrt{p_{AC}}q_{AC} + \sqrt{p_{AD}}q_{AD}\right)}{\left(\sqrt{p_{BE}}q_{BE} + \sqrt{p_{BF}}q_{BF}\right)}\right)^{\frac{3}{2}}$$
$$\times \left(\frac{(\gamma_B p_{BB'}(\sqrt{p_{BE}}q_{BE} + \sqrt{p_{BF}}q_{BF}) + (1-\gamma_B)(\sqrt{p_{BF}}q_{BF}p_{BE} + \sqrt{p_{BE}}q_{BE}p_{BF}))}{(\gamma_A p_{AA'}(\sqrt{p_{AC}}q_{AC} + \sqrt{p_{AD}}q_{AD}) + (1-\gamma_A)(\sqrt{p_{AD}}q_{AD}p_{AC} + \sqrt{p_{AC}}q_{AC}p_{AD}))}\right)^{\frac{1}{2}}$$
$$\times \left(\frac{(\gamma_B q_{BB'}(\sqrt{p_{BE}}q_{BE} + \sqrt{p_{BF}}q_{BF}) + (1-\gamma_B)(\sqrt{p_{BF}}q_{BF}q_{BE} + \sqrt{p_{BE}}q_{BE}q_{BF}))}{(\gamma_A q_{AA'}(\sqrt{p_{AC}}q_{AC} + \sqrt{p_{AD}}q_{AD}) + (1-\gamma_A)(\sqrt{p_{AD}}q_{AD}q_{AC} + \sqrt{p_{AC}}q_{AC}q_{AD}))}\right)$$
$$= \tau_A^*. \quad (2.31)$$

Allocation Procedure

Similar to the procedure of Section 2.4 (as given by Equation (2.2) for simple difference), the adaptive allocation process for the first-stage optimal adaptive allocation ratio using odds-ratio as the objective function is,

$$E_{i-1}(T_{1i}) = \frac{\sqrt{l_{i-1}}}{\sqrt{l_{i-1}} + \sqrt{m_{i-1}}}, \quad (2.32)$$

where

$$l_{i-1} = (1+\hat{\tau}_{AC:AD,i})^{\frac{3}{2}} \left((\gamma_B \hat{p}_{BB',i-1}(1+\hat{\tau}_{BE:BF,i}) + (1-\gamma_B)(\hat{\tau}_{BE:BF,i}\hat{p}_{BE,i-1} + \hat{p}_{BF,i-1}))\right)^{\frac{1}{2}}$$

$$\times \left((\gamma_B \hat{q}_{BB',i-1}(1+\hat{\tau}_{BE:BF,i}) + (1-\gamma_B)(\hat{\tau}_{BE:BF,i}\hat{q}_{BE,i-1} + \hat{q}_{BF,i-1})) \right),$$

$$m_{i-1} = (1+\hat{\tau}_{BE:BF,i})^{\frac{3}{2}} \left((\gamma_A \hat{p}_{AA',i-1}(1+\hat{\tau}_{AC:AD,i}) + (1-\gamma_A)(\hat{\tau}_{AC:AD,i}\hat{p}_{AC,i-1} + \hat{p}_{AD,i-1})) \right)^{\frac{1}{2}}$$
$$\times \left((\gamma_A \hat{q}_{AA',i-1}(1+\hat{\tau}_{AC:AD,i}) + (1-\gamma_A)(\hat{\tau}_{AC:AD,i}\hat{q}_{AC,i-1} + \hat{q}_{AD,i-1})) \right).$$

Asymptotic Variance

Following the same procedure, as mentioned in 2.9.4, and 2.9.4, using Delta method with the function $h(x,y)$ as $\sqrt{\frac{y}{x}}\frac{1-y}{1-x}$, the variance of the first-stage optimal adaptive allocation ratio $(\hat{\tau}_{A,n})$ is obtain as,

$$Var(\hat{\tau}_{A,n}) = \frac{1}{4n}\left(\frac{v_A (1-3p_A)^2 (1-p_B)^2 p_B}{p_A^3 (1-p_A)^4} + \frac{v_B (1-3p_B)^2}{p_A (1-p_A)^2 p_B} \right),$$

where the expressions of v_A, and v_B are from 2.9.4, and p_A, and p_B are from 2.9.1.

Thus, the asymptotic distribution of the estimated first-stage optimum allocation ratio is,

$$\sqrt{n}(\hat{\tau}_{A,n} - \tau_A^*) \xrightarrow{d} N\left(0, \frac{1}{4}\left(\frac{v_A (1-3p_A)^2 (1-p_B)^2 p_B}{p_A^3 (1-p_A)^4} + \frac{v_B (1-3p_B)^2}{p_A (1-p_A)^2 p_B} \right)\right).$$

2.9.6 Optimal Adaptive Allocation Ratio for Relative-Risk

Here, we are considering the objective function as the relative-risk, for which the optimum allocation ratios are obtained as,

$$\tau^*_{AC:AD} = \left(\sqrt{\frac{p_{AC}}{p_{AD}}}\right)\left(\frac{q_{AD}}{q_{AC}}\right), \quad \tau^*_{BE:BF} = \left(\sqrt{\frac{p_{BE}}{p_{BF}}}\right)\left(\frac{q_{BF}}{q_{BE}}\right) \quad \text{and}$$

$$\tau_A^* = \left(\frac{1+\tau^*_{AC:AD}}{1+\tau^*_{BE:BF}}\right)^{\frac{1}{2}} \left(\frac{(\gamma_A p_{AA'}(1+\tau^*_{AC:AD}) + (1-\gamma_A)(\tau^*_{AC:AD}p_{AC} + p_{AD}))}{(\gamma_B p_{BB'}(1+\tau^*_{BE:BF}) + (1-\gamma_B)(\tau^*_{BE:BF}p_{BE} + p_{BF}))}\right)^{\frac{1}{2}}$$
$$\times \left(\frac{(\gamma_B q_{BB'}(1+\tau^*_{BE:BF}) + (1-\gamma_B)(\tau^*_{BE:BF}q_{BE} + q_{BF}))}{(\gamma_A q_{AA'}(1+\tau^*_{AC:AD}) + (1-\gamma_A)(\tau^*_{AC:AD}q_{AC} + q_{AD}))}\right).$$

Derivation of Second-Stage Optimal Adaptive Allocation Ratio for Relative-Risk

We consider the objective function $g(\cdot,\cdot)$ as introduced in Section 2.3 to be the relative-risk. The objective function of relative-risk for comparing the two second-stage probabilities ($p_{T_1T_2}$, and $p_{T_1T_2^*}$) is given by $\frac{1-p_{T_1T_2^*}}{1-p_{T_1T_2}}$. The optimality criterion (as defined in Section 2.3 for the first-stage allocation ratio using the asymptotic variance of the objective func-

tion $avar(g(\hat{p}_{T_1T_2}, \hat{p}^*_{T_1T_2}))$ can be expressed as

$$\frac{1}{(1-p_{T_1T_2})^2}\left(\frac{p_{T_1T_2^*}q_{T_1T_2^*}}{n_{T_1T_2^*}} + \frac{(1-p_{T_1T_2^*})^2 p_{T_1T_2}q_{T_1T_2}}{n_{T_1T_2}(1-p_{T_1T_2})^2}\right) = \epsilon_2, \text{ for some constant } \epsilon_2 > 0.$$

Note that, $\tau_{T_1T_2:T_1T_2^*} = \frac{n_{T_1T_2}}{n_{T_1T_2^*}}$. Then $n_{T_1T_2}$, and $n_{T_1T_2^*}$ can be written as,

$$n_{T_1T_2} = n^{NR}_{T_1}\left(\frac{\tau_{T_1T_2:T_1T_2^*}}{1+\tau_{T_1T_2:T_1T_2^*}}\right), n_{T_1T_2^*} = \frac{n^{NR}_{T_1}}{1+\tau_{T_1T_2:T_1T_2^*}},$$

where $n^{NR}_{T_1} = n_{T_1T_2} + n_{T_1T_2^*}$, is the total number of patients who obtained treatment T_1 at the first stage and become non-responders at the end of the first stage. Substituting the expressions of $n_{T_1T_2}$ and $n_{T_1T_2^*}$ in asymptotic variance expression obtained earlier,

$$\frac{1}{(1-p_{T_1T_2})^2}\left(\frac{p_{T_1T_2^*}q_{T_1T_2^*}}{\frac{n^{NR}_{T_1}}{1+\tau_{T_1T_2:T_1T_2^*}}} + \frac{(1-p_{T_1T_2^*})^2 p_{T_1T_2}q_{T_1T_2}}{n^{NR}_{T_1}\left(\frac{\tau_{T_1T_2:T_1T_2^*}}{1+\tau_{T_1T_2:T_1T_2^*}}\right)(1-p_{T_1T_2})^2}\right) = \epsilon_2.$$

From Section 2.3, the second-stage optimal adaptive allocation ratio is obtained as,

$$\tau^*_{T_1T_2:T_1T_2^*} = \arg\min_{\tau_{T_1T_2:T_1T_2^*}} F_2(\tau_{T_1T_2:T_1T_2^*}) \quad \text{subject to}$$

$$\frac{1}{(1-p_{T_1T_2})^2}\left(\frac{p_{T_1T_2^*}q_{T_1T_2^*}}{\frac{n^{NR}_{T_1}}{1+\tau_{T_1T_2:T_1T_2^*}}} + \frac{(1-p_{T_1T_2^*})^2 p_{T_1T_2}q_{T_1T_2}}{n^{NR}_{T_1}\left(\frac{\tau_{T_1T_2:T_1T_2^*}}{1+\tau_{T_1T_2:T_1T_2^*}}\right)(1-p_{T_1T_2})^2}\right) = \epsilon_2.$$

Thus, using the above optimality criterion, the optimal value of $\tau_{T_1T_2:T_1T_2^*}$ is,

$$\tau^*_{T_1T_2:T_1T_2^*} = \left(\sqrt{\frac{p_{T_1T_2}}{p_{T_1T_2^*}}}\right)\left(\frac{q_{T_1T_2^*}}{q_{T_1T_2}}\right). \tag{2.33}$$

As derived in 2.9.2 using Lemma 1, on equation (2.33) we have,

$$\hat{\tau}_{T_1T_2:T_1T_2^*,n} \xrightarrow{a.s} \left(\sqrt{\frac{p_{T_1T_2}}{p_{T_1T_2^*}}}\right)\left(\frac{q_{T_1T_2^*}}{q_{T_1T_2}}\right). \tag{2.34}$$

Allocation Procedure

Similar to the procedure of Section 2.4 (as given by Equation (2.1) for simple difference), the adaptive allocation process for the second-stage optimal adaptive allocation ratio

using relative-risk as the objective function is,

$$E_{i-1}(I(T_{2i}=t_2|T_{1i}=t_1,R_{T_{1i}}=0))=\frac{\sqrt{\hat{p}_{t_1t_2,i-1}}\hat{q}_{t_1t_2^*,i-1}}{\sqrt{\hat{p}_{t_1t_2,i-1}}\hat{q}_{t_1t_2^*,i-1}+\sqrt{\hat{p}_{t_1t_2^*,i-1}}\hat{q}_{t_1t_2,i-1}}. \tag{2.35}$$

Asymptotic Variance

Following the same procedure, as mentioned in 2.9.4, using Delta method with the function $h(x,y)=\sqrt{\frac{x}{y}}(\frac{1-y}{1-x})$, the variance of the two second-stage optimal adaptive allocation ratios $\hat{\tau}_{AC:AD,n}$, and $\hat{\tau}_{BE:BF,n}$ are,

$$Var(\hat{\tau}_{AC:AD,n})=\frac{1}{4n}\left(\frac{v_{AC}^{-1}\left(1+p_{AC}\right)^2\left(1-p_{AD}\right)^2}{p_{AC}\left(1-p_{AC}\right)^4p_{AD}}+\frac{v_{AD}^{-1}\left(1+p_{AD}\right)^2p_{AC}}{\left(1-p_{AC}\right)^2p_{AD}^3}\right),$$

$$Var(\hat{\tau}_{BE:BF,n})=\frac{1}{4n}\left(\frac{v_{BE}^{-1}\left(1+p_{BE}\right)^2\left(1-p_{BF}\right)^2}{p_{BE}\left(1-p_{BE}\right)^4p_{BF}}+\frac{v_{BF}^{-1}\left(1+p_{BF}\right)^2p_{BE}}{\left(1-p_{BE}\right)^2p_{BF}^3}\right),$$

where v_{AC}, v_{AD}, v_{BE}, and v_{BF} are from 2.9.4. Thus, the asymptotic distributions of the estimated second-stage optimum allocation ratios are,

$$\sqrt{n}(\hat{\tau}_{AC:AD,n}-\tau^*_{AC:AD}) \xrightarrow{d} N\left(0,\frac{1}{4}\left(\frac{v_{AC}^{-1}\left(1+p_{AC}\right)^2\left(1-p_{AD}\right)^2}{p_{AC}\left(1-p_{AC}\right)^4p_{AD}}+\frac{v_{AD}^{-1}\left(1+p_{AD}\right)^2p_{AC}}{\left(1-p_{AC}\right)^2p_{AD}^3}\right)\right),$$

$$\sqrt{n}(\hat{\tau}_{BE:BF,n}-\tau^*_{BE:BF}) \xrightarrow{d} N\left(0,\frac{1}{4}\left(\frac{v_{BE}^{-1}\left(1+p_{BE}\right)^2\left(1-p_{BF}\right)^2}{p_{BE}\left(1-p_{BE}\right)^4p_{BF}}+\frac{v_{BF}^{-1}\left(1+p_{BF}\right)^2p_{BE}}{\left(1-p_{BE}\right)^2p_{BF}^3}\right)\right).$$

Derivation of First-Stage Optimal Adaptive Allocation Ratio for Relative-Risk

We consider the objective function $g(\cdot,\cdot)$ as introduced in Section 2.3to be the relative-risk. The objective function of relative-risk for comparing the two first-stage probabilities (p_A, and p_B) is given by $\frac{1-p_B}{1-p_A}$. The optimality criterion (as defined in Section 2.3) for the first-stage allocation ratio using the asymptotic variance of the objective function $avar(g(\hat{p}_A,\hat{p}_B))$ can be expressed as

$$\frac{1}{q_A^2}\left(\frac{q_B^2p_A}{n_Aq_A}+\frac{p_Bq_B}{n_B}\right)=\epsilon_1,\ \text{for some constant } \epsilon_1>0.$$

Using the expression for first-stage success probability (p_{T_1}) and failure probability (q_{T_1}) as obtained in 2.9.1, in above equation, we get,

$$\frac{1}{\left(\gamma_A q_{AA'} + (1-\gamma_A)\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}} q_{AC} + (1-\gamma_A)\frac{1}{1+\tau_{AC:AD}} q_{AD}\right)^2} \times$$
$$\left[\frac{\left(\gamma_A p_{AA'} + (1-\gamma_A)\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}} p_{AC} + (1-\gamma_A)\frac{1}{1+\tau_{AC:AD}} p_{AD}\right)\left(\gamma_B q_{BB'} + (1-\gamma_B)\frac{\tau_{BE:BF}}{1+\tau_{BE:BF}} q_{BE} + (1-\gamma_B)\frac{1}{1+\tau_{BE:BF}} q_{BF}\right)^2}{n_A\left(\gamma_A q_{AA'} + (1-\gamma_A)\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}} q_{AC} + (1-\gamma_A)\frac{1}{1+\tau_{AC:AD}} q_{AD}\right)} \right.$$
$$\left. + \frac{\left(\gamma_B p_{BB'} + (1-\gamma_B)\frac{\tau_{BE:BF}}{1+\tau_{BE:BF}} p_{BE} + (1-\gamma_B)\frac{1}{1+\tau_{BE:BF}} p_{BF}\right)\left(\gamma_B q_{BB'} + (1-\gamma_B)\frac{\tau_{BE:BF}}{1+\tau_{BE:BF}} q_{BE} + (1-\gamma_B)\frac{1}{1+\tau_{BE:BF}} q_{BF}\right)}{n_B} \right] = \epsilon_1.$$

Since, $\tau_A = \frac{n_A}{n_B}$, n_A, and n_B can be written as,

$$n_A = n\left(\frac{\tau_A}{1+\tau_A}\right), n_B = \frac{n}{1+\tau_A}.$$

The total number of failures that is obtained after completion of SMART is,

$$F_1(\tau_A, \tau_{AC:AD}, \tau_{BE:BF}) = n_{AA'} q_{AA'} + n_{AC} q_{AC} + n_{AD} q_{AD} + n_{BB'} q_{BB'} + n_{BE} q_{BE} + n_{BF} q_{BF}.$$

Now, from Section 2.3, we have,

$$\tau_A^* = \arg\min_{\tau_A} F_1\left(\tau_A, \tau^*_{AC:AD}, \tau^*_{BE:BF}\right) \quad \text{subject to}$$
$$\frac{1}{\left(\gamma_A q_{AA'} + (1-\gamma_A)\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}} q_{AC} + (1-\gamma_A)\frac{1}{1+\tau_{AC:AD}} q_{AD}\right)^2} \times$$
$$\left[\frac{\left(\gamma_A p_{AA'} + (1-\gamma_A)\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}} p_{AC} + (1-\gamma_A)\frac{1}{1+\tau_{AC:AD}} p_{AD}\right)\left(\gamma_B q_{BB'} + (1-\gamma_B)\frac{\tau_{BE:BF}}{1+\tau_{BE:BF}} q_{BE} + (1-\gamma_B)\frac{1}{1+\tau_{BE:BF}} q_{BF}\right)^2}{n_A\left(\gamma_A q_{AA'} + (1-\gamma_A)\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}} q_{AC} + (1-\gamma_A)\frac{1}{1+\tau_{AC:AD}} q_{AD}\right)} \right.$$
$$\left. + \frac{\left(\gamma_B p_{BB'} + (1-\gamma_B)\frac{\tau_{BE:BF}}{1+\tau_{BE:BF}} p_{BE} + (1-\gamma_B)\frac{1}{1+\tau_{BE:BF}} p_{BF}\right)\left(\gamma_B q_{BB'} + (1-\gamma_B)\frac{\tau_{BE:BF}}{1+\tau_{BE:BF}} q_{BE} + (1-\gamma_B)\frac{1}{1+\tau_{BE:BF}} q_{BF}\right)}{n_B} \right] = \epsilon_1.$$

Using the above optimality criterion and the expression of n_A, n_B, we get the first-stage optimal adaptive allocation ratio as,

$$\tau_A^* = \left(\frac{1+\tau^*_{AC:AD}}{1+\tau^*_{BE:BF}}\right)^{\frac{1}{2}} \left(\frac{(\gamma_A p_{AA'}(1+\tau^*_{AC:AD}) + (1-\gamma_A)(\tau^*_{AC:AD} p_{AC} + p_{AD}))}{(\gamma_B p_{BB'}(1+\tau^*_{BE:BF}) + (1-\gamma_B)(\tau^*_{BE:BF} p_{BE} + p_{BF}))}\right)^{\frac{1}{2}}$$
$$\times \left(\frac{(\gamma_B q_{BB'}(1+\tau^*_{BE:BF}) + (1-\gamma_B)(\tau^*_{BE:BF} q_{BE} + q_{BF}))}{(\gamma_A q_{AA'}(1+\tau^*_{AC:AD}) + (1-\gamma_A)(\tau^*_{AC:AD} q_{AC} + q_{AD}))}\right). \quad (2.36)$$

Similar to the 2.9.3, using Lemma 1, and Lemma 2 on equation (2.36), we get,

$$\hat{\tau}_{A,n} \xrightarrow{a.s} \left(\frac{\left(\sqrt{p_{AC}} q_{AD} + \sqrt{p_{AD}} q_{AC}\right)}{\left(\sqrt{p_{BE}} q_{BF} + \sqrt{p_{BF}} q_{BE}\right)}\right)^{\frac{1}{2}}$$
$$\times \left(\frac{(\gamma_A p_{AA'}(\sqrt{p_{AC}} q_{AD} + \sqrt{p_{AD}} q_{AC}) + (1-\gamma_A)(\sqrt{p_{AC}} q_{AD} p_{AC} + \sqrt{p_{AD}} q_{AC} p_{AD}))}{(\gamma_B p_{BB'}(\sqrt{p_{BE}} q_{BF} + \sqrt{p_{BF}} q_{BE}) + (1-\gamma_B)(\sqrt{p_{BE}} q_{BF} p_{BE} + \sqrt{p_{BF}} q_{BE} p_{BF}))}\right)^{\frac{1}{2}}$$
$$\times \left(\frac{(\gamma_B q_{BB'}(\sqrt{p_{BE}} q_{BF} + \sqrt{p_{BF}} q_{BE}) + (1-\gamma_B)(\sqrt{p_{BE}} q_{BF} q_{BE} + \sqrt{p_{BF}} q_{BE} q_{BF}))}{(\gamma_A q_{AA'}(\sqrt{p_{AC}} q_{AD} + \sqrt{p_{AD}} q_{AC}) + (1-\gamma_A)(\sqrt{p_{AC}} q_{AD} q_{AC} + \sqrt{p_{AD}} q_{AC} q_{AD}))}\right). \quad (2.37)$$

Allocation Procedure

Similar to the procedure of Section 2.4(as given by Equation (2.2) for simple difference), the adaptive allocation process for the first-stage optimal adaptive allocation ratio using relative-risk as the objective function is,

$$E_{i-1}(T_{1i}) = \frac{\sqrt{l_{i-1}}}{\sqrt{l_{i-1}} + \sqrt{m_{i-1}}}, \tag{2.38}$$

where

$$\begin{aligned} l_{i-1} = (1+\hat{\tau}_{AC:AD,i})^{\frac{1}{2}} \left((\gamma_A \hat{p}_{AA',i-1}(1+\hat{\tau}_{AC:AD,i}) + (1-\gamma_A)(\hat{\tau}_{AC:AD,i}\hat{p}_{AC,i-1} + \hat{p}_{AD,i-1}))\right)^{\frac{1}{2}} \\ \times \left((\gamma_B \hat{q}_{BB',i-1}(1+\hat{\tau}_{BE:BF,i}) + (1-\gamma_B)(\hat{\tau}_{BE:BF,i}\hat{q}_{BE,i-1} + \hat{q}_{BF,i-1}))\right), \\ m_{i-1} = (1+\hat{\tau}_{BE:BF,i})^{\frac{1}{2}} \left((\gamma_B \hat{p}_{BB',i-1}(1+\hat{\tau}_{BE:BF,i}) + (1-\gamma_B)(\hat{\tau}_{BE:BF,i}\hat{p}_{BE,i-1} + \hat{p}_{BF,i-1}))\right)^{\frac{1}{2}} \\ \times \left((\gamma_A \hat{q}_{AA',i-1}(1+\hat{\tau}_{AC:AD,i}) + (1-\gamma_A)(\hat{\tau}_{AC:AD,i}\hat{q}_{AC,i-1} + \hat{q}_{AD,i-1}))\right). \end{aligned}$$

Asymptotic Variance

Following the same procedure, as mentioned in 2.9.4, and 2.9.4, using Delta method with the function $h(x,y)$ as $\sqrt{\frac{x}{y}}\frac{1-y}{1-x}$, the variance of the first-stage optimal adaptive allocation ratio $(\hat{\tau}_{A,n})$ is obtain as,

$$Var(\hat{\tau}_{A,n}) = \frac{1}{4n}\left(\frac{v_A\left(1+p_A\right)^2\left(1-p_B\right)^2}{p_A\left(1-p_A\right)^4 p_B} + \frac{v_B\left(1+p_B\right)^2 p_A}{\left(1-p_A\right)^2 p_B^3}\right),$$

where the expressions of v_A, and v_B are from 2.9.4, and p_A, and p_B are from 2.9.1.

