
EXACT STATISTICAL ANALYSIS FOR RESPONSE-ADAPTIVE CLINICAL TRIALS: A GENERAL AND COMPUTATIONALLY TRACTABLE APPROACH

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ABSTRACT

Response-adaptive (RA) designs of clinical trials allow targeting a given objective by skewing the allocation of participants to treatments based on observed outcomes. RA designs face greater regulatory scrutiny due to potential type I error inflation, which limits their uptake in practice. Existing approaches to type I error control either only work for specific designs, have a risk of Monte Carlo/approximation error, are conservative, or computationally intractable. We develop a general and computationally tractable approach for exact analysis in two-arm RA designs with binary outcomes. We use the approach to construct exact tests applicable to designs that use either randomized or deterministic RA procedures, allowing for complexities such as delayed outcomes, early stopping or allocation of participants in blocks. Our efficient forward recursion implementation allows for testing of two-arm trials with 1,000 participants on a standard computer. Through an illustrative computational study of trials using randomized dynamic programming we show that, contrary to what is known for equal allocation, a conditional exact test has, almost uniformly, higher power than the unconditional test. Two real-world trials with the above-mentioned complexities are re-analyzed to demonstrate the value of our approach in controlling type I error and/or improving the statistical power.

Keywords Conditional test · Design and analysis of experiments · Exact test · Markov chains · Unconditional test

1. Introduction

Product development and innovation in various industries has become dominated by the use of randomized experiments as a reliable method of analysis. Introduction and widespread adoption of randomized experiments revolutionized the field of medical research several decades ago in the form of randomized controlled trials (Bhatt, 2010) and the field of digital marketing as A/B tests in the past decade (Kohavi et al., 2020).

In more recent years, a *sequential* approach to randomized experiments has gained increased popularity, in particular for the design of clinical trials in medical research. Such experiments include *response-adaptive* (RA) designs, which

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date back to [Thompson \(1933\)](#), and which sequentially adjust the allocation of participants to treatments based on the history of participant outcomes and treatment allocations (*trial history*). A wide variety of RA designs has been developed, able to achieve different objectives, such as increasing the expected participant outcomes, statistical power, or a combination of both ([Villar et al., 2015](#); [Robertson et al., 2023](#)).

In this paper, we refer to a *design* as the complete mathematical description of a clinical trial, which includes the number of treatments, endpoint type (assumed binary in this paper), allocation procedure, interim decision points (if any beyond final), and statistical test(s). What distinguishes an RA design from a *non-response-adaptive* (NRA) design is primarily the nature of the allocation procedure used to allocate participants to treatments. An allocation procedure is referred to as an *RA procedure* if at least one participant allocation depends on the outcomes history, and a design as an RA design when its allocation procedure is RA; otherwise, we call it an NRA procedure and correspondingly an NRA design. Further, we distinguish RA procedures where the probability of allocating a participant to either treatment is strictly between 0 and 1 for every participant and all possible (finite) trial histories, which we call *response-adaptive randomization* (RAR) procedures, from RA procedures where this probability is zero or one for at least one participant, one treatment and one (finite) trial history, which we call *deterministic response-adaptive* (DRA) procedures. Note that any procedure that can pause or stop the allocation to a particular treatment (e.g., arm-dropping in a multi-arm trial) is thus considered a DRA procedure as the allocation probability for one of the treatments is zero in these cases.

There is a growing number of applications of RA designs across both exploratory and confirmatory clinical trials. DRA procedures are widespread, and heavily used in exploratory trials, e.g., in dose-finding designs ([O’Quigley et al., 1990](#)), arm-dropping designs ([US FDA, 2019](#)) or arm-adding designs ([US FDA, 2023](#)). RAR procedures have been implemented in exploratory or seamless multi-arm trials (see, e.g., [Berry and Viele \(2023\)](#)), while their implementation in confirmatory trials is rare due to ongoing discussions of their risks and benefits (see, e.g., [Robertson et al. \(2023\)](#) for an overview). A regulatory guidance on adaptive designs [US FDA \(2019\)](#), encouraged consideration of multiple design options including RA designs, while mentioning the main arguments and controversies surrounding the use of RA designs.

A proposal for a clinical trial using a (response-)adaptive design tends to be reviewed with greater scrutiny than a conventional design, partially due to concerns around type I error inflation ([Bhatt and Mehta, 2016](#)). As the (unconditional) distribution of the outcomes changes by adopting an RA design instead of an NRA design, ignoring the design in the analysis can lead to type I error inflation (e.g., in [Section 4](#) we show that Fisher’s exact test induces type I error inflation for a specific RA design). Several likelihood-based tests have been shown to asymptotically control type I error for a special class of RA designs, see, e.g., [Baldi Antognini et al. \(2022\)](#). This paper focuses on type I error control in finite samples, which is not generally attained by such tests, not even under NRA designs (see, e.g., [Appendix C](#)). Additional pitfalls occur for asymptotic tests when using an RA procedure that induces relatively large imbalances, such as a DRA procedure targeting higher expected participant outcomes, see, e.g., [Baldi Antognini et al. \(2022\)](#).

The current practice for controlling type I error (in finite samples) under an RA design consists of two approaches: simulation-based tests (see, e.g., [Smith and Villar, 2018](#), Section 3.1.1 and Appendix B) or *randomization tests* (RTs) (see, e.g., [Simon and Simon, 2011](#)). In a simulation-based test, to target type I error control, the critical values are estimated by Monte Carlo simulation of the test statistic under one or several parameter configurations. Under the population model for clinical trials, an RT is a nonparametric exact test for the null hypothesis that each treatment outcome is independent of the corresponding treatment allocation conditional on the trial history up to that allocation ([Simon and Simon, 2011](#)). RTs are robust against unmeasured confounders and time trends ([Villar et al., 2018](#)) and test the sharp null hypothesis under the randomization model for clinical trials ([Rosenberger et al., 2019](#)). In this paper, we define an exact test as a test that results in a type I error rate that is bounded above by the target significance level.

