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COVARIATE ADJUSTED RESPONSE ADAPTIVE RANDOMIZATION DESIGNS

WITH TARGETED LEARNING

by

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APPROVED:

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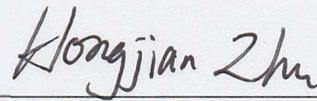
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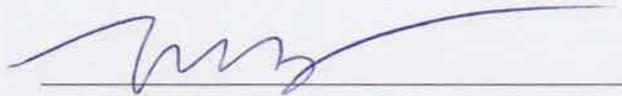
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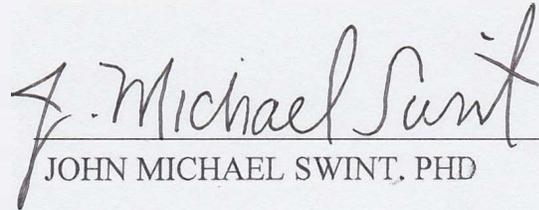
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WITH TARGETED LEARNING

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Since Food and Drug Administration (FDA) issued the very first draft guidance in 2010, adaptive designs have been considered to be one of the most promising approaches to make drug development more efficient and less costly. Two approaches, covariate-adjusted response-adaptive (CARA) randomization and adaptive seamless phase II/III design (ASD) have garnered growing attention recently. However, most of the CARA designs are based on parametric models and suffered from model misspecification. The research of incorporating CARA into ASD is also limited and whether type I error rate can be controlled has not been answered. In this dissertation, a new family of CARA emphasizing on efficiency and ethics using targeted maximum likelihood estimators (TMLE) was proposed to address public health questions as well as tackle the issue of restrictive modeling assumptions. Moreover, the combination of ASD and CARA using TMLE was studied under different scenarios. The asymptotic properties of these approaches were provided and proved rigorously. The simulation studies were carried out to check the concept further. The operating characteristics

revealed that all of the proposed approaches have well-controlled type I error rates around the

nominal level, increases in power and advantage in other ethical aspects.

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1 Introduction

1.1 Motivation and Objectives

In 2006, the US Food and Drug Administration (FDA) introduced the Critical Path Initiative (FDA et al. 2004) to help modernize drug and medical device development. In the Critical Path Opportunities List (FDA et al. 2006), FDA established the expectation in streamlining clinical trials and advancing innovative trial designs. Since then, adaptive designs have garnered growing attention and been considered to be one of the most promising approaches to make drug development more efficient and less costly. To address the increasing demand for the application of adaptive designs in clinical trials, FDA announced a new draft guidance in 2018 to replace the old draft issued in 2010. According to the draft, adaptive designs are eligible to detect drug efficacy more efficiently and reduce the number of patients exposed to inferior investigational treatments. The advantages in statistical efficiency and clinical ethics of adaptive designs make it more appealing to stakeholders than comparable non-adaptive designs (FDA et al. 2018a).

With the development of new diagnostic techologies and bioinformatics, precision medicine became one of the most popular areas in applying adaptive designs. Precision medicine naturally incorporates patients' covariates such as biomarkers and other characteristics into clinical trial designs. The flexibility of precision medicine may also allow the clinical trialists to achieve other design objectives such as optimizing power of detecting treatment effect and minimizing exposure to inferior treatments. Therefore, it is desirable to design adaptive randomized clinical trials that incorporate covariates and achieve

ethical and efficient objectives. Covariate-adjusted response-adaptive (CARA) design is one possible approach satisfying the need. CARA skews the allocation probability for a new patient based on the full history of the previous patients' and the covariates of the current patient to achieve different purposes (F. Hu and Rosenberger 2006). However, in the literature, the statistical inference of most of the CARA designs are based on parametric models and may suffer from model mis-specification and type I error inflation.

Moreover, FDA launched a new guidance to outline the use of an innovative seamless trial design to reduce the time and cost in early stages of oncology drug development (FDA et al. 2018b). FDA also emphasized its move towards the broadening acceptance of seamless trials and provided advice to sponsors to efficiently expedite the clinical development of cancer drugs through multiple expansion cohort trial designs (FDA et al. 2018b). Until 2016, there have been more than 40 active, first-in-human cancer trials that are using the seamless strategy (Prowell, Theoret, and Pazdur 2016). The seamless design has been showed to be capable of reducing the lead time and the number of trials conducted in drug evaluation programs, decreasing the sample size (Bretz, Koenig, et al. 2009). In the area of phase II and phase III study, the adaptive seamless phase II/III trials (ASD) combine the phase II and phase III into a single and seamless trial with two stages, the learning stage and the confirmatory stage, and interim analyses (Bretz, Schmidli, et al. 2006, Stallard 2010). By "adaptive", it means that in the interim analysis, a treatment arm selection is carried out and the confirmation stage is conducted according to the arm selection. The ASD has been shown to have advantage in efficiency over the standard phase II and phase III trials for efficacy confirmation (Bretz, Schmidli,

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et al. 2006).

This dissertation proposes the combination of ASD and CARA to leverage covariates and patients' historical information to achieve efficiency and ethics objectives. Furthermore, a semiparametric approach based on target maximum likelihood estimation (TMLE) is provided to tackle the issue of model mis-specification and type I error inflation and to achieve an overall better power in treatment arm selection and treatment effect detection. The theoretical properties and operating characteristics in simulation of the approach are provided.

1.2 Public Health Significance

The high cost of clinical trials has become one of the major barriers for drug development and limits patient's access to novel treatments. Drug companies' willingness to conduct clinical trials is decreased by the increasing cost of clinical research. The average cost of a phase I study conducted in the US ranged from $1.4 million to $6.6 million. A phase II study cost from $7.0 million to $19.6 million, whereas a phase III study cost ranged from $11.5 million to $52.9 million on average (Sertkaya et al. 2016).

By developing innovative approaches to adaptive seamless phase II/III clinical trials with adaptive randomization designs, one can significantly decrease the total number of patients needed to participate in clinical trials which in turn reduce the cost of new drug development. Nevertheless, the proposed method takes efficiency and ethics into account, which magnifies the power of detecting treatment effects and at the same time

diminish the exposure of patients to inferior treatments. We believe this dissertation will change the practice of implementing clinical trials, expedite the development of precision medicine, benefit the trial participants and future patients.

1.3 Three specific arms

For seamless clinical trials, it is critical to control the type I error rate which can be inflated because of the dual influence of multiplicity and selection (Bauer, Koenig, et al. 2010). In addition, adaptive randomization designs pose new challenges. First, the relationships among the treatment assignments, covariates, and responses are complicated. Second, the allocation probability functions are often not continuous, so Taylor expansion does not work. Third, the theoretical investigation of CARA and TMLE requires challenging work related to empirical processes, statistical functionals, and martingales.

To solve these problems, we conducted comprehensive researches and address the following questions. First, is there a general mathematical framework for combining ASD and adaptive randomization designs? Second, are there fundamental properties of this sequential procedure that can provide a theoretical foundation for further investigations? Third, is it possible to protect the type I error rate? Fourth, what are the advantages of the combination, especially in terms of efficiency and ethics? Fifth, can we avoid unnecessary model assumptions and address the problem of model mis-specification?

The objective is to facilitate and expedite the development of precision medicine and benefit the trial participants by studying seamless phase II/III clinical trials with

adaptive randomization designs. The three specific aims of this dissertation are:

Aim 1: Propose an innovative CARA design targeting both efficiency and ethics analyzed by using the semiparametric methodology of TMLE in two treatment scenario.

Aim 2: Extend and generalize the CARA design targeting both efficiency and ethics analyzed by using TMLE (proposed in aim 1) to multiple treatment scenario.

Aim 3: Study the feasibility of combing the seamless phase II/III clinical trials with the CARA design proposed in aim 1 and aim 2.

In aim 1 and aim 2, we provided a rigorous proof of the consistency and asymptotic normality in theory. The concept was also tested in simulations in terms of type I error rate and power. In aim 3, we conducted simulations that mimic real life clinical trials to further evaluate the operating characteristics (e.g. type I error rate, power, etc) of ASD with the proposed CARA using TMLE.

1.4   Organization of the dissertation

In section 3, we first introduced the fundamental theories and statistical methods as the basis of our proposed CARA designs and TMLE. The achievements of aim 1 and aim 2 were combined in generalized framework and presented in section 4. The detail of the allocation strategies and the asymptotic properties of the designs were introduced. The implementation of TMLE in analysis and its statistical properties were provided in section 4. In addition, extensive numerical studies were carried out to evaluate the

operating characteristics and validity of the methodology. In section 5, we introduced some basic settings and concept of adaptive seamless designs including combination test, multiple testing and closure principle. The research framework of the combination of ASD and the proposed CARA using TMLE were developed in section 6. Besides, the simulation study was conducted and presented in section 6. All corresponding proofs were relocated to the Appendix.

2 Statistical methods

In this section, we introduced some basic settings in causal inference, statistical functionals and empirical process. They set up the foundation of the nonparametric methodology, the TMLE. We adopted the same notations and terminology in "*Unified Methods for Censored Longitudinal Data and Causality*" (M. Van der Laan and Robins 2012), "*Targeted Learning*" (M. Van der Laan and Rose 2011), "*Targeted Learning in Data Science*" (M. Van der Laan and Rose 2018) and "*Introduction to Empirical Processes and Semiparametric Inference*" (Kosorok 2008).

2.1 Data structure in counterfactuals

In a statistical experiment, we denote the true data generating distribution as P_0. Let a statistical full model $\mathcal{M}^F$ representing a collection of probability distributions for P_0 that $P_0 \in \mathcal{M}^F$. $\mathcal{M}^F$ may possibly contain some parametric models, semi-parametric models or non-parametric models. The full data structure X can be written as $X = (W, (Y(a), a \in \mathbb{A}))$, where W represents the set of baseline covariates for a subject, $\mathbb{A}$ denotes a collection of all possible treatment or exposure, and Y the outcome. In many clinical trial applications, we also represent X as $X = (X(a), a \in \mathbb{A})$, where $X(a) = (W, Y(a))$. According to the concept of counterfactuals, the full data structure contains all possible realizations of Y under different intervention $a \in \mathbb{A}$. Our observed data O can be viewed as a censored version of X that $O = (A, L(A) = X(A))$. Here, censoring means that the full data structure can only be observed partially rather than

fully observed. The censoring variable A indicated windicates what component of X will be available in the experiment. For example, assume there are two treatment arms $\mathbb{A} = \{0, 1\}$, the full data structure is $X = (W, Y(1), Y(0))$. If a patient is assigned to treatment arm $A = 1$, the observed data is $O = (A = 1, X(A = 1)) = (W, Y(1))$. The information on treatment arm $A = 0$ is censored and unobservable once A is determined because no one can go back in time to assign another treatment to the same patient. We denote $\boldsymbol{O}_i = (O_1, \ldots, O_i)$ and $\boldsymbol{X}_i = (X_1, \ldots, X_i)$ as the observed data and the full data of the first i experiments respectively. Let $\boldsymbol{A}_i = (A_1, \ldots, A_i)$ denote the collection of first i observed treatment assignments. Note that here A_i is the treatment which the i-th patient is assigned to. The same notation applies to all other random variables.

2.2 Design settings and assumptions

Design settings here refers to the way how patients are assigned to available treatments or interventions. In a fixed design, the design settings for each patient is pre-determined before the trial begins. However, in an adaptive randomization trial, the design setting is typically dynamic as the trial progresses. It varies from patient to patient and it also depends on the performance of other patients. In this section, we will give out statistical definitions of fixed and adaptive design settings upon some commonly used assumptions.

Suppose in an experimental study where experiments are conducted sequentially such that each individual experiment is carried out right after the previous one and all information from previous experiments are collected and available. For the i-th experiment,

we define our design setting g_i as the conditional probability of the i-th treatment assignment A_i, given the full data $\boldsymbol{X}_i$:

$$g_i(A_i|\boldsymbol{X}_i) = \Pr(A_i|\boldsymbol{X}_i).$$

We denote $\boldsymbol{g}_n = (g_1, \ldots, g_n) \in \mathcal{G}$ as the design settings in the study, where $\mathcal{G}$ is defined as the collection of all conditional probability distribution g_i.

In 1991, Heitjan and Rubin introduced the notion of coarsening at random (CAR) to describe the general form of randomly grouped, censored, or missing data. The CAR states that the censoring mechanism satisfies coarsening at random (CAR) when the censoring distribution only depends on the observed components of X (Heitjan and Donald Rubin 1991). In this dissertation, we assume CAR assumption holds by assuming the conditional probability $\boldsymbol{g}$ is only a function of the observed data $\boldsymbol{O}$,

$$g_i(A_i|\boldsymbol{X}_i) = g_i(A_i|X_i, \boldsymbol{O}_{i-1}) = g_i(A_i|X_i(A_i), \boldsymbol{O}_{i-1}), i = 1, \ldots, n.$$

We denote $\mathcal{G}(CAR)$ as a collection of all design settings satisfying CAR assumption, then we have $g_i \in \mathcal{G}(CAR) \subset \mathcal{G}$ for all $i = 1, \ldots, n$.

In an experimental study, if one or more of the conditional distributions g_i of a single experiment is a function of $(O_1, \ldots, O_{i-1})$ and satisfies CAR assumption, then we consider $\boldsymbol{g} \in \mathcal{G}(CAR)$ as an adaptive design. If all conditional distributions g_i of a single experiment is independent from others, but not necessarily identical, $g_i \neq g_j$ for some $i \neq j$, we refer to the design settings $\boldsymbol{g}$ of the study as a fixed design $\boldsymbol{g} \in \{g : g(A|X) = h(A, X(A))$ for some measurable function $h\}$.

2.3 Probability factorization

The factorization of the data-generating distribution is essential in constructing semi-parametric parameters of interest in TMLE methodology. Under CAR assumption, the probability density of a single observation O can be factorized in a Q_0-factor and a design allocation strategy g as follows:

$$\Pr(o = (a, l)) = (a, l(x))) = Q_0((a, l(x))g(a|x)$$

where Q_0 denotes the probability density function of $l(x)$ for a given a. Q_0 only depends on the the full data distribution P_0 of X. We also utilize the notation $P_{Q_0,g}(O)$ as the probability density of O. We can easily generalize the density function of a single experiment to a joint probability density for a collection of experiments $\boldsymbol{O}_n = \{O_i, \ldots, O_n\}$ under design settings $\boldsymbol{g} = \{g_i, g_i \in \mathcal{G}(CAR) \text{ for all } i = 1, \ldots, n\}$,

$$
\begin{aligned}
P_{Q_0,\boldsymbol{g}}(\boldsymbol{o}_n) &= Q_0((a_i, l_i), i = 1, \ldots, n)\boldsymbol{g}(\boldsymbol{a}|\boldsymbol{x}) \\
&= \prod_{i=1}^{n} Q_0(a_i, l_i) \prod_{i=1}^{n} g_i(a_i|x_i, \boldsymbol{o}_{i-1}).
\end{aligned}
$$

For a fixed design with fixed design settings where $\boldsymbol{g}$ is independent of previous observations, in the i-th experiment, the observed data is constructed by randomly drawing X_i from P_0, drawing A_i from g_i and censoring $O_i = (A_i, L_i = X_i(O_i)) \sim P_{Q_0,g_i}$ (M. J. Van der Laan 2008). For an adaptive design, one can randomly draw X_i from P_0 for the i-th experiment. The A_i is drawn from the conditional distribution $g_i(\cdot|X_i, O_1, \ldots, O_{i-1})$ which is calculated based on the previous $(i-1)$ experiments. The observed data then can be expressed as $O_i \sim P_{Q_0,g_i}$ where g_i is no longer a fixed value but depends the previous data.

For example, in a k-arm randomized clinical trail (RCT), the collection of all possible treatment is defined as $\mathbb{A} = \{1, \ldots, k\}$, the baseline covariates is expressed as W. The endpoint outcome is expressed as Y. Under counterfactual concept, $Y(k)$ denotes the realization of the endpoint outcome Y when treatment k is assigned, $A = k$. Therefore the full data structure is $X = (A, W, Y(a)$ for all $a \in \mathbb{A}) \sim P_0$ while the observed data structure $O = (A, W, Y(A)) \sim P_{Q_0,g}$. The probability factorization of the observed data is

$$P_{Q_0,g}(O) = Q_0(A, W, Y)g(A|W),$$

where $Q_0(A, W, Y) = P_0(Y|A, W)P_0(W)$. One important property of this factorization is that the Q-part and g-part are orthogonal (M. Van der Laan and Rose 2011). In other word, the two parts are independent of each other, and the Q-part is the component that impacts the evaluation of our target parameter.

2.4   Empirical Process

The theory of empirical process which is a stochastic process that describes the properties of sums of independent random variables began in 1930s. It has laid a solid foundation for many subsequent researches. In this section, we will briefly introduce some important definitions and settings based on Kosorok's book (Kosorok 2008) that is closely related to this dissertation.

Let X be a random variable drawing from distribution P, $X \sim P$. We use notation F_X as its cumulative distribution function. Also, in some cases, we use F_X to represent

the corresponding distribution of X. Let f be a real-valued function, mapping $\mathbb{R} \to \mathbb{R}$, whose domain is the space of X. Let $\mathcal{F}$ be the set of these real-valued functions such that $f \in \mathcal{F}$. Consider a sample of n i.i.d. observations $X_i, \ldots, X_n$ from P. Let P_n denote the corresponding empirical distribution. We define the operators (or functions) P and P_n on a real-valued function f as following:

$$
\begin{aligned}
Pf &= \int f dP = E_P[f(X)] \\
P_n f &= \int f dP_n = \frac{1}{n} \sum_{i=1}^{n} f(x_i)
\end{aligned}
$$

Throughout this dissertation, instead of being a symbol of distribution, P and P_n can aslo be treated as a function or operator on a real-valued function. Specifically, Pf and $P_n f$ defines the Lebesgue Integral on a set of measurable functions $f \in \mathcal{F}$ (M. Van der Laan and Robins 2012).

Let $(l^\infty(\mathcal{F}), \|\cdot\|_{\mathcal{F}})$ denote a normed space of mappings which maps $\mathcal{F} \to \mathbb{R}$. If $P \in l^\infty(\mathcal{F})$, the uniform norm is defined by $\|P\|_{\mathcal{F}} = \sup_{f \in \mathcal{F}} |Pf| < \infty$. Then an empirical process G_n is defined by

$$
G_n f = \sqrt{n}(P_n f - Pf) = \sqrt{n} \left(\frac{1}{n} \sum f(X_i) - E_P f(X) \right),
$$

if $f \in \mathcal{F}$ and $\mathcal{F} \subseteq L^1(P)$ (Kosorok 2008). The empirical process G_n as well as P and P_n are elements in $(l^\infty(\mathcal{F}), \|\cdot\|_{\mathcal{F}})$. The n observations in P_n render the randomness in G_n (Kosorok 2008). A class $\mathcal{F}$ is called a P-Glivenko-Cantelli class if $\mathcal{F}$ is in $L^1(P)$ satisfying

$$
\|P_n - P\|_{f \in \mathcal{F}} = \sup_{f \in \mathcal{F}} |P_n f - Pf| \overset{a.s.}{\to} 0.
$$

The P-Glivenko-Cantelli class implies that if $\mathcal{F}$ is P-Glivenko-Cantelli, then for an em-

pirical process $\frac{1}{\sqrt{n}}G_n$ converges almost surely to zero over all $f \in \mathcal{F}$. This property can be derived directly from law of large numbers. Note that not all functions are in P-Glivenko-Cantelli class. As $\mathcal{F}$ becomes larger, it is harder to ensure all $f \in \mathcal{F}$ satisfy the strong convergence.

The P-Brownian Bridge is defined by a random element G from $l^\infty(\mathcal{F})$ which is continuous with probability one satisfying that for any k elements from $\mathcal{F}$

$$(Gf_1, \ldots, Gf_k) \sim N(0, \text{COV}_P(f_i, f_j)).$$

A typical P-Brownian Bridge G_1 is defined in a way such that for $f \in \mathcal{F}$, $G_1 f = f - Pf$. For any $f_i, f_j \in \mathcal{F}$, we have $P(Gf_i) = P(Gf_j) = 0$, and $P(Gf_1 \cdot Gf_2) = P(f_1 f_2) - Pf_1 Pf_2 = \text{COV}_P(f_1, f_2)$, which satisfies the definition of P-Brownian Bridge. Besides, the empirical process G_n can be expressed as $G_n = \frac{1}{n} \sum_{i=1}^n G_1(X_i)$. A class $\mathcal{F}$ is called a P-Donsker class if the empirical process $G_n \in (l^\infty(\mathcal{F}), \|\cdot\|_\mathcal{F})$ converges in distribution to a P-Brownian Bridge $G \in (l^\infty(\mathcal{F}), \|\cdot\|_\mathcal{F})$. Note that P-Donsker class implies a uniformly CLT property over $\mathcal{F}$. In addition, P-Donsker classes are P-Glivenko-Cantelli classes but the converse is not true. Some examples of Donsker classes are all monotone functions, all functions with uniformly bounded derivatives and the set of indicator functions $\mathcal{F} = \{I_{(-\infty, t]} : t \in \mathbb{R}\}$ (Kosorok 2008). In this dissertation, all functions used are in both P-Donsker class and P-Glivenko-Cantelli class.

2.5 Statistical Functional

Statistical functional is a common tool in nonparametric analysis. It provides an elegant way to define a population quantities as well as an estimator as a functional of the population. The notion of statistical functional acts as the foundational role in TMLE methodology. A statistical functional Ψ is a mapping that maps a function space to a d-dimensional vector of real numbers, $\Psi : (l^\infty(\mathcal{F}), \| \cdot \|_{\mathcal{F}}) \to \mathbb{R}^d$. The functional $\Psi(P)$ can be viewed as a projection from an infinity dimensional "vector" $(Pf : f \in \mathcal{F})$ to a real space $\mathbb{R}^d$. For example, if we define a functional Ψ such that $\Psi(P) = Var(X)/E(X)$ of a random variable X from a distribution P. This functional actually calculates the ratio of the variance to the expectation of a given distribution. The functional can also be written as

$$\Psi(P) = \frac{Pf_2 - (Pf_1)^2}{Pf_1},$$
$$\Psi(P_n) = \frac{P_n f_2 - (P_n f_1)^2}{P_n f_1},$$

where $f_1(X) = X$, $f_2(X) = X^2$. Therefore, Ψ maps Pf_1 and Pf_2 into a real number. In general, suppose we have n i.i.d. observations $X_1, \ldots, X_n$ from a probability distribution P_0. Let Ψ be a target parameter of interest, and let $\psi_0 = \Psi(P_0)$ be the true value of our target parameter. In addition, let P_n be the empirical distribution of $X_1, \ldots, X_n$, and let $\psi_n = \hat{\Psi}(P_n)$ be an estimator of ψ_0. We assume that $\Psi(P) = \hat{\Psi}(P)$ so that the estimator targets the desired target parameter ψ_0. If $\mathcal{F}$ is a P_0-Glivenko-Cantelli class, from continuous mapping theorem we have $\Psi(P_n) - \Psi(P_0)$ converge to zero in probability, which implied the consistency of the estimator $\hat{\Psi}(P_n)$ (Kosorok 2008).

2.6 Functional derivative

A statistical functional $\Psi : (l^\infty(\mathcal{F}), \|\cdot\|_{\mathcal{F}}) \to \mathbb{R}^d$ is Hadamard differentiable at $P \in (l^\infty(\mathcal{F}), \|\cdot\|_{\mathcal{F}})$ with derivative $d\Psi : (l^\infty(\mathcal{F}), \|\cdot\|_{\mathcal{F}}) \to \mathbb{R}^d$ if $d\Psi$ is a continuous linear map such that

$$\frac{\Psi(P + t_n h_n) - \Psi(P)}{t_n} \to d\Psi(P)(h)$$

for all scalar sequences $t_n \to 0$ and all $h_n \in l^\infty(\mathcal{F}) \to h \in l^\infty(\mathcal{F})$. Basically, there are three types of differentiability, Gateaux, Hadamard and Frechet. Frechet differentiability implies Hadamard differentiability, which implies Gateaux differentiability (Shapiro 1990).

The natural thing is that we can connect the differentiability and the asymptotic property of an estimator of statistical functional (target parameter) by using functional delta method (Fang and Santos 2014). We suppose Ψ has Hadamard derivative $d\Psi(P)$ at $P \in l^\infty(\mathcal{F})$, and the same for $P_n \in l^\infty(\mathcal{F})$. We assume that $\mathcal{F}$ is a P-Donsker class such that there exists a Brownian bridge G satisfying $G_n \equiv \sqrt{n}(P_n - P) \overset{d}{\Longrightarrow} G$. If G is Borel measurable and separable, then the functional delta method says

$$\sqrt{n}(\Psi(P_n) - \Psi(P)) \overset{d}{\Longrightarrow} d\Psi(P)(G).$$

Or equivalently,

$$\sqrt{n}(\Psi(P_n) - \Psi(P)) = d\Psi(P)(G_n) + o_P(1) = d\Psi(P)(\sqrt{n}(P_n - P)) + o_P(1).$$

$\Psi(P_n)$ is referred as an asymptotically linear estimator of $\Psi(P) \in \mathbb{R}^k$ with influence curve

$IC(P) \in \mathbb{R}^k$ if $E_P[IC(P)(X)] = 0$, $E_P(IC(P)IC(P)^T) \leq \infty$, and

$$\Psi(P_n) - \Psi(P) = (P_n - P)IC(P) + o_P(1/\sqrt{n}).$$

Note that $IC(P)$ is also a functional of P, so it is not a statistic. If $\Psi(P_n)$ is asymptotically linear for $\Psi(P)$, it is easy to show that the influence curve $IC(P)$ is formulated as

$$IC(P) = d\Psi(P)(G_1).$$

The inference about $\Psi(P_n)$ is implemented by applying CLT,

$$\sqrt{n}(\Psi(P_n) - \Psi(P)) \xrightarrow{d} N(0, \Sigma_P),$$

where $\Sigma_P = E_P(IC(P)IC(P)^T)$. Σ_P can be consistently estimated by its empirical estimator $\hat{\Sigma} = \frac{1}{n}\sum_{i=1}^{n} IC(P_n)(X_i)IC(P_n)(X_i)^T$. Then we can form asymptotically valid confidence intervals or confidence regions for $\Psi(P)$.

2.7 Nuisance tangent space

In TMLE, one essential step is to derive the influence curve of the target parameter. Let $L^2(P)$ denote a Hilbert space of functions of random variable X from P with zero expectation and finite variance endowed with inner product $\langle f_1(x), f_2(x) \rangle = \int f_1 f_2 dF_X$ where F_X is the cumulative distribution function (CDF) of the probability distribution P. Let $F_{\epsilon,g}$ denote a one-dimensional submodel of $\mathcal{M}^F$ with parameter $\epsilon \in (-\delta, \delta)$ for some small δ around zero and an index function g satisfying $F_X = F_{0,g}$. A score function $s \in L^2(P)$ indexed by g is defined as

$$s(X) = s(g)(X) = \frac{d}{d\epsilon}\log\left(\frac{dF_{\epsilon,g}}{dF_X}(X)\right)\bigg|_{\epsilon=0}.$$

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A typically used submodel is constructed as $dF_{\epsilon,g}(x) = (1 + \epsilon g(x))dF_X(x) + o(\epsilon)$ with score function $s(g)(X) = g(X)$. This one-dimensional submodel is very useful in finding functional derivatives. Note that $s(X)$ needs to be mean zero to ensure that $F_{\epsilon,s}(x)$ is a legitimate cumulative distribution function. Let $\mathcal{S}$ be the set of score functions. The tangent space $T^F(P) \subseteq L^2(P)$ is referred as the closure of the linear space spanned by $\mathcal{S}$. If the model $\mathcal{M}^F$ for P is nonparametric, then it follows immediately that the tangent space is saturated such that $T^F(P) = L^2(P)$. If the model is not nonparametric, then the tangent space is unsaturated and is a subspace of $L^2(P)$ (M. Van der Laan and Robins 2012).

For a statistical functional $\Psi : (l^\infty(\mathcal{F}), \|\cdot\|_{\mathcal{F}}) \to \mathbb{R}^d$, we assume it is Hadamard directionally differentiable (pathwise differentiable) in terms of the one-dimensional submodels, which means for every $s \in \mathcal{S}$

$$\frac{d}{d\epsilon}\Psi(P_{\epsilon,s})\big|_{\epsilon=0} = \lim_{\epsilon \to 0}\frac{\Psi(P_{\epsilon,s}) - \Psi(P)}{\epsilon} = \langle l(P), s \rangle_P$$

for an element $l(P) \in L^2(P)^d$ which is called a gradient of the pathwise derivative or the influence curve. The unique gradient $S_{eff}(P)$, defined as $S_{eff,j} = \Pi(l_j(P)|T^F(P)) \in T^F(P)$, is called canonical gradient or efficient influence curve. By unique, it means the projection of gradient $l(P)$ on $T^F(P)$ is uniquely determined. For a nonparametric full model, if influence curve exists, it is also the efficient influence curve. We give three examples of calculating influence curves. The nuisance scores are given by the scores of the models $P_{\epsilon,s}$ for which Ψ does not locally vary:

$$\left\{ s \in \mathcal{S} : \frac{d}{d\epsilon}\Psi(P_{\epsilon,s})|_{\epsilon=0} = 0 \right\} \subset \mathcal{S}$$

The nuisance tangent space $T_{nuis}(P)$ is now the closure of the linear space spanned by these nuisance scores:

$$T_{nuis}^F(P) = \overline{\left\{ s \in \mathcal{S} : \frac{d}{d\epsilon} \Psi(P_{\epsilon,s})|_{\epsilon=0} \equiv 0 \right\}} \subset T^F(P)$$

Therefore, for any one-dimensional model $P_{\epsilon,s}$ with $s \in T_{nuis}^F(P)$, we have

$$\Psi(P_{\epsilon,s}) - \Psi(P) = o(\epsilon).$$

Example 1 *Suppose we have a random variable Y from a distribution P with cumulative distribution function $F(y)$. A simple statistical functional is defined as $\Psi(P) = E(Y)$. We propose a one-dimensional sub-model $dF_{\epsilon,s}(y) = (1 + \epsilon s)dF(y)$ with a score function $s(y)$. The influence curve of Ψ can be derived as following:*

$$
\begin{aligned}
\frac{d}{d\epsilon} \left(\Psi(P_{\epsilon,s}) - \Psi(P) \right)\big|_{\epsilon=0} &= \frac{d}{d\epsilon} \left(\int_{-\infty}^{+\infty} y \, dF_{\epsilon,s}(y) - \int_{-\infty}^{+\infty} y \, dF(y) \right)\big|_{\epsilon=0} \\
&= \frac{d}{d\epsilon} \left(\int_{-\infty}^{+\infty} y(1 + \epsilon s)dF(y) - \int_{-\infty}^{+\infty} y \, dF(y) \right)\big|_{\epsilon=0} \\
&= \int_{-\infty}^{+\infty} ys \, dF(y) = \int_{-\infty}^{+\infty} (y - E(Y))s \, dF(y)
\end{aligned}
$$

Therefore the influence curve is $IC = Y - E(Y)$.