Thus, the asymptotic distribution of the estimated first-stage optimum allocation ratio is,

$$\sqrt{n}(\hat{\tau}_{A,n} - \tau_A^*) \xrightarrow{d} N\left(0, \frac{1}{4}\left(\frac{v_A\left(1+p_A\right)^2\left(1-p_B\right)^2}{p_A\left(1-p_A\right)^4 p_B} + \frac{v_B\left(1+p_B\right)^2 p_A}{\left(1-p_A\right)^2 p_B^3}\right)\right).$$

2.9.7 Derivation of the Success Probability for a Dynamic Treatment Regime.

Note that (see Section 2.2)

$$E(Y|T_1 = t_1, T_2 = t_2) = p_{t_1 t_2}. \tag{2.39}$$

Now, the success probability of the dynamic treatment regime, d_1, is obtained as

(Ghosh et al., 2020),

$$
\begin{aligned}
p_{d_1} &= E(\overline{Y}_{d_1}) \\
&= E(W^{d_1}Y), \qquad \text{where, } W^{d_1} = \frac{I(T_1 = A, T_2 = A'^{R_A}C^{1-R_A})}{\frac{\tau_A}{1+\tau_A} \times \left(\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}}\right)^{1-R_A}} \\
&= E\left(E\left[\frac{I(T_1 = A, T_2 = A'^{R_A}C^{1-R_A})Y}{\frac{\tau_A}{1+\tau_A} \times \left(\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}}\right)^{1-R_A}} \,\middle|\, T_1, T_2\right]\right) \\
&= P(T_1 = A, T_2 = A')E\left[\frac{I(T_1 = A, T_2 = A')Y}{\frac{\tau_A}{1+\tau_A}} \,\middle|\, T_1 = A, T_2 = A'\right] \\
&+ P(T_1 = A, T_2 = C)E\left[\frac{I(T_1 = A, T_2 = C)Y}{\frac{\tau_A}{1+\tau_A}\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}}} \,\middle|\, T_1 = A, T_2 = C\right] \\
&= P(T_1 = A)P(T_2 = A'|T_1 = A)E\left[\frac{Y}{\frac{\tau_A}{1+\tau_A}} \,\middle|\, T_1 = A, T_2 = A'\right] \\
&+ P(T_1 = A)P(T_2 = C|T_1 = A)E\left[\frac{Y}{\frac{\tau_A}{1+\tau_A}\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}}} \,\middle|\, T_1 = A, T_2 = C\right] \\
&= \left(\frac{\tau_A}{1+\tau_A}\right)\gamma_A\left(\frac{1}{\frac{\tau_A}{1+\tau_A}}\right)p_{AA'} + \left(\frac{\tau_A}{1+\tau_A}\right)(1-\gamma_A)\left(\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}}\right)\left(\frac{1}{\frac{\tau_A}{1+\tau_A}\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}}}\right)p_{AC} \\
&= \gamma_A p_{AA'} + (1-\gamma_A)p_{AC}.
\end{aligned}
$$

Similarly, the success probabilities of other dynamic treatment regimes are $p_{d_2} = \gamma_A p_{AA'} + (1-\gamma_A)p_{AD}$; $p_{d_3} = \gamma_B p_{BB'} + (1-\gamma_B)p_{BE}$; $p_{d_4} = \gamma_B p_{BB'} + (1-\gamma_B)p_{BF}$.

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CHAPTER 3

Optimal Adaptive SMART Design with Continuous Outcomes

3.1 Introduction

In the previous chapter, our focus was on SMART designs with binary outcomes. However, in real-world scenarios, the primary outcome variable is often continuous (e.g., change in blood sugar level or effective weight loss). Therefore, in this chapter, we aim to develop an optimal adaptive SMART design for continuous outcomes that follows a normal distribution. We assume that a lower value of the continuous outcome indicates better results. Drawing inspiration from the work of Zhang and Rosenberger (2006) in the context of two-arm randomized controlled trials, we will employ an optimality criterion that seeks to minimize the total expected outcome for all participants in a two-stage SMART. Similar to the previous chapter, we first derive the optimal adaptive allocation ratio for the second-stage randomization. This information is then recursively utilized to determine the optimal adaptive allocation ratio for the first-stage randomization in the SMART design.

While many SMART studies have focused on binary outcomes, numerous studies have utilized continuous primary outcome variables. For example, Gunlicks-Stoessel et al. (2016) conducted a pilot survey comparing four adaptive treatment strategies for adolescent depression. McKay et al. (2015) examined the impact of offering different treatment choices to patients who fail to engage in or drop out of intensive outpatient programs (IOPs) for substance dependence. Additionally, Naar-King et al. (2016) developed an adaptive behavioral treatment for African American adolescents with obesity. These examples illustrate the growing use of SMART designs with continuous outcomes. However, in all of these cases, equal randomization fails to utilize interim data to prioritize better-

performing treatments.

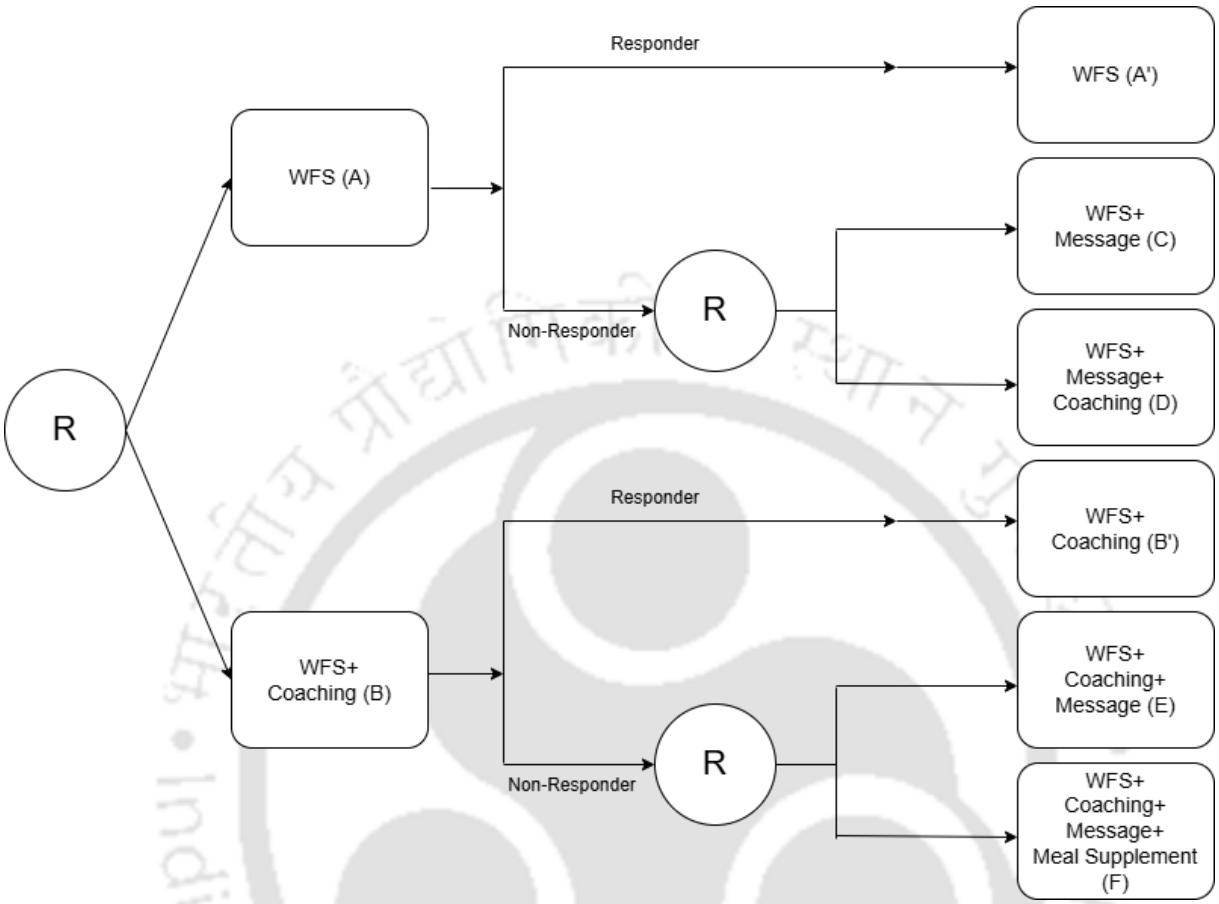


Figure 3.1: Schematic diagram of the SMART Weight Loss Management Study. The WFS denotes a wireless feedback system.

A key motivation for this chapter arises from a recent SMART study designed to evaluate the effectiveness of low-cost techniques in weight loss management compared to more expensive alternatives Spring et al. (2024). In this study, researchers investigated whether an adaptive behavioral intervention, delivered through a wireless feedback system (such as a Wi-Fi activity tracker and scale with smartphone app to provide daily feedback), could produce clinically meaningful weight loss without additional human intervention, such as coaching, messaging, or meal supplements. The study compared the effectiveness of technology-based interventions (low cost) alone versus those augmented with human support (expensive) to facilitate weight reduction. Initially, participants (see Figure 3.1), who were overweight or obese individuals, were randomized with equal probability to one of two first-stage treatments: a wireless feedback system (WFS) alone (A), or WFS plus brief telephone coaching (WFS + Coaching) (B). For those in the coaching group, weekly coaching calls (10 to 15 minutes each) were provided over the first 12 weeks. Participants' progress was then assessed at early checkpoints (weeks 2, 4, and 8). Those who did not meet specified weight loss goals (non-responder), defined as a minimum of

0.23 kg per week, were adaptively reassigned, via randomization, to either a modest or an intensive stepped-up intervention. These stepped-up interventions included options such as additional messaging, more frequent coaching, or meal replacements. The responder, who meets specified weight loss goals, continues with the same interventions assigned in the first stage. Here, $A' = A$, and $B' = B$. The second-stage interventions are: WFS plus message (C); WFS plus message and coaching (D); WFS plus coaching and message (E); and WFS plus coaching, message, and meal supplement (F). Note that interventions D and E are equivalent. Following the adaptive interventions, all participants were observed at 3, 6, and 12 months. Final weights were recorded at the end of the trial to determine which adaptive interventions were most effective.

The original study used equal randomization (probability of 0.5) to allocate interventions among eligible participants at both stages. In this chapter, to demonstrate the applicability of our proposed method, we retrospectively redesign the trial to accommodate adaptive randomization. By applying our optimal adaptive allocation methodology, we show that more participants can be assigned to the more effective treatment sequences, thereby achieving both greater ethical and statistical efficiency.

In this chapter, Section 3.2 provides a comprehensive overview of the framework and introduces the notations used for the SMART design with continuous outcome. Section 3.3 presents the development of optimal adaptive allocation ratios for both the first and second stages. The allocation procedure utilizing these optimal ratios is detailed in Section 3.4. To support our theoretical findings, a simulation study is presented in Section 3.5. Finally, in Section 3.6, we retrospectively apply our optimal adaptive allocation procedure to a real-world SMART study on weight loss management. This chapter ends with a discussion at Section 3.7.

3.2 General Framework for continuous SMART

This section provides the notational framework for the two-stage SMART design depicted in Figure 3.1. Let Y denote the continuous (non-zero positive values) outcome for each participant at the end of the trial, with lower values indicating better outcomes throughout this chapter. Most of the notations remain the same as in the previous chapter. However, due to the use of a continuous outcome, some notations need to be changed and a few new ones introduced. For clarity and brevity, we present the necessary notations again in this chapter to avoid any confusion. The generic treatments assigned to participants are denoted by A, A', B, B', C, D, E, and F, as illustrated in Figure 3.1. Upon entering the trial, participants are initially randomized at the first stage to either treatment A or B. Let T_1 represent the first-stage randomized treatment, where $T_1 \in \{A, B\}$. Based on the outcomes of certain tailoring variables at the end of the first stage, participants

are categorized as either responders or non-responders. Responders exhibit promising outcomes following the first-stage treatment, whereas non-responders show no significant effect. Responders continue with a similar or enhanced version of their initial treatment in the second stage, denoted A' for those initially assigned A and B' for those initially assigned B. Non-responders are re-randomized: those who received A at the first stage are allocated to either treatment C or D, and those who initially received B are allocated to either treatment E or F. Thus, $T_2 \in \{A', C, D\}$ if $T_1 = A$; otherwise, $T_2 \in \{B', E, F\}$ if $T_1 = B$. The complete treatment sequence for any participant is represented as $\{T_1, T_2\}$. Let R_{T_1}, where $T_1 \in \{A, B\}$, denote the indicator variable for the intermediate response that determines responder status: $R_{T_1} = 1$ for responders and $R_{T_1} = 0$ for non-responders. The number of participants assigned to the treatment sequence $\{T_1, T_2\}$ is denoted by $n_{T_1T_2}$. The number of participants receiving first-stage treatment A is $n_A = n_{AA'} + n_{AC} + n_{AD}$, corresponding to those assigned to sequences (A, A), (A, C), or (A, D). Similarly, the total number of participants for first-stage treatment B is $n_B = n_{BB} + n_{BE} + n_{BF}$.

The primary objective of this chapter is to determine the optimal adaptive allocation ratios that minimize the total expected outcome (with lower values being better) for all participants. The SMART design incorporates three randomizations: one at the first stage and two at the second stage (corresponding to each possible first-stage treatment). Consequently, there are three allocation ratios: $\tau_A = \frac{n_A}{n_B}$ for first-stage randomization, and $\tau_{AC:AD} = \frac{n_{AC}}{n_{AD}}$, $\tau_{BE:BF} = \frac{n_{BE}}{n_{BF}}$ for the second-stage randomizations following $T_1 = A$ and $T_1 = B$, respectively. The corresponding optimal ratios are determined using an optimality criterion that seeks to minimize the total expected outcome for all participants in a two-stage SMART, for a fixed asymptotic variance to maintain test power (Zhang and Rosenberger, 2006).

In this chapter, we first apply the methodology proposed by Zhang and Rosenberger (2006) in the context of two-arm randomized controlled trials to determine the optimal adaptive allocation ratios for the second stage. Determining the optimal adaptive allocation ratio for the first stage is more challenging. We address this by recursively using the second-stage optimal ratios to inform the first-stage allocation, thereby optimizing the entire trial. A similar approach was also considered for binary outcomes in the previous chapter. To characterize and compare the continuous outcomes along each specific treatment sequence, we use the mean and variance as summary statistics. For a particular treatment sequence $\{T_1, T_2\}$, the mean outcome is denoted by $\mu_{T_1T_2}$ and the variance by $\sigma^2_{T_1T_2}$. For the first-stage randomization, these statistics are defined in terms of the corresponding second-stage statistics. Specifically, the mean outcome for participants receiving treatment A in the first stage is denoted by μ_A, where

$$\mu_A = \gamma_A \mu_{AA'} + \left(\frac{1 - \gamma_A}{1 + \tau_{AC:AD}}\right)(\tau_{AC:AD}\mu_{AC} + \mu_{AD}),$$

see Section 3.8.1 for details. The variance of the outcome for participants receiving first-stage treatment A is

$$\sigma_A^2 = \Bigg[\gamma_A\left(\sigma_{AA'}^2 + (\mu_{AA'})^2\right) + (1-\gamma_A)\left(\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}}\right)\left(\sigma_{AC}^2 + (\mu_{AC})^2\right) \\ +(1-\gamma_A)\left(\frac{1}{1+\tau_{AC:AD}}\right)\left(\sigma_{AD}^2 + (\mu_{AD})^2\right)\Bigg] - \left(\gamma_A\mu_{AA'} + (1-\gamma_A)\left(\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}}\mu_{AC} + \frac{1}{1+\tau_{AC:AD}}\mu_{AD}\right)\right)^2.$$

A detailed derivation of the first-stage mean and variance is provided in Section 3.8.1. Similarly, the mean and variance of the outcomes for participants who receive treatment B at the first stage are derived in the same way.

3.3 Optimal Adaptive Allocation Ratios

In this section, we outline the general approach for determining the optimal adaptive allocation ratio for the two-stage SMART design with continuous outcome (Figure 3.1). We obtain the optimal adaptive allocation ratio, corresponding to a specific randomization process, by minimizing the total expected outcome for all participants followed by that specific randomization process. This optimization is done subject to the condition that the asymptotic variance of an objective function $g(\cdot,\cdot)$, which compares the two means (with respect to the treatments being taken for the allocation ratio), is constant, say ζ. The fixed asymptotic variance reflects the power of the corresponding hypothesis test (Rosenberger et al., 2001).

We begin by optimizing the allocation ratios for the second stage. Let $\tau_{T_1T_2:T_1T_2^*}$ denote the second-stage allocation ratio corresponding to the treatment sequence $\{T_1, T_2\}$, where $T_1 \in \{A, B\}$, and $T_2 \in \{C, D\}$ if $T_1 = A$, or $T_2 \in \{E, F\}$ if $T_1 = B$. The total expected outcome corresponding to each treatment sequence $\{T_1, T_2\}$ is considered. For the second stage, the total expected outcome for all those participants, followed by that specific randomization process. Thus, for non-responder participants initially treated with T_1 and subsequently assigned to either T_2 or T_2^* at the second stage, the total expected outcome is given by

$$F_2(\tau_{T_1T_2:T_1T_2^*}) = n_{T_1T_2}\mu_{T_1T_2} + n_{T_1T_2^*}\mu_{T_1T_2^*} = \frac{n_{T_1}(1-\gamma_{T_1})}{1+\tau_{T_1T_2:T_1T_2^*}}\left[\tau_{T_1T_2:T_1T_2^*}\mu_{T_1T_2} + \mu_{T_1T_2^*}\right]. \quad (3.1)$$

Here, we consider the objective function $g(\mu_{T_1T_2}, \mu_{T_1T_2^*}) = \mu_{T_1T_2} - \mu_{T_1T_2^*}$. The optimization criterion of the function in (3.1), subject to a constraint on the asymptotic variance, yields the optimal adaptive allocation ratio $\tau_{T_1T_2:T_1T_2^*}$. The criterion is given as,

$$\tau^*_{T_1T_2:T_1T_2^*} = \arg\min_{\tau_{T_1T_2:T_1T_2^*}} F_2(\tau_{T_1T_2:T_1T_2^*}) \text{ subject to } avar(\hat{\mu}_{T_1T_2} - \hat{\mu}_{T_1T_2^*}) = \zeta_2, \quad (3.2)$$

for some constant $\zeta_2 > 0$. From (3.2), we have,

$$\tau^*_{T_1T_2:T_1T_2^*} = \frac{\sqrt{\mu_{T_1T_2^*}}\sigma_{T_1T_2}}{\sqrt{\mu_{T_1T_2}}\sigma_{T_1T_2^*}}. \tag{3.3}$$

Thus, the second-stage optimal adaptive allocation ratios corresponding to first-stage treatments A and B are given by,

$$\tau^*_{AC:AD} = \frac{\sqrt{\mu_{AD}}\sigma_{AC}}{\sqrt{\mu_{AC}}\sigma_{AD}}, \qquad \text{and} \qquad \tau^*_{BE:BF} = \frac{\sqrt{\mu_{BF}}\sigma_{BE}}{\sqrt{\mu_{BE}}\sigma_{BF}}. \tag{3.4}$$

Now, for the first stage, it should be noted that the total expected outcome is contributed by all participants in the entire SMART. Thus, the total expected outcome at the first stage is given by,

$$\begin{aligned}
& F_1(\tau_A, \tau_{AC:AD}, \tau_{BE:BF}) \\
= \; & (n_{AA'}\mu_{AA'} + n_{AC}\mu_{AC} + n_{AD}\mu_{AD}) + (n_{BB'}\mu_{BB'} + n_{BE}\mu_{BE} + n_{BF}\mu_{BF}) \\
= \; & \frac{n}{1+\tau_A}\Bigg[\tau_A\gamma_A\mu_{AA'} + \tau_A\frac{(1-\gamma_A)}{1+\tau_{AC:AD}}\Big(\tau_{AC:AD}\mu_{AC} + \mu_{AD}\Big) \\
& + \gamma_B\mu_{BB'} + \frac{(1-\gamma_B)}{1+\tau_{BE:BF}}\Big(\tau_{BE:BF}\mu_{BE} + \mu_{BF}\Big)\Bigg].
\end{aligned}$$

Thus, using second-stage optimal adaptive allocation ratios from (3.4), the first-stage optimal adaptive allocation ratio (τ_A) is given by,

$$\tau^*_A = \arg\min_{\tau_A} F_1(\tau_A, \tau^*_{AC:AD}, \tau^*_{BE:BF}) \text{ subject to } avar\{\hat{\mu}_A - \hat{\mu}_B\} = \zeta_1,$$

for some constant $\zeta_1 > 0$. Thus, the first stage optimal adaptive allocation ratio is obtained as,

$$\tau^*_A = \frac{\left[\sqrt{\gamma_B\mu_{BB'} + (1-\gamma_B)\left(\frac{\tau^*_{BE:BF}}{1+\tau^*_{BE:BF}}\mu_{BE} + \frac{1}{1+\tau^*_{BE:BF}}\mu_{BF}\right)}\right]\sigma_A}{\left[\sqrt{\gamma_A\mu_{AA'} + (1-\gamma_A)\left(\frac{\tau^*_{AC:AD}}{1+\tau^*_{AC:AD}}\mu_{AC} + \frac{1}{1+\tau^*_{AC:AD}}\mu_{AD}\right)}\right]\sigma_B}. \tag{3.5}$$

It can be observed that the optimal adaptive allocation ratios are derived using theoretical values. However, these values are not available during the actual trial. Therefore, it is necessary to develop an adaptive allocation procedure that ensures the estimated allocation ratios converge to the optimal adaptive allocation ratios. In the next section, we describe this adaptive allocation procedure in detail.

3.4 Adaptive Allocation Procedure

The expression for optimal adaptive allocation ratio obtained in Equations (3.4) and (3.5) is a function of the population mean and variances. However, as the trial progresses, the population statistics are not available. Hence, we need to develop an adaptive allocation (randomization) procedure that assigns participants to available treatments such that the allocation procedure can mimic the optimal conditions described in Section 3.3. It is also desirable for the proposed sequential design to ensure that the estimated allocation ratios converge to their corresponding optimal values. Let Y_i denote the continuous primary outcome (non-zero positive values and lower the better) for the i^{th} participant ($i = 1, \ldots, n$). T_{1i} and T_{2i} represent the first- and second-stage treatments assigned to the i^{th} participant, respectively.

Thus, as we have done in the previous chapter for binary outcome, the total number of participants assigned to the treatment sequence $\{T_1, T_2\}$ out of k participants is given by $n_{T_1T_2,k} = \sum_{i=1}^{k} I(T_{1i} = T_1, T_{2i} = T_2)$, where T_1 and T_2 take values as specified in Section 3.2, and $n_{T_1T_2,n} = n_{T_1T_2}$. The corresponding estimates of mean and variance for the treatment sequence $\{T_1, T_2\}$ are expressed as as $\hat{\mu}_{T_1T_2,k} = \left(\sum_{i=1}^{k} I(T_{1i} = T_1, T_{2i} = T_2)Y_i\right)/n_{T_1T_2,k}$, and $\hat{\sigma}^2_{T_1T_2,k} = \left(\sum_{i=1}^{k} I(T_{1i} = T_1, T_{2i} = T_2)(Y_i - \hat{\mu}_{T_1T_2,k})^2\right)/n_{T_1T_2,k}$. Now, let us express the historical information as, $\mathscr{F}_i = \{Y_1, Y_2, ..., Y_i, T_{11}, T_{12}, ..., T_{1i}, T_{21}, T_{22}, ..., T_{2i}\}$ comprising of primary outcomes and first- and second-stage assigned treatments for the first i participants. Define, $E_i(\cdot) = E(\cdot \mid \mathscr{F}_i)$ as the conditional expectation.