Our focus is on conditional and unconditional exact tests for the parametric setting where potential outcomes are binary and have a Bernoulli distribution with unknown success rates. Examples of conditional and unconditional tests for NRA designs in this setting are, respectively, Fisher’s exact test ([Fisher, 1934](#)) and Barnard’s test ([Barnard, 1945](#)). Such tests (henceforth referred to as *exact tests*) have been less studied in the recent literature for RA designs. Reasons for this might be that exact tests are less straightforward to apply to RA designs and are less computationally tractable than simulation-based tests. Furthermore, in comparison to randomization tests, exact tests have additional assumptions on the outcomes distribution and are less readily applicable to other outcome types and covariate adaptive randomization. However, such tests also have important advantages. The advantage of an exact test is the guarantee of controlling type I error, whereas a simulation-based test, which relies on an estimated critical value is at risk of type I error inflation due to Monte Carlo error ([Robertson et al., 2023](#)). The advantage of exact tests over RTs is that exact tests can be unconditional or can condition only on certain summary statistics, while, in the population model for a clinical trial, an RT is a conditional test that conditions on the entire sequence of outcomes. In response-adaptive designs, the number of

histories of allocations leading the sequence of outcomes may be small, inducing a very discrete test with lower power, especially when using DRA procedures (Villar et al., 2018).

This paper focuses on (finite-sample) type I error control for tests on binary outcomes (treatment success/failure) collected from a clinical trial with a control and treatment group (arms) using any RA procedure. The focus on binary outcomes is justified by the fact that most response-adaptive designs both in the literature and in practice consider binary primary outcomes. The contributions of the paper are as follows: (1) We generalize the Markov chain of summary statistics first introduced in Wei et al. (1990) to allow for, e.g., known fixed delays, batched designs, and optional stopping at interim analyses. (2) We generalize Yi (2013, eq. (1)) to such Markov chains and to outcomes coming from a finite exchangeable sequence, showing the generality of this formula. (3) Drawing on pioneering statistical developments such as Fisher (1934) and Barnard (1945), we use the generalization of Yi (2013, eq. (1)) to develop an algorithm and provide code to construct and evaluate conditional and unconditional exact tests for trials with binary outcomes that use a, possibly deterministic, RA procedure. While Wei et al. (1990) first proposed the idea of conditional and unconditional exact tests for RA designs, the trial size considered in that paper was at most 20 participants, which is an unrealistically small size for two-armed confirmatory clinical trials. In contrast, the current paper uses the computational developments in Jacko (2019) to calculate the policy-dependent coefficients in the generalized version of Yi (2013, eq. (1)), allowing for trials with up to 960 participants computed on a standard computer. (4) We present a computational study where a conditional exact test is shown to have higher power for rejecting the null of no treatment effect in comparison to the unconditional exact approach. (5) We illustrate the applicability of the proposed methodology for constructing exact tests through two real examples, one of which is an RA design using a DRA procedure and the other one involves optional stopping at interim analyses.

The paper is structured as follows: Section 2 summarizes relevant literature on exact tests for binary outcomes in two-arm trials, Section 3 introduces the model and methods to construct exact tests based on binary outcomes collected under an RA procedure, Section 4 provides results of an illustrative computational study comparing the rejection rates (i.e., type I error and power) for different exact tests and statistics under the randomized dynamic programming RA procedure, Section 5 provides the results of our real-world application of the test procedures in a case study, and Section 6 concludes the paper and indicates topics of future research.

2. Conditional and unconditional exact tests

In this section, we summarize relevant literature on *conditional exact* (CX) and *unconditional exact* (UX) tests for the null of no treatment effect based on two-arm trials with binary outcomes.

CX tests were introduced for NRA designs in Fisher (1934) and an exact test for binary outcomes conditioning on the total amount of successes and allocations to both treatment groups is often referred to as *Fisher's exact test* (FET). In a CX test, the critical value is determined using the conditional null distribution of the sufficient statistic for the parameter of interest (e.g., the treatment effect) where conditioning is done on the sufficient statistics for the nuisance parameters (e.g., the probability of success for the control treatment) (Agresti, 2002, Section 3.5.7). The UX test for binary outcomes, using the critical value that bounds the maximum type I error for all parameter values under the null hypothesis from above by the significance level, was introduced for NRA designs in Barnard (1945).

A discussion on CX versus UX tests for binary outcomes under an NRA design was given in Agresti (2002, Section 3.5.6). The arguments for a CX or UX test are both practical and philosophical. A philosophical argument mentioned in Agresti (2002) considers the sampling model under the null. If the total sum of treatment successes is assumed to be a random variable, then a UX test is reasonable. This assumption might be justified when the trial participants can be considered as a random sample from the set of people eligible for the trial. In rare disease trials, the trial contains a large proportion of the people eligible for inclusion in the trial. In the latter case, it could be more natural to assume that, under the null, the total sum of treatment successes in the trial is fixed. Conditional tests might be more appropriate in such settings, as they control type I error for models with both a random and fixed sum of successes (see, e.g., Corollary 3). Another philosophical argument in favour of a CX test over a UX test is the notion that to construct a reference set for the candidate test one should not include situations with severely less (or more) informative allocations than those observed (Fisher, 1945).

To the best of our knowledge, the first source discussing CX and UX tests for RA designs was Wei et al. (1990), proposing conditioning on both the total number of successes and the numbers of allocations to each arm at the end of the trial. The philosophical argument mentioned above (on the use of less informative allocations to construct p-values) was also made for RA designs in Begg (1990) with a recommendation to condition on the number of allocations to each

arm in a CX test. In Fleming (1990), the issue was raised that such conditioning might lead to a loss of information on the treatment effect, and the suggestion was made to only use the total number of successes.

Two practical arguments given in Agresti (2002) are that UX tests are less discrete than CX tests for NRA designs and have more power as a result, while CX tests are less computationally intensive. However, these arguments do not apply in general for binary outcomes in RA designs. The power comparison heavily depends on the RA procedure and scenario considered. We will also show in Section 4 that there are situations where a CX test has higher power than a UX test.

The computational complexity of both CX and UX tests and RT remains to be perceived as prohibitive in realistic trial sizes (i.e., exact computation for these approaches may quickly become intractable). Simon and Simon (2011); Villar et al. (2018) approximate the exact critical values of the RT, which can be viewed as a CX test, due to computational intractability for a trial size of 100 participants while Begg (1990) considered CX tests for a trial with a size of 12 participants. However, computational cost is not a practical issue today and in many cases, RT can be relatively well approximated by simulation. We illustrate the computational tractability of exact tests in Section 4 where we provide and evaluate critical values for UX tests for trial sizes of 960 participants.