Example 2 *Suppose we have an observation $O = (Y, A, W)$ from a distribution P with cumulative distribution function $F(y, a, w)$. A simple statistical functional is defined as $\Psi(P) = E(Y|A = a_i, W = w_i)$. We propose a one-dimensional sub-model*

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$dF_{\epsilon,s}(y, a, w) = (1 + \epsilon s)dF(y, a, w)$ *with a score function* $s(y, a, w)$. *Without generaliz-ability, all integrals become summation when the underlying variable is discrete. Then the statistical functional can be re-written in integral form as*

$$\Psi(P) = E(Y|A = a_i, W = w_i) = \frac{\int_{-\infty}^{+\infty} y I_{a_i,w_i} dF}{\int_{-\infty}^{+\infty} I_{a_i,w_i} dF}$$

and

$$
\begin{aligned}
\Psi(P_{\epsilon,s}) &= \frac{\int_{-\infty}^{+\infty} y I_{a_i,w_i} dF_{\epsilon,s}}{\int_{-\infty}^{+\infty} I_{a_i,w_i} dF_{\epsilon,s}} \\
&= \frac{\int_{-\infty}^{+\infty} y I_{a_i,w_i} dF + \epsilon \int_{-\infty}^{+\infty} y I_{a_i,w_i} sdF}{\int_{-\infty}^{+\infty} I_{a_i,w_i} dF + \epsilon \int_{-\infty}^{+\infty} I_{a_i,w_i} sdF} \\
&= \frac{\int_{-\infty}^{+\infty} y I_{a_i,w_i} dF}{\int_{-\infty}^{+\infty} I_{a_i,w_i} dF} + \frac{\epsilon \int_{-\infty}^{+\infty} y I_{a_i,w_i} sdF}{\int_{-\infty}^{+\infty} I_{a_i,w_i} dF} \\
&\quad - \frac{\epsilon \left(\int_{-\infty}^{+\infty} y I_{a_i,w_i} dF \right) \left(\int_{-\infty}^{+\infty} y I_{a_i,w_i} sdF \right)}{\left(\int_{-\infty}^{+\infty} I_{a_i,w_i} dF \right)^2} + o(\epsilon)
\end{aligned}
$$

The influence curve of Ψ *can be derived as following:*

$$
\begin{aligned}
\frac{d}{d\epsilon} \left(\Psi(P_{\epsilon,s}) - \Psi(P) \right) \Big|_{\epsilon=0} &= \frac{\int_{-\infty}^{+\infty} y I_{a_i,w_i} sdF}{\int_{-\infty}^{+\infty} I_{a_i,w_i} dF} - \frac{\left(\int_{-\infty}^{+\infty} y I_{a_i,w_i} dF \right) \left(\int_{-\infty}^{+\infty} I_{a_i,w_i} sdF \right)}{\left(\int_{-\infty}^{+\infty} I_{a_i,w_i} dF \right)^2} \\
&= \int_{-\infty}^{+\infty} sdF \left(\frac{y I_{a_i,w_i}}{\int_{-\infty}^{+\infty} I_{a_i,w_i} dF} - \frac{\left(\int_{-\infty}^{+\infty} y I_{a_i,w_i} dF \right) I_{a_i,w_i}}{\left(\int_{-\infty}^{+\infty} I_{a_i,w_i} dF \right)^2} \right)
\end{aligned}
$$

It is easy to confirm that the expression inside the parentheses has expectation zero. Therefore the influence curve is

$$IC(O) = \frac{I(A = a_i, W = w_i)}{P(A = a_i, W = w_i)} \left(Y - E(Y|A = a_i, W = w_i) \right).$$

Example 3 *Suppose we have an observation $O = (Y, A, W)$ from a distribution P with cumulative distribution function $F(y, a, w)$. A simple statistical functional is defined as $\Psi(P) = E(Y|A = 1)$. We propose a one-dimensional sub-model $dF_{\epsilon,s}(y, a, w) = (1 + \epsilon s)dF(y, a, w)$ with a score function $s(y, a, w)$. Without generalizability, all integrals become summation when the underlying variable is discrete. The statistical functional can be re-written in integral form as*

$$\Psi(P) = E(Y|A = 1) = \int_{-\infty}^{+\infty} \left(\frac{\int_{-\infty}^{+\infty} yI(a = 1, w = w')dF(y, a, w)}{\int_{-\infty}^{+\infty} I(a = 1, w = w')dF(y, a, w)} \right) dF(y', a', w')$$

and

$$
\begin{aligned}
\Psi(P_{\epsilon,s}) &= \int_{-\infty}^{+\infty} \left(\frac{\int_{-\infty}^{+\infty} yI(a = 1, w = w')dF_{\epsilon,s}(y, a, w)}{\int_{-\infty}^{+\infty} I(a = 1, w = w')dF_{\epsilon,s}(y, a, w)} \right) dF_{\epsilon,s}(y', a', w') \\
&= \int_{-\infty}^{+\infty} \left(\frac{\int_{-\infty}^{+\infty} yI_{1,w'}dF + \epsilon \int_{-\infty}^{+\infty} yI_{1,w'}sdF}{\int_{-\infty}^{+\infty} I_{1,w'}dF + \epsilon \int_{-\infty}^{+\infty} I_{1,w'}sdF} \right) dF(y', a', w') \\
&\quad + \epsilon \int_{-\infty}^{+\infty} \left(\frac{\int_{-\infty}^{+\infty} yI_{1,w'}dF + \epsilon \int_{-\infty}^{+\infty} yI_{1,w'}sdF}{\int_{-\infty}^{+\infty} I_{1,w'}dF + \epsilon \int_{-\infty}^{+\infty} I_{1,w'}sdF} \right) sdF(y', a', w') \\
&= \int_{-\infty}^{+\infty} dF(y', a', w') \left(\frac{\int_{-\infty}^{+\infty} yI_{1,w'}dF}{\int_{-\infty}^{+\infty} I_{1,w'}dF} + \frac{\epsilon \int_{-\infty}^{+\infty} yI_{1,w'}sdF}{\int_{-\infty}^{+\infty} I_{1,w'}dF} \right. \\
&\quad \left. - \frac{\epsilon \left(\int_{-\infty}^{+\infty} yI_{1,w'}dF \right) \left(\int_{-\infty}^{+\infty} yI_{1,w'}sdF \right)}{\left(\int_{-\infty}^{+\infty} I_{1,w'}dF \right)^2} + o(\epsilon) \right) \\
&\quad + \epsilon \int_{-\infty}^{+\infty} \left(\frac{\int_{-\infty}^{+\infty} yI_{1,w'}dF}{\int_{-\infty}^{+\infty} I_{1,w'}dF} + o(\epsilon) \right) s(y', a', w')dF(y', a', w')
\end{aligned}
$$

The influence curve of Ψ can be derived as following:

$$
\begin{aligned}
\frac{d}{d\epsilon}\left(\Psi(P_{\epsilon,s}) - \Psi(P)\right)\Big|_{\epsilon=0} &= \int_{-\infty}^{+\infty} dF(y', a', w') \left(\frac{\int_{-\infty}^{+\infty} y I_{1,w'} s dF}{\int_{-\infty}^{+\infty} I_{1,w'} dF}\right. \\
&\quad - \frac{\left(\int_{-\infty}^{+\infty} y I_{1,w'} dF\right)\left(\int_{-\infty}^{+\infty} y I_{1,w'} s dF\right)}{\left(\int_{-\infty}^{+\infty} I_{1,w'} dF\right)^2} \\
&\quad \left. + s\frac{\int_{-\infty}^{+\infty} y I_{1,w'} dF}{\int_{-\infty}^{+\infty} I_{1,w'} dF}\right) \\
&= \int_{-\infty}^{+\infty} dF(y', a', w') \int_{-\infty}^{+\infty} dF(y, a, w) \\
&\quad \times s(y, a, w)\frac{I_{1,w'}}{P(1, w')}(y - E(Y|1, w')) \\
&\quad + \int_{-\infty}^{+\infty} dF(y', a', w') s(y', a', w') E(Y|1, w') \\
&= \int_{-\infty}^{+\infty} dF(y, a, w) s(y, a, w) \int_{-\infty}^{+\infty} dF(y', a', w') \\
&\quad \times \frac{I_{a=1, w'=w}}{P(1, w')}(y - E(Y|1, w')) \\
&\quad + \int_{-\infty}^{+\infty} dF(y', a', w') s(y', a', w') \left(E(Y|1, w') - E(Y|1)\right) \\
&= \int_{-\infty}^{+\infty} dF(y, a, w) s(y, a, w) \frac{I_1}{P(a=1|w)}(y - E(Y|1, w)) \\
&\quad + \int_{-\infty}^{+\infty} dF(y, a, w) s(y, a, w) \left(E(Y|1, w) - E(Y|1)\right)
\end{aligned}
$$

Therefore, the influence curve of $\Psi(P)$ is

$$
IC(O) = \frac{I(A=1)}{P(A=1|W)}\left(Y - E(Y|A=1, W)\right) + E(Y|A=1, W) - \Psi(P).
$$

3 A family of CARA designs driven by TMLE emphasizing on efficiency and ethics

3.1 Background

Since Food and Drug Administration (FDA) issued the very first draft guidance in 2010, adaptive designs have garnered growing attention and been considered to be one of the most promising approaches to make drug development more efficient and less costly. To address the increasing demand for the application of adaptive designs in clinical trials, FDA announced a new draft guidance in 2018 to replace the old draft issued in 2010. According to the draft, adaptive designs are eligible to detect drug efficacy more efficiently and reduce the number of patients exposed to inferior investigational treatments. The advantages in statistical efficiency and clinical ethics of adaptive designs make it more appealing to stakeholders than comparable non-adaptive designs (FDA et al. 2018a). However, the draft also addressed some limitations and questions such as the risk of type I error rate inflation and statistical bias in the estimation of treatment effects which is relatively less well-studied (FDA et al. 2018a). To further utilize the advantages of adaptive designs and to tackle FDA's concerns, we proposed a family of covariate-adjusted response-adaptive (CARA) designs emphasizing on efficiency and ethics. We also established a theoretical foundation for the family of CARA and employed target maximum likelihood estimation (TMLE) in data analysis to facilitate its application in practice.

Adaptive randomization procedures are classified into four categories: restricted randomization (RR), covariate adaptive randomization (CAR), response adaptive randomization (RAR) and CARA (F. Hu and Rosenberger 2006). CAR dynamically shift treatment assignment of a patient based on his or her baseline characteristics, e.g., to ensure that the imbalance between treatment groups on potentially prognostic covariates is controlled, which has an advantage in increasing the statistical power of a trial. While in the scheme of RAR, the allocation probability of a newly-enrolled patient is based on the accumulating history of previously enrolled patients. CARA designs combine both features of CAR and RAR in a way that skews the allocation probability for a newly-enrolled patient based on his or her baseline covariates and the full history of the previous patients' treatment assignments, responses, and baseline covariates to achieve a particular objective (Bandyopadhyay and Biswas 2001, Rosenberger, Vidyashankar, and Agarwal 2001, Bandyopadhyay, Biswas, and Bhattacharya 2007, F. Hu, Y. Hu, et al. 2015). However, unlike CAR and RCT which have been extensively studied in theory and real applications, the research in CARA is still in its infancy, and the application of CARA is limited due to its technical difficulties. Here, we briefly mention some CARA related papers in the literature. Zhang et al. 2007 and Zhu 2015 have studied the asymptotic properties of CARA. Some Bayesian approaches in CARA have been implemented by Inoue, Thall, and Berry 2002, Berry et al. 2004, Berry 2012, Atkinson and Biswas 2005, Schmidli, Bretz, and Racine-Poon 2007, Thall and Wathen 2007, Brannath et al. 2009, Huang et al. 2009, Yuan, Huang, and Liu 2011, Zang and Lee 2014, J. Hu, Zhu, and F. Hu 2015, J. Lin, L. Lin, and Sankoh 2016 and Villar and Rosenberger 2018. However, the above

papers on CARA have only provided valid statistical inference for CARA under correctly specified parametric models or showed controlled type I error rate in simulations.

TMLE is a novel statistical method first introduced by M. Van der Laan and Daniel Rubin 2006. It has been well acknowledged as a versatile tool in causal inference, observational study, etc. TMLE is semiparametric based and avoids assuming possibly misspecified parametric models when conducting statistical analysis. It aims to obtain an unbiased estimator for a target parameter of interest instead of the whole distribution and other nuisance parameters. It is worth noting that TMLE is a double-robust substitution estimator which holds desirable statistical properties and remains computationally feasible. TMLE has been successfully used in many applications, e.g., Bembom et al. 2009, Lendle, Fireman, and M. Van der Laan 2013, Schnitzer et al. 2014, Balzer et al. 2016, Pang et al. 2016, Pirracchio et al. 2018, Akosile et al. 2018, etc. In order to tackle model misspecification in clinical trials, M. J. Van der Laan 2008 extended TMLE to the regime of adaptive designs and established a TMLE based framework in which robust approaches were offered under semiparametric settings. Later on, Chambaz and M. Van der Laan 2014 and Zheng, Chambaz, and M. Van der Laan 2015 studied some specific CARA designs using the TMLE based framework. Many other works regarding clinical trials have been accomplished using TMLE, such as Moore and M. Van der Laan 2009a, Colantuoni and Rosenblum 2015, etc. Although the advantages of CARA have been studied in the literature listed above, the application of TMLE is hindered by its theoretical complexities.

In this dissertation, we proposed an innovative family of CARA design which is capa-

ble of addressing efficiency and ethics simultaneously. The proposed design also offered flexibility to adjust the balance between trial efficiency and ethical concerns to meet different research needs. Accordingly, TMLE approach was applied in the estimation of the target parameter and the corresponding hypothesis testing. We provided rigorous derivation and proof for its asymptotical properties under the semiparametric setting. Besides, numerical studies were carried out to compare the proposed CARA design and other commonly used randomizations and to investigate the issue of type I error rate inflation. A similar study has been studied by Chambaz and M. Van der Laan 2014. They incorporated Neyman allocation under CARA framework such that the asymptotic variance of the TMLE for the target parameter is minimized. In their study, the dynamic allocation probability was evaluated by applying TMLE for each patient sequentially enrolled. Though we shared a similar big picture, our approaches varied from different angles: 1) Instead of targeting an optimal design, we offered flexibility in a different manner which can meet different research needs, 2) We used martingale estimating equation based estimator in evaluating the allocation probability instead of using TMLE. By doing this, we eased the computational intensity while still ensured theoretical validity. 3) The working model and fluctuation model in TMLE were carefully selected to have good interpretability.

3.2 CARA designs based on semiparametric estimators

Trial settings and Data structure

Consider a clinical trial with K experimental arms and one control arm. Assume that n patients sequentially enter the trial. Let $A_i \in \mathbb{A} = \{0, 1, \ldots, K\}$, $i = 1, \ldots, n$ denote the treatment assignment of the ith patient. Let Y_i be the one-dimensional primary endpoint of the ith patient, where it can be either binary $Y_i \in \{0, 1\}$ or continuous $Y_i \in \mathbb{R}$. For the ith patient, $\boldsymbol{W}_i = (W_{i,1}, \ldots, W_{i,n_W}) \in \mathbb{W}$ represents the ith patient's baseline characteristics, where $\mathbb{W}$ is the domain of $\boldsymbol{W}$. Assume we are interested in a biomarker/subgroup indicator V_i that is a function of the baseline characteristics denoted as $V_i = f_V(\boldsymbol{W}_i) \in \mathbb{V} = \{v_1, \ldots, v_q\}$. The choice of V might be from previous translational research and represent a comprehensive understanding about the impact of baseline characteristics on the treatment effects. The definition of V will solve this problem by collapsing the categories from $\boldsymbol{W} \in \mathbb{W}$. Let $X = (Y(a), a \in \mathbb{A}, \boldsymbol{W}) \sim P_0$ be the full data structure, where $Y(a)$ denotes the realization of Y under $A = a$ and P_0 represents the true data-generating probability distribution. According to the notation of counterfactuals (M. Van der Laan and Rose 2011), the full data structure X contains all possible realizations of Y under different treatments $a \in \mathbb{A}$. The observed data for the ith patient is a censored version of X_i denoted as $O_i = (Y_i(A_i), A_i, \boldsymbol{W}_i)$. Except for the response from the treatment arm A_i which the patient is assigned to, all the other realizations of Y_i in X_i are not observable.

We use $G_i(\cdot)$ to denote the censoring mechanism of the ith patient. For CARA de-

signs, $G_i(\cdot)$ is the conditional probability of treatment assignment A_i given $(X_1, \ldots, X_i)$. Based on the coarsening at random assumption that the censoring mechanism only depends on the observed data (Heitjan and Donald Rubin 1991), we assume that G_i is conditioned on the historical observed data $\boldsymbol{O}_{i-1} = (O_1, \ldots, O_{i-1})$ and the baseline characteristics $\boldsymbol{W}_i$ through the subgroup indicator V_i. Mathematically, $G_i(a, v) = Pr(A_i = a | V_i = f_V(\boldsymbol{W}_i) = v, \boldsymbol{O}_{i-1})$. For convenience, we use short notation G_i for the conditional probability and omit the $\boldsymbol{O}_{i-1}$ in this dissertation. The likelihood of the ith observed data O_i is factorized as $P_0(O_i) = Q_0(Y_i, A_i, \boldsymbol{W}_i)G_i(A_i, V_i)$, where $Q_0(Y_i, A_i, \boldsymbol{W}_i) = P_0(Y_i|A_i, \boldsymbol{W}_i)P_0(\boldsymbol{W}_i)$ is a parameter of the full data distribution P_0. We use notation $Q_0 G_i$ in subscript to denote the data generating mechanism for the ith observed data. We also denote $N_{a,v}(n)/n$ as the proportion of n patients that has been assigned to treatment a in subgroup v.

A family of CARA designs

Clinical trials may have a variety of design objectives such as assigning more patients to the superior treatment group with higher efficiency of detecting the treatment effects. In addition, patients with different baseline characteristics may respond to the treatments differently. We propose a family of CARA designs to take into account both efficiency and ethics simultaneously, acknowledge the heterogeneity of patients, and avoid unnecessary model assumptions by using semiparametric estimators.

We first define our design parameter vector $\boldsymbol{\theta}_0 = \{\boldsymbol{\theta}_0^{a,v}, a \in \mathbb{A}, v \in \mathbb{V}\}$, where $\boldsymbol{\theta}_0^{a,v} =$

$(\theta_{0,1}^{a,v}, \theta_{0,2}^{a,v})$ for all pairs of (a, v), such that

$$\theta_{0,1}^{a,v} = E_{P_0}(Y | A = a, V = v), \quad \theta_{0,2}^{a,v} = E_{P_0}(Y^2 | A = a, V = v). \tag{1}$$

These parameters are the conditional first moment and second moment of Y. We define an extra parameter $\sigma_0^{a,v} = \theta_{0,2}^{a,v} - (\theta_{0,1}^{a,v})^2$ that is the conditional variance of Y given $(A, V) = (a, v)$ under the true probability distribution P_0. Note that when Y is binary, $\theta_{0,2}^{a,v}$ are redundant and $\sigma_0^{a,v} = \theta_{0,1}^{a,v}(1 - \theta_{0,1}^{a,v})$.

Next, we discuss how to obtain an appropriate semiparameter estimator $\hat{\boldsymbol{\theta}}_n = \{\hat{\boldsymbol{\theta}}_n^{a,v}, a \in \mathbb{A}, v \in \mathbb{V}\}$ based on the accumulated data $\boldsymbol{O}_n$, where $\hat{\boldsymbol{\theta}}_n^{a,v} = (\hat{\theta}_{n1}^{a,v}, \hat{\theta}_{n2}^{a,v})$ and the subscript n refers to the sample size. For an arbitrary parameter $\theta \in \Theta$, we first define two estimating functions $M_1^{a,v}(\theta)(\boldsymbol{O}_i)$ and $M_2^{a,v}(\theta)(\boldsymbol{O}_i)$ for all pairs of (a, v) as follow:

$$M_1^{a,v}(\theta)(\boldsymbol{O}_i) = \frac{I_i(a, v) (Y_i - \theta)}{G_i(a, v)(\boldsymbol{O}_{i-1})}, \quad M_2^{a,v}(\theta)(\boldsymbol{O}_i) = \frac{I_i(a, v) (Y_i^2 - \theta)}{G_i(a, v)(\boldsymbol{O}_{i-1})}, \tag{2}$$

where $I_i(a, v)$ is the shorthand notation of $I(A_i = a, V_i = v)$. We can re-define $\theta_{0,1}^{a,v}$ and $\theta_{0,2}^{a,v}$ as the true parameters of the martingale estimating functions (2) such that $E_{Q_0 G_i}\left[M_1^{a,v}(\theta_{0,1}^{a,v})(\boldsymbol{O}_i)\right] = 0$ and $E_{Q_0 G_i}\left[M_2^{a,v}(\theta_{0,2}^{a,v})(\boldsymbol{O}_i)\right] = 0$ for all (a, v). The estimators $\hat{\boldsymbol{\theta}}_n$ are the solutions of $\sum_{i=1}^n \left[M_1^{a,v}(\theta_{n,l}^{a,v})(\boldsymbol{O}_i)\right] = 0$, $l = 1, 2$, with the closed form

$$\hat{\theta}_{n,1}^{a,v} = \frac{\sum_{i=1}^n \frac{I_i(a,v)}{G_i(a,v)} Y_i}{\sum_{i=1}^n \frac{I_i(a,v)}{G_i(a,v)}}, \quad \hat{\theta}_{n,2}^{a,v} = \frac{\sum_{i=1}^n \frac{I_i(a,v)}{G_i(a,v)} Y_i^2}{\sum_{i=1}^n \frac{I_i(a,v)}{G_i(a,v)}}. \tag{3}$$

The calculated weight can potentially improve the efficiency and reduce the bias of unweighted estimators. Moreover, by incorporating the weight rather than simply calculating the first and second moments of Y, the martingale estimating equations (see in appendix) defined by the estimating functions $M_1^{a,v}(\theta)(\boldsymbol{O}_i)$ and $M_2^{a,v}(\theta)(\boldsymbol{O}_i)$ become independent of the CARA allocation probability G_i.

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The specific design setup is inspired by J. Hu, Zhu, and F. Hu 2015, however, our work is extended to nonparametric setting. We define $d(a, v, \boldsymbol{\theta}_0)$ and $e(a, v, \boldsymbol{\theta}_0), a \in \mathbb{A}, v \in \mathbb{V}$, as finite one-dimensional quantities of efficiency and ethics measurements of treatment a in subgroup v, respectively, where $d(\cdot, \cdot, \cdot)$ and $e(\cdot, \cdot, \cdot)$ are certain given functions. For example, we can use the reciprocal of the failure rate as an ethics measurement and the variance of response as an efficiency measurement. The choice of the efficiency and ethics measurements are determined by different design objectives, and will lead to different target allocation proportions. Here, we allow these measurements to vary with the subgroups V, which is consistent with the idea of precision medicine. We propose a family of CARA designs that assign the ith subject in subgroup $V_i = v$ to treatment a with probability

$$G_i(a, v) = Pr(A_i = a | V_i = v, \hat{\boldsymbol{\theta}}_{i-1}) = \frac{e(a, v, \hat{\boldsymbol{\theta}}_{i-1})^{\gamma_1} d(a, v, \hat{\boldsymbol{\theta}}_{i-1})^{\gamma_2}}{\sum_{k \in \mathbb{A}} e(k, v, \hat{\boldsymbol{\theta}}_{i-1})^{\gamma_1} d(k, v, \hat{\boldsymbol{\theta}}_{i-1})^{\gamma_2}}, \qquad (4)$$

where $(\gamma_1, \gamma_2) \in [0, +\infty)^2$ are two tuning parameters determining the balance between ethics and efficiency. The ratio form makes the allocation function a legitimate probability and guarantees the scale invariant property of the efficiency and ethics measurements. This family of CARA designs has very few restrictions about the efficiency and ethics component, so that it can satisfy diverse practical needs in clinical trials.

Asymptotic results of the CARA designs

We introduce the following conditions for the asymptotic results:

Condition 1 $\sup_{a \in \mathbb{A}, v \in \mathbb{V}} E_0(Y^2 | A = a, V = v) < \infty.$

Condition 2 G_i is bounded in $[g_L, g_U]$, where $0 < g_L < g_U < 1$.

Condition 3 For any fixed pair $(a, v) \in \mathbb{A} \times \mathbb{V}$, $d(a, v, \boldsymbol{\theta})$ and $e(a, v, \boldsymbol{\theta})$ are both continuous in terms of $\boldsymbol{\theta}$.

The first condition ensures that the expectation and the variance of Y is defined conditioned on all possible A, V pairs under P_0. The second condition indicates that the CARA designs should avoid assigning zero probability or probability of one to any treatments when allocating patients. The third condition requires the ethics and efficiency measurements to be continuous in $\boldsymbol{\theta}$.

Theorem 1 Under Conditions (1), (2) and (3)

$$\hat{\boldsymbol{\theta}}_n \xrightarrow{a.s.} \boldsymbol{\theta}_0 , \quad G_n(a, v) \xrightarrow{a.s.} G_0(a, v) , \quad N_{a,v}(n)/n \xrightarrow{a.s.} p_0(v)G_0(a, v) \tag{5}$$

for all (a, v) as $n \to \infty$, where $p_0(v) = P_0(V = v)$ is the marginal probability of $V = v$, and

$$G_0(a, v) = Pr(A = a | V = v) = \frac{e(a, v, \boldsymbol{\theta}_0)^{\gamma_1} d(a, v, \boldsymbol{\theta}_0)^{\gamma_2}}{\sum_{k \in \mathbb{A}} e(k, v, \boldsymbol{\theta}_0)^{\gamma_1} d(k, v, \boldsymbol{\theta}_0)^{\gamma_2}}.$$

(See Appendix Page 117 for proof.)

Theorem 1 shows the consistency of $\hat{\boldsymbol{\theta}}_n$, G_n, and $N_{a,v}(n)/n$. To study the asymptotic normality of the semiparameter estimator and the allocation proportions of the CARA design, we introduce the following conditions.

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Condition 4 $\sup\limits_{a\in\mathbb{A},v\in\mathbb{V}} E_0(Y^4|A=a,V=v)<\infty.$

Condition 5 *For any fixed pair $(a,v)\in\mathbb{A}\times\mathbb{V}$, $d(a,v,\boldsymbol{\theta})$ and $e(a,v,\boldsymbol{\theta})$ are both differentiable in terms of $\boldsymbol{\theta}$.*

Theorem 2 *Under Conditions (1), (2), (3), (4) and (5)*

$$\sqrt{n}(\hat{\boldsymbol{\theta}}_n-\boldsymbol{\theta}_0) \xrightarrow{D} N(0,\boldsymbol{\Sigma}_0^{CARA}), \tag{6}$$

$$\sqrt{n}\left(N_{a,v}(n)/n-p_0(v)G_0(a,v)\right) \xrightarrow{D} N\left(0,p_0(v)G_0(a,v)-p_0(v)^2G_0(a,v)^2\right), \tag{7}$$

where $\boldsymbol{\Sigma}_0^{CARA} = \mathrm{diag}\{\Sigma_0^{a,v},(a,v)\in\mathbb{A}\times\mathbb{V}\}$ is a diagonal block matrix. Each element matrix of $\boldsymbol{\Sigma}_0^{CARA}$ is in the form of

$$\Sigma_0^{a,v} = \frac{1}{p_0(v)G_0(a,v)}\begin{pmatrix} \theta_{0,2}^{a,v}-(\theta_{0,1}^{a,v})^2 & \theta_{0,3}^{a,v}-(\theta_{0,1}^{a,v})\theta_{0,2}^{a,v} \\ \theta_{0,3}^{a,v}-(\theta_{0,1}^{a,v})\theta_{0,2}^{a,v} & \theta_{0,3}^{a,v}-(\theta_{0,2}^{a,v})^2 \end{pmatrix},$$

where $\theta_{0,3}^{a,v}$ and $\theta_{0,4}^{a,v}$ are defined as the 3rd and 4th conditional moment of Y given $(A,V)=(a,v)$ under P_0. (See Appendix Page 120 for proof.)

3.3 Analysis of clinical trials with CARA designs based on semiparametric approaches

As introduced in the introduction, traditional analysis methods in CARA designs either have difficulties in addressing the issue of dependent observations or have to assume a possibly misspecified model. In this paper, we propose to use innovative semiparametric approaches such as TMLE to perform data analysis in clinical trials with CARA designs.

Target parameters of the designs

In the proposed CARA designs, the target parameter in TMLE can be defined as a $(K+1)$-dimensional parameter $\boldsymbol{\psi}_0 = \Psi(P_0) = (\psi_{0,0}, \psi_{0,1}, \ldots, \psi_{0,K})$, where Ψ is the target mapping $\Psi : \mathcal{M} \to \mathbb{R}^{k+1}$, and

$$\psi_{0,j} = E_{P_0}(Y|A = j), j = 0, 1, \ldots, K. \tag{8}$$

At the end of the trial, we perform the following hypothesis test

$$H_0 : C\boldsymbol{\psi}_0 = \mathbf{0} \text{ versus } H_1 : C\boldsymbol{\psi}_0 \neq \mathbf{0}, \tag{9}$$

where C is a $K \times (K+1)$ contrast matrix representing the additive treatment differences between K experimental arms and the control arm:

$$C_{K \times (K+1)} = \begin{bmatrix} -1 & 1 & & \cdots & \\ -1 & & 1 & & \\ \vdots & & & \ddots & \\ -1 & & & & 1 \end{bmatrix}.$$

Other target parameters such as relative risk and odds ratio in the scenarios of binary outcome can be easily transformed by taking logarithm of the target parameter.

As a two-step approach, TMLE obtains an initial estimator through some parametric models or semi-parametric approaches such as machin learning in the first step. In the second step, an update is applied to achieve asymptotic unbiasness through a valid loss function and a parametric fluctuation working model (M. Van der Laan and Daniel Rubin 2006).

In next subsections, we offer technique details about how to perform TMLE in clinical trials with CARA designs. At the end, we provided asymptotic results for statistical inferences of the target parameters.

An initial estimator of Q_0

Suppose the response Y is re-scaled in $[0,1]$ and it can be either binary or continuous bounded in $[0,1]$. Note that the re-scale can be implemented either through a linear transformation or any other continuous mapping. For instance, for any set of observations, a linear transformation $Y' = \frac{Y-Y_{\min}}{Y_{\max}-Y_{\min}}$ can be implemented. Also, for $Y \in \mathbb{R}$, $Y' = \mathrm{logit}\, Y$ is bounded in $[0,1]$. The re-scaling is practical because all real life measurement are always truncated to have a lowest and a highest reading. This is a linear transformation that has no impact on our inferences and conclusions. All results can be transformed back to the original scale.

Let $Q_{0,Y|A,W}(P_0) = P_0(Y|A,\boldsymbol{W})$ be the conditional distribution of Y and $Q_{0,W} = Q_W(P_0) = P_0(\boldsymbol{W})$ be the marginal distribution of W. Define $\bar{Q}_0(A,\boldsymbol{W}) = E_{P_0}(Y|A,\boldsymbol{W})$ as the conditional expectation of Y given $(A,\boldsymbol{W})$. Our target parameter $\Psi(P_0)$ only depends on the true data generating distribution P_0 through $Q_0(A,\boldsymbol{W}) = (\bar{Q}_0(A,\boldsymbol{W}), Q_{0,W}(\boldsymbol{W}))$ and it can be written as $\psi_0 = \Psi(P_0) = \Psi(Q_0)$ (rigorously we should use $\Psi(P_0) = \Psi(Q_0(P_0))$, but for convenience we use this notation as in M. Van der Laan and Rose 2011). For an arbitrary estimator Q_n of Q_0, the substitution estimator of the target parameter is $\hat{\psi}_n = \Psi(Q_n)$. To make an initial estimate of $Q_0(A,\boldsymbol{W})$, we introduce a

parametric model $\bar{Q}_n^0(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n)(A, \boldsymbol{W})$ as follows:

$$\bar{Q}_n^0(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n)(A, \boldsymbol{W}) \;=\; \frac{1}{1 + (1/\hat{\theta}_{n,1}^{A,V} - 1) \exp(-\boldsymbol{W}\hat{\boldsymbol{\beta}}_n)}, \tag{10}$$

$$Q_{n,W}^0(\boldsymbol{W}) \;=\; \frac{1}{n} \sum_{i=1}^{n} I(\boldsymbol{W} = \boldsymbol{W}_i), \tag{11}$$

for all $(A, V) \in \mathbb{A} \times \mathbb{V}$, where $V = f_V(\boldsymbol{W})$, and

$$\hat{\boldsymbol{\beta}}_n = \arg\max_{\boldsymbol{\beta}} \sum_{i=1}^{n} \frac{G_n^\star(A_i, V_i)}{G_i(A_i, V_i)} \log\left[\operatorname{expit}(\mu_i)\right]^{Y_i} \left[1 - \operatorname{expit}(\mu_i)\right]^{1-Y_i}, \tag{12}$$

where $\operatorname{expit}(x) = \exp(x)/(1 + \exp(x))$, $\mu_i = \operatorname{logit} \hat{\theta}_{n,1}^{A_i, V_i} + \boldsymbol{W}_i \boldsymbol{\beta}$.

Remark 1 $\hat{\boldsymbol{\beta}}_n$ *is the resulting coefficient of the baseline covariates in the logistic model of* $\operatorname{logit} Y_i = \operatorname{logit} \hat{\theta}_{n1}^{A_i, V_i} + \boldsymbol{W}_i \boldsymbol{\beta}$ *with weight* $w_n(O_i) = G_n^\star(A_i, V_i)/G_i(A_i, V_i)$. *The offset term in the logistic model is the group-wise information that can be brought from* $\hat{\boldsymbol{\theta}}_n$. *The second term adds more information about the within group heterogeneity from the baseline charateristics.* $\hat{\boldsymbol{\beta}}_n$ *is a consistent estimator of the true parameter* $\boldsymbol{\beta}_0$ *such that* $\hat{\boldsymbol{\beta}}_n \xrightarrow{P} \boldsymbol{\beta}_0$, *where* $\boldsymbol{\beta}_0$ *is defined as*

$$\boldsymbol{\beta}_0 = \arg\max_{\boldsymbol{\beta}} E_{Q_0 G_0} \log\left[\operatorname{expit}(\mu_0(\boldsymbol{W}, \boldsymbol{\beta}))\right]^{Y} \left[1 - \operatorname{expit}(\mu_0(\boldsymbol{W}, \boldsymbol{\beta}))\right]^{1-Y},$$

where $\mu_0(\boldsymbol{W}, \boldsymbol{\beta}) = \operatorname{logit} \theta_{0,1}^{A,V} + \boldsymbol{W}\boldsymbol{\beta}$. *The logistic model on continuous outcomes in* $[0, 1]$ *was originally used by Wedderburn 1974 and McCullagh et al. 1983. It has also been adopted and widely used in the field of TMLE (M. Van der Laan and Rose 2011, M. Van der Laan and Rose 2018, Gruber and M. Van der Laan 2010). Note that this parametric model is in general misspecified and is biased in terms of the target parameter* $\boldsymbol{\psi}_0$. *Therefore, in the second step, an update is needed to eliminate the unbiasness introduced in the first step.*

Update the initial estimate with the parametric fluctuation working model

To update the initial fit and find an asymptotic unbiased estimator of $\boldsymbol{\psi}_0$, we introduce a parametric fluctuation model. The procedure is described below.