As described in the previous Section, we have taken the objective function as the simple difference of the mean of two different treatment sequences. Based on the first $(i-1)$ observation, the second-stage adaptive allocation process can be explained as,

$$\begin{aligned} & E_{i-1}(I(T_{2i} = t_2 | T_{1i} = t_1, R_{T_{1i}} = 0)) \\ = \; & \sqrt{\hat{\mu}_{t_1t_2^*,i-1}}\hat{\sigma}_{t_1t_2,i-1} \Big/ \left(\sqrt{\hat{\mu}_{t_1t_2^*,i-1}}\hat{\sigma}_{t_1t_2,i-1} + \sqrt{\hat{\mu}_{t_1t_2,i-1}}\hat{\sigma}_{t_1t_2^*,i-1}\right), \end{aligned} \tag{3.6}$$

where, $t_2, t_2^* \in \{C, D\}$ if $t_1 = A$ or $t_2, t_2^* \in \{E, F\}$ if $t_1 = B$ and $t_2^* \neq t_2$ and $R_{T_{1i}}$ is the same as defined in Section 3.2 for the i^{th} participant. In Equation (3.6), the estimation of the second-stage mean and variances $\hat{\mu}_{t_1t_2,i}$, $\hat{\sigma}^2_{t_1t_2,i}$ is based on the first $(i-1)$ sequentially enrolled participants. These estimates are used to compute the adaptive randomization probability for the i^{th} participant, represented by equation (3.6). Similarly, the first-stage adaptive allocation process can be expressed as,

$$E_{i-1}(T_{1i}) = \sqrt{l_{i-1}} \Big/ \left(\sqrt{l_{i-1}} + \sqrt{m_{i-1}}\right), \tag{3.7}$$

where $l_{i-1} = \left[\gamma_B\hat{\mu}_{BB,i-1} + (1-\gamma_B)\left(\frac{\hat{\tau}^*_{BE:BF,i}}{1+\hat{\tau}^*_{BE:BF,i}}\hat{\mu}_{BE,i-1} + \frac{1}{1+\hat{\tau}^*_{BE:BF,i}}\hat{\mu}_{BF,i-1}\right)\right]\hat{\sigma}^2_{A,i-1}$

and $m_{i-1} = \left[\gamma_A \hat{\mu}_{AA,i-1} + (1-\gamma_A)\left(\frac{\hat{\tau}^*_{AC:AD,i}}{1+\hat{\tau}^*_{AC:AD,i}}\hat{\mu}_{AC,i-1} + \frac{1}{1+\hat{\tau}^*_{AC:AD,i}}\hat{\mu}_{AD,i-1}\right)\right]\hat{\sigma}^2_{B,i-1}$. Here, $\hat{\tau}_{AC:AD,i} = \frac{\sqrt{\hat{\mu}_{AD,i-1}}\hat{\sigma}_{AC,i-1}}{\sqrt{\hat{\mu}_{AC,i-1}}\hat{\sigma}_{AD,i-1}}$, $\hat{\tau}_{BE:BF,i} = \frac{\sqrt{\hat{\mu}_{BF,i-1}}\hat{\sigma}_{BE,i-1}}{\sqrt{\hat{\mu}_{BE,i-1}}\hat{\sigma}_{BF,i-1}}$ denote the estimated second-stage allocation ratios for the i^{th} participant (who were assigned either A or B at the first stage and is a non-responder, respectively) based on the history of $(i-1)$ participants. As discussed in Section 3.2, the first-stage allocation process recursively uses the estimated allocation ratios $\hat{\tau}_{AC:AD,i}$ and $\hat{\tau}_{BE:BF,i}$ from the second stage. It is evident that this allocation process substitutes the unknown mean and variance of the outcomes of treatment sequences in the optimal adaptive allocation ratios derived in Section 3.3 with the current estimates of the mean and variance for each treatment sequence, namely $\hat{\mu}_{t_1t_2,i-1}$ and $\hat{\sigma}_{t_1t_2,i-1}$.

In practice, the investigator assigns participants to the available treatments using the allocation procedures described in (3.6) and (3.7) for the second and first stages, respectively. Hence, it is desirable that the limiting allocation ratio, as determined by (3.6) and (3.7), is optimal. Based on the results of Rosenberger et al. (2001), Melfi et al. (2001) and Sokol and Rønn-Nielsen (2013), for second-stage randomization with the objective function defined as the simple difference of the mean of two different treatment sequences, $\hat{\tau}_{AC:AD,n} \xrightarrow{a.s.} \frac{\sqrt{\mu_{AD}}\sigma_{AC}}{\sqrt{\mu_{AC}}\sigma_{AD}}$, and $\hat{\tau}_{BE:BF,n} \xrightarrow{a.s.} \frac{\sqrt{\mu_{BF}}\sigma_{BE}}{\sqrt{\mu_{BE}}\sigma_{BF}}$, where $a.s.$ denotes almost sure convergence as n becomes large. Similarly, using the results from 3.8.1, we have

$$\hat{\tau}_{A:B,n} \xrightarrow{a.s.} \frac{\left[\sqrt{\gamma_B\mu_{BB'} + (1-\gamma_B)\left(\frac{\tau^*_{BE:BF}}{1+\tau^*_{BE:BF}}\mu_{BE} + \frac{1}{1+\tau^*_{BE:BF}}\mu_{BF}\right)}\right]\sigma_A}{\left[\sqrt{\gamma_A\mu_{AA'} + (1-\gamma_A)\left(\frac{\tau^*_{AC:AD}}{1+\tau^*_{AC:AD}}\mu_{AC} + \frac{1}{1+\tau^*_{AC:AD}}\mu_{AD}\right)}\right]\sigma_B}, \tag{3.8}$$

where $\hat{\tau}_{A:B,n}$ represents the estimated first-stage allocation ratio for the n^{th} participant, based on the outcomes of the preceding $(n-1)$ participants. These asymptotic results are derived in detailed manner in Sections 3.8.3 and 3.8.4.

3.5 Simulation

Simulations are conducted to assess the viability and evaluate the adaptive allocation procedure described in Section 3.4. In this simulation study, our objective is to empirically examine how the adaptive allocation procedure facilitates the estimation of allocation ratios ($\hat{\tau}$) relative to the true optimal adaptive allocation ratios (τ). We assess this using the sample standard error (SSE), asymptotic standard error (ASE), and coverage probability (CP) under different choices of model parameters.

Here, we consider a two-stage SMART as described in Figure 3.1, with a continuous primary outcome (non-zero positive values and lower the better) and a sample size of 500. Similar simulations with a sample size of 1000 have also been conducted in this section. In

all simulations, the response probabilities γ_A and γ_B are assumed to be constant at 0.45 and 0.50, respectively. The second column of Table 3.1 presents the assumed values of the population means and variances (μ, σ^2) corresponding to the six feasible combinations of first- and second-stage treatments $\{T_1, T_2\}$. These values are used to generate the outcome values for participants with a specific treatment sequence. However, these means and variances are unknown to the investigator and must be estimated from interim data obtained from the SMART in order to implement the adaptive allocation (randomization) procedure described in Section 3.4. Accordingly, an initial 30 participants (or any greater number) sequentially enrolled in the SMART are randomized with equal probabilities at both stages. The initial estimates of the parameters $(\hat{\mu}_{t_1t_2,i}, \hat{\sigma}_{t_1t_2,i})$ are based on the observed Y_i, for $i = 1, \cdots, 30$. Using these estimated parameter values, the allocation ratios for the first stage $(\hat{\tau}_{A,i})$ and the second stage $(\hat{\tau}_{AC:AD,i}; \hat{\tau}_{BE:BF,i})$ are estimated for the 31^{st} $(i = 31)$ participant. The 31^{st} participant is then randomized using the adaptive randomization probability $E_{30}(T_{1\ 31})$ at the first stage. If the 31^{st} participant is a non-responder, depending on the treatment assigned at the first stage, the participant is further randomized using the estimated probability, $E_{30}(I(T_{2\ 31} = C|T_{1\ 31} = A, R_{A\ 31} = 0)$ or $E_{30}(I(T_{2\ 31} = E|T_{1\ 31} = B, R_{B\ 31} = 0)$. This process of re-estimation of allocation probabilities (or corresponding allocation ratios) with updated interim data, followed by adaptive randomization, is repeated for each subsequent participant until the conclusion of the trial.

Table 3.1 shows a total of 9 scenarios (rows), where the true values of the optimal adaptive allocation ratios τ_A, $\tau_{AC:AD}$, and $\tau_{BE:BF}$ are taken less than 1, close to 1, and a value more than 1. In most of the considered scenarios, the coverage probability $(\hat{CP})$ is close to 0.95. In row 4 of Table 3.1, the $\hat{CP}$ corresponding to the allocation ratio $\tau_{AC:AD}$ is 0.856, which can be explained by the parameter values chosen for simulating row 4. We observe that the assumed parameter values for μ_{AC} and μ_{AD} are 53 and 59, respectively, which are far apart. It is unlikely that such substantial differences in means would need to be compared in a real-life scenario, as results from previous phases of the clinical trial would typically reveal much earlier which treatment sequence is more effective, making further comparison unnecessary in a SMART design. However, in other scenarios, when the means of the treatment sequences are close, the estimated coverage probability is near 0.95, and the SSE and ASE are fairly close to each other. Table 3.1 shows that for nearly all scenarios, the estimated optimal adaptive allocation ratio and the true optimal adaptive allocation ratios are nearly the same, except row 4. It can be observed that only when the difference in the means of the treatment sequences is farther apart, the estimated and true optimal adaptive allocation ratios are different. Similarly, corresponding ASE and SSE are also different, thus implying a difference in the values from the very beginning. However, as the number of participants increased, this initial difference can be overcome, as can be seen comparing the same row results from Table 3.2.

Table 3.2 shows the simulation study with 1000 participants enrolled in the trial. The results in Table 3.2 are consistent with the ones in Table 3.1, thus indicating consistency in the developed optimal adaptive allocation procedure.

Table 3.1: Estimated first-stage ($\hat{\tau}_A$) and second-stage ($\hat{\tau}_{AC:AD}, \hat{\tau}_{BE:BF}$) allocation ratios along with corresponding SSE, ASE and CP based on 5000 simulations. τ_A, $\tau_{AC:AD}$, and $\tau_{BE:BF}$ denote true values of optimum allocation ratios. Here, $\gamma_A = 0.45$, and $\gamma_B = 0.50$, with the sample size as **500**.

No.	$(\mu_{AA'}, \mu_{AC}, \mu_{AD}, \mu_{BB'}, \mu_{BE}, \mu_{BF})$ $(\sigma_{AA'}, \sigma_{AC}, \sigma_{AD}, \sigma_{BB}, \sigma_{BE}, \sigma_{BF})$	$\tau_A(\hat{\tau}_A, SSE, ASE, \hat{CP})$	$\tau_{AC:AD}(\hat{\tau}_{AC:AD}, SSE, ASE, \hat{CP})$	$\tau_{BE:BF}(\hat{\tau}_{BE:BF}, SSE, ASE, \hat{CP})$
1	(47.0, 53.0, 51.0, 50.0, 51.0, 47.0) (5.00, 4.50, 4.80, 5.35, 5.30, 4.20)	1.011 (1.017, 0.004, 0.004, 0.946)	0.920 (0.971, 0.012, 0.012, 0.941)	1.211 (1.224, 0.025, 0.023, 0.937)
2	(38.0, 49.5, 51.2, 50.0, 51.0, 49.0) (4.30, 6.50, 4.80, 5.35, 5.30, 4.20)	1.616 (1.624, 0.010, 0.010, 0.954)	1.377 (1.452, 0.023, 0.022, 0.943)	1.237 (1.252, 0.035, 0.031, 0.934)
3	(47.0, 54.0, 51.0, 50.0, 51.0, 42.0) (5.00, 4.50, 4.80, 5.35, 5.30, 3.80)	0.882 (0.888, 0.003, 0.003, 0.950)	0.911 (0.980, 0.013, 0.013, 0.935)	1.266 (1.282, 0.027, 0.024, 0.935)
4	(38.0, 53.0, 59.0, 50.0, 51.0, 47.0) (4.30, 5.25, 4.00, 5.35, 5.30, 4.20)	1.859 (1.866, 0.012, 0.012, 0.951)	1.385 (1.562, 0.025, 0.025, 0.856)	1.211 (1.237, 0.061, 0.035, 0.935)
5	(38.0, 49.5, 51.2, 50.0, 53.6, 48.3) (4.30, 6.50, 4.80, 5.35, 3.80, 5.20)	1.551 (1.561, 0.009, 0.009, 0.950)	1.377 (1.456, 0.023, 0.023, 0.947)	0.694 (0.696, 0.011, 0.010, 0.930)
6	(38.0, 42.5, 46.2, 50.0, 53.6, 48.3) (4.30, 4.50, 8.80, 5.35, 3.80, 5.60)	1.490 (1.492, 0.011, 0.011, 0.943)	0.533 (0.549, 0.003, 0.003, 0.953)	0.644 (0.646, 0.009, 0.008, 0.929)
7	(38.0, 42.5, 46.2, 50.0, 53.6, 50.3) (4.30, 4.50, 8.80, 5.35, 5.80, 5.60)	1.434 (1.435, 0.010, 0.010, 0.943)	0.533 (0.549, 0.004, 0.004, 0.950)	1.003 (1.015, 0.021, 0.019, 0.933)
8	(53.2, 52.5, 56.2, 30.0, 33.6, 30.3) (4.30, 4.50, 4.80, 5.35, 5.80, 5.60)	0.633 (0.633, 0.002, 0.002, 0.948)	0.970 (0.974, 0.017, 0.016, 0.934)	0.984 (0.990, 0.013, 0.012, 0.938)
9	(53.2, 52.5, 56.2, 30.0, 30.6, 34.3) (4.30, 4.50, 4.80, 5.35, 5.80, 3.60)	0.667 (0.668, 0.002, 0.002, 0.946)	0.970 (0.977, 0.016, 0.015, 0.940)	1.706 (1.729, 0.046, 0.040, 0.936)

3.6 Application in SMART Weight Loss Management

In Figure 3.1 and in the Introduction, we described the SMART Weight Loss Management Study (Spring et al., 2024). In this section, we present the implementation of the developed optimal adaptive allocation procedure using the data from this study. The continuous outcome of interest is the ratio of participants' weight after 12 months to their baseline weight (lower the better). Notably, this weight-ratio, constructed from the data, follows a normal distribution, approximately. The SMART Weight Loss Manage-

Table 3.2: Estimated first-stage ($\hat{\tau}_A$) and second-stage ($\hat{\tau}_{AC:AD}, \hat{\tau}_{BE:BF}$) allocation ratios along with corresponding SSE, ASE and CP based on 5000 simulations. τ_A, $\tau_{AC:AD}$, and $\tau_{BE:BF}$ denote true values of optimum allocation ratios. Here, $\gamma_A = 0.45$, and $\gamma_B = 0.50$, with the sample size as **1000**.

No.	$(\mu_{AA'}, \mu_{AC}, \mu_{AD}, \mu_{BB'}, \mu_{BE}, \mu_{BF})$ $(\sigma_{AA'}, \sigma_{AC}, \sigma_{AD}, \sigma_{BB}, \sigma_{BE}, \sigma_{BF})$	$\tau_A(\hat{\tau}_A, SSE, ASE, \hat{CP})$	$\tau_{AC:AD}(\hat{\tau}_{AC:AD}, SSE, ASE, \hat{CP})$	$\tau_{BE:BF}(\hat{\tau}_{BE:BF}, SSE, ASE, \hat{CP})$
1	(47.0, 53.0, 51.0, 50.0, 51.0, 47.0) (5.00, 4.50, 4.80, 5.35, 5.30, 4.20)	1.011 (1.015, 0.002, 0.002, 0.945)	0.920 (0.946, 0.006, 0.006, 0.946)	1.211 (1.217, 0.012, 0.011, 0.942)
2	(38.0, 49.5, 51.2, 50.0, 51.0, 49.0) (4.30, 6.50, 4.80, 5.35, 5.30, 4.20)	1.616 (1.621, 0.005, 0.005, 0.952)	1.377 (1.416, 0.011, 0.010, 0.939)	1.237 (1.244, 0.016, 0.015, 0.946)
3	(47.0, 54.0, 51.0, 50.0, 51.0, 42.0) (5.00, 4.50, 4.80, 5.35, 5.30, 3.80)	0.882 (0.884, 0.001, 0.001, 0.951)	0.911 (0.946, 0.006, 0.006, 0.946)	1.266 (1.272, 0.012, 0.011, 0.948)
4	(38.0, 53.0, 59.0, 50.0, 51.0, 47.0) (4.30, 5.25, 4.00, 5.35, 5.30, 4.20)	1.859 (1.863, 0.006, 0.006, 0.953)	1.385 (1.477, 0.011, 0.011, 0.895)	1.211 (1.221, 0.018, 0.016, 0.938)
5	(38.0, 49.5, 51.2, 50.0, 53.6, 48.3) (4.30, 6.50, 4.80, 5.35, 3.80, 5.20)	1.551 (1.557, 0.004, 0.004, 0.950)	1.377 (1.418, 0.011, 0.011, 0.944)	0.694 (0.693, 0.005, 0.005, 0.938)
6	(38.0, 42.5, 46.2, 50.0, 53.6, 48.3) (4.30, 4.50, 8.80, 5.35, 3.80, 5.60)	1.490 (1.491, 0.006, 0.005, 0.947)	0.533 (0.542, 0.002, 0.002, 0.953)	0.644 (0.645, 0.004, 0.004, 0.939)
7	(38.0, 42.5, 46.2, 50.0, 53.6, 50.3) (4.30, 4.50, 8.80, 5.35, 5.80, 5.60)	1.434 (1.436, 0.005, 0.005, 0.950)	0.533 (0.541, 0.002, 0.002, 0.948)	1.003 (1.009, 0.010, 0.009, 0.945)
8	(53.2, 52.5, 56.2, 30.0, 33.6, 30.3) (4.30, 4.50, 4.80, 5.35, 5.80, 5.60)	0.633 (0.633, 0.001, 0.001, 0.949)	0.970 (0.970, 0.008, 0.008, 0.943)	0.984 (0.985, 0.006, 0.006, 0.938)
9	(53.2, 52.5, 56.2, 30.0, 30.6, 34.3) (4.30, 4.50, 4.80, 5.35, 5.80, 3.60)	0.667 (0.667, 0.001, 0.001, 0.948)	0.970 (0.974, 0.008, 0.007, 0.947)	1.706 (1.720, 0.021, 0.019, 0.944)

ment Study was originally conducted using an equal randomization scheme. Here, our objective is to demonstrate the potential benefits that could have been realized had the adaptive allocation procedure been employed instead of equal randomization in assigning participants to different treatment sequences. Specifically, we show that the proposed procedure would have reduced the total expected outcome for all participants compared to the non-adaptive SMART. Additionally, more participants would have been assigned to adaptive interventions that are associated with a lower total expected outcome.

For analysis, we use participants' record data to retrospectively allocate the treatment sequence based on the time stamp, utilizing our developed optimal adaptive allocation ratios. Initially, all participants' records are arranged in increasing order of the combined time stamp, which refers to the entry time into the trial together with the time at which the participant was re-randomized in the second stage. Originally, 400 participants were enrolled in the trial; however, due to dropouts, only 378 participants remained at the end.

Therefore, our analysis focuses on these 378 participants. By design, there was no control arm in this trial. Initially, we randomize the first 30 participants using equal randomization probabilities. The outcomes of these 30 participants are then used to estimate the adaptive allocation ratios for both stages. These first 30 participants are removed from the dataset, and the remaining participants, sorted by time stamp, are considered for further allocation. The 31^{st} participant is selected from among the remaining participants who received the randomly generated treatment sequence using the estimated adaptive allocation ratio. For illustration, if the randomly generated treatment sequence based on the estimated adaptive allocation ratio is (A, C), the first participant in the sorted list who received (A, C) is designated as the 31^{st} participant. The outcome of this participant is recorded and combined with the previous outcome set. The adaptive allocation ratios are then re-estimated based on the updated outcome set, and that participant is removed from the list. This allocation procedure is repeated until all participants are exhausted from at least one of the treatment sequence arms.

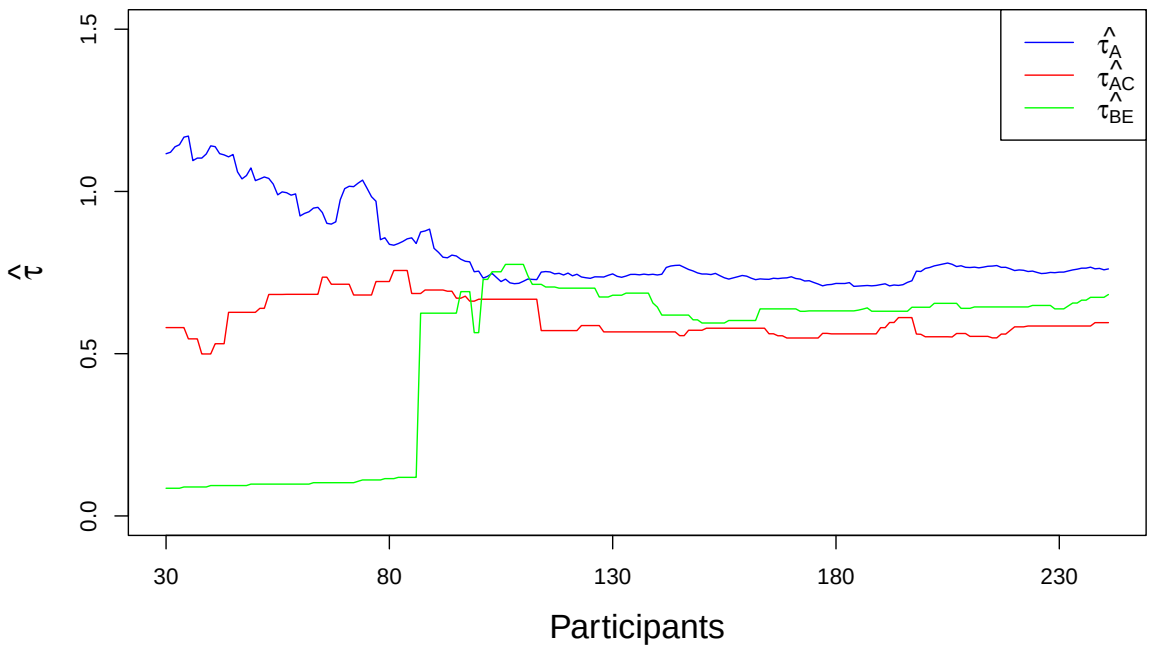


Figure 3.2: Convergence patterns of estimated optimal adaptive allocation ratios $\hat{\tau}_A$, $\hat{\tau}_{AC:AD}$, and $\hat{\tau}_{BE:BF}$ in application of OAA in the SMART Weight Loss Management study.

Figure 3.2 shows the estimated adaptive allocation ratios as the trial progresses. $\hat{\tau}_A$ and $\hat{\tau}_{AC}$ exhibit a clear convergence pattern, approaching values of 0.8 and 0.5, respectively. It can also be observed that $\hat{\tau}_{BE}$ converges to approximately 0.75. Overall, these results indicate that the estimated adaptive allocation ratios display a convergent trend, even

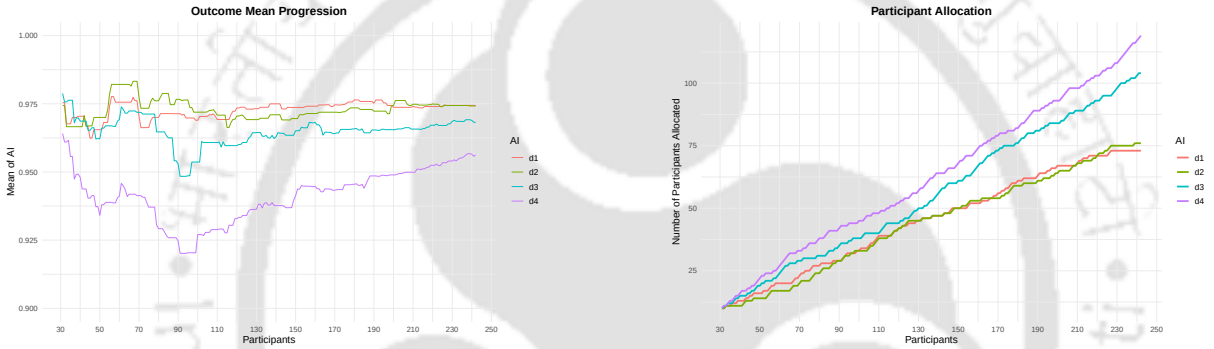
with a relatively small number of participants. Thus, we can reasonably conclude that the estimated optimal adaptive allocation ratios converge to the corresponding true optimal adaptive allocation ratios as the number of participants increases.

Table 3.3: Allocated participants and mean of outcomes (in parentheses) following optimal adaptive allocation (OAA) and 1:1 allocation in the SMART Weight Loss Management study. The OAA has to stop after 241 participants, as the treatment sequence $\{B, F\}$ of the SMART Weight Loss data has no available participants.

DTR	Optimal Adaptive Allocation (OAA)		SMART Weight Loss Allocation		SMART Weight Loss allocation (end of study)
	Participants with OAA	Remaining participants	Till 240 participants	Remaining 99 participants	All participants
d_1	47 + 26 = 73 (0.975)	38 + 15 = 53 (0.978)	59 + 31 = 90 (0.974)	26 + 10 = 36 (0.971)	85 + 41 = 126 (0.973)
d_2	47 + 29 = 76 (0.974)	38 + 9 = 47 (0.980)	59 + 31 = 90 (0.975)	26 + 7 = 33 (0.972)	85 + 38 = 123 (0.974)
d_3	84 + 20 = 104 (0.968)	8 + 12 = 20 (0.979)	68 + 26 = 94 (0.955)	24 + 6 = 30 (0.970)	92 + 32 = 124 (0.959)
d_4	84 + 35 = 119 (0.956)	8 + 0 = 8 (0.975)	68 + 26 = 94 (0.945)	24 + 9 = 33 (0.981)	92 + 35 = 127 (0.955)
Total	241	82	241	82	323

In Table 3.3, we present a comparative analysis of the retrospective application of adaptive randomization using our developed approach with the equal randomization method used in the SMART Weight Loss Management Study. The table considers 241 participants in the optimal adaptive allocation (OAA) method, as the number of participants in the (B, F) arm is exhausted at this point, necessitating the termination of the retrospective application using the OAA method. To ensure a fair comparison, we also consider the first 241 participants from the equal randomization in the original study, using the time stamp. Among these 241 participants, it can be seen that our developed optimal design was able to allocate a larger number of participants to the better AIs. Here, "better" refers to an AI through which a greater reduction in the total expected outcome can be achieved. In the second column, the allocation of participants (in increasing order) to each AI exactly matches the decreasing order of the estimated mean outcomes (in parentheses), indicating that the OAA method successfully allocates more participants to AIs associated with higher weight reduction. This is not the case (order of fours AIs) with equal randomization, as shown by the numbers in the last column of Table 3.3, which correspond to the allocations from the SMART Weight Loss Management Study. Similarly, considering only 241 participants from the original study with equal randomization, the column four of Table 3.3 shows that the AI with the lowest mean outcome was assigned the same number of participants as the AI with the second lowest mean outcome. Similarly, the AI with the highest mean outcome received the same number of participants as the AI with the second-highest mean outcome. By contrast, the OAA method achieves a more advantageous allocation by assigning more participants to the better-performing AIs compared to equal randomization.