3. Exact analysis for response-adaptive procedures

This section presents the theoretical results of this paper. Subsection 3.1 introduces the model and notation for a two-arm trial with binary outcomes using an RA procedure. In Subsection 3.2, the evolution of the trial history, describing the accrual of information in the trial, is summarized by a lower-dimensional Markov chain generalizing the Markov chain in Wei et al. (1990) to allow for complex RA designs, which is illustrated by three examples. In Subsection 3.3 we show that this Markov chain formulation leads to a simple expression of the data likelihood, extending, e.g., Yi (2013, eq. (1)), and we show that the expression also holds when it is only guaranteed that the outcomes are exchangeable. In Subsection 3.4, we use this expression of the data likelihood to provide methods for constructing conditional and unconditional exact tests for binary outcomes collected using an RA procedure.

Throughout the paper, calligraphic font is used for sets, Greek and lowercase letters for deterministic variables, uppercase letters for random variables, bold weight for vectors and matrices, and blackboard bold font for probability and expectation operators, as well as indicators. Furthermore, tuples are denoted by round brackets, closed intervals by square brackets, half-closed intervals by round and square brackets, and sets by curly brackets. Notation $x : y : z$ is used to denote a set of values with step-size y starting at x and ending at z . We let \wedge (\vee) denote logical *and* (*or*) and define $\min(\emptyset) = \infty$ with \emptyset the empty set.

3.1. Two-arm response-adaptive design with binary data

In this section, we define the parametric population model, which is the model in which we evaluate the considered (non-parametric) exact tests. Let $\theta = (\theta_C, \theta_D)$ contain the (unknown) success probabilities, where C denotes the control treatment and D denotes the developmental treatment. In the following, the same convention (i.e., first C then D) will be used to construct tuples from variables for the control and developmental treatment. Let $\mathbf{Y}_C = (Y_{C,i})_{i=1}^{\bar{i}}$, $\mathbf{Y}_D = (Y_{D,i})_{i=1}^{\bar{i}}$ be two sequences of independent Bernoulli random variables, where $\mathbb{P}_\theta(Y_{a,i} = 1) = \theta_a$ for $a \in \{C, D\}$ and \bar{i} is a natural number denoting the (predetermined) maximum trial size. The random variable $Y_{a,i}$ denotes a potential outcome for trial participant i under treatment a , which comes from one of two (i.i.d. Bernoulli) populations.

The adoption of an RA design brings forth the following additions to the population model described above. For an RA design, participants $i \in \mathcal{I} = \{1, 2, \dots, \bar{i}\}$ arrive sequentially and each participant i is allocated to a treatment arm A_i , after which the binary response $Y_{A_i,i} \in \{0, 1\}$ is collected (where A_i and $Y_{A_i,i}$ are observed given that the trial has not stopped before the arrival of participant i). Let $\mathbf{H}_i = (A_1, Y_{A_1,1}, A_2, \dots, A_i, Y_{A_i,i})$ be the trial history up to participant $i \in \mathcal{I}$, and let $\mathbf{H}_0 = ()$. Let $\mathcal{H} = \bigcup_{i=0}^{\bar{i}} \mathcal{H}_i$ where $\mathcal{H}_0 = \{()\}$, $\mathcal{I}_i = \{1, \dots, i\}$ for all $i \leq \bar{i}$, and

$$\mathcal{H}_i = \{(a_1, y_1, a_2, y_2, \dots, a_i, y_i) : y_w \in \{0, 1\}, a_w \in \{C, D\}, \forall w \in \mathcal{I}_i\}$$

be the support of \mathbf{H}_i .

An RA procedure is a function $\pi : \mathcal{H} \mapsto [0, 1]$, where it is assumed that the distribution of A_{i+1} is non-anticipating and thus only depends on \mathbf{H}_i , i.e., π is such that

$$\pi(\mathbf{H}_i) := \mathbb{P}(A_{i+1} = C \mid \mathbf{H}_i) = 1 - \mathbb{P}(A_{i+1} = D \mid \mathbf{H}_i).$$

Henceforth, the probability measure for the outcomes and allocations will be denoted by \mathbb{P}_θ^π . We can now make the distinction between a RAR and DRA procedure: the procedure π is called a RAR procedure if $0 < \pi(\mathbf{H}_i) < 1$ (almost surely) for all $i \in \mathcal{I}$, otherwise π is called a DRA procedure.

After every trial participant i , an analysis of outcomes data is modelled by introducing a real-valued test statistic $T_{\mathcal{H}}$ and rejection region $\mathcal{R}_{\mathcal{H}}$ taking as input the trial history \mathbf{H}_i . The null hypothesis is rejected and the trial is stopped after participant i when $T_{\mathcal{H}}(\mathbf{H}_i) \in \mathcal{R}_{\mathcal{H}}(\mathbf{H}_i)$. The definition of the rejection region must reflect the particular null hypothesis to be tested (e.g., two-sided or one-sided), as we will specify in [Subsection 3.4](#); when trial stopping is not allowed, the rejection region is empty for every i .

3.2. Markov chain model formulation

In this section, we define a Markov chain which we will use to determine the operating characteristics with a given exact test in a specific RA design. We consider a set of *update times* $t \in \mathcal{T} = \{0, 1, \dots, \bar{t}\}$ for a natural number \bar{t} . At update time $t \in \mathcal{T}$ we have access to information of the trial up to trial participant $i_t \in \mathcal{I}_0 = \{0, 1, \dots, \bar{i}\}$, where $i_t = 0$ refers to the information before participant $i = 1$, $i_{t+1} \geq i_t$ for all $t \in \mathcal{T} \setminus \{\bar{t}\}$ and we have $i_{\bar{t}} = \bar{i}$. We now define a stochastic process $(\mathbf{X}_t)_{t \in \mathcal{T}}$, denoted in short by $(\mathbf{X}_t)_t$, which only contains information in $(\mathbf{H}_i)_{i \in \mathcal{I}}$ needed for the analysis, and hence would typically have lower dimension than $(\mathbf{H}_i)_{i \in \mathcal{I}}$. For all update times t , we have $\mathbf{X}_t = x_t(\mathbf{H}_{i_t})$ where x_t is a function of the history up to trial participant i_t , i.e., $x_t : \mathcal{H}_{i_t} \mapsto \mathcal{X}_t$ for a (countable, multi-dimensional) set \mathcal{X}_t .