Let $\bar{Q}_{n,G_n^\star}(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \boldsymbol{\epsilon})(A, \boldsymbol{W})$ be a sub-model of $\bar{Q}_n^0(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n)(A, \boldsymbol{W})$ indexed by $G_n^\star$ with a fluctuating parameter $\boldsymbol{\epsilon} = (\epsilon_0, \epsilon_1, \ldots, \epsilon_K) \in \mathbb{R}^{K+1}$ satisfying $\bar{Q}_{n,G_n^\star}(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \boldsymbol{0})(A, \boldsymbol{W}) = \bar{Q}_n^0(\hat{\boldsymbol{\theta}}_n)(A, \boldsymbol{W})$ and

$$\text{logit} \frac{\bar{Q}_{n,G_n^\star}(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \boldsymbol{\epsilon})(A, \boldsymbol{W})}{1 - \bar{Q}_{n,G_n^\star}(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \boldsymbol{\epsilon})(A, \boldsymbol{W})} = \text{logit} \frac{\bar{Q}_n^0(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n)(A, \boldsymbol{W})}{1 - \bar{Q}_n^0(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n)(A, \boldsymbol{W})} + \boldsymbol{H}(G_n^\star)(A_i, \boldsymbol{W}_i)\hat{\boldsymbol{\epsilon}}, \tag{13}$$

where $\boldsymbol{H}(G_n^\star)(A, \boldsymbol{W}) = (H_0(G_n^\star)(A, \boldsymbol{W}), \ldots, H_K(G_n^\star)(A, \boldsymbol{W})), H_j(G_n^\star)(A, \boldsymbol{W}) = \frac{I(A=j)}{G_n^\star(A, f_V(\boldsymbol{W}))}$. The optimal value of the fluctuating parameter $\boldsymbol{\epsilon}$ is determined by

$$\hat{\boldsymbol{\epsilon}} = \arg\max_{\boldsymbol{\epsilon}} \sum_{i=1}^n \frac{G_n^\star(A_i, V_i)}{G_i(A_i, V_i)} \log\left([\bar{Q}_n(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \boldsymbol{\epsilon})(A_i, \boldsymbol{W}_i)]^{Y_i}[1 - \bar{Q}_n(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \boldsymbol{\epsilon})(A_i, \boldsymbol{W}_i)]^{1-Y_i}\right).$$

Alternatively, it is equivalent to fit the logistic regression $\text{logit} Y_i = \text{logit} \bar{Q}_n^0(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n)(A_i, \boldsymbol{W}_i) + \boldsymbol{H}(G_n^\star)(A_i, \boldsymbol{W}_i)\boldsymbol{\epsilon}$ with weight $w_n(O_i) = G_n^\star(A_i, V_i)/G_i(A_i, V_i)$. Then $\hat{\boldsymbol{\epsilon}}$ is the fitted coefficient of $\boldsymbol{H}(G_n^\star)$. Also, the marginal distribution of $\boldsymbol{W}$ is updated to $Q_{n,W,\boldsymbol{G}_{n+1}}(\boldsymbol{W}_i) = w_i / \sum_i^n w_i$, where the subscript $\boldsymbol{G}_{n+1} = (G_1, \ldots, G_{n+1})$ is the vector of all allocation functions. We adopt the notation $Q_n^\star = (\bar{Q}_n^\star(A, \boldsymbol{W}), Q_{n,W}^\star(\boldsymbol{W})), \bar{Q}_n^\star(A, \boldsymbol{W}) = \bar{Q}_{n,G_n^\star}(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\epsilon}})(A, \boldsymbol{W})$, $Q_{n,W}^\star = Q_{n,W,\boldsymbol{G}_{n+1}}(\boldsymbol{W}_i)$ to denote the updated estimator of Q_0. Hence, the updated estimator is $Q_n^\star(A, \boldsymbol{W}) = (\bar{Q}_n^\star(A, \boldsymbol{W}), Q_{n,W}^\star(\boldsymbol{W}))$,

$$\bar{Q}_n^\star(A, \boldsymbol{W}) = \frac{1}{1 + (1/\bar{Q}_n^0(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n)(A, \boldsymbol{W}) - 1)\exp(-\sum_{j=0}^K \hat{\epsilon}_{n,j} H_j(G_n^\star)(A, \boldsymbol{W}))} \tag{14}$$

$$Q_{n,W}^\star(\boldsymbol{W}) = \frac{1}{\sum_{j=1}^n w_n(O_j)} \sum_{i=1}^n w_n(O_i) I(\boldsymbol{W} = \boldsymbol{W}_i). \tag{15}$$

The logic of this procedure is described below.

Let **IC** denote the influence curve of Ψ. The influence curve is defined as the gradient of the pathwise derivative of the statistical functional Ψ. In this dissertation, the influence curve of our target parameter is $(K+1)$-dimensional. The jth element of the IC at $P = QG$ and $O = (Y, A, \boldsymbol{W})$ is

$$\text{IC}_j(Q, G)(O) = H_j(G)(A, \boldsymbol{W})\left(Y - \bar{Q}(A, \boldsymbol{W})\right) + \bar{Q}(j, \boldsymbol{W}) - \psi_j, \, j = 0, 1, \ldots, K, \quad (16)$$

where ψ_j is defined under under Q. The influence curve can be decomposed into

$$\text{IC}_{j,Y|A,W} = \frac{I(A = j)}{G(A, \boldsymbol{W})}\left(Y - \bar{Q}(A, \boldsymbol{W})\right), \quad \text{IC}_{j,W} = \bar{Q}(j, \boldsymbol{W}) - \psi_j. \quad (17)$$

The two components are orthogonal and are the projections of the influence curve onto the tangent space of $Y|A, \boldsymbol{W}$ and $\boldsymbol{W}$ respectively. The inner product of the two components in the Hilbert space $L^2(QG)$ is zero (M. Van der Laan and Rose 2011). The influence curve has the property that $E_{QG}\,\text{IC}(Q, G)(O) = 0$. However, when the Q and G where the IC is evaluated are not coincident with the Q and G endorsed by the expectation, the zero expectation is not guaranteed.

In the CARA design, it has been acknowledged that under conditions (1), (2) and (3), $\Psi(Q_n)$ is an asymptotic unbiased estimator of $\boldsymbol{\psi}_0$ if

$$\frac{1}{n}\sum_{i=1}^{n}\text{IC}(Q_n, G_n^\star)(O_i)\frac{G_n^\star(A_i, V_i)}{G_i(A_i, V_i)} = \boldsymbol{0} \quad (18)$$

(M. J. Van der Laan 2008). TMLE is used to update the initial estimator to achieve (18). First, we define a quasi-log-likelihood loss function $L(Q)(O) = -Y\log(\bar{Q}(A, V) - (1 - Y)\log(1 - Q(A, V) - \log Q_W(W))$. This loss function is valid not only for binary

outcome Y but also for continuous outcome $Y \in [0, 1]$ (Gruber and M. Van der Laan 2010). Second, we define a fluctuating model parametric model $Q_G(\boldsymbol{\epsilon})$, $\boldsymbol{\epsilon} = (\boldsymbol{\epsilon}_1, \boldsymbol{\epsilon}_2)$, indexed by G as

$$\text{logit } \bar{Q}(\boldsymbol{\epsilon}_1)(A, \boldsymbol{W}) = \text{logit } \bar{Q}(A, \boldsymbol{W}) + \boldsymbol{\epsilon}_1 \boldsymbol{H}(G)(A, \boldsymbol{W}), \tag{19}$$

$$\log Q_W(\boldsymbol{\epsilon}_2)(\boldsymbol{W}) = \log Q_W(\boldsymbol{W}) + \log(1 + \sum_{j=0}^{K} \epsilon_{2j}(\bar{Q}(j, \boldsymbol{W}) - \psi_j)). \tag{20}$$

In general, one can also adopt other valid loss functions and any parametric fluctuating models satisfying $dQ_G(\boldsymbol{\epsilon}) = (1 + \boldsymbol{\epsilon}\mathbf{IC}(Q, G) + o(\boldsymbol{\epsilon}))dQ$, e.g., the squared error loss function $L(\bar{Q}) = (Y - \bar{Q}(A, \boldsymbol{W}))^2$ and $\bar{Q}_G(\boldsymbol{\epsilon}) = \bar{Q} + \boldsymbol{\epsilon}\mathbf{IC}(Q, G)\bar{Q}(1 - \bar{Q})$. However, it is believed to be less robust since they may result in a linear regression model which breaks the global constraints (M. Van der Laan and Daniel Rubin 2006). In addition, the logit based sub-model of $\bar{Q}$ is widely used in TMLE because of its good properties such as one-step update. We have the following theorem.

Theorem 3 *With the loss function and the parametric model defined, we define the true $\boldsymbol{\epsilon}_0$ of our CARA design as $\boldsymbol{\epsilon}_0 = \arg\min_{\boldsymbol{\epsilon}} E_{Q_0 G_0} L(Q_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}))$, where G_0 is the target allocation probability and depends on $\boldsymbol{\theta}_0$. Then, the target mapping Ψ maps Q_0 and $Q_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0)$ to the same value: $\Psi(Q_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0)) = \Psi(Q_0) = \psi_0$. (See Appendix Page 121 for proof.)*

In the CARA design, all observations are not independent and are not sampled from $Q_0 G_0$ which is endorsed under the expectation in the definition of $\boldsymbol{\epsilon}_0$. To estimate $\boldsymbol{\epsilon}_0$, we denote $L_n^\star(Q)(O_i) = L(Q)(O_i)w_n(O_i)$ as a weighted quasi-likelihood loss function for the

ith patient, where $w_n(O_i) = G_n(A_i, V_i)/G_i(A_i, V_i)$. Then we define an estimator $\hat{\boldsymbol{\epsilon}}_n$ as

$$\hat{\boldsymbol{\epsilon}}_n = \arg\min_{\boldsymbol{\epsilon}} \sum_{i=1}^{n} w_n(O_i) L^\star(Q_{n,G_n^\star}(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \boldsymbol{\epsilon}))(O_i). \tag{21}$$

In general, the second step of TMLE involves an iterative update procedure such that

$$\hat{\boldsymbol{\epsilon}}_n^{(k+1)} = \arg\min_{\boldsymbol{\epsilon}} \sum_{i=1}^{n} w_n(O_i) L^\star(Q_{n,G_n^\star}^{(k)}(\boldsymbol{\epsilon}))(O_i), \tag{22}$$

where $Q_{n,G_n^\star}^{(k)} = Q_{n,G_n^\star}^{(k-1)}(\hat{\boldsymbol{\epsilon}}_n^{(k)})$. The iterative process stops when $\hat{\boldsymbol{\epsilon}}_n^{(k)} \approx 0$. M. Van der Laan and Gruber 2016 have showed that the logit based submodel is also a universal least favorable submodel in which the iterative process stops at one step in i.i.d. setting. It is easy to verify that in the CARA design, TMLE is achieved in one step. Specifically, the MLE of ϵ_1 can be solved in one step through a weighted logistic regression. In i.i.d. setting, the MLE of ϵ_2 is zero, which indicates no update is needed for the empirical distribution of $\boldsymbol{W}$. However, there is no solution in general for the MLE of ϵ_2 in the CARA design. The updated (15) along with (14) solve the estimating equation (18). One can also use the empirical distribution $1/n$ because of the fact that $Q_{n,W}^\star(\boldsymbol{W}) \xrightarrow{a.s.} 1/n$ as $n \to \infty$. The following theorem gives the asymptotic property of this estimator.

Condition 6 $E_0(W_j^2) < \infty$ for all $j \in \{1, \ldots, n_W\}$.

Theorem 4 *Under condition (1), (2), (5) and (6), we have*

$$(\hat{\boldsymbol{\beta}}_n, \hat{\boldsymbol{\epsilon}}_n) \xrightarrow{a.s.} (\boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0). \tag{23}$$

The updated estimator $Q_{n,G_n^\star}(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \hat{\boldsymbol{\epsilon}})$ solves the estimating equation (18). (See Appendix Page 122 for proof.)

Statistical inference

From previous section, we obtained the updated estimator $Q_n^\star = (\bar{Q}_n^\star(A, \boldsymbol{W}), Q_{n,W}^\star(\boldsymbol{W}))$.

The TMLE of $\boldsymbol{\psi}_0$ is calculated as

$$\hat{\psi}_{n,j}^{TMLE} = \sum_{i=1}^n Q_{n,W}^\star(\boldsymbol{W}_i)\bar{Q}_n^\star(j, \boldsymbol{W}_i), \quad j \in \{0, 1, \ldots, K\}.$$

The asymptotic property of $\hat{\psi}_n^{TMLE}$ can be studied through $(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \hat{\boldsymbol{\epsilon}})$ by Theorem 8

(M. J. Van der Laan 2008). In this dissertation, our main focus is the behavior and

asymptotic property of $\hat{\psi}_n^{TMLE}$. Moreover, we have multiple treatment arms, which

causes extra complexities. Thus, we construct the normality of $\hat{\psi}_n^{TMLE}$ directly through

the martingale estimating equation (18). The following theorem establishes the asymp-

totic normality of $\hat{\psi}_n^{TMLE}$.

Theorem 5

$$\sqrt{n}\left(\hat{\psi}_n^{TMLE} - \boldsymbol{\psi}_0\right) \xrightarrow{D} N(0, \Sigma_0^{TMLE}) \ as \ n \to \infty, \tag{24}$$

where Σ_0^{TMLE} is a $(K+1) \times (K+1)$ covariance matrix with

$$\sigma_0^{TMLE}(j, k) = E_{Q_0 G_0}\left(\mathrm{IC}_j(Q_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0), G_0)\,\mathrm{IC}_k(Q_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0), G_0)\right).$$

$\sigma_0^{TMLE}(j, k)$ *can be consistently estimated by*

$$\hat{\sigma}_n^{TMLE}(j, k) = \frac{1}{n}\sum_{i=1}^n \left(\frac{G_n^\star(A_i, V_i)}{G_i(A_i, V_i)}\right)^2 \left(\mathrm{IC}_j(Q_n^\star, G_n^\star)(O_i)\,\mathrm{IC}_k(Q_n^\star, G_n^\star)(O_i)\right).$$

The hypothesis [9] can be tested using the statistic

$$T^\star = (C\hat{\psi}_n^{TMLE})^T(\frac{1}{n}C\hat{\boldsymbol{\Sigma}}_n^{TMLE}C^T)^{-1}(C\hat{\psi}_n^{TMLE}).$$

The null hypothesis is rejected at level α if $T > \chi_K^2(1-\alpha)$. (See Appendix Page 125 for proof.)

In this section, we showed the advancement of TMLE in dealing with non-i.i.d data in the proposed CARA designs. Without additional model assumption, TMLE approach holds the consistence property and asymptotic property through theorem 3 and 4 theorem 4. In addition, the double robust nature of TMLE ensures its asymptotic efficiency in the light of semiparametric statistical model efficiency theory (M. Van der Laan and Rose 2011).

3.4   Numerical studies

Having obtained the asymptotic properties of the proposed family of CARA designs, in this section we numerically evaluated its finite-sample performance regarding the Type I error rate, power, unbiasness, and ethics properties. We considered four scenarios: (1) two treatment arms with binary endpoints; (2) three treatment arms with binary endpoints; (3) two treatment arms with continuous endpoints; (4) three treatment arms with continuous endpoints. We also studied four different CARA designs representing different ethics measurements:

CARA$_1$: $e(a, v, \hat{\boldsymbol{\theta}}_{i-1}) = \hat{\theta}_{i-1,1}^{a,v}$, $d(a, v, \hat{\boldsymbol{\theta}}_{i-1}) = \sqrt{\hat{\theta}_{i-1,2}^{a,v} - (\hat{\theta}_{i-1,1}^{a,v})^2}$

CARA$_2$: $e(a, v, \hat{\boldsymbol{\theta}}_{i-1}) = (1 - \hat{\theta}_{i-1,1}^{a,v})^{-1}$, $d(a, v, \hat{\boldsymbol{\theta}}_{i-1}) = \sqrt{\hat{\theta}_{i-1,2}^{a,v} - (\hat{\theta}_{i-1,1}^{a,v})^2}$

CARA$_3$: $e(a, v, \hat{\boldsymbol{\theta}}_{i-1}) = \hat{\theta}_{i-1,1}^{a,v} * (1 - \hat{\theta}_{i-1,1}^{a,v})^{-1}$, $d(a, v, \hat{\boldsymbol{\theta}}_{i-1}) = \sqrt{\hat{\theta}_{i-1,2}^{a,v} - (\hat{\theta}_{i-1,1}^{a,v})^2}$

$$\text{CARA}_4: e(a, v, \hat{\boldsymbol{\theta}}_{i-1}) = \Phi(\hat{\theta}_{i-1,1}^{a,v} - \frac{1}{n_A}\sum_{k=1}^{n_A}\hat{\theta}_{i-1,1}^{k,v}), d(a, v, \hat{\boldsymbol{\theta}}_{i-1}) = \sqrt{\hat{\theta}_{i-1,2}^{a,v} - (\hat{\theta}_{i-1,1}^{a,v})^2},$$

where n_A denotes the number of treatment arms, and $\Phi(\cdot)$ denotes the CDF of a standard normal distribution. All the four ethics measurements return larger value for the superior treatment arm in terms of additive treatment effect. The efficiency measurement was chosen based on the idea of Neyman allocation. The tuning parameters γ_1 and γ_2 can be assigned to different values to further examine the validity and demonstrate the flexibility. In the Tables, we used $\text{CARA}_k(\gamma_1, \gamma_2)$ to represent the above kth CARA design with tuning parameters γ_1 and γ_2.

We compared four design and analysis combinations: 1) the proposed CARA design with TMLE; 2) the proposed CARA design with t-test (chi-square test for three-treatment scenario); 3) complete randomization (CR) with TMLE; 4) complete randomization with t-test (chi-square test for three treatment). In the simulation, the first 20% of patients were assigned to the treatments with the stratified permuted block (SPB) randomization and the rest patients were allocated using TMLE. In all the scenarios, we pre-specified the significance level at $\alpha = 0.05$, and all the results were based on $10,000$ replications.

Scenario 1: two treatments with binary endpoints

Consider a clinical trial with two treatments with binary endpoints. Suppose we have a covariate vector $\boldsymbol{W} = (W_1, W_2, W_3)$ and a binary subgroup indicator $V(\boldsymbol{W}) = I(W_1 + W_2 + W_3 > 1.6)$, where W_1, W_2, W_3 independently follow uniform distribution in $[0, 1]$

and $I(\cdot)$ is the indicator function. Assume the success rate of the binary endpoint Y is:

$$p = \Phi\left(\beta_0 + \beta_A A + \beta_V V + \beta_{AV} AV + \sum_{p=1}^{3} \beta_{W,p} * W_p\right),$$

where $(\beta_0, \beta_A, \beta_V, \beta_{AV}, \beta_{W,1}, \beta_{W,2}, \beta_{W,3})$ are unknown parameters. Note that the true model of Y is a generalized linear model with a probit link function. In Tables 1.1, 1.2a and 1.2b, we fix $(\beta_0, \beta_V, \beta_{W,1}, \beta_{W,2}, \beta_{W,3}) = (-0.5, -0.1, 0.22, -0.17, -0.1)$ while adjusting the values of (β_A, β_{AV}) to study the Type I error rate, power, and other properties of our design.

In Table 1.1, we reported the Type I error rate with $(\beta_A, \beta_{AV}) = (0, 0)$. When CR is used, the Type I error rate is close to 0.05 for both TMLE and t-test. For all types of CARA designs, the Type I error rate is well-controlled for both TMLE and t-test. In Tables 1.2a and Table 1.2b, power, allocation proportions (ρ_1, ρ_2), bias in estimation of additive treatment effect (ATE) and overall response rate (ORR) are reported. Three different types of data generating distributions were considered: (1) only additive treatment effect exists with $(\beta_A, \beta_{AV}) = (0.32, 0)$; (2) only interaction treatment effect exists with $(\beta_A, \beta_{AV}) = (0, 0.75)$; (3) both interaction treatment effect and additive treatment effect exist with $(\beta_A, \beta_{AV}) = (0.18, 0.30)$. Under CR, TMLE gives higher power than t-test does. Under CARA, when t-test returns higher power than TMLE, we can see that it may be due to the bias in estimation of ATE. Note that TMLE always returns unbiased estimates of ATE. In addition, CARA is able to assign more patients to the superior treatment group than CR.

Table 1.1: Type I error rate (in %) under CR and different CARA designs in clinical trials with two treatment arms and binary endpoints.

Allocation	N	Type I error (%)		N	Type I error (%)	
		TMLE	t-test		TMLE	t-test
CR	400	4.93	4.62	600	5.49	5.25
$CARA_1(0,1)$	400	5.46	5.15	600	5.39	5.12
$CARA_1(1,0)$	400	5.43	5.37	600	5.46	5.23
$CARA_1(1,1)$	400	5.41	5.50	600	5.48	5.71
$CARA_2(0,1)$	400	5.46	5.15	600	5.39	5.12
$CARA_2(1,0)$	400	5.44	5.13	600	5.51	5.22
$CARA_2(1,1)$	400	5.43	5.32	600	5.54	5.39
$CARA_3(0,1)$	400	5.46	5.15	600	5.39	5.12
$CARA_3(1,0)$	400	5.39	5.42	600	5.30	5.41
$CARA_3(1,1)$	400	5.32	5.59	600	5.33	5.60
$CARA_4(0,1)$	400	5.46	5.15	600	5.39	5.12
$CARA_4(1,0)$	400	5.27	4.94	600	5.46	5.10
$CARA_4(1,1)$	400	5.48	5.28	600	5.46	5.19

Table 1.2a: Power (in %), proportion of treatment (in %), bias in estimation of additive treatment effect (ATE) and overall response rate (ORR) (in %) under CR and different CARA procedures in trial with two treatment arms and binary endpoint at sample size $N = 400$.

Allocation	(β_A, β_{AV})	Power (%)		ATE Bias		Trt Prop (%)	ORR (%)
(N=400)		TMLE	t-test	TMLE	Mean		
CR	(0.4, 0)	88.1	87.2	<0.001	<0.001	50.0, 50.0	0.360
$CARA_1(0,1)$	(0.4, 0)	87.3	87.0	<0.001	<0.001	48.2, 51.8	0.363
$CARA_1(1,0)$	(0.4, 0)	86.9	87.0	<0.001	<0.001	42.0, 58.0	0.372
$CARA_1(1,1)$	(0.4, 0)	86.4	87.0	<0.001	0.002	40.4, 59.6	0.374
$CARA_2(0,1)$	(0.4, 0)	87.3	87.0	<0.001	<0.001	48.2, 51.8	0.363
$CARA_2(1,0)$	(0.4, 0)	87.2	86.9	<0.001	<0.001	45.4, 54.6	0.367
$CARA_2(1,1)$	(0.4, 0)	87.0	87.1	<0.001	0.001	43.7, 56.3	0.370
$CARA_3(0,1)$	(0.4, 0)	87.3	87.0	<0.001	<0.001	48.2, 51.8	0.363
$CARA_3(1,0)$	(0.4, 0)	85.7	87.1	<0.001	0.002	38.2, 61.8	0.378
$CARA_3(1,1)$	(0.4, 0)	85.2	87.1	<0.001	0.003	37.0, 63.0	0.379
$CARA_4(0,1)$	(0.4, 0)	87.3	87.0	<0.001	<0.001	48.2, 51.8	0.363
$CARA_4(1,0)$	(0.4, 0)	87.4	86.9	<0.001	<0.001	47.7, 52.3	0.363
$CARA_4(1,1)$	(0.4, 0)	87.6	87.2	<0.001	<0.001	45.9, 54.1	0.366
CR	(0, 0.9)	87.5	86.0	<0.001	<0.001	50.0, 50.0	0.359
$CARA_1(0,1)$	(0, 0.9)	87.0	87.0	<0.001	0.003	49.1, 50.9	0.362

Continued on next page

Table 1.2a – *Continued from previous page*

Allocation (N=400)	(β_A, β_{AV})	Power (%)		ATE Bias		Trt Prop (%)	ORR (%)
		TMLE	t-test	TMLE	Mean		
$CARA_1(1,0)$	(0, 0.9)	85.2	92.4	<0.001	0.018	43.6, 56.4	0.381
$CARA_1(1,1)$	(0, 0.9)	84.5	93.2	<0.001	0.019	43.1, 56.9	0.383
$CARA_2(0,1)$	(0, 0.9)	87.0	87.0	<0.001	0.003	49.1, 50.9	0.362
$CARA_2(1,0)$	(0, 0.9)	86.0	90.7	<0.001	0.013	45.0, 55.0	0.376
$CARA_2(1,1)$	(0, 0.9)	85.6	91.6	<0.001	0.015	44.2, 55.8	0.379
$CARA_3(0,1)$	(0, 0.9)	87.0	87.0	<0.001	0.003	49.1, 50.9	0.362
$CARA_3(1,0)$	(0, 0.9)	82.3	94.6	<0.001	0.023	40.9, 59.1	0.390
$CARA_3(1,1)$	(0, 0.9)	82.1	94.9	<0.001	0.024	41.1, 58.9	0.390
$CARA_4(0,1)$	(0, 0.9)	87.0	87.0	<0.001	0.003	49.1, 50.9	0.362
$CARA_4(1,0)$	(0, 0.9)	86.7	88.3	<0.001	0.006	47.8, 52.2	0.366
$CARA_4(1,1)$	(0, 0.9)	86.4	89.6	<0.001	0.008	46.9, 53.1	0.369
CR	(0.25, 0.35)	87.8	87.3	<0.001	<0.001	50.0, 50.0	0.360
$CARA_1(0,1)$	(0.25, 0.35)	87.1	86.8	<0.001	<0.001	48.3, 51.7	0.363
$CARA_1(1,0)$	(0.25, 0.35)	86.0	87.1	<0.001	0.002	42.2, 57.8	0.373
$CARA_1(1,1)$	(0.25, 0.35)	85.5	87.0	<0.001	0.003	40.8, 59.2	0.376
$CARA_2(0,1)$	(0.25, 0.35)	87.1	86.8	<0.001	<0.001	48.3, 51.7	0.363
$CARA_2(1,0)$	(0.25, 0.35)	86.8	86.9	<0.001	0.001	45.4, 54.6	0.368
$CARA_2(1,1)$	(0.25, 0.35)	86.6	87.1	<0.001	0.001	43.8, 56.2	0.371
$CARA_3(0,1)$	(0.25, 0.35)	87.1	86.8	<0.001	<0.001	48.3, 51.7	0.363

Table 1.2a – *Continued from previous page*

Allocation (N=400)	(β_A, β_{AV})	Power (%)		ATE Bias		Trt Prop (%)	ORR (%)
		TMLE	t-test	TMLE	Mean		
$CARA_3(1,0)$	(0.25, 0.35)	84.4	86.9	<0.001	0.013	38.6, 61.4	0.380
$CARA_3(1,1)$	(0.25, 0.35)	83.8	86.8	<0.001	0.013	37.6, 62.4	0.381
$CARA_4(0,1)$	(0.25, 0.35)	87.1	86.8	<0.001	<0.001	48.3, 51.7	0.363
$CARA_4(1,0)$	(0.25, 0.35)	87.1	86.8	<0.001	<0.001	47.7, 52.3	0.364
$CARA_4(1,1)$	(0.25, 0.35)	83.2	83.3	<0.001	0.001	46.0, 54.0	0.367

Table 1.2b: Power (in %), proportion of treatment (in %), bias in estimation of additive treatment effect (ATE) and overall response rate (ORR) (in %) under CR and different CARA procedures in trial with two treatment arms and binary endpoint at sample size $N = 600$.

Allocation (N=600)	(β_A, β_{AV})	Power (%)		ATE Bias		Trt Prop (%)	ORR (%)
		TMLE	t-test	TMLE	Mean		
CR	(0.32, 0)	85.5	84.8	<0.001	<0.001	50.0, 50.0	0.344
$CARA_1(0,1)$	(0.32, 0)	85.7	85.4	0.001	0.001	48.4, 51.6	0.346
$CARA_1(1,0)$	(0.32, 0)	85.1	85.3	0.001	0.001	43.3, 56.7	0.352
$CARA_1(1,1)$	(0.32, 0)	84.5	85.2	0.001	0.001	41.8, 58.2	0.354
$CARA_2(0,1)$	(0.32, 0)	85.7	85.4	0.001	0.001	48.4, 51.6	0.346
$CARA_2(1,0)$	(0.32, 0)	85.5	85.6	0.001	0.001	46.4, 53.6	0.349

Table 1.2b – *Continued from previous page*

Allocation (N=600)	(β_A, β_{AV})	Power (%)		ATE Bias		Trt Prop (%)	ORR (%)
		TMLE	t-test	TMLE	Mean		
$CARA_2(1,1)$	(0.32, 0)	85.7	85.7	0.001	0.001	44.8, 55.2	0.350
$CARA_3(0,1)$	(0.32, 0)	85.7	85.4	0.001	0.001	48.4, 51.6	0.346
$CARA_3(1,0)$	(0.32, 0)	84.5	85.1	0.001	0.002	40.1, 59.9	0.356
$CARA_3(1,1)$	(0.32, 0)	83.9	85.2	0.001	0.002	38.8, 61.2	0.357
$CARA_4(0,1)$	(0.32, 0)	85.7	85.4	0.001	0.001	48.4, 51.6	0.346
$CARA_4(1,0)$	(0.32, 0)	85.8	85.6	0.001	0.001	48.1, 51.9	0.347
$CARA_4(1,1)$	(0.32, 0)	85.7	85.7	0.001	0.001	46.5, 53.5	0.348
CR	(0, 0.75)	87.9	87.4	0.001	0.001	50.0, 50.0	0.346
$CARA_1(0,1)$	(0, 0.75)	88.6	89.2	0.001	0.003	48.9, 51.1	0.349
$CARA_1(1,0)$	(0, 0.75)	87.7	93.1	0.001	0.013	44.1, 55.9	0.363
$CARA_1(1,1)$	(0, 0.75)	86.8	93.6	0.001	0.014	43.4, 56.7	0.365
$CARA_2(0,1)$	(0, 0.75)	88.6	89.2	0.001	0.003	48.9, 51.1	0.349
$CARA_2(1,0)$	(0, 0.75)	88.3	91.3	0.001	0.009	46.0, 54.0	0.357
$CARA_2(1,1)$	(0, 0.75)	88.1	92.3	0.001	0.011	45.0, 55.0	0.360
$CARA_3(0,1)$	(0, 0.75)	88.6	89.2	0.001	0.003	48.9, 51.1	0.349
$CARA_3(1,0)$	(0, 0.75)	84.9	94.8	0.001	0.017	41.5, 58.6	0.370
$CARA_3(1,1)$	(0, 0.75)	84.3	95.3	0.001	0.018	41.1, 58.9	0.371
$CARA_4(0,1)$	(0, 0.75)	88.6	89.2	0.001	0.003	48.9, 51.1	0.349
$CARA_4(1,0)$	(0, 0.75)	88.6	89.9	0.001	0.005	48.1, 51.9	0.351

Table 1.2b – *Continued from previous page*

Allocation (N=600)	(β_A, β_{AV})	Power (%)		ATE Bias		Trt Prop (%)	ORR (%)
		TMLE	t-test	TMLE	Mean		
$CARA_4(1,1)$	(0, 0.75)	88.5	90.8	0.001	0.007	47.1, 52.9	0.354
CR	(0.18, 0.30)	83.2	82.7	<0.001	<0.001	50.0, 50.0	0.342
$CARA_1(0,1)$	(0.18, 0.30)	83.1	82.9	<0.001	<0.001	48.4, 51.6	0.344
$CARA_1(1,0)$	(0.18, 0.30)	82.5	83.2	<0.001	0.002	43.6, 56.4	0.351
$CARA_1(1,1)$	(0.18, 0.30)	81.8	83.3	<0.001	0.002	42.2, 57.8	0.353
$CARA_2(0,1)$	(0.18, 0.30)	83.1	82.9	<0.001	<0.001	48.4, 51.6	0.344
$CARA_2(1,0)$	(0.18, 0.30)	83.1	83.0	<0.001	0.001	46.6, 53.4	0.347
$CARA_2(1,1)$	(0.18, 0.30)	83.0	83.2	<0.001	0.011	45.0, 55.0	0.349
$CARA_3(0,1)$	(0.18, 0.30)	83.1	82.9	<0.001	<0.001	48.4, 51.6	0.344
$CARA_3(1,0)$	(0.18, 0.30)	81.4	83.3	<0.001	0.002	40.7, 59.3	0.355
$CARA_3(1,1)$	(0.18, 0.30)	80.4	83.1	<0.001	0.002	39.6, 60.4	0.356
$CARA_4(0,1)$	(0.18, 0.30)	83.1	82.9	<0.001	<0.001	48.4, 51.6	0.344
$CARA_4(1,0)$	(0.18, 0.30)	83.4	89.9	0.001	0.001	48.2, 51.8	0.345
$CARA_4(1,1)$	(0.18, 0.30)	83.2	83.3	0.001	0.001	46.7, 53.3	0.347

Scenario 2: three treatments with binary endpoint

Consider a clinical trial with three treatments with binary endpoints. Suppose that the covariate vector $\boldsymbol{W} = (W_1, W_2, W_3)$ and the binary subgroup indicator $V(\boldsymbol{W})$ are

generated in the same manner as in Scenario 1. Assume the success rate of the binary endpoint Y is

$$p = \Phi \left(\beta_{A1} I(A = 1) + \beta_{A2} I(A = 2) + \beta_V V + \beta_{AV} AV + \sum_{p=1}^{3} \beta_{W,p} * W_p \right),$$

where $(\beta_{A1}, \beta_{A2}, \beta_V, \beta_{AV}, \beta_{W,1}, \beta_{W,2}, \beta_{W,3})$ are unknown parameters. In Tables 2.1, 2.2a and 2.2b, we fix the parameter values of $(\beta_V, \beta_{W,1}, \beta_{W,2}, \beta_{W,3}) = (0.2, 0.22, -0.17, -0.1)$ while adjusting the values of $(\beta_{A1}, \beta_{A2}, \beta_{AV})$ to study the Type I error rate, power, and other properties of our design.

In Table 2.1, we reported the Type I error rate with $(\beta_A, \beta_{AV}) = (0, 0)$. Both TMLE and chi-square test lead to well-controlled type I error rate when implementing either CARA or CR. We also reported the operating characteristics of our design under H_1 in Tables 2.2a and Table 2.2b. When CR is implemented, TMLE gives higher power than chi-square test does. When CARA is implemented, chi-square test renders power inflation and large bias in ATE estimation, which makes TMLE a more reliable analysis method than chi-square test. In addition, CARA slightly leads CR when comparing the power. In terms of treatment allocation proportion, CARA is able to assign more patients to the superior treatment group and results in a better overall response rate, especially when the choice of γ_1 and γ_2 aims to emphasize the ethics properties. Unlike the power trade-off in scenario 1, the power is at the same level or better than CR even when the differences in treatment allocation proportion are large, e.g. $CARA_3(1, 0)$.