The allocation of participants to each AI using the OAA method and the corresponding mean outcomes are represented graphically in Figure 3.3. Figure 3.3(a) illustrates the progression of the mean outcomes throughout the trial as new participants are allocated, while Figure 3.3(b) shows the progression of participant allocation to each AI. It is evident that AI d_4 maintains the lowest mean outcome throughout the clinical trial, and the number of participants allocated to that AI is the highest, almost from the start of the trial (after the initial 30 participants who were randomly allocated with equal probability). Notably, the order of AIs d_4, d_3, d_2, d_1 by increasing mean outcome is the exact opposite of the order d_1, d_2, d_3, d_4 by increasing number of participants allocated using OAA. Thus, by employing the OAA method, we have been able to address ethical considerations in clinical trials by preferentially allocating more participants to better-performing AIs.



(a) Progression of μ_{d_i} with recruitment of participants

(b) Progression of participant allocation with recruitment of participants.

Figure 3.3: SMART Weight Loss Management using optimum adaptive allocation

3.7 Discussion

This chapter represents a natural extension of Chapter 2 of this thesis. In this chapter, we developed optimal adaptive allocation ratios and, consequently, an allocation procedure for SMART designs with continuous outcomes. The proposed optimal adaptive allocation procedure is intended to help clinicians reduce the number of participants allocated to comparatively less effective treatment sequences. The methodology was evaluated through various simulation scenarios to better understand its dynamics. Both simulation studies and retrospective applications to data from the SMART Weight Loss Management Study provided strong support for the methodology, demonstrating substantial gains in allocating more participants to superior treatment sequences.

In the simulation study, we observed that when the means of any two treatment sequences are close, the estimated optimal adaptive allocation ratios are close to the corresponding true values of the optimal adaptive allocation ratios, even with a relatively

small sample size of 500. In scenarios where the means of two treatment sequences are farther apart, better estimation (in terms of bias) of the allocation ratios requires a larger sample size of 1000. Furthermore, our retrospective application of the methodology to the data from the SMART Weight Loss Management Study demonstrated an increase in the number of participants allocated to the more effective treatment sequence as the trial progressed. The order of participant allocation was also aligned with the effectiveness of the treatment sequences. Notably, as the trial progressed and more participants were enrolled, the gap in the number of participants allocated to the better-performing treatment sequence widened, indicating the efficiency of the developed methodology.

As mentioned in the discussion section of the previous chapter, the issues related to the burn-in period of equal randomization (first 30 or 60 patients) to obtain preliminary parameter estimates before implementing the adaptive allocation procedure also apply to continuous outcomes. Here, too, the duration of this burn-in period is chosen heuristically, without any guarantee of optimality, similar to the binary outcome case (see Section 2.8).

Another point of concern for this developed methodology is the requirement that the primary outcome be non-negative, ensuring that the estimated statistic, namely the mean, remains positive. This is a well-known drawback in adaptive RCTs as well (Hu and Rosenberger, 2006). Therefore, for our methodology, the outcomes should be such that both the estimated and theoretical statistics are positive. If all theoretical population statistics (usually the mean) are negative, the allocation ratio does not exist (it needs the square root of the mean). If the outcome is a negative continuous variable where lower values indicate better results, the optimal adaptive allocation ratio can be determined by transforming the outcome into a positive continuous variable in which higher values correspond to better outcomes, in a similar manner. However, in cases where outcomes include a mixture of negative and positive values, the developed methodology is not applicable. Currently, there is limited literature addressing this scenario in either adaptive RCTs or adaptive SMART designs. We aim to address this limitation in future work. In our study, to ensure the primary outcome is always positive, we considered the primary outcome as the ratio of each participant's weight after 12 months to their baseline weight. Had we used the difference in weights, the outcome could have taken both positive and negative values, causing the estimated mean to fluctuate between positive and negative values.

3.8 Detailed Derivation

3.8.1 Derivation of First Stage Mean (μ_A) and Variance (σ_A^2)

In this section, we will derive the first-stage mean and variance of the primary outcome corresponding to those participants who started with the first-stage treatment $T_1 \in \{A, B\}$.

The expected outcome of a participant who started with the first-stage treatment A is,

$$\begin{aligned}\mu_A &= E(Y|T_1 = A) \\ &= P(T_2 = A'|T_1 = A)E(Y|T_1 = A, T_2 = A') \\ &+ P(T_2 = C|T_1 = A)E(Y|T_1 = A, T_2 = C) \\ &+ P(T_2 = D|T_1 = A)E(Y|T_1 = A, T_2 = D) \\ &= \gamma_A \mu_{AA'} + \left(\frac{1-\gamma_A}{1+\tau_{AC:AD}}\right)(\tau_{AC:AD}\mu_{AC} + \mu_{AD}).\end{aligned}$$

Similarly, the expected outcome of a participant who started with the first-stage treatment B is,

$$\mu_B = \gamma_B \mu_{BB'} + \left(\frac{1-\gamma_B}{1+\tau_{BE:BF}}\right)(\tau_{BE:BF}\mu_{BE} + \mu_{BF}).$$

Now, we find $\sigma^2_{T_1}$, the variance of the outcome of a participant who started with the first-stage treatment A. We show the derivation σ^2_A. The σ^2_B can be obtained similarly. Here, we have,

$$\sigma^2_A = Var(Y_A) = E(Y^2_A) - (E(Y_A))^2.$$

The first term of the above equation,

$$\begin{aligned}E(Y^2_A) &= E(Y^2|T_1 = A) \\ &= P(T_2 = A'|T_1 = A)E\left[Y^2|T_1 = A, T_2 = A'\right] \\ &+ P(T_2 = C|T_1 = A)E\left[Y^2|T_1 = A, T_2 = C\right] \\ &+ P(T_2 = D|T_1 = A)E\left[Y^2|T_1 = A, T_2 = D\right] \\ &= \gamma_A\left(\sigma^2_{AA'} + \mu^2_{AA'}\right) + (1-\gamma_A)\left(\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}}\right)\left(\sigma^2_{AC} + \mu^2_{AC}\right) \\ &+ (1-\gamma_A)\left(\frac{1}{1+\tau_{AC:AD}}\right)\left(\sigma^2_{AD} + \mu^2_{AD}\right).\end{aligned}$$

Note that,

$$E(Y_A) = \mu_A = \gamma_A \mu_{AA'} + \left(\frac{1-\gamma_A}{1+\tau_{AC:AD}}\right)(\tau_{AC:AD}\mu_{AC} + \mu_{AD}).$$

Using the expressions of $E(Y^2_A)$ and $E(Y_A)$, we get,

$$\begin{aligned}\sigma^2_A &= \gamma_A\left(\sigma^2_{AA'} + \mu^2_{AA'}\right) + (1-\gamma_A)\left(\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}}\right)\left(\sigma^2_{AC} + \mu^2_{AC}\right) \\ &+ (1-\gamma_A)\left(\frac{1}{1+\tau_{AC:AD}}\right)\left(\sigma^2_{AD} + \mu^2_{AD}\right)\end{aligned}$$

$$- \left(\gamma_A \mu_{AA'} + \left(\frac{1-\gamma_A}{1+\tau_{AC:AD}}\right)(\tau_{AC:AD}\mu_{AC} + \mu_{AD})\right)^2.$$

Similarly,

$$\begin{aligned}\sigma_B^2 = {} & \gamma_B\left(\sigma_{BB'}^2 + \mu_{BB'}^2\right) + (1-\gamma_B)\left(\frac{\tau_{BE:BF}}{1+\tau_{BE:BF}}\right)\left(\sigma_{BE}^2 + \mu_{BE}^2\right) \\ & + (1-\gamma_B)\left(\frac{1}{1+\tau_{BE:BF}}\right)\left(\sigma_{BF}^2 + \mu_{BF}^2\right) \\ & - \left(\gamma_B \mu_{BB'} + \left(\frac{1-\gamma_B}{1+\tau_{BE:BF}}\right)(\tau_{BE:BF}\mu_{BE} + \mu_{BF})\right)^2.\end{aligned}$$

It can be observed that σ_A^2 and σ_B^2 are independent of the first-stage allocation ratio, τ_A. Hence, both the variances can be treated as constant with respect to τ_A.

3.8.2 Derivation of Asymptotic Variance of Parameters : $\hat{\mu}_{T_1T_2}$, $\hat{\sigma}_{T_1T_2}$

Let us consider $\{Y_1, Y_2, ..., Y_n\}$ be the continuous primary outcome variables. The notations defined in this section are analogous to those used in the previous chapter's derivations, but are now applied to the context of a continuous outcome variable. T_{1i} and T_{2i} denote the assigned first and second stage treatments to the $i^{th} \in \{1, 2, \cdots, n\}$ participant, respectively. T_{1i} can take values A and B; $T_{2i} \in \{A', C, D\}$ where $T_{1i} = A$ and $T_{2i} \in \{B', E, F\}$ where $T_{1i} = B$. Now, $\mathscr{F}_i = \{Y_1, Y_2, ..., Y_i, T_{11}, T_{12}, ..., T_{1i}, T_{21}, T_{22}, ..., T_{2i}\}$ as the history of primary outcome variables, first and second stage allocated treatments for the first i participants. Also, the conditional expectation as, $E_{i-1}(\cdot) = E(\cdot|\mathscr{F}_{i-1})$. Let, $T_1^n = (T_{11}, T_{12}, ..., T_{1n})$, and $T_2^n = (T_{21}, T_{22}, ..., T_{2n})$ be the history of treatment assignment of the first and second stage allocated treatments, respectively; and $Y^n = (Y_1, Y_2, ..., Y_n)$ be the history of primary outcome variables. The likelihood function from the data is,

$$\begin{aligned}\mathscr{L}_n &\equiv \{Y^n, T_1^n, T_2^n\} \\ &\equiv \mathscr{L}(Y_n, T_{1n}, T_{2n}|\mathscr{F}_{n-1})\mathscr{L}_{n-1},\end{aligned}$$

where $\mathscr{L}(Y_n, T_{1n}, T_{2n}|\mathscr{F}_{n-1})$ is the likelihood contribution from the n^{th} participant given the history of earlier participants. Now,

$$\mathscr{L}_n = \prod_{i=1}^{n} \mathscr{L}(Y_i, T_{1i}, T_{2i}|\mathscr{F}_{i-1}), \tag{3.9}$$

with $\mathscr{L}_0 = 1$, where,

$$
\begin{aligned}
&\mathscr{L}(Y_i, T_{1i}, T_{2i}|\mathscr{F}_{i-1}) \\
&= \mathscr{L}(Y_i|T_{1i}, T_{2i}, \mathscr{F}_{i-1})\mathscr{L}(T_{1i}, T_{2i}|\mathscr{F}_{i-1}) = \mathscr{L}(Y_i|T_{1i}, T_{2i}, \mathscr{F}_{i-1})\mathscr{L}(T_{2i}|T_{1i}, \mathscr{F}_{i-1})\mathscr{L}(T_{1i}|\mathscr{F}_{i-1}) \\
&= \left[\frac{1}{\sqrt{2\pi}\sigma_{AC}} e^{-\frac{1}{2}\left(\frac{Y_i-\mu_{AC}}{\sigma_{AC}}\right)^2}\right]^{I(T_{1i}=A,T_{2i}=C)} \times \left[\frac{1}{\sqrt{2\pi}\sigma_{AD}} e^{-\frac{1}{2}\left(\frac{Y_i-\mu_{AD}}{\sigma_{AD}}\right)^2}\right]^{I(T_{1i}=A,T_{2i}=D)} \times \\
&\left[\frac{1}{\sqrt{2\pi}\sigma_{AA'}} e^{-\frac{1}{2}\left(\frac{Y_i-\mu_{AA'}}{\sigma_{AA'}}\right)^2}\right]^{I(T_{1i}=A,T_{2i}=A')} \times \left[\frac{1}{\sqrt{2\pi}\sigma_{BE}} e^{-\frac{1}{2}\left(\frac{Y_i-\mu_{BE}}{\sigma_{BE}}\right)^2}\right]^{I(T_{1i}=B,T_{2i}=E)} \times \\
&\left[\frac{1}{\sqrt{2\pi}\sigma_{BF}} e^{-\frac{1}{2}\left(\frac{Y_i-\mu_{BF}}{\sigma_{BF}}\right)^2}\right]^{I(T_{1i}=B,T_{2i}=F)} \times \left[\frac{1}{\sqrt{2\pi}\sigma_{BB'}} e^{-\frac{1}{2}\left(\frac{Y_i-\mu_{BB'}}{\sigma_{BB'}}\right)^2}\right]^{I(T_{1i}=B,T_{2i}=B')} \times \\
&\{E_{i-1}(I(T_{2i} = A'|T_{1i} = A))\}^{I(T_{1i}=A,T_{2i}=A')} \times \\
&\left[\{E_{i-1}(I(T_{2i} = C|T_{1i} = A))\}^{I(T_{1i}=A,T_{2i}=C)}\right]^{1-I(T_{1i}=A,T_{2i}=A')} \times \\
&\left[\{E_{i-1}(1 - I(T_{2i} = C|T_{1i} = A))\}^{I(T_{1i}=A,T_{2i}=D)}\right]^{1-I(T_{1i}=A,T_{2i}=A')} \times \\
&\{E_{i-1}(I(T_{2i} = B'|T_{1i} = B))\}^{I(T_{1i}=B,T_{2i}=B')} \times \\
&\left[\{E_{i-1}(I(T_{2i} = E|T_{1i} = B))\}^{I(T_{1i}=B,T_{2i}=E)}\right]^{1-I(T_{1i}=B,T_{2i}=B')} \times \\
&\left[\{E_{i-1}(1 - I(T_{2i} = E|T_{1i} = B))\}^{I(T_{1i}=B,T_{2i}=F)}\right]^{1-I(T_{1i}=B,T_{2i}=B')} \times \\
&\{E_{i-1}(I(T_{1i} = A))\}^{I(T_{1i}=A)}\{E_{i-1}(1 - I(T_{1i} = A))\}^{I(T_{1i}=B)}. \qquad (3.10)
\end{aligned}
$$

Thus, using (3.10), the equation (3.9) can be expressed as,

$$
\begin{aligned}
&\mathscr{L}_n \\
&= \left(\frac{1}{\sqrt{2\pi}\sigma_{AC}}\right)^{\sum_{i=1}^n I(T_{1i}=A,T_{2i}=C)} \left[e^{-\frac{1}{2}\sum_{i=1}^n\left(\frac{Y_i-\mu_{AC}}{\sigma_{AC}}\right)^2 I(T_{1i}=A,T_{2i}=C)}\right] \times \\
&\left(\frac{1}{\sqrt{2\pi}\sigma_{AD}}\right)^{\sum_{i=1}^n I(T_{1i}=A,T_{2i}=D)} \left[e^{-\frac{1}{2}\sum_{i=1}^n\left(\frac{Y_i-\mu_{AD}}{\sigma_{AD}}\right)^2 I(T_{1i}=A,T_{2i}=D)}\right] \times \\
&\left(\frac{1}{\sqrt{2\pi}\sigma_{AA'}}\right)^{\sum_{i=1}^n I(T_{1i}=A,T_{2i}=A')} \left[e^{-\frac{1}{2}\sum_{i=1}^n\left(\frac{Y_i-\mu_{AA'}}{\sigma_{AA'}}\right)^2 I(T_{1i}=A,T_{2i}=A')}\right] \times \\
&\left(\prod_{i=1}^n \{E_{i-1}(I(T_{2i} = A'|T_{1i} = A))\}^{I(T_{1i}=A,T_{2i}=A')}\right) \times \\
&\left(\prod_{i=1}^n \left[\{E_{i-1}(I(T_{2i} = C|T_{1i} = A))\}^{I(T_{1i}=A,T_{2i}=C)}\right]^{1-I(T_{1i}=A,T_{2i}=A')}\right) \times \\
&\left(\prod_{i=1}^n \left[\{E_{i-1}(1 - I(T_{2i} = C|T_{1i} = A))\}^{I(T_{1i}=A,T_{2i}=D)}\right]^{1-I(T_{1i}=A,T_{2i}=A')}\right) \times \\
&\left(\frac{1}{\sqrt{2\pi}\sigma_{BE}}\right)^{\sum_{i=1}^n I(T_{1i}=B,T_{2i}=E)} \left[e^{-\frac{1}{2}\sum_{i=1}^n\left(\frac{Y_i-\mu_{BE}}{\sigma_{BE}}\right)^2 I(T_{1i}=B,T_{2i}=E)}\right] \times
\end{aligned}
$$

$$\left(\frac{1}{\sqrt{2\pi}\sigma_{BF}}\right)^{\sum_{i=1}^{n} I(T_{1i}=B,T_{2i}=F)} \left[e^{-\frac{1}{2}\sum_{i=1}^{n}\left(\frac{Y_i-\mu_{BF}}{\sigma_{BF}}\right)^2 I(T_{1i}=B,T_{2i}=F)}\right] \times$$
$$\left(\frac{1}{\sqrt{2\pi}\sigma_{BB'}}\right)^{\sum_{i=1}^{n} I(T_{1i}=B,T_{2i}=B')} \left[e^{-\frac{1}{2}\sum_{i=1}^{n}\left(\frac{Y_i-\mu_{BB'}}{\sigma_{BB'}}\right)^2 I(T_{1i}=B,T_{2i}=B')}\right] \times$$
$$\left(\prod_{i=1}^{n}\{E_{i-1}(I(T_{2i}=B'|T_{1i}=B))\}^{I(T_{1i}=B,T_{2i}=B')}\right) \times$$
$$\left(\prod_{i=1}^{n}\left[\{E_{i-1}(I(T_{2i}=E|T_{1i}=B))\}^{I(T_{1i}=B,T_{2i}=E)}\right]^{1-I(T_{1i}=B,T_{2i}=B')}\right) \times$$
$$\left(\prod_{i=1}^{n}\left[\{E_{i-1}(1-I(T_{2i}=E|T_{1i}=B))\}^{I(T_{1i}=B,T_{2i}=F)}\right]^{1-I(T_{1i}=B,T_{2i}=B')}\right) \times$$
$$\left(\prod_{i=1}^{n}(E_{i-1}(I(T_{1i}=A))^{I(T_{1i}=A)}(1-E_{i-1}(I(T_{1i}=A)))^{I(T_{1i}=B)}\right). \tag{3.11}$$

Now, using the equation $(A3)$ of Rosenberger 1997, $-n^{-1}\sum_{i=1}^{n} E_{i-1}\{\frac{\partial^2 log\mathscr{L}_i}{\partial\mu_{AC}^2}\}$ from (3.10) becomes

$$\begin{aligned}
&n^{-1}\sum_{i=1}^{n}\left[\frac{1}{\sigma_{AC}^2}E_{i-1}\left(I(T_{1i}=A,T_{2i}=C)\right)\right]\\
=&n^{-1}\sum_{i=1}^{n}\left[\frac{1}{\sigma_{AC}^2}P\left(T_{1i}=A,T_{2i}=C|\mathscr{F}_{i-1}\right)\right]\\
\xrightarrow{a.s}&\left(\frac{1}{\sigma_{AC}^2}\right)(1-\gamma_A)\left(\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}}\right)\left(\frac{\tau_A}{1+\tau_A}\right)\equiv v_{\mu_{AC}}.
\end{aligned} \tag{3.12}$$

Thus, the variance of $\hat{\mu}_{AC}(\equiv\hat{\mu}_{AC,n})$ is $\frac{1}{n}v_{\mu_{AC}}^{-1}$. Now, using the equation $(A3)$ of Rosenberger 1997, $-n^{-1}\sum_{i=1}^{n} E_{i-1}\{\frac{\partial^2 log\mathscr{L}_i}{\partial\sigma_{AC}^2}\}$ from (3.10) becomes

$$\begin{aligned}
&-n^{-1}\sum_{i=1}^{n}\left[\left(\frac{1}{\sigma_{AC}^2}\right)E_{i-1}\left(I(T_{1i}=A,T_{2i}=C)\right)-\left(\frac{3}{\sigma_{AC}^4}\right)E_{i-1}\left((Y_i-\mu_{AC})^2 I(T_{1i}=A,T_{2i}=C)\right)\right]\\
&=n^{-1}\sum_{i=1}^{n}\left[\left(-\frac{1}{\sigma_{AC}^2}\right)E_{i-1}\left(I(T_{1i}=A,T_{2i}=C)\right)+\left(\frac{3}{\sigma_{AC}^4}\right)E_{i-1}\left((Y_i-\mu_{AC})^2 I(T_{1i}=A,T_{2i}=C)\right)\right]\\
&=n^{-1}\sum_{i=1}^{n}\left[\left(-\frac{1}{\sigma_{AC}^2}\right)E_{i-1}\left(I(T_{1i}=A,T_{2i}=C)\right)+\left(\frac{3}{\sigma_{AC}^2}\right)E_{i-1}\left(I(T_{1i}=A,T_{2i}=C)\right)\right]\\
&=n^{-1}\sum_{i=1}^{n}\left[\left(\frac{2}{\sigma_{AC}^2}\right)P\left(I(T_{1i}=A,T_{2i}=C)|\mathscr{F}_{i-1}\right)\right]\\
&\xrightarrow{a.s}\left(\frac{2}{\sigma_{AC}^2}\right)(1-\gamma_A)\left(\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}}\right)\left(\frac{\tau_A}{1+\tau_A}\right)\equiv v_{\sigma_{AC}}.
\end{aligned} \tag{3.13}$$

Thus, the variance of $\hat{\sigma}_{AC}(\equiv \hat{\sigma}_{AC,n})$ is $\frac{1}{n}v^{-1}_{\sigma_{AC}}$. Now, using the equation $(A3)$ of Rosenberger 1997, $-n^{-1}\sum_{i=1}^{n} E_{i-1}\{\frac{\partial^2 log\mathscr{L}_i}{\partial \mu^2_{AD}}\}$ from (3.10) becomes

$$\begin{aligned}
&n^{-1}\sum_{i=1}^{n}\left[\frac{1}{\sigma^2_{AD}}E_{i-1}\left(I(T_{1i}=A,T_{2i}=D)\right)\right]\\
&=n^{-1}\sum_{i=1}^{n}\left[\frac{1}{\sigma^2_{AD}}P\left(T_{1i}=A,T_{2i}=D|\mathscr{F}_{i-1}\right)\right]\\
&\xrightarrow{a.s}\left(\frac{1}{\sigma^2_{AD}}\right)(1-\gamma_A)\left(\frac{1}{1+\tau_{AC:AD}}\right)\left(\frac{\tau_A}{1+\tau_A}\right)\equiv v_{\mu_{AD}}. \qquad (3.14)
\end{aligned}$$

Thus, the variance of $\hat{\mu}_{AD}(\equiv \hat{\mu}_{AD,n})$ is $\frac{1}{n}v^{-1}_{\mu_{AD}}$. Now, using the equation $(A3)$ of Rosenberger 1997, $-n^{-1}\sum_{i=1}^{n} E_{i-1}\{\frac{\partial^2 log\mathscr{L}_i}{\partial \sigma^2_{AD}}\}$ from (3.10) becomes

$$\begin{aligned}
&=-n^{-1}\sum_{i=1}^{n}\left[\left(\frac{1}{\sigma^2_{AD}}\right)E_{i-1}\left(I(T_{1i}=A,T_{2i}=D)\right)-\left(\frac{3}{\sigma^4_{AD}}\right)E_{i-1}\left((Y_i-\mu_{AD})^2I(T_{1i}=A,T_{2i}=D)\right)\right]\\
&=n^{-1}\sum_{i=1}^{n}\left[\left(-\frac{1}{\sigma^2_{AD}}\right)E_{i-1}\left(I(T_{1i}=A,T_{2i}=D)\right)+\left(\frac{3}{\sigma^4_{AD}}\right)E_{i-1}\left((Y_i-\mu_{AD})^2I(T_{1i}=A,T_{2i}=D)\right)\right]\\
&=n^{-1}\sum_{i=1}^{n}\left[\left(-\frac{1}{\sigma^2_{AD}}\right)E_{i-1}\left(I(T_{1i}=A,T_{2i}=D)\right)+\left(\frac{3}{\sigma^2_{AD}}\right)E_{i-1}\left(I(T_{1i}=A,T_{2i}=D)\right)\right]\\
&=n^{-1}\sum_{i=1}^{n}\left[\left(\frac{2}{\sigma^2_{AD}}\right)P\left(I(T_{1i}=A,T_{2i}=D)|\mathscr{F}_{i-1}\right)\right]\\
&\xrightarrow{a.s}\left(\frac{2}{\sigma^2_{AD}}\right)(1-\gamma_A)\left(\frac{1}{1+\tau_{AC:AD}}\right)\left(\frac{\tau_A}{1+\tau_A}\right)\equiv v_{\sigma_{AD}}. \qquad (3.15)
\end{aligned}$$