We assume that process $(\mathbf{X}_t)_t$ has some particular properties. First, we require that \mathbf{X}_t contains the total number of successes and allocations to each arm a up to trial participant i_t , i.e., letting

$$S_{a,i} = \sum_{i'=1}^i Y_{A_{i'},i'} \mathbb{I}(A_{i'} = a), \quad N_{a,i} = \sum_{i'=1}^i \mathbb{I}(A_{i'} = a),$$

for all $a \in \{C, D\}$, $i \in \mathcal{I}_0$ be the total sum of successes and allocations, respectively, to treatment arms up to trial participant i ; we have $S_{a,i_t} = s_a(\mathbf{X}_t)$ and $N_{a,i_t} = n_a(\mathbf{X}_t)$ for functions $s : \mathcal{X} \mapsto \mathcal{I}_0^2$, $n : \mathcal{X} \mapsto \mathcal{I}_0^2$, where $\mathcal{X} = \cup_t \mathcal{X}_t$. Second, we require the existence of a test statistic T and rejection region \mathcal{R} such that (early) rejection of the null can be determined from $\mathbf{X}_{\bar{t}}$, i.e., $T(\mathbf{X}_{\bar{t}}) \in \mathcal{R}(\mathbf{X}_{\bar{t}}) \iff \exists i : T_{\mathcal{H}}(\mathbf{H}_i) \in \mathcal{R}_{\mathcal{H}}(\mathbf{H}_i)$. Third, we focus on RA designs where we have that $(\mathbf{X}_t)_t$ is a Markov chain with transition structure

$$\mathbb{P}_\theta^\pi(\mathbf{X}_{t+1} = \mathbf{x}_{t+1} \mid \mathbf{X}_t = \mathbf{x}_t) = q^\pi(\mathbf{x}_t, \mathbf{x}_{t+1}) \cdot p_\theta(\partial s(\mathbf{x}_t, \mathbf{x}_{t+1}) \mid \partial n(\mathbf{x}_t, \mathbf{x}_{t+1})) \quad (1)$$

for all $\mathbf{x}_t \in \mathcal{X}_t$, $\mathbf{x}_{t+1} \in \mathcal{X}_{t+1}$, where q^π is a function depending solely on the RA procedure, we define

$$\partial s(\mathbf{x}_t, \mathbf{x}_{t+1}) = s(\mathbf{x}_{t+1}) - s(\mathbf{x}_t), \quad \partial n(\mathbf{x}_t, \mathbf{x}_{t+1}) = n(\mathbf{x}_{t+1}) - n(\mathbf{x}_t)$$

for all $\mathbf{x}_t \in \mathcal{X}_t$ and $\mathbf{x}_{t+1} \in \mathcal{X}_{t+1}$, and, letting $\mathcal{D} = \{-\bar{i}, \dots, -1, 0, 1, \dots, \bar{i}\}$ denote the range of $\partial s_a, \partial n_a$ for all $a \in \{C, D\}$ and $\mathbf{Y}'_C, \mathbf{Y}'_D$ be distributed as $\mathbf{Y}_C, \mathbf{Y}_D$ under \mathbb{P}_θ as defined above,

$$p_\theta(\partial s' \mid \partial n') = \prod_{a \in \{C, D\}} \mathbb{P}_\theta \left(\sum_{i=1}^{\partial n'_a} Y'_{a,i} = \partial s'_a \right) \quad \forall \partial s', \partial n' \in \mathcal{D}^2. \quad (2)$$

A few things are of note considering the definitions above. The right-hand side of (1) decomposes the distribution of the outcomes collected using an RA procedure in the distribution over allocations to each arm given the RA procedure (represented by q^π) times the distribution over outcomes given the allocations to each arm and the parameters (represented by p_θ). We require $\sum_{a \in \{C, D\}} \partial n_a(\mathbf{x}_t, \mathbf{x}_{t+1}) = i_{t+1} - i_t$ and hence the number of additional participants between update times is deterministic. The Markov chain $(\mathbf{X}_t)_t$ generalizes the Markov chain introduced in [Wei et al. \(1990\)](#), which allows the analysis of more complex trials.

In the following examples, we first present a generic Markov chain and then show how our model can be used for known fixed delays and blocked RA procedures with early stopping. These examples are further extended in [Section 5](#).

Example 1 (Summary statistics Markov chain). *For several RA procedures known from the literature, the allocation probability is a function of the summary statistics, i.e., we have $\pi(\mathbf{H}_i) = \pi_C((\mathbf{S}_i, \mathbf{N}_i))$ for all $i \in \mathcal{I}$ ([Yi, 2013](#)). In this case, the summary statistics follow a Markov chain, i.e., letting $i_t = t$ for all t (i.e., we update after every participant)*

and $\mathbf{X}_t = (\mathbf{S}_t, \mathbf{N}_t)$, $(\mathbf{X}_t)_t$ is a Markov chain with initial state $\mathbf{X}_0 = ((0, 0), (0, 0))$, state space $\mathcal{X} = \cup_t \mathcal{X}_t$, where

$$\mathcal{X}_t = \mathcal{X}_t^{SS} = \{((s'_C, s'_D), (n'_C, n'_D)) : \mathbf{s}', \mathbf{n}' \in \mathcal{I}_0^2, \mathbf{s}' \leq \mathbf{n}', \sum_a n'_a = t\},$$

and transition structure (1) with

$$q^\pi(\mathbf{x}_t, \mathbf{x}_{t+1}) = \begin{cases} \pi_C(\mathbf{x}_t), & \text{if } \partial n_C(\mathbf{x}_t, \mathbf{x}_{t+1}) = 1 \text{ and } \partial n_D(\mathbf{x}_t, \mathbf{x}_{t+1}) = 0, \\ 1 - \pi_C(\mathbf{x}_t), & \text{if } \partial n_C(\mathbf{x}_t, \mathbf{x}_{t+1}) = 0 \text{ and } \partial n_D(\mathbf{x}_t, \mathbf{x}_{t+1}) = 1, \\ 0, & \text{else,} \end{cases}$$

for all $\mathbf{x}_t \in \mathcal{X}_t$, $\mathbf{x}_{t+1} \in \mathcal{X}_{t+1}$. For instance, this property holds for Thompson sampling (Thompson, 1933) where, assuming a prior \mathbb{Q} for θ , by Bayes' rule for all $\mathbf{x}_t \in \mathcal{X}_t$

$$\pi_C(\mathbf{x}_t) = \mathbb{Q}(\theta_C \geq \theta_D \mid \mathbf{X}_t = \mathbf{x}_t) = \frac{\int_{\theta_C \geq \theta_D} \prod_{a \in \{C, D\}} \theta_a^{s_a(\mathbf{x}_t)} (1 - \theta_a)^{n_a(\mathbf{x}_t) - s_a(\mathbf{x}_t)} \mathbb{Q}(d\theta)}{\int \prod_{a \in \{C, D\}} \theta_a^{s_a(\mathbf{x}_t)} (1 - \theta_a)^{n_a(\mathbf{x}_t) - s_a(\mathbf{x}_t)} \mathbb{Q}(d\theta)}. \quad (3)$$

Other examples in which $(\mathbf{X}_t)_t$ is a Markov chain are randomized play-the-winner (described, e.g., in Wei et al. (1990)), the randomized dynamic programming-based procedure introduced in (Cheng and Berry, 2007), and index-based procedures provided in (Villar et al., 2015).