Table 2.1: Type I error rate (in %) under CR and different CARA procedures in trial with three treatment arms and binary endpoint.

Allocation	N	Type I error (%)		N	Type I error (%)	
		TMLE	chi-sq		TMLE	chi-sq
CR	600	5.80	5.44	800	5.58	5.21
$CARA_1(0,1)$	600	5.78	5.11	800	5.58	5.13
$CARA_1(1,0)$	600	5.66	5.25	800	5.66	5.54
$CARA_1(1,1)$	600	5.67	5.32	800	5.66	5.41
$CARA_2(0,1)$	600	5.78	5.11	800	5.58	5.13
$CARA_2(1,0)$	600	5.43	5.37	800	5.76	5.63
$CARA_2(1,1)$	600	5.75	5.57	800	5.65	5.49
$CARA_3(0,1)$	600	5.78	5.11	800	5.58	5.13
$CARA_3(1,0)$	600	5.59	5.66	800	5.41	5.63
$CARA_3(1,1)$	600	5.40	5.38	800	5.45	5.59
$CARA_4(0,1)$	600	5.78	5.11	800	5.58	5.13
$CARA_4(1,0)$	600	5.78	5.39	800	5.54	5.21
$CARA_4(1,1)$	600	5.83	5.34	800	5.47	5.01

Table 2.2a: Power (in %), proportion of treatment (in %), bias in estimation of additive treatment effect (ATE) and overall response rate (ORR) (in %) under CR and different CARA procedures in trial with three treatment arms and binary endpoint at sample size $N = 600$.

Allocation (N=600)	(β_A, β_{AV})	Power (%) TMLE	t-test	ATE Bias TMLE	Mean	Trt Prop (%)	ORR (%)
CR	(0.25,0.20)	86.4	84.6	(<0.001, <0.001)	(0.001, 0.001)	33.3, 33.3, 33.3	0.585
$CARA_1(0,1)$	(0.25,0.20)	86.4	82.3	(<0.001, <0.001)	(0.001, 0.005)	34.3, 33.9, 31.8	0.583
$CARA_1(1,0)$	(0.25,0.20)	87.4	88.5	(<0.001, <0.001)	(0.002, 0.004)	30.7, 32.0, 37.3	0.592
$CARA_1(1,1)$	(0.25,0.20)	87.5	85.8	(<0.001, <0.001)	(0.003, <0.001)	31.6, 32.7, 35.7	0.589
$CARA_2(0,1)$	(0.25,0.20)	86.4	82.3	(<0.001, <0.001)	(0.001, 0.005)	34.3, 33.9, 31.8	0.583
$CARA_2(1,0)$	(0.25,0.20)	87.6	92.1	(<0.001, <0.001)	(0.001, 0.013)	28.9, 30.6, 40.6	0.598
$CARA_2(1,1)$	(0.25,0.20)	87.6	90.4	(<0.001, <0.001)	(0.002, 0.009)	29.7, 31.3, 39.0	0.595
$CARA_3(0,1)$	(0.25,0.20)	86.4	82.3	(<0.001, <0.001)	(0.001, 0.005)	34.3, 33.9, 31.8	0.583
$CARA_3(1,0)$	(0.25,0.20)	87.1	92.8	(<0.001, <0.001)	(0.002, 0.016)	26.8, 28.9, 44.2	0.603
$CARA_3(1,1)$	(0.25,0.20)	87.1	92.0	(<0.001, <0.001)	(0.003, 0.013)	27.5, 29.7, 42.9	0.601
$CARA_4(0,1)$	(0.25,0.20)	86.4	82.3	(<0.001, <0.001)	(0.001, 0.005)	34.3, 33.9, 31.8	0.583
$CARA_4(1,0)$	(0.25,0.20)	87.4	87.2	(<0.001, <0.001)	(0.001, 0.003)	32.0, 32.7, 35.2	0.589
$CARA_4(1,1)$	(0.25,0.20)	87.3	84.4	(<0.001, <0.001)	(0.001, 0.002)	33.0, 33.4, 33.6	0.586

Table 2.2b: Power (in %), proportion of treatment (in %), bias in estimation of additive treatment effect (ATE) and overall response rate (ORR) (in %) under CR and different CARA procedures in trial with three treatment arms and binary endpoint at sample size $N = 800$.

Allocation (N=800)	(β_A, β_{AV})	Power (%)		ATE Bias		Trt Prop (%)	ORR (%)
		TMLE	t-test	TMLE	Mean		
CR	(0.22,0.17)	87.7	86.6	(<0.001, <0.001)	(0.001, 0.001)	33.3, 33.3, 33.3	0.578
$CARA_1(0,1)$	(0.22,0.17)	87.4	84.4	(<0.001, <0.001)	(<0.001, 0.004)	34.1, 33.8, 32.1	0.576
$CARA_1(1,0)$	(0.22,0.17)	88.1	89.3	(<0.001, <0.001)	(0.002, 0.004)	30.9, 32.1, 37.0	0.583
$CARA_1(1,1)$	(0.22,0.17)	87.9	87.5	(<0.001, <0.001)	(0.002, <0.001)	31.7, 32.6, 35.7	0.581
$CARA_2(0,1)$	(0.22,0.17)	87.4	84.4	(<0.001, <0.001)	(<0.001, 0.004)	34.1, 33.8, 32.1	0.576
$CARA_2(1,0)$	(0.22,0.17)	88.1	91.2	(<0.001, <0.001)	(0.001, 0.011)	29.5, 31.0, 39.5	0.587
$CARA_2(1,1)$	(0.22,0.17)	88.3	90.7	(<0.001, <0.001)	(0.002, 0.007)	30.2, 31.5, 38.2	0.585
$CARA_3(0,1)$	(0.22,0.17)	87.4	84.4	(<0.001, <0.001)	(<0.001, 0.004)	34.1, 33.8, 32.1	0.576
$CARA_3(1,0)$	(0.22,0.17)	87.7	93.0	(<0.001, <0.001)	(0.002, 0.013)	27.4, 29.5, 43.0	0.592
$CARA_3(1,1)$	(0.22,0.17)	87.9	92.0	(<0.001, <0.001)	(0.003, 0.010)	28.0, 30.1, 41.9	0.590
$CARA_4(0,1)$	(0.22,0.17)	87.4	84.4	(<0.001, <0.001)	(<0.001, 0.004)	34.1, 33.8, 32.1	0.576
$CARA_4(1,0)$	(0.22,0.17)	88.0	88.2	(<0.001, <0.001)	(0.001, 0.002)	32.2, 32.8, 35.0	0.580
$CARA_4(1,1)$	(0.22,0.17)	87.8	86.0	(<0.001, <0.001)	(0.001, 0.001)	32.9, 33.3, 33.8	0.578

Scenario 3: Two treatments with continuous endpoint

Consider a clinical trial with two arms and bounded continuous endpoint $Y \in \mathbb{R}$. Suppose that the covariate vector $\boldsymbol{W} = (W_1, W_2, W_3)$ and the binary subgroup indicator $V(\boldsymbol{W})$ are generated in the same manner. In order to study the robustness of the CARA, we proposed the following two models to generate the endpoint Y:

$$\text{M1:} \quad \mu = \mu_0 + (1 + \beta_A A) \left(1 + \beta_V V + \sum_{p=1}^{3} \beta_{W,p} * W_p \right),$$

$$\sigma = \frac{1 + \beta_A A}{1 + \beta_V V},$$

$$Y \sim \mathrm{N}(\mu, \sigma^2), Y \text{ is truncated if } Y < 0 \text{ or } Y > 12.$$

$$\text{M2:} \quad a = 1 + (1 + \beta_A A)(1 + \beta_V V) + \sum_{p=1}^{3} \beta_{W,p} * W_p,$$

$$b = \frac{1 + \beta_A A}{1 + \beta_V V},$$

$$Y \sim \mathrm{Gamma}(a, b), Y \text{ is truncated if } Y > 10.$$

For a given A and V, M1 generates a symmetric distribution of Y while M2 generates a skewed distribution of Y. The complexity in the models acknowledges not only the treatment effect and the difference between subgroups but also their interaction effect and within group heterogeneity due to unmeasured factors. We fixed the parameter values $\beta_V = 0.2, \beta_{W,1} = -2.2, \beta_{W,2} = 0.8, \beta_{W,3} = -1.7$ in model M1 and $\beta_V = -0.2, \beta_{W,1} = 0.73, \beta_{W,2} = -1.2, \beta_{W,3} = 0.56$ in model M2. The change of values of β_A was used to study the properties of the proposed CARA design.

In Table 3.1a and Table 3.1b, we reported the Type I error rate for sample size $n = 400$

and $n = 600$ respectively. In both model M1 and model M2, TMLE demonstrates well-controlled type I error rate under both CR and all types of CARA designs. However, when t-test is conducted the type I error rate is controlled in CR but inflated in most CARA designs especially for $\gamma_2 = 2$.

We reported the operating characteristics of our design under H_1 in Table 3.2a and Table 3.2b. TMLE dominates t-test in power under CR and all types of CARA designs. In addition, the estimation bias in TMLE is smaller and more stable compared to t-test, which makes TMLE a more reliable analysis method. When comparing CARA and CR with respect to treatment allocation, CARA is able to assign more than 20% patients to the treatment arm while still holds the same power or even a higher power in model M1. In model M2, CARA can still assign more patients to the treatment arm and retain a good power. However, the power of CARA drops when there is a significant difference in allocation proportion. In this case, we achieved ethics advantages by sacrificing the efficiency properties. In practice, the choice of the designs including the values of γ_1 and γ_2 depends on the practical need and more numerical studies.

Table 3.1a: Type I error rate (in %) under CR and different CARA procedures in trial with two treatment arms and continuous endpoint at sample size $N = 400$.

Allocation (N=400)	Model	Type I error (%) TMLE	t-test	Model	Type I error (%) TMLE	t-test
CR	M1	5.29	5.11	M2	5.35	5.49
$CARA_1(0,1)$	M1	5.36	6.04	M2	5.11	5.17
$CARA_1(0,2)$	M1	5.34	9.47	M2	5.58	6.68
$CARA_1(0.5,0)$	M1	5.42	4.81	M2	5.11	4.95
$CARA_1(0.5,1)$	M1	5.42	5.86	M2	5.12	5.60
$CARA_1(0.5,2)$	M1	5.36	9.12	M2	6.03	6.95
$CARA_1(1,0)$	M1	5.21	4.67	M2	5.06	5.22
$CARA_1(1,1)$	M1	5.50	5.83	M2	5.39	6.04
$CARA_1(1,2)$	M1	5.53	8.81	M2	6.47	7.88
$CARA_2(0,1)$	M1	5.36	6.04	M2	5.11	5.17
$CARA_2(0,2)$	M1	5.34	9.47	M2	5.58	6.68
$CARA_2(0.5,0)$	M1	5.36	4.90	M2	5.08	4.93
$CARA_2(0.5,1)$	M1	5.35	5.93	M2	5.11	5.38
$CARA_2(0.5,2)$	M1	5.42	9.21	M2	5.79	6.96
$CARA_2(1,0)$	M1	5.26	4.74	M2	5.10	4.83

Table 3.1a – *Continued from previous page*

Allocation (N=400)	Model	Type I error (%)		Model	Type I error (%)	
		TMLE	t-test		TMLE	t-test
$CARA_2(1,1)$	M1	5.49	5.94	M2	5.16	5.49
$CARA_2(1,2)$	M1	5.40	9.14	M2	5.81	6.77
$CARA_3(0,1)$	M1	5.36	6.04	M2	5.11	5.17
$CARA_3(0,2)$	M1	5.34	9.47	M2	5.58	6.68
$CARA_3(0.5,0)$	M1	5.14	4.71	M2	5.05	5.08
$CARA_3(0.5,1)$	M1	5.48	5.90	M2	5.39	5.82
$CARA_3(0.5,2)$	M1	5.41	8.85	M2	6.15	7.13
$CARA_3(1,0)$	M1	5.15	4.56	M2	5.37	5.27
$CARA_3(1,1)$	M1	5.29	5.71	M2	5.36	6.24
$CARA_3(1,2)$	M1	5.50	8.75	M2	7.19	8.42
$CARA_4(0,1)$	M1	5.36	6.04	M2	5.11	5.17
$CARA_4(0,2)$	M1	5.34	9.47	M2	5.58	6.68
$CARA_4(0.5,0)$	M1	5.28	4.98	M2	5.16	4.81
$CARA_4(0.5,1)$	M1	5.35	6.01	M2	4.99	5.21
$CARA_4(0.5,2)$	M1	5.32	9.36	M2	5.68	6.72
$CARA_4(1,0)$	M1	5.27	4.92	M2	5.04	4.97
$CARA_4(1,1)$	M1	5.38	6.02	M2	5.09	5.46

Table 3.1a – *Continued from previous page*

Allocation (N=400)	Model	Type I error (%) TMLE	t-test	Model	Type I error (%) TMLE	t-test
$CARA_4(1,2)$	M1	5.52	9.31	M2	5.85	6.93

Table 3.1b: Type I error rate (in %) under CR and different CARA procedures in trial with two treatment arms and continuous endpoint at sample size $N = 600$.

Allocation (N=600)	Model	Type I error (%) TMLE	t-test	Model	Type I error (%) TMLE	t-test
CR	M1	5.33	4.97	M2	5.26	4.91
$CARA_1(0,1)$	M1	5.15	5.79	M2	5.59	5.71
$CARA_1(0,2)$	M1	5.01	8.45	M2	5.52	6.68
$CARA_1(0.5,0)$	M1	5.07	4.70	M2	5.07	5.18
$CARA_1(0.5,1)$	M1	5.19	5.50	M2	5.61	6.05
$CARA_1(0.5,2)$	M1	5.00	8.36	M2	5.54	7.02
$CARA_1(1,0)$	M1	5.02	4.48	M2	5.56	5.60
$CARA_1(1,1)$	M1	5.13	5.12	M2	5.26	6.21
$CARA_1(1,2)$	M1	5.20	8.20	M2	5.69	7.36

Table 3.1b – *Continued from previous page*

Allocation (N=600)	Model	Type I error (%)		Model	Type I error (%)	
		TMLE	t-test		TMLE	t-test
$CARA_2(0,1)$	M1	5.15	5.79	M2	5.59	5.71
$CARA_2(0,2)$	M1	5.01	8.45	M2	5.52	6.68
$CARA_2(0.5,0)$	M1	5.19	4.80	M2	5.38	5.13
$CARA_2(0.5,1)$	M1	5.18	5.65	M2	5.59	5.72
$CARA_2(0.5,2)$	M1	5.09	8.45	M2	5.41	6.78
$CARA_2(1,0)$	M1	5.02	4.79	M2	5.07	5.10
$CARA_2(1,1)$	M1	5.25	5.47	M2	5.63	5.85
$CARA_2(1,2)$	M1	5.26	8.57	M2	5.55	6.72
$CARA_3(0,1)$	M1	5.15	5.79	M2	5.59	5.71
$CARA_3(0,2)$	M1	5.01	8.45	M2	5.52	6.68
$CARA_3(0.5,0)$	M1	5.08	4.70	M2	5.26	5.23
$CARA_3(0.5,1)$	M1	5.20	5.36	M2	5.52	6.08
$CARA_3(0.5,2)$	M1	5.21	8.35	M2	5.56	7.14
$CARA_3(1,0)$	M1	5.12	4.73	M2	5.27	5.52
$CARA_3(1,1)$	M1	5.26	5.34	M2	5.36	6.24
$CARA_3(1,2)$	M1	5.26	8.09	M2	5.84	7.78
$CARA_4(0,1)$	M1	5.15	5.79	M2	5.59	5.71

Table 3.1b – *Continued from previous page*

Allocation (N=600)	Model	Type I error (%) TMLE	t-test	Model	Type I error (%) TMLE	t-test
$CARA_4(0,2)$	M1	5.01	8.45	M2	5.52	6.68
$CARA_4(0.5,0)$	M1	5.22	4.90	M2	5.23	5.05
$CARA_4(0.5,1)$	M1	5.18	5.68	M2	5.62	5.79
$CARA_4(0.5,2)$	M1	5.12	8.52	M2	5.40	6.66
$CARA_4(1,0)$	M1	5.13	4.73	M2	5.22	5.11
$CARA_4(1,1)$	M1	5.25	5.64	M2	5.60	5.83
$CARA_4(1,2)$	M1	5.12	8.41	M2	5.47	6.70

Table 3.2a: Power (in %), proportion of treatment (in %), bias in estimation of additive treatment effect (ATE) under CR and different CARA procedures in trial with two treatment arms and continuous endpoint at sample size $N = 400$.

Allocation (N=400)	Model (β_A)	Power (%) TMLE	t-test	ATE Bias (SE) TMLE	Mean	Trt Prop (%)
CR	M1 (0.55)	86.2	78.8	0.001 (0.0016)	0.002 (0.0017)	50.0, 50.0
$CARA_1(0,1)$	M1 (0.55)	87.4	78.3	0.001 (0.0016)	0.008 (0.0017)	41.7, 58.3
$CARA_1(0,2)$	M1 (0.55)	85.2	73.9	0.001 (0.0016)	0.018 (0.0018)	33.7, 66.3

Table 3.2a – *Continued from previous page*

Allocation (N=400)	Model (β_A)	Power (%) TMLE	Power (%) t-test	ATE Bias (SE) TMLE	ATE Bias (SE) Mean	Trt Prop (%)
$CARA_1(0.5,0)$	M1 (0.55)	86.8	79.5	0.001 (0.0016)	0.002 (0.0017)	49.1, 50.9
$CARA_1(0.5,1)$	M1 (0.55)	87.4	79.0	0.001 (0.0016)	0.006 (0.0017)	40.8, 59.2
$CARA_1(0.5,2)$	M1 (0.55)	84.9	74.3	0.001 (0.0016)	0.015 (0.0018)	32.9, 67.1
$CARA_1(1,0)$	M1 (0.55)	87.0	80.0	0.001 (0.0016)	0.003 (0.0017)	48.2, 51.8
$CARA_1(1,1)$	M1 (0.55)	87.3	79.5	0.001 (0.0016)	0.005 (0.0017)	39.9, 60.1
$CARA_1(1,2)$	M1 (0.55)	84.7	74.6	0.001 (0.0016)	0.014 (0.0018)	32.2, 67.8
$CARA_2(0.5,0)$	M1 (0.55)	86.7	79.6	0.001 (0.0016)	0.005 (0.0017)	49.0, 51.0
$CARA_2(0.5,1)$	M1 (0.55)	87.4	79.3	0.001 (0.0016)	0.004 (0.0017)	40.7, 59.3
$CARA_2(0.5,2)$	M1 (0.55)	85.0	74.6	0.001 (0.0016)	0.013 (0.0019)	32.9, 67.1
$CARA_2(1,0)$	M1 (0.55)	87.1	80.6	0.001 (0.0016)	0.008 (0.0017)	48.1, 51.9
$CARA_2(1,1)$	M1 (0.55)	87.2	80.2	0.001 (0.0016)	0.001 (0.0017)	39.8, 60.2
$CARA_2(1,2)$	M1 (0.55)	84.6	75.3	0.001 (0.0016)	0.008 (0.0017)	32.1, 67.9
$CARA_3(0.5,0)$	M1 (0.55)	87.1	80.3	0.001 (0.0016)	0.005 (0.0017)	48.2, 51.8
$CARA_3(0.5,1)$	M1 (0.55)	87.3	79.9	0.001 (0.0016)	0.003 (0.0017)	39.9, 60.1
$CARA_3(0.5,2)$	M1 (0.55)	84.8	74.9	0.001 (0.0016)	0.011 (0.0019)	32.2, 67.8
$CARA_3(1,0)$	M1 (0.55)	87.0	82.0	0.001 (0.0016)	0.011 (0.0017)	46.4, 53.6
$CARA_3(1,1)$	M1 (0.55)	87.5	80.3	0.001 (0.0016)	0.003 (0.0017)	38.2, 61.8
$CARA_3(1,2)$	M1 (0.55)	83.7	75.9	0.001 (0.0016)	0.004 (0.0019)	30.7, 69.3
$CARA_4(0.5,0)$	M1 (0.55)	86.6	79.0	0.001 (0.0016)	0.002 (0.0017)	49.6, 50.4

Table 3.2a – *Continued from previous page*

Allocation	Model (β_A)	Power (%)		ATE Bias (SE)		Trt Prop (%)
(N=400)		TMLE	t-test	TMLE	Mean	
$CARA_4(0.5,1)$	M1 (0.55)	87.5	78.8	0.001 (0.0016)	0.007 (0.0017)	41.3, 58.7
$CARA_4(0.5,2)$	M1 (0.55)	85.3	74.4	0.001 (0.0016)	0.016 (0.0018)	33.4, 66.6
$CARA_4(1,0)$	M1 (0.55)	86.7	79.3	0.001 (0.0016)	0.003 (0.0017)	49.3, 50.7
$CARA_4(1,1)$	M1 (0.55)	87.4	79.0	0.001 (0.0016)	0.006 (0.0017)	41.0, 59.0
$CARA_4(1,2)$	M1 (0.55)	85.1	74.4	0.001 (0.0016)	0.015 (0.0018)	33.1, 66.9
CR	M2 (0.16)	87.7	84.0	0.001 (0.0017)	0.001 (0.0018)	50.0, 50.0
$CARA_1(0,1)$	M2 (0.16)	87.2	83.7	0.001 (0.0017)	0.002 (0.0018)	46.1, 53.9
$CARA_1(0,2)$	M2 (0.16)	84.1	83.1	0.001 (0.0018)	0.004 (0.0018)	42.2, 57.8
$CARA_1(0.5,0)$	M2 (0.16)	88.1	84.4	0.001 (0.0017)	0.001 (0.0018)	47.5, 52.5
$CARA_1(0.5,1)$	M2 (0.16)	87.0	83.8	0.001 (0.0017)	0.003 (0.0018)	43.6, 56.4
$CARA_1(0.5,2)$	M2 (0.16)	82.4	82.6	0.001 (0.0019)	0.005 (0.0019)	39.9, 60.1
$CARA_1(1,0)$	M2 (0.16)	87.7	84.0	0.001 (0.0017)	0.001 (0.0018)	45.1, 54.9
$CARA_1(1,1)$	M2 (0.16)	85.8	83.0	0.001 (0.0017)	0.003 (0.0018)	41.3, 58.7
$CARA_1(1,2)$	M2 (0.16)	80.1	81.6	0.004 (0.0021)	0.009 (0.0019)	37.6, 62.4
$CARA_2(0.5,0)$	M2 (0.16)	87.7	84.0	0.001 (0.0017)	0.001 (0.0018)	49.2, 50.8
$CARA_2(0.5,1)$	M2 (0.16)	87.2	83.9	0.001 (0.0017)	0.002 (0.0018)	45.3, 54.7
$CARA_2(0.5,2)$	M2 (0.16)	83.7	83.0	0.001 (0.0018)	0.005 (0.0018)	41.5, 58.5
$CARA_2(1,0)$	M2 (0.16)	87.9	84.2	0.001 (0.0017)	0.002 (0.0018)	48.4, 51.6
$CARA_2(1,1)$	M2 (0.16)	87.0	83.9	0.001 (0.0017)	0.003 (0.0018)	44.5, 55.5

Table 3.2a – *Continued from previous page*

Allocation (N=400)	Model (β_A)	Power (%)		ATE Bias (SE)		Trt Prop (%)
		TMLE	t-test	TMLE	Mean	
$CARA_2(1,2)$	M2 (0.16)	83.1	82.8	0.001 (0.0018)	0.005 (0.0019)	40.7, 59.3
$CARA_3(0.5,0)$	M2 (0.16)	87.6	83.9	0.001 (0.0017)	0.001 (0.0018)	46.8, 53.2
$CARA_3(0.5,1)$	M2 (0.16)	86.6	83.9	0.001 (0.0017)	0.003 (0.0018)	42.9, 57.1
$CARA_3(0.5,2)$	M2 (0.16)	81.8	82.4	0.002 (0.0019)	0.006 (0.0019)	39.2, 60.8
$CARA_3(1,0)$	M2 (0.16)	87.4	83.8	0.001 (0.0017)	0.002 (0.0018)	43.6, 56.4
$CARA_3(1,1)$	M2 (0.16)	84.6	82.6	0.001 (0.0018)	0.005 (0.0018)	39.9, 60.1
$CARA_3(1,2)$	M2 (0.16)	78.1	80.9	0.008 (0.0022)	0.012 (0.0020)	36.3, 63.7
$CARA_4(0.5,0)$	M2 (0.16)	87.7	84.0	0.001 (0.0017)	0.002 (0.0018)	49.5, 50.5
$CARA_4(0.5,1)$	M2 (0.16)	87.4	83.8	0.001 (0.0017)	0.002 (0.0018)	45.6, 54.4
$CARA_4(0.5,2)$	M2 (0.16)	83.8	83.1	0.001 (0.0018)	0.004 (0.0018)	41.7, 58.3
$CARA_4(1,0)$	M2 (0.16)	87.6	83.9	0.001 (0.0017)	0.001 (0.0018)	49.0, 51.0
$CARA_4(1,1)$	M2 (0.16)	87.2	83.9	0.001 (0.0017)	0.002 (0.0018)	45.1, 54.9
$CARA_4(1,2)$	M2 (0.16)	83.5	82.9	0.001 (0.0018)	0.005 (0.0019)	41.3, 58.7

Table 3.2b: Power (in %), proportion of treatment (in %), bias in estimation of additive treatment effect (ATE) under CR and different CARA procedures in trial with two treatment arms and continuous endpoint at sample size $N = 600$.

Allocation (N=600)	Model (β_A)	Power (%) TMLE	t-test	ATE Bias (SE) TMLE	Mean	Trt Prop (%)
CR	M1 (0.43)	86.9	79.3	0.001 (0.0012)	0.001 (0.0014)	50.0, 50.0
$CARA_1(0,1)$	M1 (0.43)	87.4	78.3	0.001 (0.0012)	0.006 (0.0013)	43.3, 56.7
$CARA_1(0,2)$	M1 (0.43)	86.9	74.4	0.001 (0.0012)	0.006 (0.0014)	36.8, 63.2
$CARA_1(0.5,0)$	M1 (0.43)	87.0	80.1	0.002 (0.0012)	0.002 (0.0013)	49.3, 50.7
$CARA_1(0.5,1)$	M1 (0.43)	87.8	78.9	0.001 (0.0012)	0.006 (0.0013)	42.6, 57.4
$CARA_1(0.5,2)$	M1 (0.43)	86.7	74.8	0.001 (0.0012)	0.007 (0.0014)	36.2, 63.8
$CARA_1(1,0)$	M1 (0.43)	87.4	81.1	0.002 (0.0012)	0.004 (0.0013)	48.6, 51.4
$CARA_1(1,1)$	M1 (0.43)	87.9	79.7	0.001 (0.0012)	0.004 (0.0013)	41.9, 58.1
$CARA_1(1,2)$	M1 (0.43)	86.7	75.4	0.001 (0.0012)	0.011 (0.0014)	35.5, 64.5
$CARA_2(0.5,0)$	M1 (0.43)	87.0	80.4	0.001 (0.0012)	0.004 (0.0013)	49.3, 50.7
$CARA_2(0.5,1)$	M1 (0.43)	87.7	79.2	0.001 (0.0012)	0.004 (0.0013)	42.5, 57.5
$CARA_2(0.5,2)$	M1 (0.43)	86.9	75.2	0.001 (0.0012)	0.010 (0.0014)	36.2, 63.8
$CARA_2(1,0)$	M1 (0.43)	87.2	81.6	0.002 (0.0012)	0.007 (0.0013)	48.5, 51.5
$CARA_2(1,1)$	M1 (0.43)	88.0	80.2	0.001 (0.0012)	0.001 (0.0013)	41.8, 58.2
$CARA_2(1,2)$	M1 (0.43)	86.6	75.9	0.001 (0.0012)	0.008 (0.0014)	35.5, 64.5

Table 3.2b – *Continued from previous page*

Allocation (N=600)	Model (β_A)	Power (%) TMLE	Power (%) t-test	ATE Bias (SE) TMLE	ATE Bias (SE) Mean	Trt Prop (%)
$CARA_3(0.5,0)$	M1 (0.43)	87.2	81.2	0.002 (0.0012)	0.005 (0.0013)	48.6, 51.4
$CARA_3(0.5,1)$	M1 (0.43)	88.0	80.0	0.001 (0.0012)	0.008 (0.0013)	41.9, 58.1
$CARA_3(0.5,2)$	M1 (0.43)	86.7	75.6	0.001 (0.0012)	0.009 (0.0014)	35.5, 64.5
$CARA_3(1,0)$	M1 (0.43)	87.5	82.9	0.001 (0.0012)	0.009 (0.0013)	47.1, 52.9
$CARA_3(1,1)$	M1 (0.43)	88.0	80.8	0.001 (0.0012)	0.002 (0.0013)	40.5, 59.5
$CARA_3(1,2)$	M1 (0.43)	86.2	76.7	0.001 (0.0012)	0.006 (0.0014)	34.3, 65.7
$CARA_4(0.5,0)$	M1 (0.43)	87.0	79.7	0.001 (0.0012)	0.002 (0.0013)	49.7, 50.3
$CARA_4(0.5,1)$	M1 (0.43)	88.0	78.9	0.001 (0.0012)	0.006 (0.0013)	43.0, 57.0
$CARA_4(0.5,2)$	M1 (0.43)	87.0	74.8	0.001 (0.0012)	0.012 (0.0014)	63.6, 63.4
$CARA_4(1,0)$	M1 (0.43)	87.1	80.1	0.001 (0.0012)	0.003 (0.0013)	49.4, 50.6
$CARA_4(1,1)$	M1 (0.43)	87.8	79.0	0.001 (0.0012)	0.005 (0.0013)	42.7, 57.3
$CARA_4(1,2)$	M1 (0.43)	87.0	75.1	0.001 (0.0012)	0.012 (0.0014)	36.3, 63.7
CR	M2 (0.13)	88.1	84.2	0.001 (0.0014)	0.001 (0.0014)	50.0, 50.0
$CARA_1(0,1)$	M2 (0.13)	87.3	84.0	0.001 (0.0014)	0.002 (0.0014)	46.8, 53.2
$CARA_1(0,2)$	M2 (0.13)	86.0	83.3	0.002 (0.0014)	0.002 (0.0015)	43.6, 56.4
$CARA_1(0.5,0)$	M2 (0.13)	87.5	83.8	0.001 (0.0014)	0.002 (0.0014)	47.9, 52.1
$CARA_1(0.5,1)$	M2 (0.13)	87.2	83.7	0.001 (0.0014)	0.002 (0.0014)	44.8, 55.2
$CARA_1(0.5,2)$	M2 (0.13)	85.3	82.8	0.001 (0.0014)	0.001 (0.0015)	41.7, 58.3
$CARA_1(1,0)$	M2 (0.13)	87.5	83.8	0.001 (0.0014)	0.002 (0.0014)	45.9, 54.1

Table 3.2b – *Continued from previous page*

Allocation (N=600)	Model (β_A)	Power (%)		ATE Bias (SE)		Trt Prop (%)
		TMLE	t-test	TMLE	Mean	
$CARA_1(1,1)$	M2 (0.13)	86.6	83.5	0.001 (0.0014)	0.001 (0.0015)	42.8, 57.2
$CARA_1(1,2)$	M2 (0.13)	84.2	82.4	0.001 (0.0015)	0.002 (0.0015)	39.8, 60.2
$CARA_2(0.5,0)$	M2 (0.13)	87.3	83.9	0.001 (0.0014)	0.001 (0.0014)	49.3, 50.7
$CARA_2(0.5,1)$	M2 (0.13)	87.3	84.0	0.001 (0.0014)	0.001 (0.0014)	46.1, 53.9
$CARA_2(0.5,2)$	M2 (0.13)	86.2	83.3	0.002 (0.0014)	0.001 (0.0014)	43.0, 57.0
$CARA_2(1,0)$	M2 (0.13)	87.3	83.8	0.001 (0.0014)	0.002 (0.0014)	48.7, 51.3
$CARA_2(1,1)$	M2 (0.13)	87.3	83.8	0.001 (0.0014)	0.002 (0.0014)	45.5, 54.5
$CARA_2(1,2)$	M2 (0.13)	85.9	83.2	0.002 (0.0014)	0.005 (0.0015)	42.4, 57.6
$CARA_3(0.5,0)$	M2 (0.13)	87.8	84.0	0.001 (0.0014)	0.002 (0.0014)	47.3, 52.8
$CARA_3(0.5,1)$	M2 (0.13)	87.0	83.7	0.001 (0.0014)	0.002 (0.0014)	44.1, 55.9
$CARA_3(0.5,2)$	M2 (0.13)	85.3	82.9	0.001 (0.0014)	0.002 (0.0015)	41.1, 58.9
$CARA_3(1,0)$	M2 (0.13)	87.4	83.6	0.001 (0.0014)	0.001 (0.0014)	44.7, 55.3
$CARA_3(1,1)$	M2 (0.13)	86.4	83.4	0.001 (0.0014)	0.001 (0.0015)	41.6, 58.4
$CARA_3(1,2)$	M2 (0.13)	83.3	82.0	0.001 (0.0015)	0.004 (0.0015)	38.7, 61.3
$CARA_4(0.5,0)$	M2 (0.13)	87.4	83.8	0.001 (0.0014)	0.002 (0.0014)	49.6, 50.4
$CARA_4(0.5,1)$	M2 (0.13)	87.3	84.0	0.001 (0.0014)	0.002 (0.0014)	46.4, 53.6
$CARA_4(0.5,2)$	M2 (0.13)	86.1	83.1	0.002 (0.0014)	0.001 (0.0015)	43.2, 56.8
$CARA_4(1,0)$	M2 (0.13)	87.6	83.9	0.001 (0.0014)	0.001 (0.0014)	49.2, 50.8
$CARA_4(1,1)$	M2 (0.13)	87.3	83.9	0.001 (0.0014)	0.002 (0.0014)	46.0, 54.0

Table 3.2b – *Continued from previous page*

Allocation	Model (β_A)	Power (%)		ATE Bias (SE)		Trt Prop (%)
(N=600)		TMLE	t-test	TMLE	Mean	
$CARA_4(1,2)$	M2 (0.13)	86.1	83.3	0.001 (0.0014)	0.001 (0.0015)	42.9, 57.1

Scenario 4: Three treatments with continuous endpoint

Consider a clinical trial with three arms and bounded continuous endpoint $Y \in \mathbb{R}$. Suppose that the covariate vector $\boldsymbol{W} = (W_1, W_2, W_3)$ and the binary subgroup indicator $V(\boldsymbol{W})$ are generated in the same manner. In order to study the robustness of the CARA, we proposed the following two models to generate the endpoint Y:

M3: $\qquad \mu = \mu_0 + (1 + \beta_{A1}I(A=1) + \beta_{A2}I(A=2))(1 + \beta_V V) + \sum_{p=1}^{3} \beta_{W,p} * W_p,$

$$\sigma = \frac{1 + \beta_{A1}I(A=1) + \beta_{A2}I(A=2)}{1 + \beta_V V},$$

$Y \sim \mathrm{N}(\mu, \sigma^2), Y$ is truncated if $Y < 0$ or $Y > 8$.