Thus, the variance of $\hat{\sigma}_{AD}(\equiv \hat{\sigma}_{AD,n})$ is $\frac{1}{n}v^{-1}_{\sigma_{AD}}$. Now, using the equation $(A3)$ of Rosenberger 1997, $-n^{-1}\sum_{i=1}^{n} E_{i-1}\{\frac{\partial^2 log\mathscr{L}_i}{\partial \mu^2_{AA'}}\}$ from (3.10) becomes

$$\begin{aligned}
&n^{-1}\sum_{i=1}^{n}\left[\frac{1}{\sigma^2_{AA'}}E_{i-1}\left(I(T_{1i}=A,T_{2i}=A')\right)\right]\\
&=n^{-1}\sum_{i=1}^{n}\left[\frac{1}{\sigma^2_{AA'}}P\left(T_{1i}=A,T_{2i}=A'|\mathscr{F}_{i-1}\right)\right]\\
&\xrightarrow{a.s}\left(\frac{1}{\sigma^2_{AA'}}\right)(\gamma_A)\left(\frac{\tau_A}{1+\tau_A}\right)\equiv v_{\mu_{AA'}}. \qquad (3.16)
\end{aligned}$$

Thus, the variance of $\hat{\mu}_{AA'}(\equiv \hat{\mu}_{AA',n})$ is $\frac{1}{n}v^{-1}_{\mu_{AA'}}$. Now, using the equation $(A3)$ of Rosenberger 1997, $-n^{-1}\sum_{i=1}^{n} E_{i-1}\{\frac{\partial^2 log\mathscr{L}_i}{\partial \sigma^2_{AA'}}\}$ from (3.10) becomes

$$
\begin{aligned}
&-\frac{1}{n}\sum_{i=1}^{n}\left[\left(\frac{1}{\sigma^2_{AA'}}\right)E_{i-1}\left(I(T_{1i}=A,T_{2i}=A')\right)-\left(\frac{3}{\sigma^4_{AA'}}\right)E_{i-1}\left((Y_i-\mu_{AA'})^2I(T_{1i}=A,T_{2i}=A')\right)\right]\\
&=\frac{1}{n}\sum_{i=1}^{n}\left[\left(-\frac{1}{\sigma^2_{AA'}}\right)E_{i-1}\left(I(T_{1i}=A,T_{2i}=A')\right)+\left(\frac{3}{\sigma^4_{AA'}}\right)E_{i-1}\left((Y_i-\mu_{AA'})^2I(T_{1i}=A,T_{2i}=A')\right)\right]\\
&=\frac{1}{n}\sum_{i=1}^{n}\left[\left(-\frac{1}{\sigma^2_{AA'}}\right)E_{i-1}\left(I(T_{1i}=A,T_{2i}=A')\right)+\left(\frac{3}{\sigma^2_{AA'}}\right)E_{i-1}\left(I(T_{1i}=A,T_{2i}=A')\right)\right]\\
&=\frac{1}{n}\sum_{i=1}^{n}\left[\left(\frac{2}{\sigma^2_{AA'}}\right)P\left(T_{1i}=A,T_{2i}=A'\mid\mathscr{F}_{i-1}\right)\right]\\
&\xrightarrow{a.s.}\left(\frac{2}{\sigma^2_{AA'}}\right)\cdot\gamma_A\cdot\left(\frac{\tau_A}{1+\tau_A}\right)\equiv v_{\sigma_{AA'}}. \qquad (3.17)
\end{aligned}
$$

Thus, the variance of $\hat{\sigma}_{AA'}(\equiv\hat{\sigma}_{AA',n})$ is $\frac{1}{n}v^{-1}_{\sigma_{AA'}}$. Now, using the equation $(A3)$ of Rosenberger 1997, $-n^{-1}\sum_{i=1}^{n}E_{i-1}\{\frac{\partial^2 log\mathscr{L}_i}{\partial\mu^2_{BE}}\}$ from (3.10) becomes

$$
\begin{aligned}
&n^{-1}\sum_{i=1}^{n}\left[\frac{1}{\sigma^2_{BE}}E_{i-1}\left(I(T_{1i}=B,T_{2i}=E)\right)\right]\\
&=n^{-1}\sum_{i=1}^{n}\left[\frac{1}{\sigma^2_{BE}}P\left(T_{1i}=B,T_{2i}=E|\mathscr{F}_{i-1}\right)\right]\\
&\xrightarrow{a.s}\left(\frac{1}{\sigma^2_{BE}}\right)(1-\gamma_B)\left(\frac{\tau_{BE:BF}}{1+\tau_{BE:BF}}\right)\left(\frac{1}{1+\tau_A}\right)\equiv v_{\mu_{BE}}. \qquad (3.18)
\end{aligned}
$$

Thus, the variance of $\hat{\mu}_{BE}(\equiv\hat{\mu}_{BE,n})$ is $\frac{1}{n}v^{-1}_{\mu_{BE}}$. Now, using the equation $(A3)$ of Rosenberger 1997, $-n^{-1}\sum_{i=1}^{n}E_{i-1}\{\frac{\partial^2 log\mathscr{L}_i}{\partial\sigma^2_{BE}}\}$ from (3.10) becomes

$$
\begin{aligned}
&-n^{-1}\sum_{i=1}^{n}\left[\left(\frac{1}{\sigma^2_{BE}}\right)E_{i-1}\left(I(T_{1i}=B,T_{2i}=E)\right)-\left(\frac{3}{\sigma^4_{BE}}\right)E_{i-1}\left((Y_i-\mu_{BE})^2I(T_{1i}=B,T_{2i}=E)\right)\right]\\
&=n^{-1}\sum_{i=1}^{n}\left[\left(-\frac{1}{\sigma^2_{BE}}\right)E_{i-1}\left(I(T_{1i}=B,T_{2i}=E)\right)+\left(\frac{3}{\sigma^4_{BE}}\right)E_{i-1}\left((Y_i-\mu_{BE})^2I(T_{1i}=B,T_{2i}=E)\right)\right]\\
&=n^{-1}\sum_{i=1}^{n}\left[\left(-\frac{1}{\sigma^2_{BE}}\right)E_{i-1}\left(I(T_{1i}=B,T_{2i}=E)\right)+\left(\frac{3}{\sigma^2_{BE}}\right)E_{i-1}\left(I(T_{1i}=B,T_{2i}=E)\right)\right]\\
&=n^{-1}\sum_{i=1}^{n}\left[\left(\frac{2}{\sigma^2_{BE}}\right)P\left(I(T_{1i}=B,T_{2i}=E)|\mathscr{F}_{i-1}\right)\right]\\
&\xrightarrow{a.s}\left(\frac{2}{\sigma^2_{BE}}\right)(1-\gamma_B)\left(\frac{\tau_{BE:BF}}{1+\tau_{BE:BF}}\right)\left(\frac{1}{1+\tau_A}\right)\equiv v_{\sigma_{BE}}. \qquad (3.19)
\end{aligned}
$$

Thus, the variance of $\hat{\sigma}_{BE}(\equiv\hat{\sigma}_{BE,n})$ is $\frac{1}{n}v^{-1}_{\sigma_{BE}}$. Now, using the equation $(A3)$ of Rosen-

berger 1997, $-n^{-1}\sum_{i=1}^{n} E_{i-1}\{\frac{\partial^2 log\mathscr{L}_i}{\partial\mu_{BF}^2}\}$ from (3.10) becomes

$$\begin{aligned}
&n^{-1}\sum_{i=1}^{n}\left[\frac{1}{\sigma_{BF}^2}E_{i-1}\left(I(T_{1i}=B,T_{2i}=F)\right)\right]\\
&=n^{-1}\sum_{i=1}^{n}\left[\frac{1}{\sigma_{BF}^2}P\left(T_{1i}=B,T_{2i}=F|\mathscr{F}_{i-1}\right)\right]\\
&\xrightarrow{a.s}\left(\frac{1}{\sigma_{BF}^2}\right)(1-\gamma_B)\left(\frac{1}{1+\tau_{BE:BF}}\right)\left(\frac{1}{1+\tau_A}\right)\equiv v_{\mu_{BF}}. \qquad (3.20)
\end{aligned}$$

Thus, the variance of $\hat{\mu}_{BF}(\equiv\hat{\mu}_{BF,n})$ is $\frac{1}{n}v_{\mu_{BF}}^{-1}$. Now, using the equation $(A3)$ of Rosenberger 1997, $-n^{-1}\sum_{i=1}^{n} E_{i-1}\{\frac{\partial^2 log\mathscr{L}_i}{\partial\sigma_{BF}^2}\}$ from (3.10) becomes

$$\begin{aligned}
&-n^{-1}\sum_{i=1}^{n}\left[\left(\frac{1}{\sigma_{BF}^2}\right)E_{i-1}\left(I(T_{1i}=B,T_{2i}=F)\right)-\left(\frac{3}{\sigma_{BF}^4}\right)E_{i-1}\left((Y_i-\mu_{BF})^2I(T_{1i}=B,T_{2i}=F)\right)\right]\\
&=n^{-1}\sum_{i=1}^{n}\left[\left(-\frac{1}{\sigma_{BF}^2}\right)E_{i-1}\left(I(T_{1i}=B,T_{2i}=F)\right)+\left(\frac{3}{\sigma_{BF}^4}\right)E_{i-1}\left((Y_i-\mu_{BF})^2I(T_{1i}=B,T_{2i}=F)\right)\right]\\
&=n^{-1}\sum_{i=1}^{n}\left[\left(-\frac{1}{\sigma_{BF}^2}\right)E_{i-1}\left(I(T_{1i}=B,T_{2i}=F)\right)+\left(\frac{3}{\sigma_{BF}^2}\right)E_{i-1}\left(I(T_{1i}=B,T_{2i}=F)\right)\right]\\
&=n^{-1}\sum_{i=1}^{n}\left[\left(\frac{2}{\sigma_{BF}^2}\right)P\left(I(T_{1i}=B,T_{2i}=F)|\mathscr{F}_{i-1}\right)\right]\\
&\xrightarrow{a.s}\left(\frac{2}{\sigma_{BF}^2}\right)(1-\gamma_B)\left(\frac{1}{1+\tau_{BE:BF}}\right)\left(\frac{1}{1+\tau_A}\right)\equiv v_{\sigma_{BF}}. \qquad (3.21)
\end{aligned}$$

Thus, the variance of $\hat{\sigma}_{BF}(\equiv\hat{\sigma}_{BF,n})$ is $\frac{1}{n}v_{\sigma_{BF}}^{-1}$. Now, using the equation $(A3)$ of Rosenberger 1997, $-n^{-1}\sum_{i=1}^{n} E_{i-1}\{\frac{\partial^2 log\mathscr{L}_i}{\partial\mu_{BB'}^2}\}$ from (3.10) becomes

$$\begin{aligned}
&n^{-1}\sum_{i=1}^{n}\left[\frac{1}{\sigma_{BB'}^2}E_{i-1}\left(I(T_{1i}=B,T_{2i}=B')\right)\right]\\
&=n^{-1}\sum_{i=1}^{n}\left[\frac{1}{\sigma_{BB'}^2}P\left(T_{1i}=B,T_{2i}=B'|\mathscr{F}_{i-1}\right)\right]\\
&\xrightarrow{a.s}\left(\frac{1}{\sigma_{BB'}^2}\right)(\gamma_B)\left(\frac{1}{1+\tau_A}\right)\equiv v_{\mu_{BB'}}. \qquad (3.22)
\end{aligned}$$

Thus, the variance of $\hat{\mu}_{BB'}(\equiv\hat{\mu}_{BB',n})$ is $\frac{1}{n}v_{\mu_{BB'}}^{-1}$.

Now, using the equation $(A3)$ of Rosenberger 1997, $-n^{-1}\sum_{i=1}^{n} E_{i-1}\{\frac{\partial^2 log\mathscr{L}_i}{\partial\sigma_{BB'}^2}\}$ from (3.10) becomes

$$
\begin{aligned}
&-\frac{1}{n}\sum_{i=1}^{n}\left[\left(\frac{1}{\sigma^2_{BB'}}\right)E_{i-1}\left(I(T_{1i}=B,T_{2i}=B')\right)-\left(\frac{3}{\sigma^4_{BB'}}\right)E_{i-1}\left((Y_i-\mu_{BB'})^2I(T_{1i}=B,T_{2i}=B')\right)\right]\\
&=\frac{1}{n}\sum_{i=1}^{n}\left[\left(-\frac{1}{\sigma^2_{BB'}}\right)E_{i-1}\left(I(T_{1i}=B,T_{2i}=B')\right)+\left(\frac{3}{\sigma^4_{BB'}}\right)E_{i-1}\left((Y_i-\mu_{BB'})^2I(T_{1i}=B,T_{2i}=B')\right)\right]\\
&=\frac{1}{n}\sum_{i=1}^{n}\left[\left(-\frac{1}{\sigma^2_{BB'}}\right)E_{i-1}\left(I(T_{1i}=B,T_{2i}=B')\right)+\left(\frac{3}{\sigma^2_{BB'}}\right)E_{i-1}\left(I(T_{1i}=B,T_{2i}=B')\right)\right]\\
&=\frac{1}{n}\sum_{i=1}^{n}\left[\left(\frac{2}{\sigma^2_{BB'}}\right)P\left(T_{1i}=B,T_{2i}=B'\mid\mathscr{F}_{i-1}\right)\right]\\
&\xrightarrow{a.s.}\left(\frac{2}{\sigma^2_{BB'}}\right)\cdot\gamma_B\cdot\left(\frac{1}{1+\tau_A}\right)\equiv v_{\sigma_{BB'}}. \qquad (3.23)
\end{aligned}
$$

Thus, the variance of $\hat{\sigma}_{BB'}(\equiv\hat{\sigma}_{BB',n})$ is $\frac{1}{n}v^{-1}_{\sigma_{BB'}}$.

Using equations (3.12), (3.14), (3.13), (3.15),(3.18), (3.20), (3.19), (3.21) from above, we have,

$$
\begin{aligned}
\sqrt{n}(\hat{\mu}_{AC,n}-\mu_{AC}) &\xrightarrow{d} N(0,v^{-1}_{\mu_{AC}}),\\
\sqrt{n}(\hat{\mu}_{AD,n}-\mu_{AD}) &\xrightarrow{d} N(0,v^{-1}_{\mu_{AD}}),\\
\sqrt{n}(\hat{\sigma}_{AC,n}-\sigma_{AC}) &\xrightarrow{d} N(0,v^{-1}_{\sigma_{AC}}),\\
\sqrt{n}(\hat{\sigma}_{AD,n}-\sigma_{AD}) &\xrightarrow{d} N(0,v^{-1}_{\sigma_{AD}}),\\
\sqrt{n}(\hat{\mu}_{BE,n}-\mu_{BE}) &\xrightarrow{d} N(0,v^{-1}_{\mu_{BE}}),\\
\sqrt{n}(\hat{\mu}_{BF,n}-\mu_{BF}) &\xrightarrow{d} N(0,v^{-1}_{\mu_{BF}}),\\
\sqrt{n}(\hat{\sigma}_{BE,n}-\sigma_{BE}) &\xrightarrow{d} N(0,v^{-1}_{\sigma_{BE}}),\\
\sqrt{n}(\hat{\sigma}_{BF,n}-\sigma_{BF}) &\xrightarrow{d} N(0,v^{-1}_{\sigma_{BF}}),
\end{aligned}
$$

and are asymptotically independent. Using Slutsky's theorem,

$$
\begin{aligned}
\sqrt{n}\left(\begin{bmatrix}\hat{\mu}_{AC,n}-\mu_{AC}\\ \hat{\sigma}_{AC,n}-\sigma_{AC}\\ \hat{\mu}_{AD,n}-\mu_{AD}\\ \hat{\sigma}_{AD,n}-\sigma_{AD}\end{bmatrix}\right) &\xrightarrow{d} N\left(\begin{bmatrix}0\\0\\0\\0\end{bmatrix},\begin{bmatrix}v^{-1}_{\mu_{AC}} & 0 & 0 & 0\\ 0 & v^{-1}_{\sigma_{AC}} & 0 & 0\\ 0 & 0 & v^{-1}_{\mu_{AD}} & 0\\ 0 & 0 & 0 & v^{-1}_{\sigma_{AD}}\end{bmatrix}\right),\\
\sqrt{n}\left(\begin{bmatrix}\hat{\mu}_{BE,n}-\mu_{BE}\\ \hat{\sigma}_{BE,n}-\sigma_{BE}\\ \hat{\mu}_{BF,n}-\mu_{BF}\\ \hat{\sigma}_{BF,n}-\sigma_{BF}\end{bmatrix}\right) &\xrightarrow{d} N\left(\begin{bmatrix}0\\0\\0\\0\end{bmatrix},\begin{bmatrix}v^{-1}_{\mu_{BE}} & 0 & 0 & 0\\ 0 & v^{-1}_{\sigma_{BE}} & 0 & 0\\ 0 & 0 & v^{-1}_{\mu_{BF}} & 0\\ 0 & 0 & 0 & v^{-1}_{\sigma_{BF}}\end{bmatrix}\right).
\end{aligned}
$$

3.8.3 Asymptotic distribution for second-stage allocation ratio

Using the last expression of asymptotic distribution obtained in Section 3.8.2 and multivariate delta method with function $h(x_1, x_2, x_3, x_4)$ as $\sqrt{\frac{x_1}{x_2}\frac{x_3}{x_4}}$, the variance of the estimated second-stage allocation ratios $(\hat{\tau}_{AC:AD,n})$ and $(\hat{\tau}_{BE:BF,n})$ are,

$$Var(\hat{\tau}_{AC:AD,n}) = \frac{1}{4n}\left(\frac{v^{-1}_{\mu_{AC}}\mu_{AD}\sigma^2_{AC}}{\mu^3_{AC}\sigma^2_{AD}} + \frac{4v^{-1}_{\sigma_{AC}}\mu_{AD}}{\mu_{AC}\sigma^2_{AD}} + \frac{v^{-1}_{\mu_{AD}}\sigma^2_{AC}}{\mu_{AC}\mu_{AD}\sigma^2_{AD}} + \frac{4v^{-1}_{\sigma_{AD}}\sigma_{AC}\mu_{AD}}{\mu_{AC}\sigma^4_{AD}}\right),$$

$$Var(\hat{\tau}_{BE:BF,n}) = \frac{1}{4n}\left(\frac{v^{-1}_{\mu_{BE}}\mu_{BF}\sigma^2_{BE}}{\mu^3_{BE}\sigma^2_{BF}} + \frac{4v^{-1}_{\sigma_{BE}}\mu_{BF}}{\mu_{BE}\sigma^2_{BF}} + \frac{v^{-1}_{\mu_{BF}}\sigma^2_{BE}}{\mu_{BE}\mu_{BF}\sigma^2_{BF}} + \frac{4v^{-1}_{\sigma_{BF}}\sigma_{BE}\mu_{BF}}{\mu_{BE}\sigma^4_{BF}}\right),$$

where $v_{\mu_{AC}}$, $v_{\sigma_{AC}}$, $v_{\mu_{AD}}$, $v_{\sigma_{AD}}$, $v_{\mu_{BE}}$, $v_{\sigma_{BE}}$, $v_{\mu_{BF}}$, and $v_{\sigma_{BF}}$ are as obtained in Section 3.8.2. Thus, the asymptotic distribution of the estimated second-stage allocation ratios is,

$$\sqrt{n}\left(\hat{\tau}_{AC:AD,n} - \tau^*_{AC:AD}\right) \xrightarrow{d} N\left(0, \frac{1}{4}\left(\frac{v^{-1}_{\mu_{AC}}\mu_{AD}\sigma^2_{AC}}{\mu^3_{AC}\sigma^2_{AD}} + \frac{4v^{-1}_{\sigma_{AC}}\mu_{AD}}{\mu_{AC}\sigma^2_{AD}} + \frac{v^{-1}_{\mu_{AD}}\sigma^2_{AC}}{\mu_{AC}\mu_{AD}\sigma^2_{AD}} + \frac{4v^{-1}_{\sigma_{AD}}\sigma_{AC}\mu_{AD}}{\mu_{AC}\sigma^4_{AD}}\right)\right),$$

$$\sqrt{n}\left(\hat{\tau}_{BE:BF,n} - \tau^*_{BE:BF}\right) \xrightarrow{d} N\left(0, \frac{1}{4}\left(\frac{v^{-1}_{\mu_{BE}}\mu_{BF}\sigma^2_{BE}}{\mu^3_{BE}\sigma^2_{BF}} + \frac{4v^{-1}_{\sigma_{BE}}\mu_{BF}}{\mu_{BE}\sigma^2_{BF}} + \frac{v^{-1}_{\mu_{BF}}\sigma^2_{BE}}{\mu_{BE}\mu_{BF}\sigma^2_{BF}} + \frac{4v^{-1}_{\sigma_{BF}}\sigma_{BE}\mu_{BF}}{\mu_{BE}\sigma^4_{BF}}\right)\right).$$

3.8.4 Asymptotic distribution of first-stage allocation ratio

In this section, we find the asymptotic distribution for the estimated first-stage allocation ratio. Using the obtained expressions in Section 3.8.2 and multivariate delta method with function $h(x_1, x_2, x_3, x_4)$ as $\sqrt{\frac{x_1}{x_3}\frac{x_2}{x_4}}$, the variance of the estimated first-stage allocation ratio $\hat{\tau}_{A,n}$ is,

$$\begin{aligned} Var(\hat{\tau}_{A,n}) \quad &= \left(\frac{\partial\hat{\tau}_{A,n}}{\partial\mu_{AA'}}\right)^2 v^{-1}_{\mu_{AA'}} + \left(\frac{\partial\hat{\tau}_{A,n}}{\partial\sigma_{AA'}}\right)^2 v^{-1}_{\sigma_{AA'}} + \left(\frac{\partial\hat{\tau}_{A,n}}{\partial\mu_{AC}}\right)^2 v^{-1}_{\mu_{AC}} + \left(\frac{\partial\hat{\tau}_{A,n}}{\partial\sigma_{AC}}\right)^2 v^{-1}_{\sigma_{AC}} \\ &+ \left(\frac{\partial\hat{\tau}_{A,n}}{\partial\mu_{AD}}\right)^2 v^{-1}_{\mu_{AD}} + \left(\frac{\partial\hat{\tau}_{A,n}}{\partial\sigma_{AD}}\right)^2 v^{-1}_{\sigma_{AD}} + \left(\frac{\partial\hat{\tau}_{A,n}}{\partial\mu_{BB'}}\right)^2 v^{-1}_{\mu_{BB'}} + \left(\frac{\partial\hat{\tau}_{A,n}}{\partial\sigma_{BB'}}\right)^2 v^{-1}_{\sigma_{BB'}} \\ &+ \left(\frac{\partial\hat{\tau}_{A,n}}{\partial\mu_{BE}}\right)^2 v^{-1}_{\mu_{BE}} + \left(\frac{\partial\hat{\tau}_{A,n}}{\partial\sigma_{BE}}\right)^2 v^{-1}_{\sigma_{BE}} + \left(\frac{\partial\hat{\tau}_{A,n}}{\partial\mu_{BF}}\right)^2 v^{-1}_{\mu_{BF}} + \left(\frac{\partial\hat{\tau}_{A,n}}{\partial\sigma_{BF}}\right)^2 v^{-1}_{\sigma_{BF}}. \end{aligned} \quad (3.24)$$