Example 2 (Responses with known fixed delays). *Example 1 can be extended to settings where outcomes have a known fixed delay, which is captured by a delayed response in the RA procedure, i.e. for a delay length $d \in \{1, 2, \dots, \bar{i}\}$ and initial allocation probability $p_{C,0} \in [0, 1]$ such that $\pi(\cdot) = p_{C,0}$ we have*

$$\begin{aligned} \pi(\mathbf{H}_i) &= p_{C,0}, & \forall i \in \{1, 2, \dots, d\}, \\ \pi(\mathbf{H}_i) &= \pi_C((\mathbf{S}_{i-d}, \mathbf{N}_{i-d})), & \forall i \in \{d+1, d+2, \dots, \bar{i}\}. \end{aligned}$$

Let $i_t = t$ for all t and $\mathbf{X}_t = (\mathbf{S}_t, \mathbf{N}_t, \mathbf{A}_t)$ with $\mathbf{A}_t = (A_{t+1}, \dots, A_{t+d})$. The process $(\mathbf{X}_t)_t$ is a Markov chain with state space $\mathcal{X} = \cup_t \mathcal{X}_t$, where

$$\mathcal{X}_t = \{((s'_C, s'_D), (n'_C, n'_D), \mathbf{a}) : ((s'_C, s'_D), (n'_C, n'_D)) \in \mathcal{X}_t^{SS}, \mathbf{a} \in \{C, D\}^d\},$$

initial state $\mathbf{X}_0 = ((0, 0), (0, 0), \mathbf{A}_0)$ (where, independently, $\mathbb{P}(A_{0,d'} = C) = 1 - \mathbb{P}(A_{0,d'} = D) = p_{C,0}$ for all $d' \leq d$) and, letting the function \mathbf{a} be such that $\mathbf{a}(\mathbf{X}_t) = \mathbf{A}_t$, transition structure (1) with

$$q^\pi(\mathbf{x}_t, \mathbf{x}_{t+1}) = \pi_C((\mathbf{s}(\mathbf{x}_t), \mathbf{n}(\mathbf{x}_t)))^{\mathbb{I}(a_d(\mathbf{x}_{t+1})=C)} (1 - \pi_C((\mathbf{s}(\mathbf{x}_t), \mathbf{n}(\mathbf{x}_t))))^{\mathbb{I}(a_d(\mathbf{x}_{t+1})=D)}$$

whenever $\partial n_a(\mathbf{x}_t, \mathbf{x}_{t+1}) = \mathbb{I}(a = a_1(\mathbf{x}_t))$ for $a \in \{C, D\}$, $a_{d'}(\mathbf{x}_{t+1}) = a_{d'+1}(\mathbf{x}_t)$ for all $d' \in \{1, \dots, d-1\}$, and $q^\pi(\mathbf{x}_t, \mathbf{x}_{t+1}) = 0$ otherwise. Hence, we add arm C to the top of the stack \mathbf{A}_{t+1} with probability equal to $\pi_C((\mathbf{S}_t, \mathbf{N}_t))$, while the next participant is allocated by the treatment at the start of the stack (based on \mathbf{H}_{t-d}).

Example 3 (Bayesian blocked RA design with early stopping). *Allocation is sometimes performed in groups of participants, where groups of more than one participant are allocated treatment to target an allocation probability. There are different ways to allocate participants to treatments inside groups, for instance by a biased coin, mass-weighted urn, or, most often, a (modified) permuted block design, worked out below. Furthermore, interim analyses, in addition to an analysis at the end, are often performed to reject equality of the success probabilities when at one of the interim analyses the posterior probability of control superiority, $\pi_C((\mathbf{S}_t, \mathbf{N}_t))$ determined by (3), is smaller than or equal to $1 - \pi_C^*((\mathbf{S}_t, \mathbf{N}_t))$ or larger than or equal to $\pi_C^*((\mathbf{S}_t, \mathbf{N}_t))$ where $\pi_C^*((\mathbf{S}_t, \mathbf{N}_t))$ is a critical value, determining the rejection region $\mathcal{R}_{\mathcal{H}}$ while π_C determines the test statistic $T_{\mathcal{H}}$ (see, e.g., Yannopoulos et al. (2020, pg. 6), where $\pi_C^* \equiv 0.986$).*

Letting $\mathcal{T}_t = \{0, \dots, t\}$, $i_0 = 0$ and $i_t = \sum_{t'=1}^t b_{t'}$ where $(b_t)_t$ is the sequence of group sizes, $U_t = \min(t, U_t')$ where

$$U_t' = \min(\{t' \in \mathcal{T} : \pi_C((\mathbf{S}_{t'}, \mathbf{N}_{t'})) \leq 1 - \pi_C^*((\mathbf{S}_{t'}, \mathbf{N}_{t'})) \text{ or } \pi_C((\mathbf{S}_{t'}, \mathbf{N}_{t'})) \geq \pi_C^*((\mathbf{S}_{t'}, \mathbf{N}_{t'}))\}),$$

we define $\mathbf{X}_t = (\mathbf{S}_t, \mathbf{N}_t, U_t)$.