M4: $\qquad a = 1 + (1 + \beta_{A1}I(A=1) + \beta_{A2}I(A=2))(1 + \beta_V V) + \sum_{p=1}^{3} \beta_{W,p} * W_p,$

$$b = \frac{1 + \beta_{A1}I(A=1) + \beta_{A2}I(A=2)}{1 + \beta_V V},$$

$Y \sim \mathrm{Gamma}(a, b), Y$ is truncated if $Y > 12$.

We fixed the parameter values $\beta_V = 0.22, \beta_{W,1} = -0.22, \beta_{W,2} = -0.7, \beta_{W,3} = -0.1$ in model M3, and $\beta_V = -0.4, \beta_{W,1} = 0.26, \beta_{W,2} = -0.37, \beta_{W,3} = 0.44$ in model M4. The

values of β_{A1} and β_{A1} in the two models are adjusted to obtain Type I error rate and power.

In Tables 4.1a and Table 4.1b, we reported the Type I error rate. In model M3, both TMLE and chi-square test demonstrates well-controlled type I error under CR and all Type of CARA designs. In model M4, TMLE and chi-square test both are able to control Type I error rate when implemented under CR. However, when CARA is conducted, TMLE outperforms chi-square test in terms of much lower Type I error. TMLE and chi-square test both give inflated Type I error rate when sample size is relatively small, $n = 600$. When sample size is increased to $n = 800$, TMLE controls Type I error rate, though when implemented under some CARA the Type I error rate is slight over 0.06, while chi-square test keeps rendering inflated Type I error rate when implemented under all types of CARA designs.

In Tables 4.2a and Table 4.2b, power, proportion of treatment, bias in estimation of ATE are compared under CR and CARA procedures for sample size $n = 600$ and $n = 800$ respectively. TMLE dominates chi-square test in power for CR and all CARAs. In addition, TMLE gives a more accurate estimation of the ATE than chi-square test does. When comparing designs, in model 1, many CARAs are able to assign more than 40% patients to the treatment group and increase power by 3% simultaneously. In model 2, CARAs can also assign more than 40% to the treatment group and without losing power.

Table 4.1a: Type I error rate (in %) under CR and different CARA procedures in trial with three treatment arms and continuous endpoint at sample size $N = 600$.

Allocation (N=600)	Model	Type I error (%) TMLE	chi-sq	Model	Type I error (%) TMLE	chi-sq
CR	M3	5.85	5.20	M4	5.81	5.52
$CARA_1(0,1)$	M3	5.08	4.85	M4	6.15	8.14
$CARA_1(0,2)$	M3	5.51	5.00	M4	7.10	16.47
$CARA_1(0.5,0)$	M3	5.19	4.86	M4	5.94	6.12
$CARA_1(0.5,1)$	M3	4.98	4.94	M4	6.31	10.01
$CARA_1(0.5,2)$	M3	5.62	5.14	M4	7.79	20.31
$CARA_1(1,0)$	M3	5.07	4.98	M4	6.10	7.30
$CARA_1(1,1)$	M3	5.18	4.97	M4	6.77	12.62
$CARA_1(1,2)$	M3	5.63	5.17	M4	9.51	24.09
$CARA_2(0.5,0)$	M3	5.18	4.85	M4	5.62	5.59
$CARA_2(0.5,1)$	M3	4.95	4.94	M4	6.34	8.81
$CARA_2(0.5,2)$	M3	5.54	5.05	M4	7.32	17.52
$CARA_2(1,0)$	M3	4.96	4.91	M4	5.93	5.94
$CARA_2(1,1)$	M3	5.16	4.98	M4	6.34	9.60
$CARA_2(1,2)$	M3	5.52	5.13	M4	7.24	18.47

Table 4.1a – *Continued from previous page*

Allocation (N=600)	Model	Type I error (%)		Model	Type I error (%)	
		TMLE	chi-sq		TMLE	chi-sq
$CARA_3(0.5,0)$	M3	5.04	4.92	M4	5.85	6.39
$CARA_3(0.5,1)$	M3	5.15	4.98	M4	6.27	10.78
$CARA_3(0.5,2)$	M3	5.66	5.18	M4	7.92	21.61
$CARA_3(1,0)$	M3	5.08	4.83	M4	6.18	8.56
$CARA_3(1,1)$	M3	5.29	4.99	M4	6.74	14.63
$CARA_3(1,2)$	M3	5.61	5.25	M4	10.02	26.94
$CARA_4(0.5,0)$	M3	5.27	4.88	M4	5.77	5.35
$CARA_4(0.5,1)$	M3	4.98	4.89	M4	6.32	8.60
$CARA_4(0.5,2)$	M3	5.47	5.12	M4	7.17	17.14
$CARA_4(1,0)$	M3	5.12	4.83	M4	5.78	5.67
$CARA_4(1,1)$	M3	5.04	4.81	M4	6.16	8.94
$CARA_4(1,2)$	M3	5.74	5.10	M4	7.25	17.79

Table 4.1b: Type I error rate (in %) under CR and different CARA procedures in trial with three treatment arms and continuous endpoint at sample size $N = 800$.

Allocation (N=800)	Model	Type I error (%) TMLE	chi-sq	Model	Type I error (%) TMLE	chi-sq
CR	M3	5.31	5.17	M4	5.41	5.22
$CARA_1(0,1)$	M3	5.58	5.27	M4	5.52	7.73
$CARA_1(0,2)$	M3	5.70	5.55	M4	5.83	15.05
$CARA_1(0.5,0)$	M3	5.57	5.14	M4	5.47	5.75
$CARA_1(0.5,1)$	M3	5.61	5.26	M4	5.59	9.46
$CARA_1(0.5,2)$	M3	5.68	5.33	M4	6.04	18.06
$CARA_1(1,0)$	M3	5.49	5.05	M4	5.32	7.01
$CARA_1(1,1)$	M3	5.65	5.21	M4	5.65	11.96
$CARA_1(1,2)$	M3	5.41	5.22	M4	6.75	21.76
$CARA_2(0.5,0)$	M3	5.50	5.11	M4	5.65	5.15
$CARA_2(0.5,1)$	M3	5.65	5.30	M4	5.71	8.43
$CARA_2(0.5,2)$	M3	5.64	5.31	M4	5.92	16.14
$CARA_2(1,0)$	M3	5.56	5.12	M4	5.52	5.62
$CARA_2(1,1)$	M3	5.66	5.24	M4	5.45	8.90
$CARA_2(1,2)$	M3	5.46	5.26	M4	6.06	16.75

Table 4.1b – *Continued from previous page*

Allocation (N=800)	Model	Type I error (%) TMLE	chi-sq	Model	Type I error (%) TMLE	chi-sq
$CARA_3(0.5,0)$	M3	5.58	5.08	M4	5.37	6.10
$CARA_3(0.5,1)$	M3	5.69	5.21	M4	5.61	10.11
$CARA_3(0.5,2)$	M3	5.41	5.19	M4	6.42	19.39
$CARA_3(1,0)$	M3	5.28	4.92	M4	5.70	8.23
$CARA_3(1,1)$	M3	5.47	5.04	M4	5.64	13.36
$CARA_3(1,2)$	M3	5.54	5.39	M4	6.88	24.14
$CARA_4(0.5,0)$	M3	5.45	5.10	M4	5.50	4.97
$CARA_4(0.5,1)$	M3	5.57	5.23	M4	5.65	8.26
$CARA_4(0.5,2)$	M3	5.71	5.44	M4	5.88	15.62
$CARA_4(1,0)$	M3	5.54	5.09	M4	5.57	5.20
$CARA_4(1,1)$	M3	5.66	5.27	M4	5.61	8.42
$CARA_4(1,2)$	M3	5.68	5.27	M4	5.98	16.23

Table 4.2a: Power (in %), proportion of treatment (in %), bias in estimation of additive treatment effect (ATE) under CR and different CARA procedures in trial with three treatment arms and continuous endpoint at sample size $N = 600$.

Allocation (N=600)	Model (β_A)	Power (%)		ATE Bias		Trt Prop (%)
		TMLE	chi-sq	TMLE	Mean	
CR	M3 (0, 0.25)	87.6	83.7	(0.002, 0.001)	(0.002, 0.001)	33.3, 33.3, 33.3
$CARA_1(0,1)$	M3 (0, 0.25)	90.2	86.9	(0.001, 0.001)	(0.001, 0.001)	31.0, 31.0, 37.9
$CARA_1(0,2)$	M3 (0, 0.25)	91.0	87.4	(0.001, 0.001)	(0.001, 0.002)	28.6, 28.6, 42.8
$CARA_1(0.5,0)$	M3 (0, 0.25)	88.0	85.1	(0.001, 0.001)	(0.001, 0.002)	33.0, 33.0, 34.0
$CARA_1(0.5,1)$	M3 (0, 0.25)	90.4	87.7	(0.001, 0.001)	(0.001, 0.002)	30.7, 30.7, 38.7
$CARA_1(0.5,2)$	M3 (0, 0.25)	92.3	87.7	(0.001, 0.001)	(0.001, 0.003)	28.2, 28.2, 43.6
$CARA_1(1,0)$	M3 (0, 0.25)	88.2	85.9	(0.001, 0.001)	(0.001, 0.003)	32.6, 32.6, 34.7
$CARA_1(1,1)$	M3 (0, 0.25)	90.2	88.1	(0.001, 0.001)	(0.001, 0.004)	30.3, 30.3, 39.4
$CARA_1(1,2)$	M3 (0, 0.25)	91.0	88.3	(0.001, 0.001)	(0.001, 0.004)	27.8, 27.8, 44.4
$CARA_2(0.5,0)$	M3 (0, 0.25)	88.0	85.5	(0.001, 0.001)	(0.001, 0.004)	32.9, 32.9, 34.2
$CARA_2(0.5,1)$	M3 (0, 0.25)	90.4	88.2	(0.001, 0.001)	(0.001, 0.004)	30.6, 30.6, 38.9
$CARA_2(0.5,2)$	M3 (0, 0.25)	91.2	88.3	(0.001, 0.001)	(0.001, 0.005)	28.1, 28.1, 43.8
$CARA_2(1,0)$	M3 (0, 0.25)	88.5	86.9	(0.001, 0.001)	(0.001, 0.007)	32.5, 32.5, 35.1
$CARA_2(1,1)$	M3 (0, 0.25)	90.3	89.0	(0.001, 0.001)	(0.001, 0.007)	30.1, 30.1, 39.8
$CARA_2(1,2)$	M3 (0, 0.25)	91.1	89.1	(0.001, 0.001)	(0.001, 0.008)	27.7, 27.7, 44.7

Table 4.2a – *Continued from previous page*

Allocation (N=600)	Model (β_A)	Power (%)		ATE Bias		Trt Prop (%)
		TMLE	chi-sq	TMLE	Mean	
$CARA_3(0.5,0)$	M3 (0, 0.25)	88.3	86.5	(0.001, 0.001)	(0.001, 0.005)	32.5, 32.5, 34.9
$CARA_3(0.5,1)$	M3 (0, 0.25)	90.3	88.6	(0.001, 0.001)	(0.001, 0.005)	30.2, 30.2, 39.6
$CARA_3(0.5,2)$	M3 (0, 0.25)	91.0	88.6	(0.001, 0.001)	(0.001, 0.006)	27.8, 27.7, 44.6
$CARA_3(1,0)$	M3 (0, 0.25)	88.8	88.4	(0.001, 0.001)	(0.001, 0.009)	31.7, 31.8, 36.5
$CARA_3(1,1)$	M3 (0, 0.25)	90.4	90.1	(0.001, 0.001)	(0.001, 0.010)	29.4, 29.3, 41.3
$CARA_3(1,2)$	M3 (0, 0.25)	91.0	90.0	(0.001, 0.001)	(0.001, 0.011)	26.9, 26.8, 46.3
$CARA_4(0.5,0)$	M3 (0, 0.25)	87.8	84.4	(0.001, 0.001)	(0.001, 0.001)	33.2, 33.2, 33.6
$CARA_4(0.5,1)$	M3 (0, 0.25)	90.4	87.4	(0.001, 0.001)	(0.001, 0.002)	30.9, 30.9, 38.3
$CARA_4(0.5,2)$	M3 (0, 0.25)	91.2	87.4	(0.001, 0.001)	(0.001, 0.003)	28.5, 28.4, 43.2
$CARA_4(1,0)$	M3 (0, 0.25)	87.9	85.0	(0.001, 0.001)	(0.001, 0.002)	33.0, 33.0, 34.0
$CARA_4(1,1)$	M3 (0, 0.25)	90.5	87.7	(0.001, 0.001)	(0.001, 0.003)	30.7, 30.7, 38.6
$CARA_4(1,2)$	M3 (0, 0.25)	91.3	87.7	(0.001, 0.001)	(0.001, 0.003)	28.3, 28.2, 43.5
CR	M4 (0.16)	86.5	83.6	(0.001, 0.003)	(0.001, 0.003)	33.3, 33.3, 33.3
$CARA_1(0,1)$	M4 (0.16)	86.8	83.4	(0.001, 0.001)	(0.001, 0.006)	30.8, 32.4, 36.7
$CARA_1(0,2)$	M4 (0.16)	84.0	81.9	(0.001, 0.001)	(0.001, 0.009)	28.3, 31.4, 40.3
$CARA_1(0.5,0)$	M4 (0.16)	87.4	84.1	(0.001, 0.001)	(0.002, 0.003)	31.8, 32.8, 35.4
$CARA_1(0.5,1)$	M4 (0.16)	86.5	83.0	(0.001, 0.001)	(0.001, 0.008)	29.3, 31.8, 38.9
$CARA_1(0.5,2)$	M4 (0.16)	82.8	81.9	(0.002, 0.003)	(0.001, 0.008)	26.8, 30.8, 42.4
$CARA_1(1,0)$	M4 (0.16)	87.8	83.8	(0.001, 0.001)	(0.001, 0.008)	30.3, 32.2, 37.5

Table 4.2a – *Continued from previous page*

Allocation (N=600)	Model (β_A)	Power (%) TMLE	chi-sq	ATE Bias TMLE	Mean	Trt Prop (%)
$CARA_1(1,1)$	M4 (0.16)	86.0	82.9	(0.001, 0.001)	(0.001, 0.009)	27.8, 31.1, 41.0
$CARA_1(1,2)$	M4 (0.16)	80.9	81.5	(0.003, 0.006)	(0.001, 0.008)	25.5, 30.0, 44.5
$CARA_2(0.5,0)$	M4 (0.16)	87.2	84.5	(0.001, 0.001)	(0.001, 0.003)	32.9, 33.1, 34.0
$CARA_2(0.5,1)$	M4 (0.16)	86.7	83.4	(0.001, 0.001)	(0.001, 0.004)	30.4, 32.2, 37.4
$CARA_2(0.5,2)$	M4 (0.16)	83.5	82.4	(0.001, 0.001)	(0.001, 0.006)	27.8, 31.2, 40.9
$CARA_2(1,0)$	M4 (0.16)	87.3	84.7	(0.001, 0.001)	(0.001, 0.005)	32.4, 32.9, 34.6
$CARA_2(1,1)$	M4 (0.16)	86.7	83.9	(0.001, 0.001)	(0.001, 0.001)	29.9, 32.0, 38.1
$CARA_2(1,2)$	M4 (0.16)	83.3	82.6	(0.001, 0.002)	(0.001, 0.002)	27.4, 31.0, 41.6
$CARA_3(0.5,0)$	M4 (0.16)	87.7	84.6	(0.001, 0.001)	(0.001, 0.001)	31.4, 32.6, 36.0
$CARA_3(0.5,1)$	M4 (0.16)	86.3	83.5	(0.001, 0.001)	(0.001, 0.005)	28.9, 31.6, 39.6
$CARA_3(0.5,2)$	M4 (0.16)	82.1	81.7	(0.003, 0.004)	(0.001, 0.005)	26.4, 30.5, 43.1
$CARA_3(1,0)$	M4 (0.16)	87.7	84.5	(0.001, 0.001)	(0.001, 0.001)	29.4, 31.8, 38.8
$CARA_3(1,1)$	M4 (0.16)	85.7	82.9	(0.002, 0.002)	(0.003, 0.001)	27.0, 30.7, 42.3
$CARA_3(1,2)$	M4 (0.16)	79.6	81.6	(0.006, 0.009)	(0.005, 0.001)	24.7, 29.6, 45.7
$CARA_4(0.5,0)$	M4 (0.16)	87.0	84.0	(0.001, 0.002)	(0.001, 0.002)	33.1, 33.2, 33.7
$CARA_4(0.5,1)$	M4 (0.16)	86.8	83.4	(0.001, 0.001)	(0.001, 0.005)	30.5, 32.3, 37.1
$CARA_4(0.5,2)$	M4 (0.16)	84.0	82.3	(0.002, 0.002)	(0.001, 0.007)	28.0, 31.3, 40.7
$CARA_4(1,0)$	M4 (0.16)	87.2	84.4	(0.001, 0.001)	(0.001, 0.002)	32.8, 33.1, 34.1
$CARA_4(1,1)$	M4 (0.16)	86.8	83.6	(0.001, 0.001)	(0.001, 0.004)	30.3, 32.2, 37.5

Table 4.2a – *Continued from previous page*

Allocation (N=600)	Model (β_A)	Power (%)		ATE Bias		Trt Prop (%)
		TMLE	chi-sq	TMLE	Mean	
$CARA_4(1,2)$	M4 (0.16)	83.4	82.2	(0.003, 0.001)	(0.001, 0.006)	27.7, 31.2, 41.1

Table 4.2b: Power (in %), proportion of treatment (in %), bias in estimation of additive treatment effect (ATE) under CR and different CARA procedures in trial with three treatment arms and continuous endpoint at sample size $N = 800$.

Allocation (N=800)	Model (β_A)	Power (%)		ATE Bias		Trt Prop (%)
		TMLE	chi-sq	TMLE	Mean	
CR	M3 (0, 0.2)	83.5	80.0	(0.002, 0.001)	(0.002, 0.001)	33.3, 33.3, 33.3
$CARA_1(0,1)$	M3 (0, 0.2)	86.4	82.1	(0.001, 0.001)	(0.001, 0.001)	31.5, 31.5, 37.0
$CARA_1(0,2)$	M3 (0, 0.2)	87.2	83.0	(0.001, 0.001)	(0.001, 0.001)	29.6, 29.5, 40.9
$CARA_1(0.5,0)$	M3 (0, 0.2)	84.2	81.1	(0.001, 0.001)	(0.001, 0.001)	33.1, 33.0, 33.9
$CARA_1(0.5,1)$	M3 (0, 0.2)	86.2	82.7	(0.001, 0.001)	(0.001, 0.001)	31.2, 31.2, 37.6
$CARA_1(0.5,2)$	M3 (0, 0.2)	87.4	83.5	(0.001, 0.001)	(0.001, 0.002)	29.3, 29.2, 41.6
$CARA_1(1,0)$	M3 (0, 0.2)	84.6	81.8	(0.001, 0.001)	(0.001, 0.002)	32.8, 32.8, 34.5
$CARA_1(1,1)$	M3 (0, 0.2)	86.4	83.9	(0.001, 0.001)	(0.001, 0.002)	30.9, 30.9, 38.2
$CARA_1(1,2)$	M3 (0, 0.2)	87.3	83.9	(0.001, 0.001)	(0.001, 0.003)	28.9, 28.9, 42.2
$CARA_2(0.5,0)$	M3 (0, 0.2)	84.3	81.8	(0.001, 0.001)	(0.001, 0.002)	33.0, 33.0, 34.0

Table 4.2b – *Continued from previous page*

Allocation (N=800)	Model (β_A)	Power (%)		ATE Bias		Trt Prop (%)
		TMLE	chi-sq	TMLE	Mean	
$CARA_2(0.5,1)$	M3 (0, 0.2)	86.4	83.3	(0.001, 0.001)	(0.001, 0.002)	31.1, 31.1, 37.8
$CARA_2(0.5,2)$	M3 (0, 0.2)	87.4	83.8	(0.001, 0.001)	(0.001, 0.003)	29.2, 29.1, 41.7
$CARA_2(1,0)$	M3 (0, 0.2)	84.7	83.0	(0.001, 0.001)	(0.001, 0.004)	32.6, 32.6, 34.7
$CARA_2(1,1)$	M3 (0, 0.2)	86.5	84.7	(0.001, 0.001)	(0.001, 0.005)	30.8, 30.7, 38.5
$CARA_2(1,2)$	M3 (0, 0.2)	87.5	84.7	(0.001, 0.001)	(0.001, 0.005)	28.8, 28.8, 42.4
$CARA_3(0.5,0)$	M3 (0, 0.2)	84.6	82.4	(0.001, 0.001)	(0.001, 0.003)	32.7, 32.7, 34.6
$CARA_3(0.5,1)$	M3 (0, 0.2)	86.4	84.3	(0.001, 0.001)	(0.001, 0.004)	30.8, 30.8, 38.4
$CARA_3(0.5,2)$	M3 (0, 0.2)	87.5	84.5	(0.001, 0.001)	(0.001, 0.004)	28.9, 28.8, 42.3
$CARA_3(1,0)$	M3 (0, 0.2)	84.9	84.6	(0.001, 0.001)	(0.001, 0.007)	32.1, 32.1, 35.8
$CARA_3(1,1)$	M3 (0, 0.2)	86.7	85.9	(0.001, 0.001)	(0.001, 0.007)	30.2, 30.1, 39.7
$CARA_3(1,2)$	M3 (0, 0.2)	87.5	85.9	(0.001, 0.001)	(0.001, 0.008)	28.2, 28.1, 43.7
$CARA_4(0.5,0)$	M3 (0, 0.2)	84.2	80.5	(0.001, 0.001)	(0.001, 0.001)	33.2, 33.2, 33.6
$CARA_4(0.5,1)$	M3 (0, 0.2)	86.2	82.4	(0.001, 0.001)	(0.001, 0.001)	31.4, 31.3, 37.3
$CARA_4(0.5,2)$	M3 (0, 0.2)	87.2	83.2	(0.001, 0.001)	(0.001, 0.001)	29.4, 29.4, 41.2
$CARA_4(1,0)$	M3 (0, 0.2)	84.1	81.1	(0.001, 0.001)	(0.001, 0.001)	33.1, 33.1, 33.8
$CARA_4(1,1)$	M3 (0, 0.2)	86.2	82.7	(0.001, 0.001)	(0.001, 0.001)	31.2, 31.2, 37.6
$CARA_4(1,2)$	M3 (0, 0.2)	87.4	83.5	(0.001, 0.001)	(0.001, 0.002)	29.3, 29.2, 41.5
CR	M4 (0.04, 0.16)	88.7	86.8	(0.001, 0.003)	(0.001, 0.003)	33.3, 33.3, 33.3
$CARA_1(0,1)$	M4 (0.04, 0.16)	89.1	86.0	(0.001, 0.001)	(0.002, 0.006)	31.2, 32.4, 36.4

Table 4.2b – *Continued from previous page*

Allocation (N=800)	Model (β_A)	Power (%)		ATE Bias		Trt Prop (%)
		TMLE	chi-sq	TMLE	Mean	
$CARA_1(0,2)$	M4 (0.04, 0.16)	87.9	84.4	(0.001, 0.001)	(0.003, 0.010)	29.0, 31.5, 39.6
$CARA_1(0.5,0)$	M4 (0.04, 0.16)	89.5	87.1	(0.001, 0.001)	(0.001, 0.003)	32.0, 32.8, 35.2
$CARA_1(0.5,1)$	M4 (0.04, 0.16)	89.0	85.6	(0.001, 0.001)	(0.003, 0.008)	29.9, 31.8, 38.3
$CARA_1(0.5,2)$	M4 (0.04, 0.16)	87.2	84.1	(0.002, 0.002)	(0.003, 0.010)	27.7, 30.8, 41.5
$CARA_1(1,0)$	M4 (0.04, 0.16)	89.6	86.4	(0.001, 0.001)	(0.002, 0.005)	30.7, 32.2, 37.1
$CARA_1(1,1)$	M4 (0.04, 0.16)	88.9	85.3	(0.001, 0.001)	(0.003, 0.009)	28.6, 31.2, 40.3
$CARA_1(1,2)$	M4 (0.04, 0.16)	86.7	83.8	(0.001, 0.004)	(0.002, 0.009)	26.4, 30.0, 43.5
$CARA_2(0.5,0)$	M4 (0.04, 0.16)	89.5	87.3	(0.001, 0.001)	(0.001, 0.002)	33.0, 33.1, 33.9
$CARA_2(0.5,1)$	M4 (0.04, 0.16)	89.2	86.0	(0.001, 0.001)	(0.002, 0.004)	30.8, 32.2, 37.0
$CARA_2(0.5,2)$	M4 (0.04, 0.16)	87.6	84.6	(0.001, 0.002)	(0.002, 0.007)	28.6, 31.3, 40.2
$CARA_2(1,0)$	M4 (0.04, 0.16)	89.5	87.3	(0.001, 0.001)	(0.001, 0.004)	32.6, 33.0, 34.5
$CARA_2(1,1)$	M4 (0.04, 0.16)	89.1	86.1	(0.001, 0.001)	(0.002, 0.002)	30.4, 32.0, 37.6
$CARA_2(1,2)$	M4 (0.04, 0.16)	87.3	85.0	(0.001, 0.001)	(0.002, 0.005)	28.2, 31.0, 40.8
$CARA_3(0.5,0)$	M4 (0.04, 0.16)	89.5	86.9	(0.001, 0.001)	(0.001, 0.001)	31.6, 32.6, 35.8
$CARA_3(0.5,1)$	M4 (0.04, 0.16)	89.1	85.8	(0.001, 0.001)	(0.003, 0.006)	29.5, 31.6, 38.9
$CARA_3(0.5,2)$	M4 (0.04, 0.16)	87.0	84.2	(0.001, 0.003)	(0.002, 0.007)	27.3, 30.6, 42.1
$CARA_3(1,0)$	M4 (0.04, 0.16)	89.7	86.7	(0.001, 0.001)	(0.001, 0.001)	29.9, 31.8, 38.2
$CARA_3(1,1)$	M4 (0.04, 0.16)	88.8	85.5	(0.001, 0.002)	(0.002, 0.004)	27.8, 30.8, 41.5
$CARA_3(1,2)$	M4 (0.04, 0.16)	85.3	83.7	(0.002, 0.004)	(0.001, 0.004)	25.7, 29.7, 44.6

Table 4.2b – *Continued from previous page*

Allocation (N=800)	Model (β_A)	Power (%)		ATE Bias		Trt Prop (%)
		TMLE	chi-sq	TMLE	Mean	
$CARA_4(0.5,0)$	M4 (0.04, 0.16)	89.3	87.2	(0.001, 0.001)	(0.001, 0.001)	33.1, 33.2, 33.7
$CARA_4(0.5,1)$	M4 (0.04, 0.16)	89.1	85.8	(0.001, 0.001)	(0.002, 0.005)	30.9, 32.3, 36.7
$CARA_4(0.5,2)$	M4 (0.04, 0.16)	87.8	84.6	(0.001, 0.001)	(0.003, 0.009)	28.7, 31.3, 39.9
$CARA_4(1,0)$	M4 (0.04, 0.16)	89.5	87.2	(0.001, 0.001)	(0.001, 0.001)	32.9, 33.1, 34.0
$CARA_4(1,1)$	M4 (0.04, 0.16)	89.1	86.0	(0.001, 0.001)	(0.003, 0.005)	30.7, 32.2, 37.1
$CARA_4(1,2)$	M4 (0.04, 0.16)	87.6	84.5	(0.001, 0.001)	(0.002, 0.007)	28.5, 31.2, 40.3

3.5   Conclusions

In this section, we proposed an innovative framework of CARA design with TMLE. Under the framework, we demonstrated how to set up the allocation of a patient based on the full history of the previous patients' treatment assignments, responses, and covariates, and the covariates of the current patient to achieve different objectives. The TMLE is used to handle the "messy" data which is caused by the adaption in CARA design. In the theory part, we showed the consistency and asymptotic properties of the proposed family of CARA designs. In addition, the TMLE has been prove to have asymptotic normality in the proposed CARA designs under certain conditions.

Furthermore, the simulation studies above successfully verified the concept of the designs in different angels. The advantage of the proposed framework lies on two major points. First, the proposed framework is very flexible in terms of the efficiency measure and ethics measure. And it is capable of addressing trial efficiency and ethics simultaneously. The diversity of the measures of trial efficiency and ethics as well as the tuning parameters endures us the ability to assign more patients to superior treatment arm while retain the same power or even gain more power. Second, the nonparametric nature of TMLE can avoid model mis-specification and control Type I error rate under different and complicated data generating distributions. Particularly, when the normality of the data is invalid, which is always true in real applications, our proposed framework showed superior robustness through a two-step approach than tradition methods with respect to type I error control, power and ATE estimation.

4 Principles of Adaptive Seamless II/III Designs

4.1 Background

The drive to reduce development costs and shorten the time-to-market of new therapies has led to the development of the methodology of ASD. Typically, such trials combine the phase II and phase III into a single and seamless trial with two stages, the learning stage and the confirmatory stage, and interim analyses (Bretz, Schmidli, et al. 2006, Stallard 2010). The ASD has been shown to have advantage in efficiency over the standard phase II and phase III trials for efficacy confirmation (Bretz, Schmidli, et al. 2006). In the learning stage which is typically a phase II trial, the primary goal is to compare multiple experimental treatments or drug doses simultaneously. In the interim analysis, the most promising candidates are selected for further investigation in the confirmation stage which corresponds to a phase III trial or the study is stopped due to futility. The final analysis combines the "learnt data" and the "confirm data" and addresses the overall type I error rate in statistical testing at a pre-specified level independent of the interim analysis.

In practice, hypothesis testing with type I error control is the primary focus of a seamless phase II/III trial, with estimation being an important but secondary target (Cohen and Sackrowitz 1989, Troendle and Yu 1999, Posch et al. 2005, Stallard and Friede 2008, Bowden and Glimm 2008, Bowden and Glimm 2014, Todd and Stallard 2005). A critical problem in the seamless phase II/III clinical trial is to combine the data from the two stages and control the familywise error rate (FWER).

The most crucial aspect of the problem is how to utilize the accumulating data while

control the FWER. When the "learnt data" is used to make selection decision or used to estimate design parameters in the interim analysis, a simple combination of the "learnt data" and the "confirm data" to make statistical inference can considerable compromise the FWER. That is, not only the type I error on the selected hypotheses but also the family of the hypotheses of the adaptive trial need to be controlled at pre-specified level (Wang, Hung, and O'Neill 2010). Certain combination methods such as the inverse χ^2 method (Bauer and Kohne 1994) and the weighted inverse normal method (Lehmacher and Wassmer 1999) have been proposed to combine data from the two stages in the final hypothesis test and to achieve a strong control of the FWER.

The control of the FWER in ASD also involves dealing with multiplicity. Multiplicity is the potential inflation of type I error rate in clinical trials where the simultaneous assessments of multiple testing are carried out. It is a common issue in clinical trials when evaluating multiple end points, conducting subgroup analysis and comparing several treatment arms (Dmitrienko and D'Agostino 2018, Li et al. 2016). There are many common statistical methods and approaches that have been proposed to address multiplicity issues. Generally, the statistical methods are classified into two categories: single step methods and stepwise methods (FDA et al. 2017, Bretz, Hothorn, and Westfall 2016). The single step methods reject or accept a single hypothesis independently and do not rely on the decision of any other hypothesis, e.g., Bonferroni method, Simes method and Dunnett method. On the contrary the stepwise methods make decision of a single hypothesis on the basis of the decisions of other hypotheses, e.g., Holm method (stepdown Bonferroni method), Hochberg test (stepwise Simes method) and stepdown

Dunnett method.

4.2 Combination tests

Combination test is a common approach used in meta-analysis. It combines p-values from independent data or studies (Heard and Rubin-Delanchy 2018). The idea of using combination function to combine stagewise p-values was first proposed by Bauer and Kohne 1994 and then it was applied in treatment selection by Bauer and Kieser 1999. In ASD, a simple combination of the "learnt data" and the "confirm data" to make statistical inference can considerable compromise the FWER. Combination test is used to tackle this issue and achieve a strong control of the FWER.