Now, the partial derivatives with respect to the treatment sequences for first-stage treatment A are expressed as,

$$\frac{\partial \hat{\tau}_{A,n}}{\partial \mu_{AA'}} = \sqrt{\frac{\mu_B}{\mu_A}} \cdot \frac{\gamma_A}{\sigma_B \sigma_A}(\mu_{AA'} - \mu_A) - \frac{\gamma_A \sqrt{\mu_B}\sigma_A}{2\sigma_B \mu_A^{3/2}},$$

$$\frac{\partial \hat{\tau}_{A,n}}{\partial \sigma_{AA'}} = \sqrt{\frac{\mu_B}{\mu_A}} \cdot \frac{\gamma_A \sigma_{AA'}}{\sigma_B \sigma_A},$$

$$\frac{\partial \hat{\tau}_{A,n}}{\partial \mu_{AC}} = \sqrt{\frac{\mu_B}{\mu_A}} \cdot \frac{(1-\gamma_A)}{2\sigma_A \sigma_B} \left[\frac{4\mu_{AC}^2 \sigma_{AD}\sqrt{\mu_{AD}}\sigma_{AC} + 4\mu_{AD}\sigma_{AC}^2 \mu_{AC}^{3/2} + \sigma_{AD}\sigma_{AC}\mu_{AD}^{5/2} + \sqrt{\mu_{AD}}\sigma_{AC}\sigma_{AD}^3 - \sqrt{\mu_{AD}}\sigma_{AC}\sigma_{AD}\mu_{AC}^2 - \sqrt{\mu_{AD}}\sigma_{AD}\sigma_{AC}^3}{2\sqrt{\mu_{AC}}(\sigma_{AD}\sqrt{\mu_{AC}} + \sigma_{AC}\sqrt{\mu_{AD}})^2} \right.$$
$$\left. - \mu_A \cdot \frac{2\sqrt{\mu_{AC}}\mu_{AD}\sigma_{AC}^2 + \mu_{AC}\sqrt{\mu_{AD}}\sigma_{AC}\sigma_{AD} + \sigma_{AC}\sigma_{AD}\mu_{AD}^{3/2}}{\sqrt{\mu_{AC}}(\sigma_{AD}\sqrt{\mu_{AC}} + \sigma_{AC}\sqrt{\mu_{AD}})^2} \right]$$
$$- \frac{\sqrt{\mu_B}\sigma_A}{2\sigma_B \mu_A^{3/2}}(1-\gamma_A) \left(\frac{2\sqrt{\mu_{AC}}\mu_{AD}\sigma_{AC}^2 + \mu_{AC}\sqrt{\mu_{AD}}\sigma_{AC}\sigma_{AD} + \sigma_{AC}\sigma_{AD}\mu_{AD}^{3/2}}{2\sqrt{\mu_{AC}}(\sigma_{AD}\sqrt{\mu_{AC}} + \sigma_{AC}\sqrt{\mu_{AD}})^2} \right),$$

$$\frac{\partial \hat{\tau}_{A,n}}{\partial \sigma_{AC}} = \sqrt{\frac{\mu_B}{\mu_A}} \cdot \frac{(1-\gamma_A)}{2\sigma_A \sigma_B} \left[\frac{3\sqrt{\mu_{AC}}\sqrt{\mu_{AD}}\sigma_{AD}\sigma_{AC}^2 + 2\mu_{AD}\sigma_{AC}^3 + \sqrt{\mu_{AD}}\sigma_{AD}\mu_{AC}^{\frac{5}{2}} - \sqrt{\mu_{AC}}\sigma_{AD}\mu_{AD}^{\frac{5}{2}} - \sqrt{\mu_{AC}}\sqrt{\mu_{AD}}\sigma_{AD}^3}{(\sigma_{AD}\sqrt{\mu_{AC}} + \sigma_{AC}\sqrt{\mu_{AD}})^2} \right.$$
$$\left. - 2\mu_A \cdot \frac{\sqrt{\mu_{AD}}\mu_{AC}^{\frac{3}{2}}\sigma_{AD} - \sqrt{\mu_{AC}}\sigma_{AD}\mu_{AD}^{\frac{3}{2}}}{(\sigma_{AD}\sqrt{\mu_{AC}} + \sigma_{AC}\sqrt{\mu_{AD}})^2} \right]$$
$$- \frac{\sqrt{\mu_B}\sigma_A}{2\sigma_B \mu_A^{3/2}}(1-\gamma_A) \left(\frac{\sqrt{\mu_{AD}}\mu_{AC}^{\frac{3}{2}}\sigma_{AD} - \sqrt{\mu_{AC}}\sigma_{AD}\mu_{AD}^{\frac{3}{2}}}{(\sigma_{AD}\sqrt{\mu_{AC}} + \sigma_{AC}\sqrt{\mu_{AD}})^2} \right),$$

$$\frac{\partial \hat{\tau}_{A,n}}{\partial \mu_{AD}} = \sqrt{\frac{\mu_B}{\mu_A}} \cdot \frac{(1-\gamma_A)}{2\sigma_A \sigma_B} \left[\frac{4\mu_{AD}^2 \sigma_{AC}\sqrt{\mu_{AC}}\sigma_{AD} + 4\mu_{AC}\sigma_{AD}^2 \mu_{AD}^{3/2} + \sigma_{AC}\sigma_{AD}\mu_{AC}^{5/2} + \sqrt{\mu_{AC}}\sigma_{AD}\sigma_{AC}^3 - \sqrt{\mu_{AC}}\sigma_{AD}\sigma_{AC}\mu_{AD}^2 - \sqrt{\mu_{AC}}\sigma_{AC}\sigma_{AD}^3}{2\sqrt{\mu_{AD}}(\sigma_{AD}\sqrt{\mu_{AC}} + \sigma_{AC}\sqrt{\mu_{AD}})^2} \right.$$
$$\left. - \mu_A \cdot \frac{2\sqrt{\mu_{AD}}\mu_{AC}\sigma_{AD}^2 + \mu_{AD}\sqrt{\mu_{AC}}\sigma_{AD}\sigma_{AC} + \sigma_{AD}\sigma_{AC}\mu_{AC}^{3/2}}{\sqrt{\mu_{AD}}(\sigma_{AD}\sqrt{\mu_{AC}} + \sigma_{AC}\sqrt{\mu_{AD}})^2} \right]$$
$$- \frac{\sqrt{\mu_B}\sigma_A}{2\sigma_B \mu_A^{3/2}}(1-\gamma_A) \left(\frac{2\sqrt{\mu_{AD}}\mu_{AC}\sigma_{AD}^2 + \mu_{AD}\sqrt{\mu_{AC}}\sigma_{AD}\sigma_{AC} + \sigma_{AD}\sigma_{AC}\mu_{AC}^{3/2}}{2\sqrt{\mu_{AD}}(\sigma_{AD}\sqrt{\mu_{AC}} + \sigma_{AC}\sqrt{\mu_{AD}})^2} \right),$$

$$\frac{\partial \hat{\tau}_{A,n}}{\partial \sigma_{AD}} = \sqrt{\frac{\mu_B}{\mu_A}} \cdot \frac{(1-\gamma_A)}{2\sigma_A \sigma_B} \left[\frac{3\sqrt{\mu_{AD}}\sqrt{\mu_{AC}}\sigma_{AC}\sigma_{AD}^2 + 2\mu_{AC}\sigma_{AD}^3 + \sqrt{\mu_{AC}}\sigma_{AC}\mu_{AD}^{\frac{5}{2}} - \sqrt{\mu_{AD}}\sigma_{AC}\mu_{AC}^{\frac{5}{2}} - \sqrt{\mu_{AD}}\sqrt{\mu_{AC}}\sigma_{AC}^3}{(\sigma_{AD}\sqrt{\mu_{AC}} + \sigma_{AC}\sqrt{\mu_{AD}})^2} \right.$$
$$\left. - 2\mu_A \cdot \frac{\sqrt{\mu_{AC}}\mu_{AD}^{\frac{3}{2}}\sigma_{AC} - \sqrt{\mu_{AD}}\sigma_{AC}\mu_{AC}^{\frac{3}{2}}}{(\sigma_{AD}\sqrt{\mu_{AC}} + \sigma_{AC}\sqrt{\mu_{AD}})^2} \right]$$
$$- \frac{\sqrt{\mu_B}\sigma_A}{2\sigma_B \mu_A^{3/2}}(1-\gamma_A) \left(\frac{\sqrt{\mu_{AC}}\mu_{AD}^{\frac{3}{2}}\sigma_{AC} - \sqrt{\mu_{AD}}\sigma_{AC}\mu_{AC}^{\frac{3}{2}}}{(\sigma_{AD}\sqrt{\mu_{AC}} + \sigma_{AC}\sqrt{\mu_{AD}})^2} \right).$$

Similarly along the same lines, the partial derivates $\frac{\partial \hat{\tau}_{A,n}}{\partial \mu_{BB'}}$, $\frac{\partial \hat{\tau}_{A,n}}{\partial \sigma_{BB'}}$, $\frac{\partial \hat{\tau}_{A,n}}{\partial \mu_{BE}}$, $\frac{\partial \hat{\tau}_{A,n}}{\partial \sigma_{BE}}$, $\frac{\partial \hat{\tau}_{A,n}}{\partial \mu_{BF}}$, and $\frac{\partial \hat{\tau}_{A,n}}{\partial \sigma_{BF}}$ are computed for the treatment arm starting with first-stage treatment B. These obtained expressions are substituted in Equation (3.24) to obtain the final simplified expression for the asymptotic variance of the estimated first-stage allocation ratio ($\hat{\tau}_{A,n}$). Thus, the asymptotic distribution of the estimated first-stage allocation ratio is,

$$\sqrt{n}\left(\hat{\tau}_{A,n} - \tau_A^*\right) \xrightarrow{d} N(0, Var(\hat{\tau}_{A,n})).$$

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CHAPTER 4

Covariate-Adjusted Adaptive SMART Designs with Binary Outcomes

4.1 Introduction

In Chapters 2 and 3, we established the foundation of adaptive (randomization) SMART designs with binary and continuous outcomes, respectively, focusing on optimizing designs based solely on final outcomes. However, further personalization and optimization can be achieved by incorporating covariate information (Biswas et al., 2004). Covariate adjustment in adaptive clinical trial designs allows for more precise treatment effect estimation, enhances statistical power, and improves ethical allocation by tailoring treatments to individual profiles (Atkinson and Biswas, 2013). Covariates such as systolic or diastolic blood pressure, body mass index (BMI), gender, and race can significantly impact treatment effectiveness (Wester et al., 2022). In randomized controlled trials (RCTs), covariate adjustment is a widely accepted practice due to its benefits in increasing statistical power and protecting against chance imbalances (Pirondini et al., 2022; Tackney et al., 2023). As a result, several adaptive methodologies incorporating covariate adjustment have been developed and implemented in RCTs. For example, Rosenberger et al. (2001) proposed a covariate-adjusted, outcome-driven adaptive randomization approach for a binary outcome in the context of two-arm RCTs. Other examples of covariate-adjusted adaptive RCTs include studies in cardiovascular diseases (Pirondini et al., 2022), stroke (Hu et al., 2006), epilepsy (Biswas et al., 2004), cancer (Yin and Zhou, 2016; Zhou et al., 2017), and depression (Liu et al., 2011).

As discussed in the earlier chapters, the use of adaptive randomization is gaining mo-

mentum in SMART studies (Ghosh et al., 2024; Wang et al., 2022; Yang et al., 2024). However, there has been comparatively little work focused on incorporating covariate adjustment within adaptive SMART designs. Cheung et al. (2015) introduced SMART-AR, which adapts randomization probabilities using a Q-learning framework. This method determines empirical randomization probabilities by maximizing the Q-functions based on the interim data. In practical applications, however, the true Q-functions are unknown and must be estimated from the available data. This estimation process can be challenging due to the use of pseudo-outcomes, which serve as proxies for the quantity under expectation in the definition of the first-stage Q-function (Chakraborty et al., 2016).

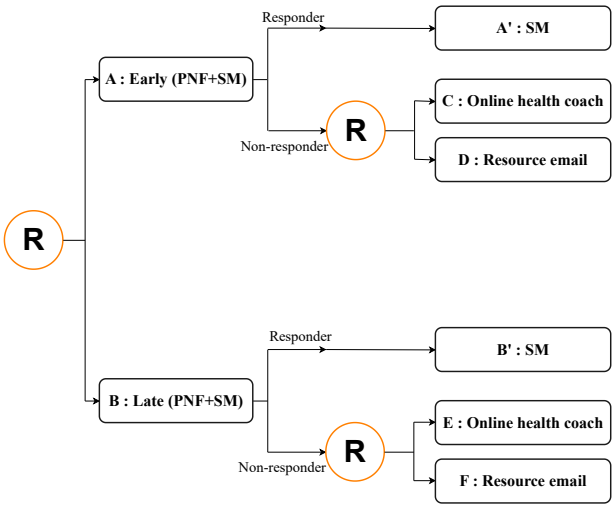
In this chapter, building on the foundation developed in Chapter 2, we incorporate covariate information into the allocation ratio using logistic regression. Specifically, we model the second-stage success probabilities ($p_{T_1T_2}$) as functions of covariates by applying the logit link within a generalized linear model framework (Rosenberger et al., 2001). Similar to the previous two chapters, we also recursively incorporate the second-stage allocation information into the first stage to determine the allocation ratio for the first stage. This approach is much simpler and more intuitive, as it does not rely on the complex structure of the Q-function.

Section 4.2 introduces the necessary notational framework for this chapter, while Section 4.3 develops the covariate-adjusted allocation ratio. Section 4.4 describes the adaptive procedure for patient allocation. Extensive simulation studies are presented in Section 4.5, and a real-world application using data from the M-Bridge study is provided in Section 4.6. The chapter concludes with a discussion in Section 4.7.

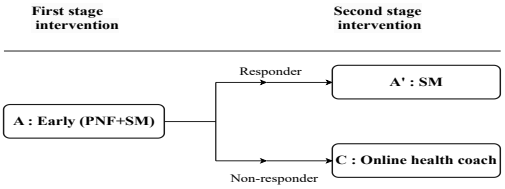
4.2 General Framework for Covariate Adjustment

The notational framework employed in this section for covariate-adjusted, adaptive two-stage SMART designs with binary outcomes closely follows that of Chapter 2. For ease of understanding, we reintroduce the relevant notation here, along with new symbols to incorporate covariates into the adaptive randomization process.

Let Y denote the binary primary outcome (success or failure) observed at the end of a two-stage SMART. As illustrated in Figure 4.1(a) (It is identical to Figure 2.1), participants are first randomized to treatment A (early PNF + SM) or B (late PNF + SM), denoted by $T_1 \in \{A, B\}$. In Figure 4.1(a), *"R in circle"* denotes randomization process. After the first stage, responders continue with A' or B' (SM only), while non-responders are re-randomized: to C (online health coach) or D (resource email) if $T_1 = A$, and to E (online health coach) or F (resource email) if $T_1 = B$. Note that C and E (likewise D and F) may represent the same or different treatments depending on the SMART design. Thus, $T_2 \in \{A', C, D\}$ if $T_1 = A$, and $T_2 \in \{B', E, F\}$ if $T_1 =$



(a) A schematic diagram of a 2-Stage SMART following M-Bridge study. Here R represents randomization.



(b) An example dynamic treatment regime (DTR) to reduce heavy drinking and related risks among college students from M-Bridge study.

Figure 4.1

B, with the treatment sequence represented by $\{T_1, T_2\}$. Let $n_{T_1T_2}$ be the number of participants receiving $\{T_1, T_2\}$, and R_{T_1} (1 for responder, 0 for non-responder) the response indicator for first-stage treatment T_1. Let X denote the k-dimensional vector of covariates corresponding to a patient, $X \in \mathbb{R}^k, k \geq 1$. The covariates can be binary, categorical, or continuous.

4.3 Covariate-Adjusted Allocation Ratio

In Chapter 2, we obtained optimal adaptive allocation ratios corresponding to both first- and second-stage randomization processes by minimizing the total expected number of failures from the entire SMART. This minimization is subject to an objective function $g(\cdot, \cdot)$ that compares two binomial success probabilities, under the constraint of a fixed asymptotic variance ($avar$) of the same objective function. Considering the objective function as the simple difference of the success probabilities, those ratios (see Section

2.3.1) solely depend on different success probabilities $p_{T_1T_2}$ as

$$\tau_{AC:AD} = \sqrt{\frac{p_{AC}}{p_{AD}}}, \quad \tau_{BE:BF} = \sqrt{\frac{p_{BE}}{p_{BF}}}, \text{ and } \tau_A = \sqrt{\frac{p_A}{p_B}},$$

where the last one corresponds to the first stage and the other two to the second stage. Note that, here, $p_A = \gamma_A p_{AA'} + (1-\gamma_A)\frac{\tau_{AC:AD}}{1+\tau_{AC:AD}} p_{AC} + (1-\gamma_A)\frac{1}{1+\tau_{AC:AD}} p_{AD}$, and $p_B = \gamma_B p_{BB'} + (1-\gamma_B)\frac{\tau_{BE:BF}}{1+\tau_{BE:BF}} p_{BE} + (1-\gamma_B)\frac{1}{1+\tau_{BE:BF}} p_{BF}$.

In this chapter, we aim to incorporate covariate information into the allocation ratios. The motivation for this approach stems from the fact that the effects of treatments may depend on specific covariates. For example, a particular medication (or, for instance, a weight-loss intervention) may work differently for males and females. Similarly, a diabetes medication may demonstrate substantially different effectiveness in Americans compared to Asians, due to differences in genetic structure (i.e., racial factors) (Berg et al., 2024). As the above allocation ratios are functions of success probabilities, we model $p_{T_1T_2}$ as a function of covariates using logistic regression, which is the most natural choice in this case. We have

$$\begin{aligned} \log\left(\frac{p_{T_1T_2}}{1-p_{T_1T_2}}\right) &= \beta'_{T_1T_2} X \\ \implies p_{T_1T_2} &= \frac{1}{1+e^{-\beta'_{T_1T_2}X}}, \end{aligned} \tag{4.1}$$

where, $\beta_{T_1T_2}$ is the unknown coefficient vector of $X \in \mathbb{R}^k$ corresponding to the participants who obtained the treatment sequence $\{T_1, T_2\}$. Now, we substitute the expression for $p_{T_1T_2}$ from equation (4.1) into the allocation ratios. Therefore, we have the second-stage adaptive allocation ratios as follows,

$$\tau_{AC:AD}(X) = \sqrt{\frac{1+e^{-\beta'_{AD}X}}{1+e^{-\beta'_{AC}X}}}, \quad \tau_{BE:BF}(X) = \sqrt{\frac{1+e^{-\beta'_{BF}X}}{1+e^{-\beta'_{BE}X}}}, \text{ and,} \tag{4.2}$$

and the first-stage adaptive allocation ratio is obtained as follows:

$$\tau_A(X) = \sqrt{\frac{\frac{\gamma_A}{1+e^{-\beta'_{AA'}X}} + \frac{(1-\gamma_A)}{(1+\tau_{AC:AD}(X))}\left[\frac{\tau_{AC:AD}(X)}{1+e^{-\beta'_{AC}X}} + \frac{1}{1+e^{-\beta'_{AD}X}}\right]}{\frac{\gamma_B}{1+e^{-\beta'_{BB'}X}} + \frac{(1-\gamma_B)}{(1+\tau_{BE:BF}(X))}\left[\frac{\tau_{BE:BF}(X)}{1+e^{-\beta'_{BE}X}} + \frac{1}{1+e^{-\beta'_{BF}X}}\right]}}. \tag{4.3}$$

Note that the optimal adaptive allocation ratios obtained in Chapter 2 for a two-stage SMART with a binary primary outcome are fixed. However, the adaptive allocation ratios in (4.2) and (4.3) are functions of covariates. Therefore, in this chapter, we have only adaptive allocation ratios instead of optimal adaptive allocation ratios.

In this chapter, we develop adaptive allocation ratios that vary according to participants' covariate information (baseline covariates), making treatment allocation more personalized than the optimal adaptive allocation procedure developed in Chapter 2. By combining the approaches of this chapter and Chapter 2, we argue that the total expected number of failures in the entire SMART can be further minimized, compared to Chapter 2, by utilizing information about the impact of covariates on treatment effectiveness for given participants. Note that the adaptive allocation ratios in (4.2) and (4.3) reduce to the corresponding optimal adaptive allocation ratios if, for all $\{T_1, T_2\}$, all components of the coefficient vector $\beta_{T_1T_2}$ except the intercept are zero. Here, we have used the optimal adaptive allocation ratios from Chapter 2, which were derived using the simple difference as the objective function. Similarly, we can obtain the covariate-adjusted adaptive allocation ratios for the other two objective functions: odds-ratio and relative-risk.

In Section 2.9.5 of Chapter 2, we derived the optimal adaptive allocation ratio for the odds-ratio with a binary outcome, without covariate adjustment. Here, we substitute the expression for $p_{T_1T_2}$ from (4.1) into the optimal adaptive allocation ratios, where the objective function is the odds-ratio. Thus, the second-stage covariate-adjusted allocation ratios are given by,

$$\begin{aligned}\tau_{AC:AD}(X) &= \left(\frac{e^{-\beta'_{AD}X}}{e^{-\beta'_{AC}X}}\right)\left(\frac{1+e^{-\beta'_{AC}X}}{1+e^{-\beta'_{AD}X}}\right)^{\frac{3}{2}},\\ \tau_{BE:BF}(X) &= \left(\frac{e^{-\beta'_{BF}X}}{e^{-\beta'_{BE}X}}\right)\left(\frac{1+e^{-\beta'_{BE}X}}{1+e^{-\beta'_{BF}X}}\right)^{\frac{3}{2}}.\end{aligned} \tag{4.4}$$

The first-stage adaptive allocation ratio is obtained as follows,

$$\begin{aligned}\tau_A(X) = \left(\frac{1+\tau_{AC:AD}(X)}{1+\tau_{BE:BF}(X)}\right)^{\frac{3}{2}} &\times \left(\sqrt{\frac{\frac{\gamma_B(1+\tau_{BE:BF}(X))}{1+e^{-\beta'_{BB'}X}} + (1-\gamma_B)\left[\frac{\tau_{BE:BF}(X)}{1+e^{-\beta'_{BE}X}} + \frac{1}{1+e^{-\beta'_{BF}X}}\right]}{\frac{\gamma_A}{1+e^{-\beta'_{AA'}X}} + \frac{(1-\gamma_A)}{1+\tau_{AC:AD}(X)}\left[\frac{\tau_{AC:AD}(X)}{1+e^{-\beta'_{AC}X}} + \frac{1}{1+e^{-\beta'_{AD}X}}\right]}}\right)\\ &\times \left(\frac{\frac{\gamma_B e^{-\beta'_{BB'}X}(1+\tau_{BE:BF}(X))}{1+e^{-\beta'_{BB'}X}} + (1-\gamma_B)\left[\frac{\tau_{BE:BF}(X)e^{-\beta'_{BE}X}}{1+e^{-\beta'_{BE}X}} + \frac{e^{-\beta'_{BF}X}}{1+e^{-\beta'_{BF}X}}\right]}{\frac{\gamma_A e^{-\beta'_{AA'}X}(1+\tau_{AC:AD}(X))}{1+e^{-\beta'_{AA'}X}} + (1-\gamma_A)\left[\frac{\tau_{AC:AD}(X)e^{-\beta'_{AC}X}}{1+e^{-\beta'_{AC}X}} + \frac{e^{-\beta'_{AD}X}}{1+e^{-\beta'_{AD}X}}\right]}\right).\end{aligned} \tag{4.5}$$

Similarly, from the developed optimal adaptive allocation ratio (in Section 2.9.6) for the objective function relative-risk, the second-stage covariate-adjusted allocation ratio is obtained as,

$$\begin{aligned}\tau_{AC:AD}(X) &= \left(\frac{e^{-\beta'_{AD}X}}{e^{-\beta'_{AC}X}}\right)\left(\sqrt{\frac{1+e^{-\beta'_{AC}X}}{1+e^{-\beta'_{AD}X}}}\right),\\ \tau_{BE:BF}(X) &= \left(\frac{e^{-\beta'_{BF}X}}{e^{-\beta'_{BE}X}}\right)\left(\sqrt{\frac{1+e^{-\beta'_{BE}X}}{1+e^{-\beta'_{BF}X}}}\right).\end{aligned} \tag{4.6}$$

The first-stage adaptive allocation ratio is obtained as follows,

$$\tau_A(X) = \left(\frac{1+\tau_{AC:AD}(X)}{1+\tau_{BE:BF}(X)}\right)^{\frac{1}{2}} \times \left(\sqrt{\frac{\frac{\gamma_A(1+\tau_{AC:AD}(X))}{1+e^{-\beta'_{AA'}X}} + (1-\gamma_A)\left[\frac{\tau_{AC:AD}(X)}{1+e^{-\beta'_{AC}X}} + \frac{1}{1+e^{-\beta'_{AD}X}}\right]}{\frac{\gamma_B(1+\tau_{BE:BF}(X))}{1+e^{-\beta'_{BB'}X}} + (1-\gamma_B)\left[\frac{\tau_{BE:BF}(X)}{1+e^{-\beta'_{BE}X}} + \frac{1}{1+e^{-\beta'_{BF}X}}\right]}} \right)$$
$$\times \left(\frac{\frac{\gamma_B(1+\tau_{BE:BF}(X))}{1+e^{-\beta'_{BB'}X}} + (1-\gamma_B)\left[\frac{\tau_{BE:BF}(X)}{1+e^{-\beta'_{BE}X}} + \frac{1}{1+e^{-\beta'_{BF}X}}\right]}{\frac{\gamma_A(1+\tau_{AC:AD}(X))}{1+e^{-\beta'_{AA'}X}} + (1-\gamma_A)\left[\frac{\tau_{AC:AD}(X)}{1+e^{-\beta'_{AC}X}} + \frac{1}{1+e^{-\beta'_{AD}X}}\right]} \right). \tag{4.7}$$

4.4 Adaptive Allocation Procedure

In Sections 2.4 and 3.4, adaptive allocation procedures are designed to implement the developed adaptive allocation approach in a real SMART, in the respective chapters. Here, we also outline the procedure for the method developed in the previous section after incorporating covariate information into the adaptive allocation ratios. The notational structure is similar to that in Section 2.4.