Assume that allocation within blocks is done using a permuted block design. Then, letting u be a function such that $u(\mathbf{X}_t) = U_t$, the process $(\mathbf{X}_t)_t$ is a Markov chain with state space $\mathcal{X} = \cup_t \mathcal{X}_t$ where

$$\mathcal{X}_t = \{((s'_C, s'_D), (n'_C, n'_D), u') : ((s'_C, s'_D), (n'_C, n'_D)) \in \mathcal{X}_t^{SS}, u' \in \mathcal{T}_t\},$$

initial state equal to $\mathbf{X}_0 = ((0, 0), (0, 0), 0)$ and transition structure (1) with $q^\pi(\mathbf{x}_t, \mathbf{x}_{t+1})$ targeting an allocation of $\pi_C(\mathbf{x}_t)b_t$ participants to the control group, in particular we have that $q^\pi(\mathbf{x}_t, \mathbf{x}_{t+1})$ equals:

$$\begin{cases} \pi_C(\mathbf{x}_t)b_t - \lfloor \pi_C(\mathbf{x}_t)b_t \rfloor, & \text{if } \partial \mathbf{n}(\mathbf{x}_t, \mathbf{x}_{t+1}) = (\lceil \pi_C(\mathbf{x}_t)b_t \rceil, b_t - \lceil \pi_C(\mathbf{x}_t)b_t \rceil), \\ & 1 - \pi_C^*(\mathbf{x}_t) < \pi_C(\mathbf{x}_t) < \pi_C^*(\mathbf{x}_t) \text{ and } u(\mathbf{x}_{t+1}) = u(\mathbf{x}_t) + 1, \\ \lceil \pi_C(\mathbf{x}_t)b_t \rceil - \pi_C(\mathbf{x}_t)b_t, & \text{if } \partial \mathbf{n}(\mathbf{x}_t, \mathbf{x}_{t+1}) = (\lfloor \pi_C(\mathbf{x}_t)b_t \rfloor, b_t - \lfloor \pi_C(\mathbf{x}_t)b_t \rfloor), \\ & 1 - \pi_C^*(\mathbf{x}_t) < \pi_C(\mathbf{x}_t) < \pi_C^*(\mathbf{x}_t) \text{ and } u(\mathbf{x}_{t+1}) = u(\mathbf{x}_t) + 1, \\ 1 & \text{if } ((1 - \pi_C^*(\mathbf{x}_t) \geq \pi_C(\mathbf{x}_t)) \vee (\pi_C^*(\mathbf{x}_t) \leq \pi_C(\mathbf{x}_t))) \wedge (\mathbf{x}_{t+1} = \mathbf{x}_t), \\ 0, & \text{else,} \end{cases}$$

for all $\mathbf{x}_t \in \mathcal{X}_t, \mathbf{x}_{t+1} \in \mathcal{X}_{t+1}$, where $\lceil \delta \rceil = \lceil \delta \rceil - 1$ for all $\delta \in \mathcal{D}$, $\pi_C(\mathbf{x}_t) = \pi_C((\mathbf{s}(\mathbf{x}_t), \mathbf{n}(\mathbf{x}_t)))$, and $\pi_C^*(\mathbf{x}_t)$ is defined similarly for all $\mathbf{x}_t \in \mathcal{X}_t$. The (random) number of participants included in the trial is captured by $i_{u(\mathbf{X}_t)}$. Lastly, $\mathbb{T}(\mathbf{X}_{\bar{t}}) \in \mathcal{R} \iff \exists i : \mathbb{T}_{\mathcal{H}}(\mathbf{H}_i) \in \mathcal{R}_{\mathcal{H}}(\mathbf{H}_i)$ where $\mathcal{R} = \{1\}$ and

$$\mathbb{T}(\mathbf{X}_{\bar{t}}) = \mathbb{I}(u(\mathbf{X}_{\bar{t}}) < \bar{t}, \pi_C(\mathbf{X}_{\bar{t}}) \leq 1 - \pi_C^*(\mathbf{X}_{\bar{t}}), \text{ or } \pi_C(\mathbf{X}_{\bar{t}}) \geq \pi_C^*(\mathbf{X}_{\bar{t}})),$$

i.e., the null hypothesis is rejected when the trial stops early or either treatment has a high enough posterior probability of being superior at the end.

3.3. Data likelihood for a two-arm response-adaptive design

In order to construct exact tests after treatment allocation using an RA procedure and to compute associated operating characteristics, we build upon Subsection 3.1 and we need the following result (the proof can be found in Appendix A), where $\mathcal{B}([0, 1]^2)$ denotes the Borel sigma algebra on $[0, 1]^2$.

Theorem 1.

Assume there is a signed measure μ on $([0, 1]^2, \mathcal{B}([0, 1]^2))$ such that for all $\mathbf{y}_C, \mathbf{y}_D \in \{0, 1\}^{\bar{t}}$

$$\mathbb{P}(\mathbf{Y}_a = \mathbf{y}_a \quad \forall a \in \{C, D\}) = \int_{[0, 1]^2} \prod_{a \in \{C, D\}} \theta_a^{\sum_{i=1}^{\bar{t}} y_{a,i}} (1 - \theta_a)^{\sum_{i=1}^{\bar{t}} (1 - y_{a,i})} \mu(d\boldsymbol{\theta}) \quad (4)$$

and the process $(\mathbf{X}_t)_t$ has transition structure (1) with the factor $p_{\boldsymbol{\theta}}(\partial \mathbf{s}(\mathbf{x}_t, \mathbf{x}_{t+1}) \mid \partial \mathbf{n}(\mathbf{x}_t, \mathbf{x}_{t+1}))$ replaced by $p(\partial \mathbf{s}(\mathbf{x}_t, \mathbf{x}_{t+1}) \mid \partial \mathbf{n}(\mathbf{x}_t, \mathbf{x}_{t+1}), \mathbf{n}(\mathbf{x}_t), \mathbf{s}(\mathbf{x}_t))$ where

$$p(\partial \mathbf{s}' \mid \partial \mathbf{n}', \mathbf{n}', \mathbf{s}') = \mathbb{P} \left(\sum_{i=n'_a+1}^{n'_a + \partial n'_a} Y_{a,i} = \partial s'_a \quad \forall a \in \{C, D\} \mid \sum_{i=1}^{n'_a} Y_{a,i} = s'_a \quad \forall a \in \{C, D\} \right) \quad (5)$$

for all $\mathbf{s}', \mathbf{n}' \in \mathcal{I}_0^2, \partial \mathbf{s}', \partial \mathbf{n}' \in \mathcal{D}^2$, then

$$\mathbb{P}^\pi(\mathbf{X}_t = \mathbf{x}_t) = g_t^\pi(\mathbf{x}_t) \int_{[0, 1]^2} \prod_{a \in \{C, D\}} \theta_a^{s_a(\mathbf{x}_t)} (1 - \theta_a)^{n_a(\mathbf{x}_t) - s_a(\mathbf{x}_t)} \mu(d\boldsymbol{\theta}) \quad \forall \mathbf{x}_t \in \mathcal{X}_t, \quad (6)$$

where, letting $\binom{n}{k}$ denote the binomial coefficient for natural numbers n, k , for all $t, \mathbf{x}_t \in \mathcal{X}_t$

$$g_0^\pi(\mathbf{x}_0) = 1, g_t^\pi(\mathbf{x}_t) = \sum_{\mathbf{x}_{t-1} \in \mathcal{X}_{t-1}} \left(\prod_{a \in \{C, D\}} \binom{\partial n_a(\mathbf{x}_{t-1}, \mathbf{x}_t)}{\partial s_a(\mathbf{x}_{t-1}, \mathbf{x}_t)} \right) g_{t-1}^\pi(\mathbf{x}_{t-1}) q^\pi(\mathbf{x}_{t-1}, \mathbf{x}_t). \quad (7)$$