Suppose we have n p-values $(p_1, \ldots, p_n)$ from the hypothesis test of n independent studies. Under the null hypotheses for $i = 1, \ldots, n$,

$$H_0 : p_i \sim U[0, 1].$$

There are variate of different combination methods available. Two commonly used combination statistics are Fisher's statistic (Bauer and Kohne 1994)

$$S_F = \sum_{i=1}^{n} \log p_i$$

and Pearson's statistic

$$S_P = \sum_{i=1}^{n} \log(1 - p_i).$$

Under the null hypothesis H_0, both $-2S_F$ and $-2S_P$ are distributed as χ_{2n}^2. The combined

p-values can be expressed as

$$C_F(p_1, \ldots, p_n) = \Pr(X \geq -2S_F), \quad C_P(p_1, \ldots, p_n) = \Pr(X \geq -2S_P). \qquad (25)$$

Fisher's statistic is more sensitive to small p-values while Pearson's statistic is more sensitive to large p-values. In a two stage adaptive seamless design, one can reject the joint null hypothesis at level α if

$$-2S_F \leq \chi^2_{4,1-\alpha} \quad \text{and} \quad -2S_P \leq \chi^2_{4,1-\alpha},$$

or equivalently

$$p_1 p_2 \leq \exp(-\frac{1}{2}\chi^2_{4,1-\alpha}) \quad \text{and} \quad (1-p_1)(1-p_2) \leq \exp(-\frac{1}{2}\chi^2_{4,1-\alpha}).$$

Another commonly used combination method is the weighted inverse normal method (Lehmacher and Wassmer 1999)

$$S_W = 1 - \Phi\left(\frac{\sum_{i=1}^{n} w_i \Phi^{-1}(1-p_i)}{\sqrt{\sum_{i=1}^{n} w_i^2}}\right),$$

where $0 < w_i < 1$ are arbitrary weighted. Under the null hypothesis H_0, S_W is distributed as $U[0,1]$ and is also the combined p-value. The weights are suggested to be proportional to the expected difference between the H_0 and H_1 and be inversely proportional to the standard deviation of the statistic used in the i-th experiment (Liptak 1958, Won et al. 2009). Under circumstance that no further information is available, a widely used weight is $w_i \propto \sqrt{n_i}$ where n_i is the sample size of the i-th study. Similarly, in the final analysis of a two stage adaptive seamless design, one can reject the joint null hypothesis at level α if

$$C_W(p_1, \ldots, p_n) = S_W = 1 - \Phi\left(w_1 \Phi^{-1}(1-p_1) + w_2 \Phi^{-1}(1-p_2)\right) \leq \alpha, \qquad (26)$$

where $w_i = \sqrt{n_i/(n_1 + n_2)}, i = 1, 2$.

4.3 Multiple testing methods

In this section, the three single step methods, Bonferroni method, Simes method and Dunnett method are introduced.

Bonferroni method

Bonferroni method is a single step nonparametric test. Suppose we have a family of hypotheses with n single hypothesis $(H_1, \ldots, H_n)$. Let H denote the global null hypothesis such that

$$H = H_1 \cap H_2 \cap \ldots \cap H_n.$$

Let p_i denote the corresponding p-values for each individual hypothesis H_i for $i = 1, \ldots, n$. The Bonferroni test rejects an individual hypothesis H_i at the FWER α if

$$p_i \leq \alpha/n \quad \text{or} \quad \min(np_i, 1) \leq \alpha.$$

Correspondingly, Bonferroni method rejects the global hypothesis H at the FWER α if one or more individual hypothesis H_i is rejected. Bonferroni method controls the FWER at level α following from the Boole's inequality such that

$$\text{FWER} = \Pr\left\{\bigcup_{i=1}^{n}\left(p_i \leq \frac{\alpha}{n}\right)\right\} \leq \sum_{i=1}^{n}\left\{\Pr\left(p_i \leq \frac{\alpha}{n}\right)\right\} = \alpha.$$

Though the FWER is controlled at a pre-specified α level, Bonferroi method is rarely used in practice. The Bonferroni method is rather conservative if there are a large number

of hypotheses and/or the test statistics are strongly positively correlated. As a trade-off of the strong control FWER, the Bonferroni method reduces statistical power.

Simes method

Simes method, proposed by Simes 1986, is also a single step nonparametric test. Unlike Bonferroni method, Simes method assumes non-negative correlations between each individual p-values. Let $p_{(i)}, i = 1, \ldots, n$ be the ordered p-values such that $p_{(1)} < p_{(2)} < \ldots < p_{(n)}$. The Simes method rejects the global hypothesis H at the FWER α if

$$p_{(i)} \leq i\alpha/n \text{ for at least one } i$$

or equivalently if

$$\min_i \{np_{(i)}/i\} \leq \alpha.$$

Unlike Bonferroni method, Simes method can only be used to test the global hypothesis H but not the individual hypothesis H_i. However, Simes method is more powerful than the global test using Bonferroni method.

Dunnett method

For scenarios that multiple treatment arms are compared with a control, Dunnett method can be used to exploit the correlation between the p-values. Dunnett method, proposed by Dunnett 1955, is a parametric method and assumes normality. When correctly specified, Dunnett method provides a less conservative control of FWER and is more powerful than the nonparametric methods such as Bonferroni method and Simes method.

Suppose we have $(K+1)$ arms with K treatment arms and 1 control arm. Each arm has n_i observations for $i = 0, 1, \ldots, K$. We assume the following parametric model for observation Y_{ij},

$$Y_{ij} = \mu_i + \epsilon_{ij}, \quad i = 0, 1, \ldots, K, \quad j = 1, \ldots, n_i,$$

where μ_i is the treatment effect of arm i and ϵ_{ij} is the i.i.d. normal term of Y_{ij}. We assume $\epsilon_{ij} \sim N(0, \sigma^2)$. For the multi-arm trial, we would like to test the K treatments against the control:

$$H_i : \mu_i - \mu_0 = 0, \quad i = 1, \ldots, K$$

According to the normality assumption above, we can obtain K t-test statistics,

$$t_i = \frac{\hat{\mu}_i - \hat{\mu}_0}{\hat{\sigma}\sqrt{\frac{1}{n_i} + \frac{1}{n_0}}}, \quad i = 1, \ldots, K,$$

where $\hat{\mu}_i$ and $\hat{\sigma}$ are estimators of μ_i and σ. The key point is that under the null hypotheses, $t_i \sim t_\nu$, where t_ν is a univariate t-distribution with degree of freedom $\nu = \sum_{i=0}^{K} n_i - K - 1$. In addition, under the global null hypothesis $H = \bigcap_{i=1}^{K} H_i$, $(t_1, \ldots, t_K)$ is a K-variate t-distribution with degree of freedom ν and correlation matrix $\{\rho_{ij}\}_{K \times K}$, where

$$\rho_{ij} = \sqrt{\frac{n_i n_j}{(n_i + n_0)(n_j + n_0)}}, \quad i = 1, \ldots, K, \quad j = 1, \ldots, K.$$

The individual hypothesis H_i is rejected at the FWER α if

$$t_i \geq c_{K, 1-\alpha},$$

where $c_{K, 1-\alpha}$ satisfies $\Pr[(t_1, \ldots, t_K) \leq (c_{K, 1-\alpha}, \ldots, c_{K, 1-\alpha})] = 1 - \alpha$ which can be calculated based on the K-variate t-distribution with degree of freedom ν and correlation

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matrix $\{\rho_{ij}\}_{K \times K}$. Also, Dunnett method rejects the global hypothesis H at the FWER α if one or more individual hypothesis H_i is rejected. In practice, the multivariate t-distribution can be approximated by a multivariate normal distribution when ν is large.

Dunnett method performs better than Bonferroni method and Simes method in term of FWER and power because of the ability of adjusting for the correlations between test statistics. Furthermore, Dunnett test can also be extend to linear models, generalized linear models and any other methods with an asymptotically normal distributed statistic such as TMLE. An example and discussion will be shown in section 4.

4.4   Closure principle

The closure principle proposed by Marcus, Eric, and Gabriel 1976 is the fundamental principle in building FWER-controlling multiple testing procedures. It has been used to construct virtually all multiple testing methods arising in clinical trial and pharmaceutical applications. Since closure principle based procedures strongly control FWER, it has been applied in all confirmatory clinical trials (Dmitrienko and D'Agostino 2013). Because of this important property, we will use the closure principle in the final stage of our proposed ASD.

Suppose we have n hypothesis $(H_1, \ldots, H_n)$ in a study, $n \geq 2$. The hypothesis testing of the individual hypothesis H_i can be carried out at a local α level based on its own test statistic t_i and asymptotic property. Let p_i denote the corresponding p-value of the individual hypothesis testing for $i = 1, \ldots, n$. We form an intersection hypothesis H_I for

an arbitrary subset $I \subseteq \{1, \ldots, n\}$ and $|I| \geq 2$ such that

$$H_I = \bigcap_{i \in I} H_i.$$

The hypothesis testing of all intersection hypotheses can be implemented at a local α level using either the p-values or test statistics of the individual hypotheses through multiple testing methods, e.g., Bonferroni method, Simes method and Dunnett method. The closure principle says that an individual hypothesis H_i is rejected at FWER α if all such intersection hypothesis H_I with $i \in I$ are rejected at local α level (Bretz, Schmidli, et al. 2006).

4.5 Multiple testing in adaptive designs

In general, the idea of conducting multiple testing in adaptive designs is: a) using a suitable combination test to fuse p-values of each individual hypothesis between trial stages; b) constructing all intersection hypotheses and using multiple testing method on them based on combined p-values at a local α level; c) using closure principle to conduct a global test at FWER level α.

Suppose in a two stage adaptive design, there are two individual hypothesis H_1 and H_2 and let H_{12} denote the intersection hypothesis. According to the closure principle, the individual hypothesis H_1, H_2 and the intersection hypothesis H_{12} need to be tested in both stages. Let $p_{i,j}$ denote the p-value for hypothesis H_j, $j \in \{1, 2, 12\}$ at stage i, $i = 1, 2$. The p-value of the intersection hypotheses $H_{i,12}$ can be obtained through any suitable multiple testing method. By applying Fisher's/Pearson's combination test in

(25) or weighted inverse normal combination test in (26), we have the combined p-values of the two stages as $C(p_{1,j}, p_{2,j})$, $j \in \{1, 2, 12\}$. According to the closure principle, H_1 is rejected globally at a FWER α level if simultaneously

$$C(p_{1,1}, p_{2,1}) \leq \alpha, \text{ and } C(p_{1,12}, p_{2,12}) \leq \alpha.$$

In a treatment/dose selection ASD where two experimental arms are compared with a control arm in the first stage, H_{12} degenerate to either H_1 or H_2 in the second stage since one experimental arm is dropped during interim analysis. If H_2 is dropped, then H_1 is rejected globally at a FWER α level if simultaneously

$$C(p_{1,1}, p_{2,1}) \leq \alpha, \text{ and } C(p_{1,12}, p_{2,1}) \leq \alpha.$$

5 An Adaptive Seamless Design with CARA and TMLE

In this section, the framework for the adaptive seamless phase II/III trials with CARA and TMLE was discussed. The generalized version of the proposed CARA design presented in section 3 is the realization of aim 3 and is applied in the first stage of the ASD. The special case of the proposed CARA design with only two arms is the realization of aim 2 and is used as the allocation strategy in the second stage of the ASD. In this section, we adopted the same notation as we presented in section 3.

5.1 Framework of the ASD with CARA designs

Suppose in a typical scenario where there are $(K+1)$ treatment arms under investigation in a clinical phase II and III study. Among the $(K+1)$ arms, K treatment arms are compared with one control arm. Let $A_i \in \mathbb{A} = \{0, 1, \ldots, K\}$ denote the treatment assignment of the ith patient. Let Y_i be the one-dimensional primary endpoint outcome of the ith patient, where it can be either binary $Y_i \in \{0, 1\}$ or continuous $Y_i \in \mathbb{R}$. For the ith patient, $\boldsymbol{W}_i = (W_{i,1}, \ldots, W_{i,n_W}) \in \mathbb{W}$ represents the patient's baseline characteristics. Assume we are interested in a biomarker/subgroup indicator V_i that is a function of the baseline characteristics denoted as $V_i = f_V(\boldsymbol{W}_i) \in \mathbb{V} = \{v_1, \ldots, v_q\}$ for the ith patient. The choice of V might be from previous translational research and represent a comprehensive understanding about the impact of baseline characteristics on the treatment

effects.

In such scenario, an ASD can be carried out to reduce the costs and shorten the time in the clinical trial. In addition to the good properties of ASD, we would also be interested in assigning more patients to the superior treatment group with higher efficiency of detecting the treatment effects. Therefore, we incorporated the ASD with CARA emphasizing on ethics and efficiency. To operate a CARA randomization as discussed in section 3, we first define the design parameter vector $\boldsymbol{\theta}_0 = \{\boldsymbol{\theta}_0^{a,v}, a \in \mathbb{A}, v \in \mathbb{V}\}$, where $\boldsymbol{\theta}_0^{a,v} = (\theta_{0,1}^{a,v}, \theta_{0,2}^{a,v})$ for all pairs of (a, v), such that

$$\theta_{0,1}^{a,v} = E_{P_0}(Y|A = a, V = v), \ \theta_{0,2}^{a,v} = E_{P_0}(Y^2|A = a, V = v).$$

According to section 3, the estimator of $\boldsymbol{\theta}_0$, $\hat{\boldsymbol{\theta}}_n = \{\hat{\boldsymbol{\theta}}_n^{a,v}, a \in \mathbb{A}, v \in \mathbb{V}\}$, can be obtained through equation (3) as

$$\hat{\theta}_{n,1}^{a,v} = \frac{\sum_{i=1}^{n} \frac{I_i(a,v)}{G_i(a,v)} Y_i}{\sum_{i=1}^{n} \frac{I_i(a,v)}{G_i(a,v)}}, \quad \hat{\theta}_{n,2}^{a,v} = \frac{\sum_{i=1}^{n} \frac{I_i(a,v)}{G_i(a,v)} Y_i^2}{\sum_{i=1}^{n} \frac{I_i(a,v)}{G_i(a,v)}},$$

where $G_i(\cdot)$ is the conditional probability of treatment assignment A_i given $(X_1, \ldots, X_i)$ in the CARA framework. Therefore, if subjects enter the trial sequentially, one can always calculate $\hat{\boldsymbol{\theta}}_n$ after the n-th subject and use the estimate for the $(n+1)$-th subject. We also define $d(a, v, \boldsymbol{\theta}_0)$ and $e(a, v, \boldsymbol{\theta}_0), a \in \mathbb{A}, v \in \mathbb{V}$, as finite one-dimensional quantities of efficiency and ethics measurements of treatment a in subgroup v, respectively. The choice of the efficiency and ethics measurements are determined by different design objectives, and will lead to different target allocation proportions.

Suppose in the protocol of the ASD, the planned total sample size is n, and the planned sample size for the first stage is n_1. Then the sample size for the second stage is

$n_2 = n - n_1$. We proposed the following design framework of the ASD with CARA.

In the first stage, we assigns the ith subject with subgroup $V_i = v$ to treatment $A = a, a = 0, 1, \ldots, K$, with probability

$$G_i(a, v) = \Pr(A_i = a | V_i = v, \hat{\boldsymbol{\theta}}_{i-1}) = \frac{e(a, v, \hat{\boldsymbol{\theta}}_{i-1})^{\gamma_1} d(a, v, \hat{\boldsymbol{\theta}}_{i-1})^{\gamma_2}}{\sum_{k \in \mathbb{A}} e(k, v, \hat{\boldsymbol{\theta}}_{i-1})^{\gamma_1} d(k, v, \hat{\boldsymbol{\theta}}_{i-1})^{\gamma_2}},$$

where $(\gamma_1, \gamma_2) \in [0, +\infty)^2$ are two tuning parameters determining the balance between ethics and efficiency. At the end of the first stage, one treatment, say treatment $k^\star$, is chosen to enter the second stage with the control arm based on certain criteria. For instance, in this dissertation, the treatment arm with the largest test statistic $T_{j,1}$ is selected. The details were described in the following section.

In the second stage, the control arm along with the selected treatment $k^\star$ resembles a two arm trial with the planned number of remaining patients (n_2). We sequentially assigns the i-th patient (in the second stage) with subgroup $V_i = v$ to treatment $l, l = 0, k^*$, with probability

$$G_i(l, v) = \Pr(A_i = l | V_i = v, \hat{\boldsymbol{\theta}}_{i-1}) = \frac{e_l(v, \hat{\boldsymbol{\theta}}_{i-1})^{\gamma_1} d_l(v, \hat{\boldsymbol{\theta}}_{i-1})^{\gamma_2}}{e_0(v, \hat{\boldsymbol{\theta}}_{i-1})^{\gamma_1} d_0(v, \hat{\boldsymbol{\theta}}_{i-1})^{\gamma_2} + e_{k^*}(v, \hat{\boldsymbol{\theta}}_{i-1})^{\gamma_1} d_{k^*}(v, \hat{\boldsymbol{\theta}}_{i-1})^{\gamma_2}}.$$

Note that $\hat{\boldsymbol{\theta}}_{i-1}$ needs to be re-estimated in stage 2. The interim analysis regarding selection criteria and final analysis using TMLE were discussed in section 5.2.

5.2 Using TMLE in interim analysis and final analysis

The design that incorporates ASD with CARA ses the previous covariates, responses, treatment assignments, and the current covariate to update the allocation probability for

the next patient and uses the responses to determine which treatment will be continued to the second stage. It is conceptually difficult to combine these two types of adaptive designs because (1) all the responses, treatment assignments and covariates are correlated with each other in a complicated manner; (2) the data used in the treatment selection are also used for inference at the end of the trial. The challenges related to TMLE in CARA have been introduced before in section 3. In this section, we proposed the an analysis plan to overcome these difficulties.

We define a $(K+1)$-dimensional target parameter as $\boldsymbol{\psi}_0 = \Psi(P_0) = (\psi_{0,0}, \psi_{0,1}, \ldots, \psi_{0,K})$, where $\psi_{0,j} = E_{P_0}(Y|A=j)$ is the j-th treatment effect for $j = 0, 1, \ldots, K$. For the many-to-one comparison, we define K individual null hypothesis as $H_{0,j} : \psi_{0,j} - \psi_{0,0} = 0$ for $j = 1, \ldots, K$. Based on the TMLE procedure as we discussed in section 3, we have

$$\sqrt{n}\left(\hat{\boldsymbol{\psi}}_n^{TMLE} - \boldsymbol{\psi}_0\right) \xrightarrow{D} N(0, \Sigma_0^{TMLE}) \text{ as } n \to \infty,$$

where the element of Σ_0^{TMLE} can be estimated as

$$\hat{\sigma}_n^{TMLE}(j, k) = \frac{1}{n} \sum_{i=1}^n \left(\frac{G_n^\star(A_i, V_i)}{G_i(A_i, V_i)}\right)^2 \left(\mathrm{IC}_j(Q_n^\star, G_n^\star)(O_i) \, \mathrm{IC}_k(Q_n^\star, G_n^\star)(O_i)\right).$$

Then we consider the following standardized test statistics

$$T_j = \frac{\sqrt{n}(\hat{\psi}_{n,j}^{TMLE} - \hat{\psi}_{n,0}^{TMLE})}{\sqrt{\hat{\sigma}_n^{TMLE}(0,0) + \hat{\sigma}_n^{TMLE}(j,j) - 2\hat{\sigma}_n^{TMLE}(0,j)}},$$

for the j-th hypothesis. According to Theorem 5, it is easy to show that under the null, $T_j \xrightarrow{D} N(0,1)$ for all $j = 1, \ldots, K$. Therefore, each single test statistic T_j has an approximate standard normal distribution. Moreover, (T_i, T_j) has an asymptotic bi-

variate normal distribution

$$\begin{pmatrix} T_i \\ T_j \end{pmatrix} \xrightarrow{D} N\left(\mathbf{0}, \begin{bmatrix} 1 & \rho_{i,j} \\ \rho_{j,i} & 1 \end{bmatrix} \right),$$

where

$$\rho_{i,j} = \frac{\sigma_0^{TMLE}(0,0) + \sigma_0^{TMLE}(i,j) - \sigma_0^{TMLE}(0,i) - \sigma_0^{TMLE}(0,j)}{\sqrt{(\sigma_0^{TMLE}(0,0) + \sigma_0^{TMLE}(i,i) - 2\sigma_0^{TMLE}(0,i))(\sigma_0^{TMLE}(0,0) + \sigma_0^{TMLE}(j,j) - 2\sigma_0^{TMLE}(0,j))}},$$

for all $i \neq j$. If the null hypotheses are extended to the distribution-wise equivalence of any two arms, then under the null we have $\rho_{i,j} = 1/2$. Therefore, the type I error rate is controlled and asymptotically α when applying the Simes method and the Dunnett method.

The analysis procedure is described below.

Firstly, we denote the test statistic based on the data from the first stage as $T_{j,1}$ for $j = 1, \ldots, K$ (the subscript 1 stands for the first stage). In the interim analysis, the treatment arm with the largest test statistic $T_{j,1}$ is selected and is denoted as k^*. The adjusted p-values of all single hypotheses $H_j, j = 1, \ldots, K$ and all intersection hypotheses $H_I, I \subseteq \{1, \ldots, K\}$ are calculated using the Simes method or the Dunnett method at local level α. We denote these p-values as $p_{j,1}$ and $p_{I,1}$ for single hypothesis and intersection hypothesis respectively.

Secondly, the selected arm k^* is carried forward to the second stage and resembles a two-arm trial along with the control. In the final analysis, the test statistic $T_{k^*,2}$ and the corresponding p-value $p_{k^*,2}$ are calculated using TMLE based on the data from the second stage only and not on the accumulated data. The combined p-values from

the two-stage trial can be obtained using Fisher's method in (25) or weighted inverse normal method in (26). For instance, the combined p-value for a single hypothesis H_{k^*} is $p_{k^*} = C(p_{k^*,1}, p_{k^*,2})$; and the combined p-value for an intersection hypothesis H_I with $k^* \in I$ is $p_I = C(p_{I,1}, p_{k^*,2})$ since all intersection hypotheses H_I with $k^* \in I$ degenerate to H_{k^*} in the second stage.

Thirdly, to strongly control the FWER at level α, the closure principle is applied. According to the closure principle (Marcus, Eric, and Gabriel 1976), one is able to reject the null hypothesis H_{k^*} for the selected arm k^* if for any intersection hypothesis I satisfying $k^* \in I$, the combined p-value $p_{k^*} \leq \alpha$.

5.3   Simulation studies

In this section, we numerically evaluated the finite-sample operating characteristics of the ASD with CARA and TMLE regarding the Type I error rate, power and other properties. Consider an adaptive phase II/III trial with three arms in the first stage, where two treatment/dose arms are compared to the control. In the interim analysis, the promising one is chosen and carried forward to the second stage. We introduced three different scenarios in terms of the type data generating distribution of the endpoint Y: (1) binary; (2) continuous and symmetric (normally distributed); (3) continuous and skewed (e.g. gamma distribution). The three scenarios covered most basic types of data appeared in real applications and served as a test for the robustness of our proposed framework.

We also compared ASD with CARA to ASD with complete randomization (CR). For the CARA procedure, we studied four different CARA designs representing different ethics measurements:

$$\text{CARA}_1: e(a,v,\hat{\boldsymbol{\theta}}_{i-1}) = \hat{\theta}^{a,v}_{i-1,1}, \ d(a,v,\hat{\boldsymbol{\theta}}_{i-1}) = \sqrt{\hat{\theta}^{a,v}_{i-1,2} - (\hat{\theta}^{a,v}_{i-1,1})^2}$$

$$\text{CARA}_2: e(a,v,\hat{\boldsymbol{\theta}}_{i-1}) = (1 - \hat{\theta}^{a,v}_{i-1,1})^{-1}, \ d(a,v,\hat{\boldsymbol{\theta}}_{i-1}) = \sqrt{\hat{\theta}^{a,v}_{i-1,2} - (\hat{\theta}^{a,v}_{i-1,1})^2}$$

$$\text{CARA}_3: e(a,v,\hat{\boldsymbol{\theta}}_{i-1}) = \hat{\theta}^{a,v}_{i-1,1} * (1 - \hat{\theta}^{a,v}_{i-1,1})^{-1}, \ d(a,v,\hat{\boldsymbol{\theta}}_{i-1}) = \sqrt{\hat{\theta}^{a,v}_{i-1,2} - (\hat{\theta}^{a,v}_{i-1,1})^2}$$

$$\text{CARA}_4: e(a,v,\hat{\boldsymbol{\theta}}_{i-1}) = \Phi(\hat{\theta}^{a,v}_{i-1,1} - \frac{1}{n_A}\sum_{k=1}^{n_A} \hat{\theta}^{k,v}_{i-1,1}), \ d(a,v,\hat{\boldsymbol{\theta}}_{i-1}) = \sqrt{\hat{\theta}^{a,v}_{i-1,2} - (\hat{\theta}^{a,v}_{i-1,1})^2},$$

where n_A denotes the number of treatment arms ($n_A = 3$ in the first stage, $n_A = 2$ in the second stage), and $\Phi(\cdot)$ denotes the CDF of standard normal distribution. All the four ethics measurements return larger value for the superior treatment arm in terms of additive treatment effect. The efficiency measurement was chosen based on the idea of Neyman allocation. The tuning parameters γ_1 and γ_2 can be assigned to different values to further examine the validity and demonstrate the flexibility. In the Tables, we used $\text{CARA}_k(\gamma_1, \gamma_2)$ to represent the above kth CARA design with tuning parameters γ_1 and γ_2.

In the interim analysis and final analysis of the ASD, the test statistics $T_{i,j}$ and the corresponding p-values $p_{i,j}$ were obtained using TMLE as we described previously if the allocation was carried out using CARA. The standardized t-statistics or z-statistics were calculated for the complete randomization. We compared four combinations of multiple testing method and combination method: (1) Dunnett method with Fisher's method; (2)

Dunnett method with weighted inverse normal method; (3) Simes method with Fisher's method; (CR) Simes method with weighted inverse normal method. The weighted used in the weighted inverse normal method is proportional to the square root of sample size.

In the whole simulation study, we set the sample size for the first stage is $n_1 = 200$ and the sample size for the second stage is $n_2 = 500$. Moreover, when CARA was conducted, the first 25% and 10% of patients in the first and second stage were allocated using the stratified permuted block (SPB) randomization and the rest patients were allocated using TMLE. For the binary scenario, an additioal 10% (total 20%) patients in the second stage were initially assigned by SPB for a better convergency in TMLE approach. Moreover, we pre-specified the significance level at $\alpha = 0.05$, and all the results were based on $10,000$ replications.

Scenario 1: Binary endpoint

Consider an ASD with binary endpoints, suppose we have a covariate vector $\boldsymbol{W} = (W_1, W_2, W_3)$ and a binary subgroup indicator $V(\boldsymbol{W}) = I(W_1 + W_2 + W_3 > 1.6)$, where W_1, W_2, W_3 independently follow uniform distribution in $[0, 1]$ and $I(\cdot)$ is the indicator function. Assume the success rate of the binary endpoint Y is:

$$p = \Phi\left(\beta_0 + \beta_{A1}I(A = 1) + \beta_{A2}I(A = 2) + \beta_V V + \sum_{p=1}^{3} \beta_{W,p} * W_p\right),$$

where $(\beta_0, \beta_{A1}, \beta_{A2}, \beta_V, \beta_{W,1}, \beta_{W,2}, \beta_{W,3})$ are unknown parameters. Note that the true model of Y is a generalized linear model with a probit link function. In Tables 5.1, 5.2a and 5.2b, we fix $(\beta_0, \beta_V, \beta_{W,1}, \beta_{W,2}, \beta_{W,3}) = (0, 0.2, 0.22, -0.17, -0.1)$ while adjusting the

values of (β_{A1}, β_{A2}) to study the FWER, power, and other properties. Thus, the initial estimate in TMLE was from a mis-specified model.

In Table 5.1, we reported the Type I error rate with $(\beta_{A1}, \beta_{A2}) = (0,0)$. All proposed approaches and TMLE and the traditional approach control the Type I error rate at the nominal level 0.05. In Table 5.2a and Table 5.2b, power, correct selection rate (M) and the proportion of control arm in the first stage (C1) and the second stage (C2) are reported. In Table 5.2a, we considered the situation that only one arm is more effective than the control $(\beta_{A1} = 0, \beta_{A2} = 0.33)$ while in Table 5.2b, there are differential treatment effects in the two treatment arms $(\beta_{A1} = 0.15, \beta_{A2} = 0.33)$. Though the proposed ASDs do not show a dominated advantage in power and correct selection rate over the traditional approach, the proportion of control arm can be significantly dropped from 33.3% in the first stage to 30.1% and from 50.0% in the second stage to 45.3% (e.g. $CARA_2(1,1)$).

Table 5.1: Type I error rate (in %) comparison between the proposed ASD and the traditional approach based ASD with binary endpoints.

Allocation	Dunnett $\alpha(\%)$		Simes $\alpha(\%)$	
N = 200+500	Fisher's	Weighted	Fisher's	Weighted
CR (t-test)	5.39	5.37	5.18	5.00
$CARA_1(0,1)$	5.22	4.84	5.07	4.40
$CARA_1(1,0)$	5.29	5.02	5.11	4.56
$CARA_1(1,1)$	5.18	4.99	5.02	4.59

Continued on next page

Table 5.1 – *Continued from previous page*

Allocation	Dunnett α(%)		Simes α(%)	
N = 200+500	Fisher's	Weighted	Fisher's	Weighted
$CARA_2(0,1)$	5.22	4.84	5.07	4.40
$CARA_2(1,0)$	5.11	4.75	4.81	4.52
$CARA_2(1,1)$	5.34	4.99	5.10	4.63
$CARA_3(0,1)$	5.22	4.84	5.07	4.40
$CARA_3(1,0)$	5.42	5.06	5.16	4.80
$CARA_3(1,1)$	5.48	5.14	5.23	4.79
$CARA_4(0,1)$	5.22	4.84	5.07	4.40
$CARA_4(1,0)$	5.28	4.91	5.15	4.64
$CARA_4(1,1)$	5.42	4.86	5.12	4.64

Table 5.2a: Power (in %) comparison between the proposed ASD and the traditional approach based ASD with binary endpoints. Only one arm has treatment effect.

Allocation	(β_{A1}, β_{A2})	Dunnett Power(%)		Simes Power(%)		M(%)	C1(%)	C2(%)
N = 200+500		Fisher's	Weighted	Fisher's	Weighted			
CR (t-test)	(0,0.33)	85.55	87.07	84.55	85.12	92.98	33.4	50.0
$CARA_1(0,1)$	(0,0.33)	85.78	87.04	84.93	85.09	93.28	32.0	46.9

Table 5.2a – *Continued from previous page*

Allocation	(β_{A1}, β_{A2})	Dunnett Power(%)		Simes Power(%)		M(%)	C1(%)	C2(%)
N = 200+500		Fisher's	Weighted	Fisher's	Weighted			
$CARA_1(1,0)$	(0,0.33)	85.69	86.95	84.66	85.25	93.36	31.7	46.2
$CARA_1(1,1)$	(0,0.33)	85.71	86.95	84.88	85.22	93.39	30.4	43.3
$CARA_2(0,1)$	(0,0.33)	85.78	87.04	84.93	85.09	93.28	32.0	46.9
$CARA_2(1,0)$	(0,0.33)	85.52	86.92	84.50	85.15	93.36	32.9	48.9
$CARA_2(1,1)$	(0,0.33)	85.69	87.25	84.69	85.21	93.45	31.5	45.8
$CARA_3(0,1)$	(0,0.33)	85.78	87.04	84.93	85.09	93.28	32.0	46.9
$CARA_3(1,0)$	(0,0.33)	84.41	86.08	83.16	84.27	93.36	31.3	45.1
$CARA_3(1,1)$	(0,0.33)	84.82	86.26	83.56	84.66	93.37	29.9	42.3
$CARA_4(0,1)$	(0,0.33)	85.78	87.04	84.93	85.09	93.28	32.0	46.9
$CARA_4(1,0)$	(0,0.33)	85.99	87.23	85.05	85.33	93.41	33.1	49.3
$CARA_4(1,1)$	(0,0.33)	85.90	87.16	84.97	85.30	93.35	31.7	46.2

Table 5.2b: Power (in %) comparison between the proposed ASD and the traditional approach based ASD with binary endpoints. Two arms have differential treatment effect.

Allocation	(β_{A1}, β_{A2})	Dunnett Power(%)		Simes Power(%)		M(%)	C1(%)	C2(%)
N = 200+500		Fisher's	Weighted	Fisher's	Weighted			
CR (t-test)	(0.15, 0.33)	83.47	85.31	83.06	84.55	79.03	33.4	50.0

Table 5.2b – *Continued from previous page*

Allocation	(β_{A1}, β_{A2})	Dunnett Power(%)		Simes Power(%)		M(%)	C1(%)	C2(%)
N = 200+500		Fisher's	Weighted	Fisher's	Weighted			
$CARA_1(0,1)$	(0.15, 0.33)	83.90	85.47	83.43	84.71	79.47	34.0	50.9
$CARA_1(1,0)$	(0.15, 0.33)	83.20	84.98	82.71	84.32	79.36	30.6	46.1
$CARA_1(1,1)$	(0.15, 0.33)	83.19	85.15	82.70	84.30	79.45	31.3	46.9
$CARA_2(0,1)$	(0.15, 0.33)	83.90	85.47	83.43	84.71	79.47	34.0	50.9
$CARA_2(1,0)$	(0.15, 0.33)	82.63	84.71	82.14	83.81	79.34	29.7	44.6
$CARA_2(1,1)$	(0.15, 0.33)	82.95	84.80	82.54	83.88	79.35	30.1	45.3
$CARA_3(0,1)$	(0.15, 0.33)	83.90	85.47	83.43	84.71	79.47	34.0	50.9
$CARA_3(1,0)$	(0.15, 0.33)	81.19	83.78	80.79	82.85	79.25	28.3	41.1
$CARA_3(1,1)$	(0.15, 0.33)	81.61	83.84	80.94	82.91	79.21	28.3	41.7
$CARA_4(0,1)$	(0.15, 0.33)	83.90	85.47	83.43	84.71	79.47	34.0	50.9
$CARA_4(1,0)$	(0.15, 0.33)	83.70	85.32	83.15	84.25	79.61	32.1	48.2
$CARA_4(1,1)$	(0.15, 0.33)	83.56	85.37	83.20	84.57	79.40	32.7	49.0

Scenario 2: Continuous normal endpoint

Consider an ASD with bounded continuous endpoint $Y \in \mathbb{R}$. Suppose that the covariate vector $\boldsymbol{W} = (W_1, W_2, W_3)$ and the binary subgroup indicator $V(\boldsymbol{W})$ are generated in the

same manner. Assume the endpoint Y follows a normal distribution as:

$$\mu = \mu_0 + (1 + \beta_{A1}I(A=1) + \beta_{A2}I(A=2))(1 + \beta_V V) + \sum_{p=1}^{3} \beta_{W,p} * W_p,$$

$$\sigma = \frac{1 + \beta_{A1}I(A=1) + \beta_{A2}I(A=2)}{1 + \beta_V V},$$

$$Y \sim \mathrm{N}(\mu, \sigma^2), Y \text{ is truncated if } Y < 0 \text{ or } Y > 8.$$

We fixed the parameter values $(\mu_0, \beta_V, \beta_{W,1}, \beta_{W,2}, \beta_{W,3}) = (3, 0.5, 0.22, -0.17, -0.1)$. The values of β_{A1} and β_{A1} were adjusted to obtain the FWER and power.