As the trial is in progress, we need to use estimates of the allocation ratios that can approximate the corresponding developed allocation ratios. The estimate of the allocation ratios for the i^{th} participant can be obtained from the first $i-1$ participants. Assuming T_{1i} denotes the first stage treatment administered to the i^{th} patient, let $\mathscr{F}_i = \{Y_1, Y_2, ..., Y_i, T_{11}, T_{12}, ..., T_{1i}, T_{21}, T_{22}, ..., T_{2i}\}$ be the historical data available for the first i participants. Let $E(\cdot|\mathscr{F}_i) = E_i(\cdot)$, which denotes the conditional expectation. Using a similar approach as in Section 2.4, and based on the second-stage adaptive allocation ratios developed in (4.2), the second-stage treatment allocation process (i.e., the probability for the i^{th} participant to receive treatment t_2 after receiving treatment t_1 at the first stage and becoming a non-responder) can be expressed as follows,

$$E_{i-1}\left(I\left(T_{2i} = t_2 \mid T_{1i} = t_1, R_{T_{1i}} = 0\right)\right) = \frac{\sqrt{1+e^{-\hat{\beta}'_{t_1 t_2^*, i-1} X_i}}}{\sqrt{1+e^{-\hat{\beta}'_{t_1 t_2, i-1} X_i}} + \sqrt{1+e^{-\hat{\beta}'_{t_1 t_2^*, i-1} X_i}}}, \tag{4.8}$$

where, $t_2, t_2^* \in \{C, D\}$ if $t_1 = A$ or $t_2, t_2^* \in \{E, F\}$ if $t_1 = B$ and $t_2^* \neq t_2$ and $R_{T_{1i}}$ is the same as defined in Section 4.2 for the i^{th} patient. The X_i denotes the $k \geq 1$ dimensional vector of covariates corresponding to the i^{th} participant. The $\hat{\beta}_{t_1 t_2, i-1}$ denotes the estimated coefficients of X in (4.1), obtained from the data of participants who were assigned treatment sequence (t_1, t_2) among the first $(i-1)$ sequentially enrolled participants.

Similarly, for the first-stage randomization, the allocation process can be expressed as,

$$E_{i-1}(T_{1i}) = \sqrt{l_{i-1}} \Big/ \left(\sqrt{l_{i-1}} + \sqrt{m_{i-1}}\right), \tag{4.9}$$

where $l_{i-1} = \frac{\gamma_A}{1+e^{-\hat{\beta}'_{AA',i-1}X_i}} + \frac{(1-\gamma_A)}{\left(1+\hat{\tau}_{AC:AD,i}\right)}\left[\frac{\hat{\tau}_{AC:AD,i}}{1+e^{-\hat{\beta}'_{AC,i-1}X_i}} + \frac{1}{1+e^{-\hat{\beta}'_{AD,i-1}X_i}}\right]$ and $m_{i-1} = \frac{\gamma_B}{1+e^{-\hat{\beta}'_{BB',i-1}X_i}} + \frac{(1-\gamma_B)}{\left(1+\hat{\tau}_{BE:BF,i}\right)}\left[\frac{\hat{\tau}_{BE:BF,i}}{1+e^{-\hat{\beta}'_{BE,i-1}X_i}} + \frac{1}{1+e^{-\hat{\beta}'_{BF,i-1}X_i}}\right]$. Note that, $\hat{\tau}_{AC:AD,i} = \sqrt{\frac{1+e^{-\hat{\beta}'_{AD,i-1}X_i}}{1+e^{-\hat{\beta}'_{AC,i-1}X_i}}}$, $\hat{\tau}_{BE:BF,i} = \sqrt{\frac{1+e^{-\hat{\beta}'_{BF,i-1}X_i}}{1+e^{-\hat{\beta}'_{BE,i-1}X_i}}}$ denote the estimated second-stage allocation ratios for the i^{th} patient (who obtain either A or B at the first stage and is a non-responder) based on the history of $(i-1)$ participants.

In Sections 2.4 and 3.4, the adaptive allocation procedures corresponding to binary and continuous outcomes, respectively, ensured that the estimated adaptive allocation ratios converge to the corresponding true "optimal" adaptive allocation ratios almost surely as the sample size becomes large. However, the notion of convergence for covariate-adjusted adaptive allocation ratios is not valid, and there is no corresponding "true" value for these ratios. All covariate-adjusted adaptive allocation ratios are functions of the covariates (X); hence, the convergence of estimated adaptive allocation ratios is not well defined. Similarly, the covariate-adjusted adaptive allocation procedure with the objective function as the odds-ratio (using (4.4) and (4.5)) and as the relative-risk (using (4.6) and (4.7)) can be developed.

4.5 Simulation Study

In this section, we present the simulation results obtained using the adaptive allocation procedure described in Section 4.4. Similar to the simulation study presented in Section 2.6, here our objective is to empirically show that the total expected number of failures is lower when using covariate-adjusted adaptive allocation compared to the optimal adaptive SMART and non-adaptive SMART. We also show that the number of patients allocated to the AIs or dynamic treatment regimes (DTRs) is synchronized with the performance of the corresponding DTRs. Note that we do not show the empirical convergence of the estimated allocation ratios here (as was done in Section 2.6), since the allocation ratios depend on covariates and therefore vary for each combination of covariate values.

We conducted simulations with sample sizes of 500 and 1000 participants. The study began with a warm-up period, during which the first 60 participants were randomly assigned to interventions with equal probability. From 61$^{\text{st}}$ participant onwards, the stage-specific randomization probability for the i^{th} participant is determined from (4.8) or (4.9). The corresponding parameters (βs) in the appropriate logistic regression model are estimated from the outcomes and covariates of the initial $(i-1)$ participants. For this simulation, we considered two continuous covariates: X_1 (e.g., serum sodium concentration) and X_2 (e.g., body mass index (BMI)). We assumed X_1 follows a normal distribution with a mean of 135 and variance of 16, while X_2 follows a normal distribution with a mean

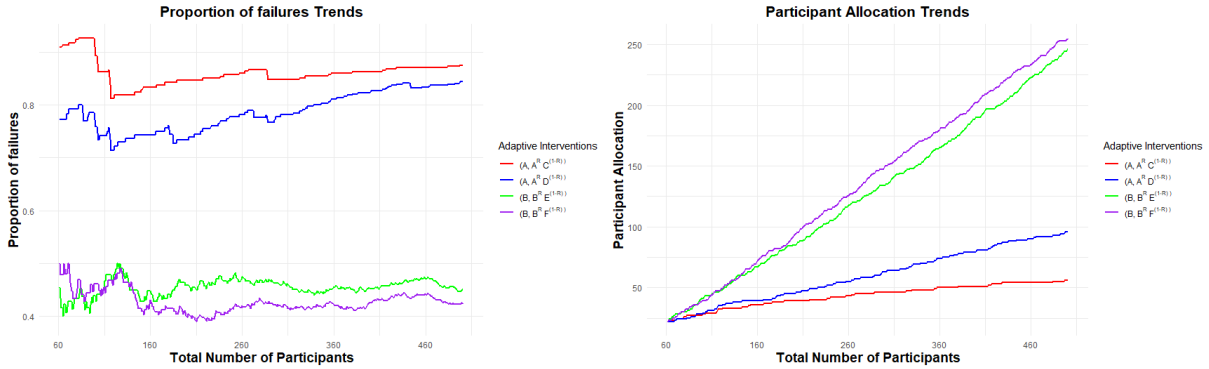
of 25 and variance of 6. Although the covariates in our framework can be both continuous and bivariate, this study focuses on these two continuous variables.

Different true values were specified for the unknown coefficients of the covariates in the consider logistic model corresponding to each intervention sequence $\{T_1, T_2\}$, denoted as $\beta_{AA',0}, \beta_{AA',1}, \beta_{AA',2}$; $\beta_{AC,0}, \beta_{AC,1}, \beta_{AC,2}$; $\beta_{AD,0}, \beta_{AD,1}$, $\beta_{AD,2}$; $\beta_{BB',0}, \beta_{BB',1}, \beta_{BB',2}$; $\beta_{BE,0}, \beta_{BE,1}, \beta_{BE,2}$; and, $\beta_{BF,0}, \beta_{BF,1}, \beta_{BF,2}$. The true values of the parameters are used to simulate the binary outcome variable using the specified logistic model. The expected number of failures was calculated by averaging results over 5000 simulation runs. At the end of the trial, the average total number of failures was compared across three allocation procedures: equal allocation, optimal adaptive allocation (proposed in Chapter 2) using simple difference as the objective function, and our developed covariate-adjusted adaptive allocation procedure, also using the simple difference function. The results are presented in Table 4.1. In Table 4.1, it can be observed that for all examples (1 to 9), the developed covariate-adjusted adaptive allocation procedure reduces the total expected number of failures compared to both the optimal adaptive allocation procedure described in Chapter 2 and the equal randomization procedure. It can be observed that the proposed method results in a reduction of 5 to 19 failures compared to the optimal adaptive allocation, in a SMART with a total sample size of 500.

In Tables 4.1, we have seen that the covariate-adjusted adaptive allocation procedure reduces the total expected number of failures compared to the optimal adaptive allocation. Next, we examine, using graphical methods, whether the procedure developed in this chapter allocates more participants to the better-performing AIs as the trial progresses. Here, for simulation, we have considered the response rates γ_A and γ_B as 0.4 and 0.3, respectively. The coefficient values of $\beta_{AA',0}, \beta_{AA',1}, \beta_{AA',2}$; $\beta_{AC,0}, \beta_{AC,1}, \beta_{AC,2}$; $\beta_{AD,0}, \beta_{AD,1}, \beta_{AD,2}$; $\beta_{BB',0}, \beta_{BB',1}, \beta_{BB',2}$; $\beta_{BE,0}, \beta_{BE,1}, \beta_{BE,2}$; $\beta_{BF,0}, \beta_{BF,1}, \beta_{BF,2}$ are taken as $1.2, -0.022, 0.01995$; $3.4, -0.0375, 0.0047$; $3.4, -0.0375, 0.0047$; $-5.5, 0.04, -0.012$; $-6.6, 0.05, 0.0088$; $4.5, -0.025$, 0.004 respectively. Figure 4.2(a) illustrates how the proportion of failures for each of the four embedded AIs evolves as the number of enrolled participants increases over the course of the trial, using the proposed covariate-adjusted adaptive allocation. We observed that the proportion of failures increases in the following order among the AIs: $(B, B^{R_B}F^{1-R_B})$, $(B, B^{R_B}E^{1-R_B})$, $(A, A^{R_A}D^{1-R_A})$, and $(A, A^{R_A}C^{1-R_A})$. Therefore, the embedded $(B, B^{R_B}F^{1-R_B})$ AI is performing the best, whereas the $(A, A^{R_A}C^{1-R_A})$ AI is performing the worst in terms of the number of failures. Thus, we expect the proposed approach to allocate more participants to the best-performing AI and the fewest participants to the worst-performing AI. At the end of the trial, Figure 4.2(b) confirms that the allocation of participants to each AI is consistent with their respective failure proportions observed in Figure 4.2(a). AIs with lower failure rates are allocated more participants.

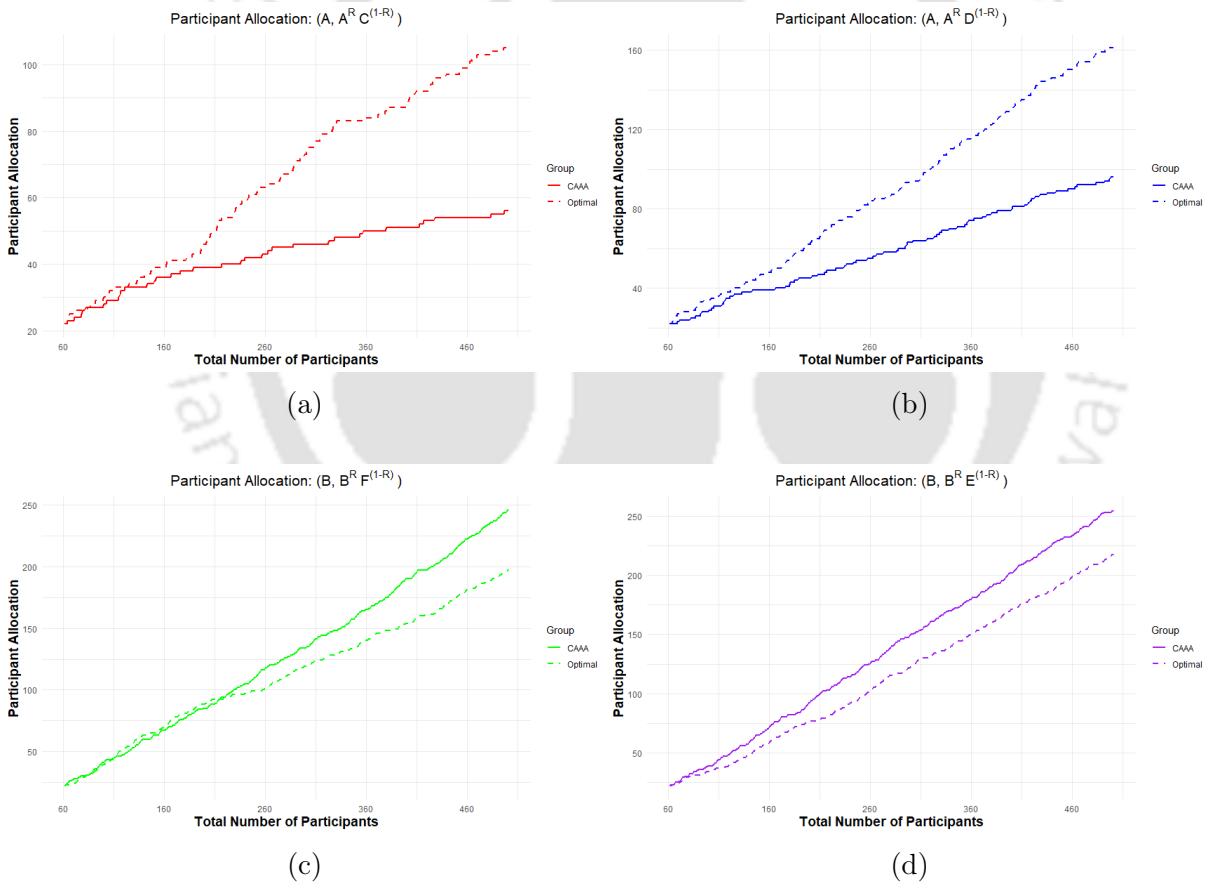
Table 4.1: Comparative study of the total expected number of failures using covariate-adjusted randomized allocation, optimal adaptive allocation, and equal allocation for different values of unknown logistic regression coefficients. Here, $\gamma_A = 0.4$, *and* $\gamma_B = 0.3$, and the sample size is **500** using the objective function as **Simple Difference**.

No.	$(\beta_{AA',0}, \beta_{AA',1}, \beta_{AA',2})$ $(\beta_{AC,0}, \beta_{AC,1}, \beta_{AC,2})$ $(\beta_{AD,0}, \beta_{AD,1}, \beta_{AD,2})$	$(\beta_{BB',0}, \beta_{BB',1}, \beta_{BB',2})$ $(\beta_{BE,0}, \beta_{BE,1}, \beta_{BE,2})$ $(\beta_{BF,0}, \beta_{BF,1}, \beta_{BF,2})$	Total expected number of failures		
			Covariate-Adjusted	Optimal	Equal
1	(1.2,-0.022,0.01995) (3.4,-0.0375,0.0047) (3.4,-0.0375,0.0047)	(-5.5,0.04,-0.012) (-6.6,0.05,0.0088) (4.5,-0.025,0.004)	261	280	309
2	(1.8,-0.02,0.0062) (0.25,0.008,0.0009) (1.20,-0.02,0.0087)	(1.5,-0.02016,0.009) (-1.2,0.009,0.0139) (-1.3,0.009,0.00964)	253	258	272
3	(0.25, 0.008, 0.0009) (1.543, 0.01, 0.00008) (0.290, 0.01, 0.0018)	(2.03, -0.02, 0.00605) (3.4, -0.0375, 0.0047) (3.4, -0.0375, 0.0047)	168	182	223
4	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (0.25, 0.008, 0.0009)	(1.5, -0.02016, 0.009) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	268	280	310
5	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (1.2, -0.02, 0.0087)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	294	308	328
6	(1.8, -0.02, 0.0052) (0.25, 0.008, 0.0009) (1.2, -0.02, 0.0087)	(1.5,-0.02016,0.009) (-1.2, 0.009, 0.0139) (-1.3, 0.009, 0.00964)	253	258	272
7	(1.8, -0.02, 0.0062) (0.25, 0.008, 0.0009) (0.25, 0.008, 0.0009)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	217	224	235
8	(1.8, -0.02, 0.0062) (0.25, 0.008, 0.0009) (0.25, 0.008, 0.0009)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (3.4, -0.0375, 0.0047)	250	257	268
9	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (1.2, -0.02, 0.0087)	(-6.6, 0.05, 0.0088) (-1.2, 0.009, 0.0139) (3.4, -0.0375, 0.0047)	296	308	328



(a) Proportion of failures over different AIs (b) Allocation of participants over different AIs

Figure 4.2: Progression of proportion of failures and allocation of participants over different AIs.



(a) (b)

(c) (d)

Figure 4.3: Comparison of allocated participants in each AI using covariate-adjusted adaptive allocation (CAAA) and optimal adaptive allocation.

Figure 4.3 illustrates the progression of participant allocation to each AI throughout the trial, comparing the covariate-adjusted adaptive allocation with the optimal adaptive allocation. In Figures 4.3(a) and 4.3(b), we observe that, by the end of the trial, the two worst-performing AIs ($(A, A^{R_A}C^{R_A})$ and $(A, A^{R_A}D^{1-R})$, respectively) receive more

participants under the optimal adaptive allocation than under the covariate-adjusted approach. In contrast, as shown in Figures 4.3(c) and 4.3(d), the two best-performing AIs receive more participants when the covariate-adjusted approach is used compared to the optimal adaptive allocation. It is also noteworthy that the covariate-adjusted adaptive allocation achieves a greater reduction in the allocation of participants to the two worst interventions, compared to its increase in allocating participants to the two better interventions. This represents a significant improvement, as minimizing the number of participants exposed to the less effective interventions is particularly important. In summary, the simulation studies demonstrate that covariate-adjusted adaptive allocation outperforms optimal adaptive allocation by both reducing the total expected number of failures and allocating more participants to better-performing AIs, while assigning fewer participants to the worse-performing AIs.

Table 4.2: Comparative study of the total expected number of failures using Covariate adjusted randomized allocation, optimal adaptive allocation, and equal allocation for different values of unknown logistic regression coefficients. Here, $\gamma_A = 0.4$, *and* $\gamma_B = 0.3$, and the sample size is **1000** using the objective function as **Simple Difference**.

No.	$(\beta_{AA',0}, \beta_{AA',1}, \beta_{AA',2})$ $(\beta_{AC,0}, \beta_{AC,1}, \beta_{AC,2})$ $(\beta_{AD,0}, \beta_{AD,1}, \beta_{AD,2})$	$(\beta_{BB',0}, \beta_{BB',1}, \beta_{BB',2})$ $(\beta_{BE,0}, \beta_{BE,1}, \beta_{BE,2})$ $(\beta_{BF,0}, \beta_{BF,1}, \beta_{BF,2})$	Total expected number of failures		
			Covariate-Adjusted	Optimal	Equal
1	(1.2,-0.022,0.01995) (3.4,-0.0375,0.0047) (3.4,-0.0375,0.0047)	(-5.5,0.04,-0.012) (-6.6,0.05,0.0088) (4.5,-0.025,0.004)	521	555	617
2	(1.8,-0.02,0.0062) (0.25,0.008,0.0009) (1.2,-0.02,0.0087)	(1.5,-0.02016,0.009) (-1.2,0.009,0.0139) (-1.3,0.009,0.00964)	504	513	542
3	(0.25, 0.008, 0.0009) (1.543, 0.01, 0.00008) (0.290, 0.01, 0.0018)	(2.03, -0.02, 0.00605) (3.4, -0.0375, 0.0047) (3.4, -0.0375, 0.0047)	334	360	447
4	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (0.25, 0.008, 0.0009)	(1.5, -0.02016, 0.009) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	533	557	619
5	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (1.2, -0.02, 0.0087)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	589	616	658
6	(1.8, -0.02, 0.0052) (0.25, 0.008, 0.0009) (1.2, -0.02, 0.0087)	(1.5,-0.02016,0.009) (-1.2, 0.009, 0.0139) (-1.3, 0.009, 0.00964)	504	513	542
7	(1.8, -0.02, 0.0062) (0.25, 0.008, 0.0009) (0.25, 0.008, 0.0009)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	433	447	469
8	(1.8, -0.02, 0.0062) (0.25, 0.008, 0.0009) (0.25, 0.008, 0.0009)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (3.4, -0.0375, 0.0047)	502	513	538
9	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (1.2, -0.02, 0.0087)	(-6.6, 0.05, 0.0088) (-1.2, 0.009, 0.0139) (3.4, -0.0375, 0.0047)	595	615	657

Table 4.3: Comparative study of the total expected number of failures using Covariate adjusted randomized allocation, optimal adaptive allocation, and equal allocation for different values of unknown logistic regression coefficients. Here, $\gamma_A = 0.4$, *and* $\gamma_B = 0.3$, and the sample size is **500** using the objective function as **Relative-Risk**.

No.	$(\beta_{AA',0}, \beta_{AA',1}, \beta_{AA',2})$ $(\beta_{AC,0}, \beta_{AC,1}, \beta_{AC,2})$ $(\beta_{AD,0}, \beta_{AD,1}, \beta_{AD,2})$	$(\beta_{BB',0}, \beta_{BB',1}, \beta_{BB',2})$ $(\beta_{BE,0}, \beta_{BE,1}, \beta_{BE,2})$ $(\beta_{BF,0}, \beta_{BF,1}, \beta_{BF,2})$	Total expected number of failures		
			Covariate-Adjusted	Optimal	Equal
1	(1.2,-0.022,0.01995) (3.4,-0.0375,0.0047) (3.4,-0.0375,0.0047)	(-5.5,0.04,-0.012) (-6.6,0.05,0.0088) (4.5,-0.025,0.004)	226	249	309
2	(1.8,-0.02,0.0062) (0.25,0.008,0.0009) (1.2,-0.02,0.0087)	(1.5,-0.02016,0.009) (-1.2,0.009,0.0139) (-1.3,0.009,0.00964)	235	239	272
3	(0.25, 0.008, 0.0009) (1.543, 0.01, 0.00008) (0.290, 0.01, 0.0018)	(2.03, -0.02, 0.00605) (3.4, -0.0375, 0.0047) (3.4, -0.0375, 0.0047)	100	107	223
4	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (0.25, 0.008, 0.0009)	(1.5, -0.02016, 0.009) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	247	252	309
5	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (1.2, -0.02, 0.0087)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	271	286	328
6	(1.8, -0.02, 0.0052) (0.25, 0.008, 0.0009) (1.2, -0.02, 0.0087)	(1.5,-0.02016,0.009) (-1.2, 0.009, 0.0139) (-1.3, 0.009, 0.00964)	235	239	272
7	(1.8, -0.02, 0.0062) (0.25, 0.008, 0.0009) (0.25, 0.008, 0.0009)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	209	213	235
8	(1.8, -0.02, 0.0062) (0.25, 0.008, 0.0009) (0.25, 0.008, 0.0009)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (3.4, -0.0375, 0.0047)	232	240	269
9	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (1.2, -0.02, 0.0087)	(-6.6, 0.05, 0.0088) (-1.2, 0.009, 0.0139) (3.4, -0.0375, 0.0047)	274	286	328

Table 4.4: Comparative study of the total expected number of failures using Covariate adjusted randomized allocation, optimal adaptive allocation, and equal allocation for different values of unknown logistic regression coefficients. Here, $\gamma_A = 0.4$, *and* $\gamma_B = 0.3$, and the sample size is **1000** using the objective function as **Relative-Risk**.