Following Jaynes (1986), the data likelihood (4) implies that the potential outcomes are participant-exchangeable, i.e., $(Y_{a,i})_{i=1}^{\bar{t}} \stackrel{d}{=} (Y_{a,\rho_{\mathcal{I}}(i)})_{i=1}^{\bar{t}}$ for all permutations $\rho_{\mathcal{I}}$ over \mathcal{I} respectively, where $\stackrel{d}{=}$ denotes equality in distribution. Note that this is a nonparametric extension of the setting of Subsection 3.1 in case $\theta_C = \theta_D$, as the outcomes are also participant-exchangeable and independent of the allocations for the two-population Bernoulli outcomes model with

equal success rates. Furthermore, μ is absolutely continuous with respect to the Dirac measure on $\{\theta : \theta_C = \theta_D\}$ if and only if the total sequence of outcomes $(Y_{a,i})_{a \in \{C,D\}, i \in \mathcal{I}}$ is independent of the allocations, i.e., $(Y_{C,i})_{i=1}^{\bar{i}} \stackrel{d}{=} (Y_{D,i})_{i=1}^{\bar{i}}$, which is a nonparametric version of the null hypothesis $\theta_C = \theta_D$ in the model of [Subsection 3.1](#). Hence, [Theorem 1](#) can be applied in these settings, i.e., in a finite population model assuming outcomes come from a participant-exchangeable sequence. Furthermore, the theorem can also be applied when the outcome sequence can be extended to an infinite exchangeable sequence, in which case the measure μ must be a probability measure by de Finetti's theorem. Lastly, if the outcomes are i.i.d. Bernoulli distributed, μ is a positive point mass on a parameter value $\theta \in [0, 1]^2$ and we obtain Equation (1) from [Yi \(2013\)](#)

$$\mathbb{P}_{\theta}^{\pi}(\mathbf{X}_t = \mathbf{x}_t) = g_t^{\pi}(\mathbf{x}_t) \prod_{a \in \{C,D\}} \theta_a^{s_a(\mathbf{x}_t)} (1 - \theta_a)^{n_a(\mathbf{x}_t) - s_a(\mathbf{x}_t)} \forall \mathbf{x}_t \in \mathcal{X}. \quad (8)$$

All settings described above assume that the outcomes collected in a clinical trial come from a population model, and hence not a randomization model ([Rosenberger et al., 2019](#)). See [Table 1](#) for an overview of the differences between the randomization model, parametric population model, and nonparametric population model for the potential outcomes.

Table 1: Differences between the parametric population model, nonparametric population model, and randomization model for the potential outcomes in a clinical trial.

	Parametric population model (Subsection 3.1)	Nonparametric population model	Randomization model
Potential outcomes	$Y_{C,1}, \dots, Y_{C,\bar{i}} \stackrel{iid}{\sim} \text{Bern}(\theta_C)$ $Y_{D,1}, \dots, Y_{D,\bar{i}} \stackrel{iid}{\sim} \text{Bern}(\theta_D)$	$(\mathbf{Y}_C, \mathbf{Y}_D) \sim \mathbb{P}$ $(Y_{a,i})_{i=1}^{\bar{i}} \stackrel{d}{=} (Y_{a,\rho_{\mathcal{I}}(i)})_{i=1}^{\bar{i}}$ for all permutations $\rho_{\mathcal{I}}$ on \mathcal{I}	Unknown, fixed $y_{C,1}, \dots, y_{C,\bar{i}}$ $y_{D,1}, \dots, y_{D,\bar{i}}$
Null hypothesis	Parametric null: $H_0 : \theta_C = \theta_D$	Nonparametric null: $H_0^{\text{NP}} : (Y_{C,i})_{i=1}^{\bar{i}} \stackrel{d}{=} (Y_{D,i})_{i=1}^{\bar{i}}$	Sharp null: $H_0^{\text{sharp}} : y_{C,i} = y_{D,i} \forall i$
Reference set	One reference set, equal to state space \mathcal{X} containing treatment group sizes and successes per arm	Several conditional reference sets $\mathcal{X}_{\zeta}(z)$ for each data summary $z \in \mathcal{Z}$	One reference set: all possible allocations given RA procedure and fixed outcomes, e.g., for DRA procedures such as PTW contains two possible paths
Probability over states	Distribution over states follows from joint probability measure $\mathbb{P}_{\theta}^{\pi}$	Conditional probability $g_{\bar{i}}^{\pi}(\mathbf{x}_{\bar{i}}) / \sum_{\mathbf{x}_{\bar{i}} \in \mathcal{X}_{\zeta}(z)} g_{\bar{i}}^{\pi}(\mathbf{x}_{\bar{i}})$ of state $\mathbf{x}_{\bar{i}}$ given $\zeta = z$	Sum of probabilities of allocation sequences given outcomes
Critical values	One (unconditional exact) min-max critical value, ensuring type I error control for all parameters under null	Several (conditional exact) critical values, one for each conditional reference set, determined by conditional probability distribution	One (unconditional exact) critical value, determined by probability distribution over allocations
Test under fixed equal treatment groups	Barnard's test	Fisher's exact test (for test statistic depending on $S_{C,\bar{i}}$)	Randomization test (in general)
Alternative hypothesis one-sided	$H_1 : \theta_D > \theta_C$	$H_1^{\text{NP}} : (Y_{D,i})_{i=1}^{\bar{i}} \stackrel{d}{>} (Y_{C,i})_{i=1}^{\bar{i}}$ $\stackrel{d}{>}$ denotes stochastic dominance	$H_1' : y_{D,i} > y_{C,i} \forall i$

We now give an application of [Theorem 1](#).