In Table 6.1, we reported the Type I error rate with $(\beta_{A1}, \beta_{A2}) = (0,0)$. All proposed approaches and TMLE and the traditional approach control the Type I error rate at the nominal level 0.05. In Table 6.2a and Table 6.2b, power, correct selection rate (M) and the proportion of control arm in the first stage (C1) and the second stage (C2) are reported. In Table 6.2a, we considered the situation that only one arm is more effective than the control $(\beta_{A1} = 0, \beta_{A2} = 0.2)$ while in Table 6.2b, there are differential treatment effects in the two treatment arms $(\beta_{A1} = 0.1, \beta_{A2} = 0.2)$. The proposed ASD with CARA and TMLE shows a significant advantage in both power and correct selection rate over the traditional approach. There is more than 3% increase in power and around 2.5% increase in correct selection rate across all types of CARAs. Besides, the proportion of control arm can be dropped to around 30% in the first stage and 45% in the second stage.

Table 6.1: Type I error rate (in %) comparison between the proposed ASD and the traditional approach based ASD with continuous normal endpoints.

Allocation	Dunnett α(%)		Simes α(%)	
N = 200+500	Fisher's	Weighted	Fisher's	Weighted
CR (t-test)	5.31	5.52	5.14	5.05
$CARA_1(0,1)$	5.16	4.98	4.87	4.62
$CARA_1(1,0)$	5.14	5.17	4.91	4.70
$CARA_1(1,1)$	5.07	4.79	4.79	4.48
$CARA_2(0,1)$	5.16	4.98	4.87	4.62
$CARA_2(1,0)$	5.02	5.03	4.77	4.50
$CARA_2(1,1)$	5.10	4.89	4.80	4.34
$CARA_3(0,1)$	5.16	4.98	4.87	4.62
$CARA_3(1,0)$	5.28	5.00	4.93	4.55
$CARA_3(1,1)$	5.08	4.79	4.81	4.34
$CARA_4(0,1)$	5.16	4.98	4.87	4.62
$CARA_4(1,0)$	5.11	5.08	4.91	4.53
$CARA_4(1,1)$	5.12	5.00	4.77	4.55

Table 6.2a: Power (in %) comparison between the proposed ASD and the traditional approach based ASD with continuous normal endpoints. Only one arm has treatment effect.

Allocation	(β_{A1}, β_{A2})	Dunnett Power(%)		Simes test Power(%)		M(%)	C1(%)	C2(%)
N = 200+500		Fisher's	Weighted	Fisher's	Weighted			
CR (t-test)	(0, 0.2)	79.57	81.61	78.32	79.27	90.01	33.4	50.0
$CARA_1(0,1)$	(0, 0.2)	83.34	84.77	82.46	82.80	91.96	31.8	46.3
$CARA_1(1,0)$	(0, 0.2)	83.04	84.61	81.97	82.72	91.44	32.9	48.9
$CARA_1(1,1)$	(0, 0.2)	83.44	84.82	82.35	82.77	91.82	31.2	45.1
$CARA_2(0,1)$	(0, 0.2)	83.34	84.77	82.46	82.80	91.96	31.8	46.3
$CARA_2(1,0)$	(0, 0.2)	83.21	84.82	82.09	82.96	91.69	32.8	48.6
$CARA_2(1,1)$	(0, 0.2)	83.52	84.84	82.39	82.77	91.93	31.1	44.9
$CARA_3(0,1)$	(0, 0.2)	83.34	84.77	82.46	82.80	91.96	31.8	46.3
$CARA_3(1,0)$	(0, 0.2)	83.29	84.65	82.22	82.68	91.71	32.3	47.5
$CARA_3(1,1)$	(0, 0.2)	83.50	84.95	82.59	82.82	92.02	30.6	43.7
$CARA_4(0,1)$	(0, 0.2)	83.34	84.77	82.46	82.80	91.96	31.8	46.3
$CARA_4(1,0)$	(0, 0.2)	83.07	84.58	82.03	82.48	91.60	33.2	49.5
$CARA_4(1,1)$	(0, 0.2)	83.38	84.84	82.45	83.01	92.00	31.5	45.8

Table 6.2b: Power (in %) comparison between the proposed ASD and the traditional approach based ASD with continuous normal endpoints. Two arms have differential treatment effect.

Allocation N = 200+500	(β_{A1}, β_{A2})	Dunnett Power(%) Fisher's	Weighted	Simes Power(%) Fisher's	Weighted	M(%)	C1(%)	C2(%)
CR (t-test)	(0.1, 0.2)	78.77	81.15	78.06	80.23	72.61	33.4	50.0
$CARA_1(0,1)$	(0.1, 0.2)	82.01	84.07	81.60	83.32	75.03	31.0	46.4
$CARA_1(1,0)$	(0.1, 0.2)	82.14	84.20	81.69	83.55	74.11	32.7	48.9
$CARA_1(1,1)$	(0.1, 0.2)	82.23	84.31	81.81	83.56	74.98	30.3	45.3
$CARA_2(0,1)$	(0.1, 0.2)	82.01	84.07	81.60	83.32	75.03	31.0	46.4
$CARA_2(1,0)$	(0.1, 0.2)	82.51	84.50	81.91	83.82	74.38	32.5	48.7
$CARA_2(1,1)$	(0.1, 0.2)	82.17	84.31	81.67	83.37	74.88	30.2	45.1
$CARA_3(0,1)$	(0.1, 0.2)	82.01	84.07	81.60	83.32	75.03	31.0	46.4
$CARA_3(1,0)$	(0.1, 0.2)	82.10	84.34	81.66	83.40	74.33	31.8	47.6
$CARA_3(1,1)$	(0.1, 0.2)	82.28	84.09	81.86	83.42	74.90	29.5	44.0
$CARA_4(0,1)$	(0.1, 0.2)	82.01	84.07	81.60	83.32	75.03	31.0	46.4
$CARA_4(1,0)$	(0.1, 0.2)	82.21	84.26	81.67	83.47	74.23	33.1	49.5
$CARA_4(1,1)$	(0.1, 0.2)	82.13	84.04	81.72	83.19	74.90	30.7	45.9

Scenario 3: Continuous skewed endpoint

Consider an ASD with bounded continuous endpoint $Y \in \mathbb{R}$. Suppose that the covariate vector $\boldsymbol{W} = (W_1, W_2, W_3)$ and the binary subgroup indicator $V(\boldsymbol{W})$ are generated in the same manner. Assume the endpoint Y follows a gamma distribution as:

$$a = 1 + (1 + \beta_{A1}I(A = 1) + \beta_{A2}I(A = 2))(1 + \beta_V V) + \sum_{p=1}^{3} \beta_{W,p} * W_p,$$

$$b = \frac{1 + \beta_{A1}I(A = 1) + \beta_{A2}I(A = 2)}{1 + \beta_V V},$$

$$Y \sim \text{Gamma}(a, b), Y \text{ is truncated if } Y > 12.$$

We fixed the parameter values $(\beta_V, \beta_{W,1}, \beta_{W,2}, \beta_{W,3}) = (-0.4, 0.26, -0.37, 0.44)$. The values of β_{A1} and β_{A1} were adjusted to obtain the FWER and power.

In Table 7.1, we reported the Type I error rate with $(\beta_{A1}, \beta_{A2}) = (0, 0)$. For some types of CARAs, Fisher's combination test results in a slight inflated type I error rate. The weighted inverse normal is able to control the type I error at the nominal level 0.05. In Table 7.2a and Table 7.2b, power, correct selection rate (M) and the proportion of control arm in the first stage (C1) and the second stage (C2) are reported. In Table 7.2a, we considered the situation that only one arm is more effective than the control $(\beta_{A1} = 0, \beta_{A2} = 0.14)$ while in Table 7.2b, there are differential treatment effects in the two treatment arms $(\beta_{A1} = 0.06, \beta_{A2} = 0.15)$. Though most CARA types appear to be more powerful than the traditional approach, we can observe some trade-offs existing in some types of CARA which show a slight drop in power and correct selection rate but significantly increase the proportion of superior arms (e.g. $CARA_1(1, 1)$ and

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$CARA_3(1, 1)$).

Table 7.1: Type I error rate (in %) comparison between the proposed ASD and the traditional approach based ASD with continuous skewed endpoints.

Allocation	Dunnett α(%)		Simes α(%)	
N = 200+500	Fisher's	Weighted	Fisher's	Weighted
CR (t-test)	4.88	4.91	4.69	4.53
$CARA_1(0, 1)$	5.52	5.39	5.26	4.80
$CARA_1(1, 0)$	5.39	5.09	5.19	4.81
$CARA_1(1, 1)$	6.23	5.55	6.01	5.22
$CARA_2(0, 1)$	5.52	5.39	5.26	4.80
$CARA_2(1, 0)$	5.08	5.23	4.89	4.77
$CARA_2(1, 1)$	5.68	5.23	5.30	4.88
$CARA_3(0, 1)$	5.52	5.39	5.26	4.80
$CARA_3(1, 0)$	5.46	5.03	5.30	4.82
$CARA_3(1, 1)$	6.72	5.67	6.54	5.37
$CARA_4(0, 1)$	5.52	5.39	5.26	4.80
$CARA_4(1, 0)$	5.22	5.13	4.97	4.77
$CARA_4(1, 1)$	5.56	5.24	5.30	4.77

Table 7.2a: Power (in %) comparison between the proposed ASD and the traditional approach based ASD with continuous skewed endpoints. Only one arm has treatment effect.

Allocation	(β_{A1}, β_{A2})	Dunnett Power(%)		Simes Power(%)		M(%)	C1(%)	C2(%)
N = 200+500		Fisher's	Weighted	Fisher's	Weighted			
CR (t-test)	(0, 0.14)	83.03	84.60	81.90	82.77	92.43	33.4	50.0
$CARA_1(0,1)$	(0, 0.14)	84.05	85.91	83.03	83.93	93.01	32.0	46.9
$CARA_1(1,0)$	(0, 0.14)	84.23	85.92	83.21	83.96	92.90	31.7	46.2
$CARA_1(1,1)$	(0, 0.14)	83.32	84.66	82.21	82.88	92.33	30.4	43.3
$CARA_2(0,1)$	(0, 0.14)	84.05	85.91	83.03	83.93	93.01	32.0	46.9
$CARA_2(1,0)$	(0, 0.14)	84.80	86.08	83.86	84.10	93.12	32.9	48.9
$CARA_2(1,1)$	(0, 0.14)	83.56	85.38	82.43	83.46	92.61	31.5	45.8
$CARA_3(0,1)$	(0, 0.14)	84.05	85.91	83.03	83.93	93.01	32.0	46.9
$CARA_3(1,0)$	(0, 0.14)	84.06	85.89	83.27	83.94	93.04	31.3	45.1
$CARA_3(1,1)$	(0, 0.14)	82.38	84.35	81.23	82.10	92.10	29.9	42.3
$CARA_4(0,1)$	(0, 0.14)	84.05	85.91	83.03	83.93	93.01	32.0	46.9
$CARA_4(1,0)$	(0, 0.14)	84.88	86.38	83.72	84.33	93.13	33.1	49.3
$CARA_4(1,1)$	(0, 0.14)	83.98	85.74	83.00	83.88	93.03	31.7	46.2

Table 7.2b: Power (in %) comparison between the proposed ASD and the traditional approach based ASD with continuous skewed endpoints. Two arms have differential treatment effect.

Allocation	(β_{A1}, β_{A2})	Dunnett Power(%)		Simes Power(%)		M(%)	C1(%)	C2(%)
N = 200+500		Fisher's	Weighted	Fisher's	Weighted			
CR (t-test)	(0.06, 0.15)	84.61	86.24	84.28	85.51	81.93	33.4	50.0
$CARA_1(0,1)$	(0.06, 0.15)	85.49	86.95	85.12	86.01	82.60	31.4	46.8
$CARA_1(1,0)$	(0.06, 0.15)	85.60	87.19	84.99	86.33	82.61	31.0	46.1
$CARA_1(1,1)$	(0.06, 0.15)	84.23	86.21	83.74	85.33	82.01	29.2	43.0
$CARA_2(0,1)$	(0.06, 0.15)	85.49	86.95	85.12	86.01	82.60	31.4	46.8
$CARA_2(1,0)$	(0.06, 0.15)	85.62	87.14	85.24	86.36	82.53	32.6	48.8
$CARA_2(1,1)$	(0.06, 0.15)	85.37	86.58	84.88	85.93	82.51	30.7	45.6
$CARA_3(0,1)$	(0.06, 0.15)	85.49	86.95	85.12	86.01	82.60	31.4	46.8
$CARA_3(1,0)$	(0.06, 0.15)	85.56	87.09	85.07	86.52	82.81	30.4	44.9
$CARA_3(1,1)$	(0.06, 0.15)	83.67	85.92	83.20	85.01	81.76	28.6	41.9
$CARA_4(0,1)$	(0.06, 0.15)	85.49	86.95	85.12	86.01	82.60	31.4	46.8
$CARA_4(1,0)$	(0.06, 0.15)	86.06	87.29	85.68	86.66	82.62	32.9	49.3
$CARA_4(1,1)$	(0.06, 0.15)	85.19	86.69	84.94	85.93	82.58	30.9	46.1

5.4   Discussion and Conclusions

In this section, we proposed an innovative framework of ASD with CARA and TMLE. Under the framework, we demonstrated how to carry out an ASD using CARA randomization in both stages and applying TMLE to handle the "messy" data. Simulation studies have been conducted to verify the concept through the Type I error rates and to compare the power between the proposed ASD and the traditional ASD. We also put the two combination methods and two multiple testing methods side-by-side to further investigate their operating characteristics under different simulation settings.

The Simes method is more conservative than Dunnett method in all conditions for both type I error and power. Both Fisher's method and weighted inverse normal method are able to control the type I error at nominal level 0.05 except that when the endpoint is skewed, Fisher's method inflates the type I error up to 0.067. In terms of power, weighted inverse normal method dominated Fisher's method in every single situation. This phenomenon has also been discussed in other literature, e.g. Zaykin 2011, Liptak 1958, Won et al. 2009. In general, Dunnett method with weighted inverse normal method has an overall better performance than other combinations.

Furthermore, the advantage of the proposed framework lies on two major points. First, the proposed framework is very flexible in terms of the efficiency measure and ethics measure. And it is capable of addressing trial efficiency and ethics simultaneously. The diversity of the measures of trial efficiency and ethics as well as the tuning parameters endures us the ability to assign more patients to superior treatment arm while retain

the same power or even gain more power. Second, the nonparametric nature of TMLE can avoid model mis-specification and control Type I error rate under different and complicated data generating distributions. Particularly, when the normality of the data is invalid, which is always true in real applications, our proposed framework showed superior robustness through a two-step approach than tradition methods with respect to type I error control, power and correct selection rate.

It is worth mentioning that in scenario 1 when the endpoint was set to be binary, we didn't see a clear power gain or correct selection rate increase using the proposed ASD. During the simulation, the allocation probability $G_i(a, v)$ was restricted by a lower bound and a upper bound, which was unnecessary for other scenarios with continuous endpoint. Moreover, the initial number of patients in the second stage was also set to be one time more than in other scenarios. All these may be caused by the convergence issue in CARA where an initial estimate is needed to start the allocation procedure. A possible solution is to use the estimates of design parameters from the first stage to initiate the CARA procedure in the second stage. By doing this, we can potentially save the initial number of patients in the second stage and speed up the convergence in CARA and TMLE. However, whether or not the type I error will get compromised is unknown. A future work is needed in both theory and simulation to confirm this thought.

6 Conclusions

For the first two arms, we proposed an innovative framework of CARA design with TMLE. Under the framework, we demonstrated how to set up the allocation of a patient based on the full history of the previous patients' treatment assignments, responses, and covariates, and the covariates of the current patient to achieve different objectives. The TMLE is used to handle the "messy" data which is caused by the adaption in CARA design. In the theory part, we showed the consistency and asymptotic properties of the proposed family of CARA designs. In addition, the TMLE has been proved to have asymptotic normality in the proposed CARA designs under certain conditions. Furthermore, the simulation studies successfully verified the concept of the designs in different angels. The proposed framework shows advantage in both flexibility in terms of efficiency and ethics and robustness in terms of type I error, power and ATE estimation.

For aim 3, we introduced the concept of incorporating CARA and TMLE in ASD. Under the framework, we demonstrated how to carry out an ASD using CARA randomization in both stages and applying TMLE to handle the "messy" data in interim analysis and final analysis. Simulation studies have been conducted to justify the validity of the approach through the Type I error rates and to compare the power between the proposed approach and the traditional approach. In addition to the main results, we found that the Simes method is more conservative than Dunnett method in all conditions for both type I error and power. Both Fisher's method and weighted inverse normal method are able to control the type I error at nominal level except that Fisher's method inflates the

rate of type I error when the endpoint is highly skewed. In terms of power, weighted inverse normal method dominated Fisher's method in every single situation. In general, Dunnett method with weighted inverse normal method has an overall better performance than other combinations.

It is worth mentioning that the performance of either CARA with TMLE or ASD with CARA and TMLE doesn't dominate the tradition approaches when the trials have binary endpoint. There are two reasons for this phenomenon. First, the binary endpoint provides much less information than continuous endpoint does. This raises the difficulty in statistical inference. Second, the convergence of CARA and TMLE is the most challenge issue particularly when trial has binary endpoint. Throughout the simulation studies in this dissertation, three remedy methods were used to tackle this problem: (1) one may restrict G function in some pre-specified interval which avoids the allocation probability to be zero and one. Actually, the restriction is unnecessary for continuous endpoint. (2) instead of allocating the initial patients in a complete random manner, one may apply stratified permuted block randomization to achieve a more balanced initial allocation. (3) one can increase the initial number of patients and give CARA more time to find a more accurate estimation of the design parameters.

In summary, we accomplished the three arms in the dissertation. The proposed design frameworks are based on semiparametric approaches and avoid making model assumptions. This desirable feature makes it more appealing to biostatisticians than other parametric methods. Moreover, the proposed design framework provides the flexibility of balancing trial efficiency and ethics. This innovative property may further encourage

clinicalists in practicing adaptive designs in real applications.

7 Appendix: Proofs

Lemma 1: Suppose there is a class of estimating function $M_h^B(\phi)(\boldsymbol{O}_i)$ of a parameter $\phi \in \mathbb{R}$ indexed by h has the following form $M_h^B(\phi)(\boldsymbol{O}_i) = \frac{I_B((A_i, V_i))}{G_i(A_i, V_i)}(h(O_i) - \phi)$, where the indexed function $h : \mathbb{R} \to \mathbb{R}$ is bounded in $[h_L, h_U]$, the indicator function $I_B(x) = 1$ if the $x \in B$. Let $S_n^B(\phi)$ denote the martingale $S_n^B(\phi) = \sum_{i=1}^n \left(M_h^B(\phi)(\boldsymbol{O}_i) - E_{Q_0, G_i} M_h^B(\phi)(\boldsymbol{O}_i) \right)$. Then $\frac{1}{n} S_n^B(\phi) \xrightarrow{a.s.} 0$ if G_i is bounded in $[g_L, g_U]$ for all i and $0 < g_L < g_U < 1$.

Proof of Lemma 1: Let s_n^B denote the martingale difference $s_n^B = M_h^B(\phi)(\boldsymbol{O}_n) - E_{Q_0, G_n} M_h^B(\phi)(\boldsymbol{O}_n)$. Define the true parameter of $M_h^B(\phi)(\boldsymbol{O}_i)$ as $E_{Q_0 G_i} M_h^B(\phi_0)(\boldsymbol{O}_i) = 0$. ϕ_0 can be expressed explicitly as $\sum_{\{a,v\} \in B} \{E_{Q_0}(h(Y)|A = a, V = v)p_0(v)\}/p_{0,B}(v)$, where $p_{0,B}(v) = \sum_{\{a,v\} \in B} p_0(v)$. We use the short notation $I_B(i)$ to denote the indicator function $I_B(\{A_i, V_i\})$. For $p = 1$, $E\left(|s_i^B|^p|\mathcal{O}_{i-1}\right) = 0$. For any $1 < p \leq 2$, we have

$$
\begin{aligned}
E\left(|s_i^B|^p|\mathcal{O}_{i-1}\right) &= E\left(|s_i^B|^p|\mathcal{O}_{i-1}\right) \\
&= E\left(\left|\frac{I_B(i)}{G_i(A_i, V_i)}(h(O_i) - \phi) - p_{0,B}(v)(\phi_0 - \phi)\right|^p \Big| \mathcal{O}_{i-1}\right) \\
&= E\left(\left|\phi\left(p_{0,B}(v) - \frac{I_B(i)}{G_i(A_i, V_i)}\right) + \frac{I_B(i)}{G_i(A_i, V_i)}h(O_i) - p_{0,B}(v)\phi_0\right|^p \Big| \mathcal{O}_{i-1}\right) \\
&\leq E\left(\left|\phi\left(p_{0,B}(v) - \frac{I_B(i)}{G_i(a, v)}\right)\right|^p + \left|\frac{I_B(i)}{G_i(A_i, V_i)}h(O_i) - p_{0,B}(v)\phi_0\right|^p \Big| \mathcal{O}_{i-1}\right) \\
&\leq E\left(\left|\phi\left(p_{0,B}(v) - \frac{I_B(i)}{G_i(A_i, V_i)}\right)\right|^p \Big| \mathcal{O}_{i-1}\right) \\
&\quad + E\left(\left|\frac{I_B(i)}{G_i(a, v)}h(O_i) - p_{0,B}(v)\phi_0\right|^p \Big| \mathcal{O}_{i-1}\right)
\end{aligned}
$$

For the first term on the right hand side,

$$E\left(\left|\phi\left(p_{0,B}(v)-\frac{I_B(i)}{G_i(A_i,V_i)}\right)\right|^p\bigg|\mathcal{O}_{i-1}\right)=\phi^p E\left(\left|p_{0,B}(v)-\frac{I_B(i)}{G_i(A_i,V_i)}\right|^p\bigg|\mathcal{O}_{i-1}\right)$$

by Hölder's inequality

$$<\phi^p\left(E_{Q_0 G_i}\left(p_{0,B}(v)^2-\frac{2p_{0,B}(v)}{G_i(A_i,V_i)}I_B(i)+\frac{I_B(i)}{G_i(A_i,V_i)^2}\right)\right)^{p/2}$$

$$\leq\phi^p\left(1+\frac{1}{g_L^2}\right)^{p/2}$$

For the second term on the right hand side,

$$E\left(\left|\frac{I_B(i)}{G_i(A_i,V_i)}h(O_i)-p_{0,B}(v)\phi_0\right|^p\bigg|\mathcal{O}_{i-1}\right)<\left(E_{Q_0 G_i}\left(\frac{I_B(i)}{G_i(A_i,V_i)}h(O_i)-p_{0,B}(v)\phi_0\right)^2\right)^{p/2}$$

by Hölder's inequality

$$\leq\left(E_{Q_0 G_i}\left(\frac{I_B(i)}{G_i^2(A_i,V_i)}h(O_i)^2+p_{0,B}(v)^2\phi_0^2-2\frac{p_{0,B}(v)\phi_0}{G_i(A_i,V_i)}h(O_i)I_B(i)\right)\right)^{p/2}$$

$$\leq\left(\frac{\max(h_L^2,h_U^2)}{g_L^2}+\phi_0^2\right)^{p/2}$$

Thus, $E\left(|s_i|^p|\mathcal{F}_{i-1}\right)<\phi^p\left(1+\frac{1}{g_L^2}\right)^{p/2}+\phi_0^p\left(1+\frac{\max(h_L^2,h_U^2)}{g_L^2\phi_0^2}\right)^{p/2}$. For a sequence $\{c_i=i\}_n$,

we have

$$\sum_{i=1}^{\infty}c_i^{-p}E\left(|s_i|^p|\mathcal{O}_{i-1}\right)=\sum_{i=1}^{\infty}\frac{E\left(|s_i|^p|\mathcal{O}_{i-1}\right)}{c_i^p}$$

$$=\sum_{i=1}^{\infty}\frac{\phi^p\left(1+\frac{1}{g_L^2}\right)^{p/2}+\phi_0^p\left(1+\frac{\max(h_L^2,h_U^2)}{g_L^2\phi_0^2}\right)^{p/2}}{i^p}<\infty.$$

Therefore $\sum_{i=1}^{\infty}a_i^{-p}E\left(|s_i|^p|\mathcal{O}_{i-1}\right)<\infty$ holds for all $1\leq p\leq 2$. According to the martingale strong laws of large numbers,

$$\frac{S_n}{c_n}=\frac{1}{n}\sum_{i=1}^{n}\left(M_h^B(\phi)(\boldsymbol{O}_i(i))-E_{Q_0 G_i}M_h^B(\phi)(\boldsymbol{O}_i)\right)\xrightarrow{a.s.}0,$$

for all $\phi\in\Theta$.

Proof of Theorem 1:

First, simply let $I_B(i) = I_i(a,v)$, $h(O_i) = Y_i$, $\phi = \theta_{0,1}^{a,v}$. Under conditions (1) and (2), Lemma 1 gives

$$\sum_{i=1}^{n} \frac{I_i(a,v)}{G_i(a,v)}(Y_i - \theta_{0,1}^{a,v}) = 0.$$

It follows immediately that $\hat{\theta}_{n,1}^{a,v} \xrightarrow{a.s.} \theta_{0,1}^{a,v}$. Similarly, we have $\hat{\theta}_{n,2}^{a,v} \xrightarrow{a.s.} \theta_{0,2}^{a,v}$. Thus, $\hat{\boldsymbol{\theta}}_n \xrightarrow{a.s.}$ $\boldsymbol{\theta}_0$ as $n \to \infty$. Since under condition (3), the allocation function G_i is a continuous function in terms of $\hat{\boldsymbol{\theta}}_{i-1}$ and the target allocation function G_0 is also a continuous function in terms of $\boldsymbol{\theta}_0$, by continuous mapping we have

$$G_n(a,v) \xrightarrow{a.s.} G_0(a,v).$$

Second, if we let $I_B(i) = I_i(a,v)$, $h(O_i) = G_0(A_i, V_i)$ and $\phi = 0$, we have $\phi_0 = G_0(a,v)$

$$\frac{1}{n}\sum_{i=1}^{n} \frac{I_i(a,v)}{G_i(a,v)}G_0(a,v) \xrightarrow{a.s.} p_0(v)G_0(a,v).$$

This implies that $N_{a,v}(n)/n \xrightarrow{a.s.} p_0(v)G_0(a,v)$.

Lemma 2: Suppose there are two estimating functions $M_{h_1}^{B_1}(\phi_1)(\boldsymbol{O}_i)$ and $M_{h_2}^{B_2}(\phi_2)(\boldsymbol{O}_i)$ indexed by h_1 and h_2 respectively. h_1 is bounded in $[h_{1L}, h_{1U}]$ and h_2 is bounded in $[h_{2L}, h_{2U}]$. Under the condition that $B_1 = B_2 = \{(a,v)\}$, we omit the superscript. Let $S_{n,h_1}(\phi_1)$ and $S_{n,h_2}(\phi_2)$ denote the martingales $S_{n,h_1}(\phi_1) = \sum_{i=1}^{n}(M_{h_1}(\phi_1)(\boldsymbol{O}_i) - E_{Q_0,G_i}M_{h_1}(\phi_1)(\boldsymbol{O}_i))$, $S_{n,h_2}(\phi_2) = \sum_{i=1}^{n}(M_{h_2}(\phi_2)(\boldsymbol{O}_i) - E_{Q_0,G_i}M_{h_2}(\phi_2)(\boldsymbol{O}_i))$. Then

$$\sqrt{n}\begin{bmatrix} S_{n,h_1}(\phi_{h_1,0}) \\ S_{n,h_2}(\phi_{h_2,0}) \end{bmatrix} \xrightarrow{D} N\left(\boldsymbol{0}, \frac{p_0(v)}{G_0(a,v)}\begin{bmatrix} \phi_{h_1^2,0} - \phi_{h_1,0}^2 & \phi_{h_1 h_2,0} - \phi_{h_1,0}\phi_{h_2,0} \\ \phi_{h_1 h_2,0} - \phi_{h_1,0}\phi_{h_2,0} & \phi_{h_2^2,0} - \phi_{h_2,0}^2 \end{bmatrix}\right),$$

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where $\phi_{h_1,0}$, $\phi_{h_2,0}$, $\phi_{h_1^2,0}$, $\phi_{h_2^2,0}$, $\phi_{h_1 h_2,0}$ are the true parameters of the martingale estimating functions $M_{h_1}(\phi)(\boldsymbol{O}_i)$, $M_{h_2}(\phi)(\boldsymbol{O}_i)$, $M_{h_1^2}(\phi)(\boldsymbol{O}_i)$, $M_{h_2^2}(\phi)(\boldsymbol{O}_i)$, $M_{h_1 h_2}(\phi)(\boldsymbol{O}_i)$ respectively.

Proof of Lemma 2: By Theorem 1, we have $\frac{1}{n}S_{n,h_1}(\phi_1) \xrightarrow{a.s.} 0$ and $\frac{1}{n}S_{n,h_2}(\phi_2) \xrightarrow{a.s.} 0$. Let $s_{n,h_1}(\phi_1)$ and $s_{n,h_2}(\phi_2)$ denote the corresponding martingale differences. It is easy to show that the conditional variance of s_{i,h_1}, s_{i,h_2} and their conditional covariance are

$$E_{Q_0 G_i}\left(s_{i,h_1}(\phi_1)\right)^2 = \frac{p_0(v)}{G_i(a,v)}\left(\phi_{h_1^2,0} - 2\phi_1\phi_{h_1,0} + \phi_1^2\right) - p_0(v)^2(\phi_{h_1,0} - \phi_1)^2,$$

$$E_{Q_0 G_i}\left(s_{i,h_2}(\phi_2)\right)^2 = \frac{p_0(v)}{G_i(a,v)}\left(\phi_{h_2^2,0} - 2\phi_2\phi_{h_2,0} + \phi_2^2\right) - p_0(v)^2(\phi_{h_2,0} - \phi_2)^2,$$

$$E_{Q_0 G_i}\left(s_{i,h_1}(\phi_1)s_{i,h_2}(\phi_2)\right) = \frac{p_0(v)}{G_i(a,v)}\left(\phi_{h_1 h_2,0} - \phi_1\phi_{h_2,0} - \phi_2\phi_{h_1,0} + \phi_1\phi_2\right)$$
$$-p_0(v)^2(\phi_{h_1,0} - \phi_1)(\phi_{h_2,0} - \phi_2).$$

Consider a linear combination $t_i = \alpha_1 s_{i,h_1}(\phi_1) + \alpha_2 s_{i,h_2}(\phi_2)$, $\alpha_1, \alpha_2 \in \mathbb{R}$. We rewrite it in vector form $t_i = \boldsymbol{\alpha}^T \boldsymbol{s}_i(\phi_1, \phi_2)(\boldsymbol{O}_i)$, where $\boldsymbol{\alpha}^T = (\alpha_1, \alpha_2)$, $\boldsymbol{s}_i(\phi_1, \phi_2)(\boldsymbol{O}_i) = (s_{i,h_1}(\phi_1), s_{i,h_2}(\phi_2))$. The conditional variance-covariance matrix of t_i is

$$V_{t_i} = E_{Q_0 G_i} t_i^2 = \boldsymbol{\alpha}^T \begin{bmatrix} E_{Q_0 G_i}\left(s_{i,h_1}(\phi_1)\right)^2 & E_{Q_0 G_i}\left(s_{i,h_1}(\phi_1)s_{i,h_2}(\phi_2)\right) \\ E_{Q_0 G_i}\left(s_{i,h_1}(\phi_1)s_{i,h_2}(\phi_2)\right) & E_{Q_0 G_i}\left(s_{i,h_2}(\phi_2)\right)^2 \end{bmatrix} \boldsymbol{\alpha}$$

$$= \boldsymbol{\alpha}^T \left(\frac{p_0(v)}{G_i(a,v)}\boldsymbol{m}_1 - p_0(v)^2\boldsymbol{m}_2\right)\boldsymbol{\alpha},$$

where

$$\boldsymbol{m}_1 = \begin{bmatrix} \phi_{h_1^2,0} - 2\phi_1\phi_{h_1,0} + \phi_1^2 & \phi_{h_1 h_2,0} - \phi_1\phi_{h_2,0} - \phi_2\phi_{h_1,0} + \phi_1\phi_2 \\ \phi_{h_1 h_2,0} - \phi_1\phi_{h_2,0} - \phi_2\phi_{h_1,0} + \phi_1\phi_2 & \phi_{h_2^2,0} - 2\phi_2\phi_{h_2,0} + \phi_2^2 \end{bmatrix},$$

$$\boldsymbol{m}_2 = \begin{bmatrix} (\phi_{h_1,0} - \phi_1)^2 & (\phi_{h_1,0} - \phi_1)(\phi_{h_2,0} - \phi_2) \\ (\phi_{h_1,0} - \phi_1)(\phi_{h_2,0} - \phi_2) & (\phi_{h_2,0} - \phi_2)^2 \end{bmatrix}.$$

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$\{t_n\}$ is a martingale difference sequence. Let $T_n = \sum_{i=1}^n t_i$ be the martingale sum of t_i.