No.	$(\beta_{AA',0}, \beta_{AA',1}, \beta_{AA',2})$ $(\beta_{AC,0}, \beta_{AC,1}, \beta_{AC,2})$ $(\beta_{AD,0}, \beta_{AD,1}, \beta_{AD,2})$	$(\beta_{BB',0}, \beta_{BB',1}, \beta_{BB',2})$ $(\beta_{BE,0}, \beta_{BE,1}, \beta_{BE,2})$ $(\beta_{BF,0}, \beta_{BF,1}, \beta_{BF,2})$	Total expected number of failures		
			Covariate-Adjusted	Optimal	Equal
1	(1.2,-0.022,0.01995) (3.4,-0.0375,0.0047) (3.4,-0.0375,0.0047)	(-5.5,0.04,-0.012) (-6.6,0.05,0.0088) (4.5,-0.025,0.004)	438	485	618
2	(1.8,-0.02,0.0062) (0.25,0.008,0.0009) (1.2,-0.02,0.0087)	(1.5,-0.02016,0.009) (-1.2,0.009,0.0139) (-1.3,0.009,0.00964)	462	471	542
3	(0.25, 0.008, 0.0009) (1.543, 0.01, 0.00008) (0.290, 0.01, 0.0018)	(2.03, -0.02, 0.00605) (3.4, -0.0375, 0.0047) (3.4, -0.0375, 0.0047)	177	198	448
4	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (0.25, 0.008, 0.0009)	(1.5, -0.02016, 0.009) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	483	496	620
5	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (1.2, -0.02, 0.0087)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	538	570	657
6	(1.8, -0.02, 0.0052) (0.25, 0.008, 0.0009) (1.2, -0.02, 0.0087)	(1.5,-0.02016,0.009) (-1.2, 0.009, 0.0139) (-1.3, 0.009, 0.00964)	462	471	542
7	(1.8, -0.02, 0.0062) (0.25, 0.008, 0.0009) (0.25, 0.008, 0.0009)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	413	424	469
8	(1.8, -0.02, 0.0062) (0.25, 0.008, 0.0009) (0.25, 0.008, 0.0009)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (3.4, -0.0375, 0.0047)	461	476	538
9	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (1.2, -0.02, 0.0087)	(-6.6, 0.05, 0.0088) (-1.2, 0.009, 0.0139) (3.4, -0.0375, 0.0047)	542	570	657

Table 4.5: Comparative study of the total expected number of failures using Covariate adjusted randomized allocation, optimal adaptive allocation, and equal allocation for different values of unknown logistic regression coefficients. Here, $\gamma_A = 0.4$, *and* $\gamma_B = 0.3$, and the sample size is **500** using the objective function as **Odds-Ratio**.

No.	$(\beta_{AA',0}, \beta_{AA',1}, \beta_{AA',2})$ $(\beta_{AC,0}, \beta_{AC,1}, \beta_{AC,2})$ $(\beta_{AD,0}, \beta_{AD,1}, \beta_{AD,2})$	$(\beta_{BB',0}, \beta_{BB',1}, \beta_{BB',2})$ $(\beta_{BE,0}, \beta_{BE,1}, \beta_{BE,2})$ $(\beta_{BF,0}, \beta_{BF,1}, \beta_{BF,2})$	Total expected number of failures		
			Covariate-Adjusted	Optimal	Equal
1	(1.2,-0.022,0.01995) (3.4,-0.0375,0.0047) (3.4,-0.0375,0.0047)	(-5.5,0.04,-0.012) (-6.6,0.05,0.0088) (4.5,-0.025,0.004)	302	300	309
2	(1.8,-0.02,0.0062) (0.25,0.008,0.0009) (1.2,-0.02,0.0087)	(1.5,-0.02016,0.009) (-1.2,0.009,0.0139) (-1.3,0.009,0.00964)	259	257	272
3	(0.25, 0.008, 0.0009) (1.543, 0.01, 0.00008) (0.290, 0.01, 0.0018)	(2.03, -0.02, 0.00605) (3.4, -0.0375, 0.0047) (3.4, -0.0375, 0.0047)	140	154	223
4	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (0.25, 0.008, 0.0009)	(1.5, -0.02016, 0.009) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	300	296	310
5	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (1.2, -0.02, 0.0087)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	330	325	328
6	(1.8, -0.02, 0.0052) (0.25, 0.008, 0.0009) (1.2, -0.02, 0.0087)	(1.5,-0.02016,0.009) (-1.2, 0.009, 0.0139) (-1.3, 0.009, 0.00964)	258	257	272
7	(1.8, -0.02, 0.0062) (0.25, 0.008, 0.0009) (0.25, 0.008, 0.0009)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	230	230	235
8	(1.8, -0.02, 0.0062) (0.25, 0.008, 0.0009) (0.25, 0.008, 0.0009)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (3.4, -0.0375, 0.0047)	259	261	269
9	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (1.2, -0.02, 0.0087)	(-6.6, 0.05, 0.0088) (-1.2, 0.009, 0.0139) (3.4, -0.0375, 0.0047)	330	326	328

Table 4.6: Comparative study of the total expected number of failures using Covariate adjusted randomized allocation, optimal adaptive allocation, and equal allocation for different values of unknown logistic regression coefficients. Here, $\gamma_A = 0.4$, *and* $\gamma_B = 0.3$, and the sample size is **1000** using the objective function as **Odds-Ratio**.

No.	$(\beta_{AA',0}, \beta_{AA',1}, \beta_{AA',2})$ $(\beta_{AC,0}, \beta_{AC,1}, \beta_{AC,2})$ $(\beta_{AD,0}, \beta_{AD,1}, \beta_{AD,2})$	$(\beta_{BB',0}, \beta_{BB',1}, \beta_{BB',2})$ $(\beta_{BE,0}, \beta_{BE,1}, \beta_{BE,2})$ $(\beta_{BF,0}, \beta_{BF,1}, \beta_{BF,2})$	Total expected number of failures		
			Covariate-Adjusted	Optimal	Equal
1	(1.2,-0.022,0.01995) (3.4,-0.0375,0.0047) (3.4,-0.0375,0.0047)	(-5.5,0.04,-0.012) (-6.6,0.05,0.0088) (4.5,-0.025,0.004)	599	602	618
2	(1.8,-0.02,0.0062) (0.25,0.008,0.0009) (1.2,-0.02,0.0087)	(1.5,-0.02016,0.009) (-1.2,0.009,0.0139) (-1.3,0.009,0.00964)	511	510	542
3	(0.25, 0.008, 0.0009) (1.543, 0.01, 0.00008) (0.290, 0.01, 0.0018)	(2.03, -0.02, 0.00605) (3.4, -0.0375, 0.0047) (3.4, -0.0375, 0.0047)	265	297	446
4	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (0.25, 0.008, 0.0009)	(1.5, -0.02016, 0.009) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	597	589	619
5	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (1.2, -0.02, 0.0087)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	661	653	657
6	(1.8, -0.02, 0.0052) (0.25, 0.008, 0.0009) (1.2, -0.02, 0.0087)	(1.5,-0.02016,0.009) (-1.2, 0.009, 0.0139) (-1.3, 0.009, 0.00964)	511	510	542
7	(1.8, -0.02, 0.0062) (0.25, 0.008, 0.0009) (0.25, 0.008, 0.0009)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	458	460	470
8	(1.8, -0.02, 0.0062) (0.25, 0.008, 0.0009) (0.25, 0.008, 0.0009)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (3.4, -0.0375, 0.0047)	518	521	537
9	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (1.2, -0.02, 0.0087)	(-6.6, 0.05, 0.0088) (-1.2, 0.009, 0.0139) (3.4, -0.0375, 0.0047)	661	652	657

Table 4.7: Comparative study of the total expected number of failures using Covariate adjusted randomized allocation, optimal adaptive allocation, and equal allocation for different values of unknown logistic regression coefficients. Here, $\gamma_A = 0.4$, *and* $\gamma_B = 0.3$, and the sample size is **5000** using the objective function as **Odds-Ratio**.

No.	$(\beta_{AA',0}, \beta_{AA',1}, \beta_{AA',2})$ $(\beta_{AC,0}, \beta_{AC,1}, \beta_{AC,2})$ $(\beta_{AD,0}, \beta_{AD,1}, \beta_{AD,2})$	$(\beta_{BB',0}, \beta_{BB',1}, \beta_{BB',2})$ $(\beta_{BE,0}, \beta_{BE,1}, \beta_{BE,2})$ $(\beta_{BF,0}, \beta_{BF,1}, \beta_{BF,2})$	Total expected number of failures		
			Covariate-Adjusted	Optimal	Equal
1	(1.2,-0.022,0.01995) (3.4,-0.0375,0.0047) (3.4,-0.0375,0.0047)	(-5.5,0.04,-0.012) (-6.6,0.05,0.0088) (4.5,-0.025,0.004)	2965	3001	3085
2	(1.8,-0.02,0.0062) (0.25,0.008,0.0009) (1.2,-0.02,0.0087)	(1.5,-0.02016,0.009) (-1.2,0.009,0.0139) (-1.3,0.009,0.00964)	2530	2530	2702
3	(0.25, 0.008, 0.0009) (1.543, 0.01, 0.00008) (0.290, 0.01, 0.0018)	(2.03, -0.02, 0.00605) (3.4, -0.0375, 0.0047) (3.4, -0.0375, 0.0047)	1273	1447	2237
4	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (0.25, 0.008, 0.0009)	(1.5, -0.02016, 0.009) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	2968	2941	3097
5	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (1.2, -0.02, 0.0087)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	3312	3271	3295
6	(1.8, -0.02, 0.0052) (0.25, 0.008, 0.0009) (1.2, -0.02, 0.0087)	(1.5,-0.02016,0.009) (-1.2, 0.009, 0.0139) (-1.3, 0.009, 0.00964)	2530	2530	2702
7	(1.8, -0.02, 0.0062) (0.25, 0.008, 0.0009) (0.25, 0.008, 0.0009)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (-1.2, 0.009, 0.0139)	2283	2292	2345
8	(1.8, -0.02, 0.0062) (0.25, 0.008, 0.0009) (0.25, 0.008, 0.0009)	(-6.6, 0.05, 0.0088) (3.4, -0.0375, 0.0047) (3.4, -0.0375, 0.0047)	2589	2601	2692
9	(1.8, -0.02, 0.0062) (1.2, -0.02, 0.0087) (1.2, -0.02, 0.0087)	(-6.6, 0.05, 0.0088) (-1.2, 0.009, 0.0139) (3.4, -0.0375, 0.0047)	3311	3270	3294

We have increased the sample size to 1000 in Table 4.2, using exactly the same set of parameter values as in Table 4.1. We observe a much larger reduction in the total expected number of failures achieved by the covariate-adjusted approach compared to the optimal adaptive allocation, relative to the results from the simulation with 500 participants. Tables 4.3 and 4.4 present the results for the relative-risk objective function. In both tables, we observe a similar trend to that seen with the simple difference. The covariate-

adjusted method yields a lower expected total number of failures compared to both the optimal adaptive allocation procedure and equal allocation.

We have conducted covariate-adjusted adaptive allocation with the objective function as odds-ratio, with sample sizes of 500 and 1000 in Tables 4.5, 4.6, respectively. However, we notice that in some scenarios (rows in the table), the covariate-adjusted adaptive allocation has performed worse than the optimal adaptive allocation. The reason behind this performance of the covariate-adjusted adaptive allocation with the objective function odds-ratio is its slow adaptive nature in the presence of covariate information compared to the two other objective functions, simple difference and relative-risk. Note that, in Chapter 2, we have seen one of the second stage optimal adaptive allocation ratio (without covariate-adjusted) as $\tau^*_{AC:AD} = \left(\sqrt{\frac{p_{AC}}{p_{AD}}}\right)$ for simple difference, $\tau^*_{AC:AD} = \left(\sqrt{\frac{p_{AC}}{p_{AD}}}\right)\left(\frac{q_{AD}}{q_{AC}}\right)$ for relative risk, and $\tau^*_{AC:AD} = \left(\sqrt{\frac{p_{AD}}{p_{AC}}}\right)\left(\frac{q_{AD}}{q_{AC}}\right)$ for odds-ratio. For the first two objective functions, $\frac{p_{AC}}{p_{AD}}$ appears in the optimal adaptive allocation ratios as the reciprocal of its appearance in the optimal adaptive allocation ratio with the objective function as odds-ratio. Therefore, the covariate-adjusted adaptive allocation ratio based on the odds-ratio requires a much larger sample size to achieve similar performance compared to the other two objective functions. In Table 4.7, with an increased sample size of 5000, we observe an improvement in performance for the objective function as the odds-ratio compared to the results with sample sizes of 500 and 1000.

4.6 Application to the M-bridge Data

In Section 2.7 of Chapter 2, we used data from the M-bridge study to illustrate the applicability of optimal adaptive allocation in a real SMART design. Here, we extend this analysis by incorporating covariate information from the same dataset to demonstrate the practical use of the proposed covariate-adjusted adaptive allocation methodology introduced in this chapter. Recall that the binary primary outcome of interest is defined as the frequency of consuming 4/5 or more drinks by participants within a two-hour period in the past 30 days at any of the three follow-up assessments at the end of the study. If the frequency is one or more, the binary outcome is coded as 0 (failure); otherwise, it is coded as 1 (success). It is well established that drinking habits vary with respect to gender (White, 2020). Therefore, we include the binary covariate gender in the proposed approach to evaluate its performance relative to the optimal adaptive allocation described in Chapter 2. We included the first 60 participants (ordered by their entry date and time into the study) in the warm-up period, during which treatments are assigned using equal randomization probabilities. For the next treatment allocation, we retrospectively observe the gender information of the 61^{st} participant, and then use this information in the equations (4.9) and (4.8) to obtain the first- and second-stage random allocation probabilities,

respectively. We use the estimated (β) coefficients derived from the data of the warm-up period for these calculations. Once the randomly allocated treatment sequence $\{T_1, T_2\}$ is determined, we identify the 61^{st} participant as the first individual in the ordered list (61 onwards) whose treatment sequence is consistent with $\{T_1, T_2\}$ and the gender information is the same as used in the logistic models. As stated in Section 2.7, the selected participant may have a rank higher than 61^{st} in the ordered list of participants. This process is then repeated for each subsequent participant, utilizing the historical data from all preceding participants. The allocation procedure is terminated if, during retrospective allocation, any treatment arm in the AI sequence exhausts its pool of eligible participants.

Table 4.8: Allocated participants and proportion of failures (in parentheses) following covariate-adjusted adaptive allocation (CAAA) and optimal adaptive allocation (OAA). The simple difference of the success probabilities is used as the objective function $g(\cdot, \cdot)$. The CAAA has to stop after 146 participants, as the treatment sequence $\{A, C\}$ of the M-bridge SMART has no available female participants. The proportion of failures for d_i is q_{d_i}, whereas the proportion of failures (in the last row) is the ratio of the total number of failures to the total participants.

AI	Responder (R) + Non-Responder (NR) = Total (Proportion of failures)			
	Covariate-Adjusted Adaptive Allocation (CAAA)		Optimal Adaptive Allocation (OAA)	
	Participants with CAAA	Remaining participants	Participants with OAA	Remaining participants
d_1	47 + 4 = 51 (0.275)	140 + 33 = 173 (0.236)	45 + 10 = 55 (0.337)	142 + 27 = 169 (0.244)
d_2	47 + 12 = 59 (0.251)	140 + 26 = 166 (0.295)	45 + 9 = 54 (0.206)	142 + 29 = 171 (0.293)
d_3	55 + 15 = 70 (0.174)	121 + 21 = 142 (0.322)	49 + 14 = 63 (0.253)	127 + 22 = 149 (0.293)
d_4	55 + 13 = 68 (0.197)	121 + 34 = 155 (0.276)	49 + 19 = 68 (0.192)	127 + 28 = 155 (0.263)
Total	146 (0.212)	375 (0.277)	146 (0.248)	375 (0.263)

Table 4.8 presents a comparison between the covariate-adjusted adaptive allocation and the optimal adaptive allocation approaches using the M-bridge data. This retrospective allocation process was halted after 146 participants were enrolled, as the treatment sequence $\{A, C\}$ had exhausted all available female participants. Overall, the covariate-adjusted adaptive allocation resulted in a failure rate of 0.212 among the 146 participants (approximately 31 failures), compared to 0.248 (36 failures) with the optimal adaptive allocation. This represents a reduction of about 5 failures, a benefit that is likely to increase with a larger sample size. In covariate-adjusted adaptive allocation, the best AI is d_3, which was allocated 70 participants and had a failure rate of 0.174. In comparison, the best AI under optimal adaptive allocation is d_4, with 68 participants and a higher

failure rate of 0.192. Thus, in this M-bridge study, considering 146 participants, covariate-adjusted adaptive allocation assigned more participants to the superior AI and achieved a lower failure rate. For both covariate-adjusted adaptive allocation and optimal adaptive allocation, the worst AI was d_1, but covariate-adjusted adaptive allocation allocated fewer participants to d_1 than optimal adaptive allocation.

4.7 Discussion

In this chapter, we incorporated covariate information into the allocation process by applying logistic regression to adjust the optimal adaptive allocation ratios established in Chapter 2. Although the covariate-adjusted adaptive allocation does not maintain the strict optimality criterion of the original method, our results show that this approach effectively reduces the total expected number of failures compared to the purely optimal adaptive allocation described in Chapter 2. This covariate-adjusted strategy is particularly advantageous when outcomes are influenced by participant characteristics (covariates), as it allows the allocation procedure to better account for individual differences. Note that the proposed approach fits a separate logistic regression model for each treatment sequence $\{T_1, T_2\}$. As a result, the effective sample size for each model is substantially smaller than the total sample size of the SMART study. Therefore, it is advisable to limit the number of covariates included in each logistic regression model to avoid inefficient parameter estimation due to limited data. Including too many covariates may lead to high bias in the estimation of the β parameters, which could in turn adversely affect the accuracy of the treatment allocation.

The proposed covariate-adjusted adaptive allocation approach presents several important challenges. A primary concern is the potential for allocation imbalance when certain covariate patterns are rare. In such cases, this method may inadvertently assign very few participants to specific treatment arms or covariate groups (Berger, 2007). This can reduce statistical power and limit the ability to detect treatment effects within those subgroups (Ning and Huang, 2010). In the same line, it is recommended to restrict the number of covariates to a few only; otherwise, there may be estimation issues due to a small or even zero number of participants for a specific combination of covariates. In addition, adaptive randomization methods that incorporate covariates may be less familiar to key stakeholders, such as regulatory agencies and clinicians. This lack of familiarity can create challenges for its implementation in practice. As with any adaptive randomization strategy in SMART, covariate-adjusted adaptive allocation relies on timely outcome data to guide allocation decisions. In practice, delays or missing outcome information can compromise the adaptation process, resulting in less effective treatment assignments and potentially diminishing the overall benefits of the approach (Hardwick et al., 2006). These

limitations underscore the importance of careful trial planning and transparent communication with stakeholders when implementing covariate-adjusted adaptive allocation in SMART designs.

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CHAPTER 5

Future Work

5.1 Introduction

In the previous three chapters, we developed adaptive allocation procedures for assigning interventions to participants in order to provide better treatment sequences to more participants. Chapter 2 addressed the optimal adaptive allocation ratio in SMART designs with binary outcomes, while Chapter 3 extended this approach to continuous outcomes. In Chapter 4, we incorporated covariate information into the developed allocation ratios for binary outcomes. In this final chapter, we explore potential future research directions based on the findings presented in this thesis. First, we will discuss the incorporation of covariate information into the adaptive allocation process for SMART designs with continuous outcomes. Additionally, we will explore further avenues for advancing adaptive SMART methodologies.

5.2 Covariate-Adjusted Adaptive SMART Designs with Continuous Outcomes

In Chapter 4, we observed the empirical benefits of incorporating covariate information when determining stage-wise adaptive allocation ratios, thereby assigning more participants to the better intervention. However, this analysis was limited to SMART designs with binary outcomes. Here, we focus on incorporating participant covariate information into SMART designs with continuous outcomes. Covariate adjustment has been found to significantly increase the efficiency of allocation in traditional RCTs with contin-

uous outcomes (Tsiatis et al., 2008). Although covariate-adjusted adaptive clinical trial methodologies have become popular, the use of standard regression models has not been widespread. Recently, empirical studies have demonstrated the advantages of using intuitive and commonly employed regression models for estimating and inferring treatment effects in covariate-adjusted RCTs (Ma et al., 2022). In the future, we can incorporate a linear regression model to estimate the unknown parameters for the different intervention sequences in SMART designs with continuous outcomes. More specifically, the mean outcome of each intervention sequence can be estimated using a linear regression model and then updated in the allocation ratios derived in Chapter 3. Whereas earlier estimation relied solely on historical treatment assignments and outcome data, it will now also depend on the covariates of incoming participants. Similar to Chapter 4, there will be no optimality condition here, as each adaptive allocation ratio will be a function of the covariates.

5.3 Multi-stage optimal adaptive SMART design

In this thesis, we have considered a two-stage SMART framework in which an adaptive intervention (AI) comprises two interventions corresponding to the two stages. However, in practice, an AI may consist of $K > 2$ interventions or treatments corresponding to a $K > 2$ stage SMART. For example, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) SMART design includes three stages (Rush et al., 2004). The proposed adaptive allocation strategies in this thesis can be extended to $K > 2$ stage SMART designs by appropriately defining the optimality criteria for $K > 2$ stages. First, the optimal allocation ratios (without incorporating covariates) should be determined for the final stage. Subsequently, this information can be passed to the preceding stages in sequence until reaching the first stage.

5.4 Multi-treatment optimal adaptive SMART design

The specific SMART design considered in this thesis involves two possible interventions or treatment options at each randomization point. In contrast, randomized controlled trials (RCTs) frequently employ multi-arm designs, where more than two treatments are available for random allocation to participants (Ghosh et al., 2020). Similarly, SMART designs can also incorporate multi-arm configurations, either at every stage or at specific stages, depending on the research objectives and clinical considerations (Wang et al., 2022). Expanding SMART designs to accommodate more than two interventions at a randomization point introduces additional methodological challenges, particularly in terms of defining optimal allocation strategies and ensuring statistical efficiency. The adaptive allocation

approaches developed in this thesis are not directly applicable to multi-arm SMART designs, as the constraint on the asymptotic variance is valid only for two-arm trials (in our case, stage-specific two-arm randomization). Therefore, extending the proposed methods to multi-arm SMART designs represents an important and promising direction for future research, which could enhance the flexibility and applicability of adaptive randomization in more complex clinical settings.

5.5 Optimal adaptive SMART design with randomized responders

In this thesis, the SMART design considered involves randomizing non-responders from the first stage at the second stage, while responders continue with the same or a similar treatment. However, there are SMART designs in which responders are also randomized at the second stage, similar to non-responders. For example, Kidwell et al. (2018) described a SMART design in immuno-oncology treatment in which responders are also re-randomized at the second stage. In the future, we aim to extend our methodology to incorporate the randomization of responders as well. Consequently, in the second stage, there will be four distinct optimal adaptive allocation ratios corresponding to each randomization point. The optimal adaptive allocation ratio for the first stage will then be determined based on these four second-stage allocation ratios.

5.6 Conclusion

The main objective of developing adaptive randomization methodologies in the context of SMART designs is to assign better treatment sequences to a greater number of participants, while minimizing the allocation of less effective sequences. Through the approaches developed in this thesis, we have demonstrated that it is possible to minimize the total expected number of failures in SMART designs with a binary primary outcome, or to reduce the total expected outcome in SMART designs with a continuous primary outcome (where lower outcomes are preferable).

Although the methodology was developed with potential applications in the medical domain, these adaptive approaches can also be valuable in market research, particularly in the personalized delivery of advertisements or products to online customers (Legare et al., 2022). For example, on an online platform, an adaptive intervention could recommend a second product (second stage) based on the purchase of a first product (first stage), while assessing user experience (responder/non-responder). Experimental designs such as SMART, combined with adaptive randomization procedures, can thus be employed

to develop more personalized product recommendations and reduce customer satisfaction failures.

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Journal Articles outside the thesis

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