We define V_T as

$$\frac{1}{n}V_T = \lim_{n\to\infty} \frac{1}{n}\sum_{i=1}^n E[t_i^2] = \boldsymbol{\alpha}^T \left(p_0(v)\boldsymbol{m}_1 \lim_{n\to\infty} \frac{1}{n}\sum_{i=1}^n E\left(\frac{1}{G_i(a,v)}\right) - p_0(v)^2 \boldsymbol{m}_2 \right) \boldsymbol{\alpha}$$

Since $G_i(a,v)$ depends on $\boldsymbol{O}_{i-1}$ through $\hat{\boldsymbol{\theta}}_{i-1}$, by Theorem 1 we have $\hat{\boldsymbol{\theta}}_0 \xrightarrow{a.s.} \boldsymbol{\theta}_0$. Thus,

$E\left(\frac{1}{G_i(a,v)}\right) \to \frac{1}{G_0(a,v)}$ as long as $G_i(a,v)$ is a bounded and continuous function of $\hat{\boldsymbol{\theta}}_{i-1}$.

Therefore, $\frac{1}{n}V_T \to \boldsymbol{\alpha}^T \left(\frac{p_0(v)}{G_0(a,v)}\boldsymbol{m}_1 - p_0(v)^2\boldsymbol{m}_2 \right) \boldsymbol{\alpha}$. We define W_T as

$$\frac{1}{n}W_T = \lim_{n\to\infty} \frac{1}{n}\sum_{i=1}^n E_{Q_0 G_i}[t_i^2] = \boldsymbol{\alpha}^T \left(p_0(v)\boldsymbol{m}_1 \lim_{n\to\infty} \frac{1}{n}\sum_{i=1}^n \frac{1}{G_i(a,v)} - p_0(v)^2\boldsymbol{m}_2 \right) \boldsymbol{\alpha}.$$

By Theorem 1 and continuous mapping, we have $\frac{1}{n}W_T \xrightarrow{P} \boldsymbol{\alpha}^T \left(\frac{p_0(v)}{G_0(a,v)}\boldsymbol{m}_1 - p_0(v)^2\boldsymbol{m}_2 \right) \boldsymbol{\alpha}$.

Thus, for the martingale t_i we have $W_T \xrightarrow{P} V_T$. For all $\epsilon > 0$, we have:

$$\sum_{j=1}^n \left[E\left(\left(\frac{t_j}{\sqrt{n\boldsymbol{\alpha}^T \left(\frac{p_0(v)}{G_0(a,v)}\boldsymbol{m}_1 - p_0(v)^2\boldsymbol{m}_2 \right) \boldsymbol{\alpha}}} \right)^2 \right. \right.$$

$$\left. \left. \times I\left(\left| \frac{t_j}{\sqrt{n\boldsymbol{\alpha}^T \left(\frac{p_0(v)}{G_0(a,v)}\boldsymbol{m}_1 - p_0(v)^2\boldsymbol{m}_2 \right) \boldsymbol{\alpha}}} \right| \geq \epsilon \right) \right) \right]$$

$$\leq \frac{1}{n}\sum_{j=1}^n \left[E\left(\left(\frac{\sup_j |t_j|}{\sqrt{\boldsymbol{\alpha}^T \left(\frac{p_0(v)}{G_0(a,v)}\boldsymbol{m}_1 - p_0(v)^2\boldsymbol{m}_2 \right) \boldsymbol{\alpha}}} \right)^2 \right. \right.$$

$$\left. \left. \times I\left(n \leq \frac{\sup_j (t_j^2)/\epsilon^2}{\boldsymbol{\alpha}^T \left(\frac{p_0(v)}{G_0(a,v)}\boldsymbol{m}_1 - p_0(v)^2\boldsymbol{m}_2 \right) \boldsymbol{\alpha}} \right) \right) \right]$$

$$\leq \frac{g_U \left(\alpha_1^2 \phi_1^2 + \alpha_2^2 \phi_2^2 + \rho_{12} \right)}{g_L^2 \boldsymbol{\alpha}^T \left(p_0(v)\boldsymbol{m}_1 - g_U p_0(v)^2\boldsymbol{m}_2 \right) \boldsymbol{\alpha}}$$

$$\times \left(\frac{1}{n}\sum_{j=1}^n I\left(n \leq \frac{g_U \left(\alpha_1^2 \phi_1^2 + \alpha_2^2 \phi_2^2 + \rho_{12} \right)/\epsilon^2}{g_L^2 \boldsymbol{\alpha}^T \left(p_0(v)\boldsymbol{m}_1 - g_U p_0(v)^2\boldsymbol{m}_2 \right) \boldsymbol{\alpha}} \right) \right) \longrightarrow 0,$$

where $\rho_{12} = \alpha_1^2 \max(h_{1L}^2, h_{1U}^2)) + \alpha_2^2 \max(h_{2L}^2, h_{2U}^2)$. Therefore, the Lindeberg conditions

holds. By martingale central limit theorem,

$$\frac{1}{\sqrt{n}} \sum_{i=1}^{n} \boldsymbol{\alpha}^T \boldsymbol{s}_i(\phi_1, \phi_2)(\boldsymbol{O}_i) \xrightarrow{D} N\left(0, \boldsymbol{\alpha}^T \left(\frac{p_0(v)}{G_0(a, v)} \boldsymbol{m}_1 - p_0(v)^2 \boldsymbol{m}_2\right) \boldsymbol{\alpha}\right) \qquad (27)$$

The convergence holds for all $\alpha_1, \alpha_2 \in \mathbb{R}$, by Cramer-Wold Theorem,

$$\frac{1}{\sqrt{n}} \begin{bmatrix} S_{n,h_1}(\phi_1) \\ S_{n,h_2}(\phi_2) \end{bmatrix} \xrightarrow{D} N\left(\boldsymbol{0}, \frac{p_0(v)}{G_0(a, v)} \boldsymbol{m}_1 - p_0(v)^2 \boldsymbol{m}_2\right).$$

In addition, when plugging in the true parameter we have

$$\frac{1}{\sqrt{n}} \begin{bmatrix} S_{n,h_1}(\phi_{h_1,0}) \\ S_{n,h_2}(\phi_{h_2,0}) \end{bmatrix} \xrightarrow{D} N\left(\boldsymbol{0}, \frac{p_0(v)}{G_0(a, v)} \begin{bmatrix} \phi_{h_1^2,0} - \phi_{h_1,0}^2 & \phi_{h_1 h_2,0} - \phi_{h_1,0}\phi_{h_2,0} \\ \phi_{h_1 h_2,0} - \phi_{h_1,0}\phi_{h_2,0} & \phi_{h_2^2,0} - \phi_{h_2,0}^2 \end{bmatrix}\right).$$

Proof of theorem 2: Firstly, we simply let $h_1(O_i) = Y_i$, $h_2(O_i) = Y_i^2$. Under conditions

(1), (2), (3), (4) and (5), Lemma 2 gives

$$\sqrt{n}\left((\hat{\theta}_{n,1}^{a,v}, \hat{\theta}_{n,2}^{a,v}) - (\theta_{0,1}^{a,v}, \theta_{0,2}^{a,v})\right) \xrightarrow{D} N(0, \Sigma_0^{a,v}),$$

where

$$\Sigma_0^{a,v} = \frac{1}{p_0(v)G_0(a, v)} \begin{pmatrix} \theta_{0,2}^{a,v} - (\theta_{0,1}^{a,v})^2 & \theta_{0,3}^{a,v} - (\theta_{0,1}^{a,v})\theta_{0,2}^{a,v} \\ \theta_{0,3}^{a,v} - (\theta_{0,1}^{a,v})\theta_{0,2}^{a,v} & \theta_{0,3}^{a,v} - (\theta_{0,2}^{a,v})^2 \end{pmatrix},$$

where $\theta_{0,3}^{a,v}$ and $\theta_{0,4}^{a,v}$ are defined as the 3rd and 4th conditional moment of Y given $(A, V) =$

(a, v) under P_0. Two different pairs of (a, v) is zero because the the multiplicity of the

indication functions become zero. Therefore,

$$\sqrt{n}(\hat{\boldsymbol{\theta}}_n - \boldsymbol{\theta}_0) \xrightarrow{D} N(0, \Sigma_0^{CARA}),$$

where $\Sigma_0^{CARA} = \text{diag}\{\Sigma_0^{a,v}, (a, v) \in \mathbb{A} \times \mathbb{V}\}$ is a diagonal block matrix.

Secondly, we let $h(O_i) = G_0(A_i, V_i)$ and $\phi = 0$, then the true parameter $\phi_{h_1,0} = G_0(a, v)$ and $\phi_{h_1^2,0} = G_0(a, v)^2$. Lemma 2 implies

$$\frac{1}{\sqrt{n}} \sum_{i=1}^{n} \left(\frac{I_i(a, v)}{G_i(A_i, V_i)} G_0(A_i, V_i) - p_0(v) G_0(a, v) \right) \xrightarrow{D} N(0, \frac{p_0(v)}{G_0(a, v)} G_0(a, v)^2 - p_0(v)^2 G_0(a, v)^2).$$

By simplifying the above expression, we have

$$\sqrt{n} \left(N_{a,v}(n)/n - p_0(v) G_0(a, v) \right) \xrightarrow{D} N \left(0, p_0(v) G_0(a, v) - p_0(v)^2 G_0(a, v)^2 \right).$$

Proof of Theorem 3: Consider the fluctuating model $Q_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon})$ as defined in (19) and (20). The local fluctuation model of $Q_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0)$ at $\boldsymbol{\epsilon}_0$ then is denoted as $Q_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0)(\boldsymbol{\epsilon})$. Since $\boldsymbol{\epsilon}_0$ is defined as the minimum of the expectation of the loss function defined in theorem 3 under Q_0 from the data generating distribution P_0 and the true design parameter $\boldsymbol{\theta}_0$ (or G_0), the derivative of $E_{Q_0 G_0} L(Q_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0)(\boldsymbol{\epsilon}))$ at $\boldsymbol{\epsilon} = 0$ equals zero. Thus, we have for all $j \in \{0, 1, \ldots, K\}$

$$E_{Q_0 G_0} \left(\frac{\partial}{\partial \epsilon_j} L(Q_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0)(\boldsymbol{\epsilon})) \Big|_{\epsilon_j = 0} \right) = E_{Q_0 G_0} \left(H_j(G_0)(\bar{Q}_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0) - Y) \right)$$
$$= E_{Q_0 G_0} \left(IC_{j,Y|A,W}(Q_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0), G_0) \right) = 0$$

$$E_{Q_0 G_0} \left(\frac{\partial}{\partial \epsilon_j} L(Q_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0)(\boldsymbol{\epsilon})) \Big|_{\epsilon_j = 0} \right) = E_{Q_0 G_0} \left(\bar{Q}_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0)(j, \boldsymbol{W}) - \Psi_j(Q_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0)) \right)$$
$$= E_{Q_0 G_0} \left(IC_{j,W}(Q_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0), G_0) \right) = 0$$

Simply by combining the above two equations, it follows immediately that

$$E_{Q_0 G_0} \left(IC_j(Q_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0), G_0) \right) = 0$$

According to Theorem 1.3M. Van der Laan and Robins 2012, the above equation implies

$$\psi_0 - \Psi(Q_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0)) = 0.$$

Proof of theorem 4:

By definition,

$$
\begin{aligned}
\boldsymbol{\beta}_0 &= \arg\max_{\boldsymbol{\beta}} E_{Q_0 G_0} \log \left[\operatorname{expit}(\mu_0(\boldsymbol{\theta}_0, \boldsymbol{\beta})(O)) \right]^Y \left[1 - \operatorname{expit}(\mu_0(\boldsymbol{\theta}_0, \boldsymbol{\beta})(O)) \right]^{1-Y} \\
&= \arg\max_{\boldsymbol{\beta}} E_{Q_0 G_i} \left(\frac{G_0(A_i, V_i)}{G_i(A_i, V_i)} \log \left[\operatorname{expit}(\mu_0(\boldsymbol{\theta}_0, \boldsymbol{\beta})(O_i)) \right]^{Y_i} \left[1 - \operatorname{expit}(\mu_0(\boldsymbol{\theta}_0, \boldsymbol{\beta})(O_i)) \right]^{1-Y_i} \right),
\end{aligned}
$$

where $\mu_0(\boldsymbol{\theta}_0, \boldsymbol{\beta})(O) = \operatorname{logit} \theta_{0,1}^{A,V} + \boldsymbol{W}\boldsymbol{\beta}$. Equivalently, $\boldsymbol{\beta}_0$ is the true parameter of

$$
\begin{aligned}
&E_{Q_0 G_i} \left(\frac{\partial}{\partial \beta_j} \frac{G_0(A_i, V_i)}{G_i(A_i, V_i)} \log \left[\operatorname{expit}(\mu_0(\boldsymbol{\theta}_0, \boldsymbol{\beta})(O_i)) \right]^{Y_i} \left[1 - \operatorname{expit}(\mu_0(\boldsymbol{\theta}_0, \boldsymbol{\beta})(O_i)) \right]^{1-Y_i} \Big|_{\beta_j = \beta_{0,j}} \right) \\
&= E_{Q_0 G_i} \left(\frac{G_0(A_i, V_i)}{G_i(A_i, V_i)} W_{i,j} \left(Y_i - \bar{Q}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0)(A_i, \boldsymbol{W}_i) \right) \right) = 0,
\end{aligned}
$$

for all $j \in \{1, \ldots, n_W\}$. Let $M_j(\boldsymbol{\theta}, \boldsymbol{\beta})(O_i) = \frac{G_{\boldsymbol{\theta}}(A_i, V_i)}{G_i(A_i, V_i)} W_{i,j} \left(Y_i - \bar{Q}(\boldsymbol{\theta}, \boldsymbol{\beta})(A_i, \boldsymbol{W}_i) \right)$ and then $S_{j,n}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0) = \sum_{i=1}^{n} M_j(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0)(O_i)$ is a martingale. Under condition (2), we have G_i is bounded in $[g_L, g_U]$ for all i and $0 < g_L < g_U < 1$. For $p = 1$, $E\left(|M_j(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0)(O_i)|^p | \mathcal{O}_{i-1} \right) = 0$. For any $1 < p \leq 2$, we have

$$
\begin{aligned}
E\left(|M_j(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0)(O_i)|^p | \mathcal{O}_{i-1} \right) &= E\left(\left| \frac{G_0(A_i, V_i)}{G_i(A_i, V_i)} W_{ij} \left(Y_i - \bar{Q}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0)(A_i, \boldsymbol{W}_i) \right) \right|^p \Big| \mathcal{O}_{i-1} \right) \\
&\leq \left(\frac{g_U}{g_L} \right)^p E\left(\left| W_{ij} \left(Y_i - \bar{Q}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0)(A_i, \boldsymbol{W}_i) \right) \right|^p \Big| \mathcal{O}_{i-1} \right) \\
&\leq \left(\frac{g_U}{g_L} \right)^p \max |W_j|^p < \infty.
\end{aligned}
$$

Therefore, for a sequence $\{c_i = i\}_n$, we have that $\sum_{i=1}^{\infty} c_i^{-p} E\left(|M_j(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0)(O_i)|^p | \mathcal{O}_{i-1} \right) < \infty$ holds for all $1 \leq p \leq 2$. According to the martingale strong laws of large num-

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bers, $\frac{1}{n}\sum_{i=1}^{n} M_j(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0)(O_i) \xrightarrow{a.s.} 0$ holds for all $j \in \{1, \ldots, n_W\}$. Since from theorem 1, we know $\hat{\boldsymbol{\theta}}_n \xrightarrow{a.s.} \boldsymbol{\theta}_0$. It follows immediately by continuous mapping that $\frac{1}{n}\sum_{i=1}^{n} M_j(\hat{\boldsymbol{\theta}}_n, \boldsymbol{\beta}_0)(O_i) \xrightarrow{a.s.} 0$. Since $\frac{1}{n}\sum_{i=1}^{n} M_j(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n)(O_i) = 0$, under condition (6) we have

$$
\begin{aligned}
\frac{1}{n}\sum_{i=1}^{n} \boldsymbol{M}(\hat{\boldsymbol{\theta}}_n, \boldsymbol{\beta}_0)(O_i) &= \frac{1}{n}\sum_{i=1}^{n} \left(\boldsymbol{M}(\hat{\boldsymbol{\theta}}_n, \boldsymbol{\beta}_0)(O_i) - \boldsymbol{M}(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n)(O_i) \right) \\
&= \left(\frac{1}{n}\sum_{i=1}^{n} -\frac{d}{d\boldsymbol{\beta}_0} \boldsymbol{M}(\hat{\boldsymbol{\theta}}_n, \boldsymbol{\beta}_0)(O_i) \right) (\hat{\boldsymbol{\beta}}_n - \boldsymbol{\beta}_0) \xrightarrow{a.s.} 0,
\end{aligned}
$$

where $\boldsymbol{M}(\boldsymbol{\theta}, \boldsymbol{\beta}) = (M_1(\boldsymbol{\theta}, \boldsymbol{\beta}), \ldots, M_{n_W}(\boldsymbol{\theta}, \boldsymbol{\beta}))$ is the stacked vector, and

$$
\begin{aligned}
-\frac{1}{n}\sum_{i=1}^{n} \frac{d}{d\beta_{0,j}} M_k(\hat{\boldsymbol{\theta}}_n, \boldsymbol{\beta}_0)(O_i) &= \frac{1}{n}\sum_{i=1}^{n} \frac{G_0(A_i, V_i)}{G_i(A_i, V_i)} W_{i,j} W_{i,k} \bar{Q}(\hat{\boldsymbol{\theta}}_n, \boldsymbol{\beta}_0)(1 - \bar{Q}(\hat{\boldsymbol{\theta}}_n, \boldsymbol{\beta}_0)) \\
&\xrightarrow{a.s.} E_{Q_0 G_0} \left(W_j W_k \bar{Q}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0)(1 - \bar{Q}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0)) \right) < \infty.
\end{aligned}
$$

Assume that the matrix $E_{Q_0 G_0} \left(\boldsymbol{W} \boldsymbol{W}^T \bar{Q}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0)(1 - \bar{Q}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0)) \right)$ is invertible, then we have $\hat{\boldsymbol{\beta}}_n \xrightarrow{a.s.} \boldsymbol{\beta}_0$ as $n \to \infty$. Similarly, for $\boldsymbol{\epsilon}_0$ we have

$$
\begin{aligned}
\boldsymbol{\epsilon}_0 &= \arg\max_{\boldsymbol{\epsilon}} E_{Q_0 G_0} \log \left[\bar{Q}_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}) \right]^Y \left[1 - \bar{Q}_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}) \right]^{1-Y} \\
&= \arg\max_{\boldsymbol{\epsilon}} E_{Q_0 G_i} \frac{G_0(A_i, V_i)}{G_i(A_i, V_i)} \log \left[\bar{Q}_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon})(O_i) \right]^Y \left[1 - \bar{Q}_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon})(O_i) \right]^{1-Y}.
\end{aligned}
$$

Equivalently, $\boldsymbol{\epsilon}_0$ is the true parameter of

$$
E_{Q_0 G_i} \left(\frac{G_0(A_i, V_i)}{G_i(A_i, V_i)} H_j(G_0)(A_i, \boldsymbol{W}_i) \left(Y_i - \bar{Q}_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0)(A_i, \boldsymbol{W}_i) \right) \right) = 0,
$$

for all $j \in \{0, 1, \ldots, K\}$. Let $M_j(\boldsymbol{\theta}, \boldsymbol{\beta}, \epsilon)(O_i) = \frac{G_{\boldsymbol{\theta}}(A_i, V_i)}{G_i(A_i, V_i)} H_j(G_0)(A_i, \boldsymbol{W}_i) \left(Y_i - \bar{Q}_{G_{\boldsymbol{\theta}}}(\boldsymbol{\theta}, \boldsymbol{\beta}, \epsilon)(A_i, \boldsymbol{W}_i) \right)$ and then $S_{j,n}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0) = \sum_{i=1}^{n} M_j(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0)(O_i)$ is a martingale. Under condition (2), we have G_i is bounded in $[g_L, g_U]$ for all i and $0 < g_L < g_U < 1$. Also G_0 should be

bounded in $[g_L, g_U]$. For $p = 1$, $E\left(|M_j(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0)(O_i)|^p | \mathcal{O}_{i-1}\right) = 0$. For any $1 < p \leq 2$, we have

$$
\begin{aligned}
&E\left(|M_j(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0)(O_i)|^p | \mathcal{O}_{i-1}\right) \\
\leq\ & \left(\frac{g_U}{g_L}\right)^p E\left(\left| H_j(G_0)(A_i, \boldsymbol{W}_i)\left(Y_i - \bar{Q}_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0)(A_i, \boldsymbol{W}_i)\right)\right|^p \Big| \mathcal{O}_{i-1}\right) \\
\leq\ & \left(\frac{g_U}{g_L}\right)^p \frac{1}{g_L} < \infty.
\end{aligned}
$$

Therefore, we have that $\frac{1}{n}\sum_{i=1}^n M_j(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0)(O_i) \xrightarrow{a.s.} 0$ holds for all $j \in \{0, 1, \ldots, K\}$. As previously showed that $(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n) \xrightarrow{a.s.} (\boldsymbol{\theta}_0, \boldsymbol{\beta}_0)$, it follows immediately by continuous mapping that $\frac{1}{n}\sum_{i=1}^n M_j(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \boldsymbol{\epsilon}_0)(O_i) \xrightarrow{a.s.} 0$. Since $\frac{1}{n}\sum_{i=1}^n M_j(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \hat{\boldsymbol{\epsilon}}_n)(O_i) = 0$, we have

$$
\begin{aligned}
\frac{1}{n}\sum_{i=1}^n \boldsymbol{M}(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \boldsymbol{\epsilon}_0)(O_i)\ &=\ \frac{1}{n}\sum_{i=1}^n \left(\boldsymbol{M}(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \boldsymbol{\epsilon}_0)(O_i) - \boldsymbol{M}(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \hat{\boldsymbol{\epsilon}}_n)(O_i)\right) \\
&=\ \left(\frac{1}{n}\sum_{i=1}^n -\frac{d}{d\boldsymbol{\epsilon}_0}\boldsymbol{M}(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \boldsymbol{\epsilon}_0)(O_i)\right)(\hat{\boldsymbol{\epsilon}}_n - \boldsymbol{\epsilon}_0) \xrightarrow{a.s.} 0,
\end{aligned}
$$

where $\boldsymbol{M}(\boldsymbol{\theta}, \boldsymbol{\beta}, \boldsymbol{\epsilon}) = (M_1(\boldsymbol{\theta}, \boldsymbol{\beta}, \boldsymbol{\epsilon}), \ldots, M_K(\boldsymbol{\theta}, \boldsymbol{\beta}, \boldsymbol{\epsilon}))$ is the stacked vector, and

$$
\begin{aligned}
&-\frac{1}{n}\sum_{i=1}^n \frac{d}{d\epsilon_{0,j}} M_k(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \boldsymbol{\epsilon}_0)(O_i) \\
=\ & \frac{1}{n}\sum_{i=1}^n \frac{G_0(A_i, V_i)}{G_i(A_i, V_i)} H_j(G_0) H_k(G_0)\bar{Q}(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \boldsymbol{\epsilon}_0)(1 - \bar{Q}(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \boldsymbol{\epsilon}_0)) \\
& \xrightarrow{a.s.} E_{Q_0 G_0}\left(H_j(G_0) H_k(G_0)\bar{Q}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0)(1 - \bar{Q}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0))\right).
\end{aligned}
$$

When $j \neq k$, $H_j(G_0) H_k(G_0) = 0$, the matrix $E_{Q_0 G_0}\left(\boldsymbol{H}(G_0)\boldsymbol{H}(G_0)^T \bar{Q}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0)(1 - \bar{Q}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0))\right)$ is a diagonal matrix. Hence, we put all things together that

$$
(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \hat{\boldsymbol{\epsilon}}_n) \xrightarrow{a.s.} (\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0)
$$

as $n \to \infty$.

Proof of theorem 5:

According to Theorem 3, we have $E_{Q_{G_0} G_i} \left(\frac{G_0(A_i, V_i)}{G_i(A_i, V_i)} \mathbf{IC}(Q_{G_0}, G_0)(O_i) \right) = 0$. And be-

cause $(\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \hat{\boldsymbol{\epsilon}})$ solves the estimating equation (18) according to theorem 4, we have

$\frac{1}{n} \sum_{i=1}^{n} \frac{G_n(A_i, V_i)}{G_i(A_i, V_i)} \mathbf{IC}(Q_n^\star, G_n)(O_i) = 0$. Therefore, by the definition of pathwise differentia-

bility, we have

$$
\hat{\psi}_{n,j}^{TMLE} - \psi_0 = \Psi(Q_n^\star) - \Psi(Q_{G_0}(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0))
$$

$$
= -\frac{1}{n} \sum_{i=1}^{n} E_{Q_{G_0} G_i} \left(\frac{G_n(A_i, V_i)}{G_i(A_i, V_i)} \mathbf{IC}(Q_n^\star, G_n)(O_i) \right)
$$

$$
= \frac{1}{n} \sum_{i=1}^{n} \frac{G_0(A_i, V_i)}{G_i(A_i, V_i)} \mathbf{IC}(Q_{G_0}, G_0)(O_i)
$$

$$
+ \frac{1}{n} \sum_{i=1}^{n} \left[\frac{G_n(A_i, V_i)}{G_i(A_i, V_i)} \mathbf{IC}(Q_n^\star, G_n)(O_i) - \frac{G_0(A_i, V_i)}{G_i(A_i, V_i)} \mathbf{IC}(Q_{G_0}, G_0)(O_i) \right]
$$

$$
- \frac{1}{n} \sum_{i=1}^{n} E_{Q_{G_0} G_i} \left[\frac{G_n(A_i, V_i)}{G_i(A_i, V_i)} \mathbf{IC}(Q_n^\star, G_n)(O_i) - \frac{G_0(A_i, V_i)}{G_i(A_i, V_i)} \mathbf{IC}(Q_{G_0}, G_0)(O_i) \right].
$$

We use notation $\boldsymbol{D}(\boldsymbol{\theta}, \boldsymbol{\beta}, \boldsymbol{\epsilon})(O_i) = G_{\boldsymbol{\theta}}(A_i, V_i) \mathbf{IC}(Q_{\boldsymbol{\theta}}(\boldsymbol{\theta}, \boldsymbol{\beta}, \boldsymbol{\epsilon}), G_{\boldsymbol{\theta}})(O_i)$, then we have by

Taylor expansion

$$
\frac{1}{n} \sum_{i=1}^{n} \left[\frac{G_n(A_i, V_i)}{G_i(A_i, V_i)} \mathbf{IC}(Q_n^\star, G_n)(O_i) - \frac{G_0(A_i, V_i)}{G_i(A_i, V_i)} \mathbf{IC}(Q_{G_0}, G_0)(O_i) \right]
$$

$$
= \left(\frac{1}{n} \sum_{i=1}^{n} \frac{1}{G_i} \frac{d\boldsymbol{D}(\boldsymbol{\theta}, \boldsymbol{\beta}, \boldsymbol{\epsilon})}{d(\boldsymbol{\theta}, \boldsymbol{\beta}, \boldsymbol{\epsilon})} \Big|_{(\boldsymbol{\theta}, \boldsymbol{\beta}, \boldsymbol{\epsilon})=(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0)}(O_i) \right) \left((\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \hat{\boldsymbol{\epsilon}}_n) - (\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0) \right),
$$

and

$$
\frac{1}{n} \sum_{i=1}^{n} E_{Q_{G_0} G_i} \left[\frac{G_n(A_i, V_i)}{G_i(A_i, V_i)} \mathbf{IC}(Q_n^\star, G_n)(O_i) - \frac{G_0(A_i, V_i)}{G_i(A_i, V_i)} \mathbf{IC}(Q_{G_0}, G_0)(O_i) \right]
$$

$$
= \left(\frac{1}{n} \sum_{i=1}^{n} E_{Q_{G_0} G_i} \left[\frac{1}{G_i} \frac{d\boldsymbol{D}(\boldsymbol{\theta}, \boldsymbol{\beta}, \boldsymbol{\epsilon})}{d(\boldsymbol{\theta}, \boldsymbol{\beta}, \boldsymbol{\epsilon})} \Big|_{(\boldsymbol{\theta}, \boldsymbol{\beta}, \boldsymbol{\epsilon})=(\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0)}(O_i) \right] \right) \left((\hat{\boldsymbol{\theta}}_n, \hat{\boldsymbol{\beta}}_n, \hat{\boldsymbol{\epsilon}}_n) - (\boldsymbol{\theta}_0, \boldsymbol{\beta}_0, \boldsymbol{\epsilon}_0) \right).
$$

Based on Theorem 1, we can easily have

$$\frac{1}{n}\sum_{i=1}^{n}\left(\frac{1}{G_i}\frac{d\boldsymbol{D}(\boldsymbol{\theta},\boldsymbol{\beta},\boldsymbol{\epsilon})}{d(\boldsymbol{\theta},\boldsymbol{\beta},\boldsymbol{\epsilon})(O_i)}-E_{Q_{G_0}G_i}\left[\frac{1}{G_i}\frac{d\boldsymbol{D}(\boldsymbol{\theta},\boldsymbol{\beta},\boldsymbol{\epsilon})}{d(\boldsymbol{\theta},\boldsymbol{\beta},\boldsymbol{\epsilon})(O_i)}\right]\right)\Big|_{(\boldsymbol{\theta},\boldsymbol{\beta},\boldsymbol{\epsilon})=(\boldsymbol{\theta}_0,\boldsymbol{\beta}_0,\boldsymbol{\epsilon}_0)}=o_p(1).$$

Assume all conditions in Theorem 8 in M. J. Van der Laan 2008 hold (where it is generally the case), then $\sqrt{n}\left((\hat{\boldsymbol{\theta}}_n,\hat{\boldsymbol{\beta}}_n,\hat{\boldsymbol{\epsilon}}_n)-(\boldsymbol{\theta}_0,\boldsymbol{\beta}_0,\boldsymbol{\epsilon}_0)\right)$ has an asymptotic multivariate normal distribution. Therefore,

$$\frac{1}{\sqrt{n}}\sum_{i=1}^{n}\left[\frac{G_n(A_i,V_i)}{G_i(A_i,V_i)}\mathbf{IC}(Q_n^{\star},G_n)(O_i)-\frac{G_0(A_i,V_i)}{G_i(A_i,V_i)}\mathbf{IC}(Q_{G_0},G_0)(O_i)\right]$$
$$-\frac{1}{\sqrt{n}}\sum_{i=1}^{n}E_{Q_{G_0}G_i}\left[\frac{G_n(A_i,V_i)}{G_i(A_i,V_i)}\mathbf{IC}(Q_n^{\star},G_n)(O_i)-\frac{G_0(A_i,V_i)}{G_i(A_i,V_i)}\mathbf{IC}(Q_{G_0},G_0)(O_i)\right]=o_p(1).$$

It follows immediately that

$$\sqrt{n}(\hat{\psi}_{n,j}^{TMLE}-\psi_0)=\frac{1}{\sqrt{n}}\sum_{i=1}^{n}\frac{G_0(A_i,V_i)}{G_i(A_i,V_i)}\mathbf{IC}(Q_{G_0},G_0)(O_i)+o_p(1).$$

As a martingale difference $E_{Q_{G_0}G_i}\frac{G_0(A_i,V_i)}{G_i(A_i,V_i)}\mathbf{IC}(Q_{G_0},G_0)(O_i)=0$ for all $i=1,\dots,n$, the multivariate Lindeberg-Feller condition holds according to Condition 2 and the fact that $\mathbf{IC}(\cdot)\in L^2(P)^{(K+1)}$. Thus, we have

$$\sqrt{n}\left(\hat{\boldsymbol{\psi}}_n^{TMLE}-\boldsymbol{\psi}_0\right)\xrightarrow{D}N(0,\Sigma_0^{TMLE})\text{ as }n\to\infty,$$

where Σ_0^{TMLE} is a $(K+1)\times(K+1)$ covariance matrix with

$$\sigma_0^{TMLE}(j,k)=E_{Q_0G_0}\left(\mathrm{IC}_j(Q_{G_0}(\boldsymbol{\theta}_0,\boldsymbol{\beta}_0,\boldsymbol{\epsilon}_0),G_0)\,\mathrm{IC}_k(Q_{G_0}(\boldsymbol{\theta}_0,\boldsymbol{\beta}_0,\boldsymbol{\epsilon}_0),G_0)\right)$$

with a consistent estimator

$$\hat{\sigma}_n^{TMLE}(j,k)=\frac{1}{n}\sum_{i=1}^{n}\left(\frac{G_n^{\star}(A_i,V_i)}{G_i(A_i,V_i)}\right)^2\left(\mathrm{IC}_j(Q_n^{\star},G_n^{\star})(O_i)\,\mathrm{IC}_k(Q_n^{\star},G_n^{\star})(O_i)\right).$$

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