Remark 1. In the setting of [Example 1](#), assuming i.i.d. Bernoulli distributed outcomes and the complete randomization (CR) NRA design where $\pi_C(\mathbf{x}) = 1/2$ for all $\mathbf{x} \in \mathcal{X}$, it can be verified that $g_t^\pi(\mathbf{x}_t) = \binom{t}{n_C(\mathbf{x}_t)} \binom{n_C(\mathbf{x}_t)}{s_C(\mathbf{x}_t)} \binom{n_D(\mathbf{x}_t)}{s_D(\mathbf{x}_t)} / 2^t$, hence

$$\mathbb{P}_\theta^\pi(\mathbf{X}_t = \mathbf{x}_t) = \frac{\binom{t}{n_C(\mathbf{x}_t)}}{2^t} \prod_{a \in \{C, D\}} \binom{n_a(\mathbf{x}_t)}{s_a(\mathbf{x}_t)} \theta_a^{s_a(\mathbf{x}_t)} (1 - \theta_a)^{n_a(\mathbf{x}_t) - s_a(\mathbf{x}_t)} \forall \mathbf{x}_t \in \mathcal{X}. \quad (9)$$

The recursive definition (1) leads to an efficient implementation of a forward recursion algorithm to compute $g_t^\pi(\mathbf{x}_t)$ for all states $\mathbf{x}_t \in \mathcal{X}$. This algorithm is based on the same principles for efficient calculation and storage of value functions and policies as those outlined in [Jacko \(2019\)](#), i.e., uses the conservation law for the states, a storage mapping function, and overwrites values that are not used further in the algorithm.

Equation (8) states that for the setting described above, the probability of reaching a state \mathbf{x}_t can be decomposed as the product of a coefficient $g_t^\pi(\mathbf{x}_t)$, corresponding to the uncertainty in reaching \mathbf{x}_t due to the allocation procedure, and a term proportional to the likelihood of the outcomes data conditioned on the allocations, independent of the allocation procedure. In particular, it means that if one has access to g_t^π , computation of expectations with respect to \mathbf{X}_t under different values of θ comes down to taking the inner product of g_t^π with the (scaled) likelihood under these values of θ . This procedure can be used to calculate the rejection rate $\mathbb{P}_\theta^\pi(\mathbb{T}(\mathbf{X}_{\bar{t}}) \in \mathcal{R}(\mathbf{X}_{\bar{t}}))$, making it possible to efficiently compute the exact tests in the following sections.

3.4. Exact tests

In the following, we consider a test for the null hypothesis of no treatment effect, i.e., we test

$$H_0 : \theta_C = \theta_D \text{ v.s. } H_1 : \theta_C \neq \theta_D.$$

For a chosen test statistic \mathbb{T} and upper/lower critical values \bar{c}, \underline{c} , this test rejects H_0 whenever $\mathbb{T}(\mathbf{X}_{\bar{t}}) \geq \bar{c}(\mathbf{X}_{\bar{t}})$ or $\mathbb{T}(\mathbf{X}_{\bar{t}}) \leq \underline{c}(\mathbf{X}_{\bar{t}})$. This test can be made one-sided by setting $\bar{c} \equiv \infty$ or $\underline{c} \equiv -\infty$.

3.4.1. Conditional exact tests

In this subsection, we discuss a conditional test for RA designs extending, e.g., Fisher's exact test ([Fisher, 1934](#)).

Definition 1 (Conditional Test). Let $\zeta : \mathcal{X}_{\bar{t}} \mapsto \mathcal{Z}$ be a conditioning (summary) function for $\mathbf{x}_{\bar{t}} \in \mathcal{X}_{\bar{t}}$ and $\mathcal{X}_\zeta(z)$ be the pre-image of $z \in \mathcal{Z}$ under ζ , denoted the conditional reference set of states. A conditional test based on ζ for a test statistic function \mathbb{T} , RA procedure π , and significance level $0 < \alpha < 1$ rejects when $\mathbb{T}(\mathbf{X}_{\bar{t}}) \geq \bar{c}(\zeta(\mathbf{X}_{\bar{t}}))$ or $\mathbb{T}(\mathbf{X}_{\bar{t}}) \leq \underline{c}(\zeta(\mathbf{X}_{\bar{t}}))$ where, for $0 < \bar{\alpha}, \underline{\alpha} < 1$ such that $\bar{\alpha} + \underline{\alpha} = \alpha$, we have for all $z \in \mathcal{Z}$

$$\bar{c}(z) = \min \left\{ c \in \bar{\mathbb{T}}(\mathcal{X}_\zeta(z)) : \frac{\sum_{\mathbf{x}_{\bar{t}} \in \mathcal{X}_\zeta(z) : \mathbb{T}(\mathbf{x}_{\bar{t}}) \geq c} g_{\bar{t}}^\pi(\mathbf{x}_{\bar{t}})}{\sum_{\mathbf{x}_{\bar{t}} \in \mathcal{X}_\zeta(z)} g_{\bar{t}}^\pi(\mathbf{x}_{\bar{t}})} \leq \bar{\alpha} \right\}, \quad (10)$$

$$\underline{c}(z) = \max \left\{ c \in \bar{\mathbb{T}}(\mathcal{X}_\zeta(z)) : \frac{\sum_{\mathbf{x}_{\bar{t}} \in \mathcal{X}_\zeta(z) : \mathbb{T}(\mathbf{x}_{\bar{t}}) \leq c} g_{\bar{t}}^\pi(\mathbf{x}_{\bar{t}})}{\sum_{\mathbf{x}_{\bar{t}} \in \mathcal{X}_\zeta(z)} g_{\bar{t}}^\pi(\mathbf{x}_{\bar{t}})} \leq \underline{\alpha} \right\}. \quad (11)$$

In the above, $\mathbb{T}(E)$ denotes the image of $E \subseteq \mathcal{X}_{\bar{t}}$ under \mathbb{T} , while $\bar{\mathbb{T}}(E) = \mathbb{T}(E) \cup \{-\infty, \infty\}$.

Let $s(\mathbf{x}) = \sum_{a \in \{C, D\}} s_a(\mathbf{x})$ for all $\mathbf{x} \in \mathcal{X}$. The next result, for which the proof can be found in [Appendix A](#), states that if $\zeta(\mathbf{X}_{\bar{t}})$ contains the total number of successes, a conditional test based on ζ is exact under the assumptions of [Theorem 1](#), and will be denoted the CX- ζ test.

Corollary 1. If $\zeta : \mathcal{X}_{\bar{t}} \mapsto \mathcal{Z}$, $s(\mathbf{X}_{\bar{t}}) = \tilde{s}(\zeta(\mathbf{X}_{\bar{t}}))$ for a function $\tilde{s} : \mathcal{Z} \mapsto \mathcal{I}_0$ and the assumptions of [Theorem 1](#) hold then under the nonparametric null hypothesis H_0^{NP} in [Table 1](#) we have

$$\mathbb{P}_\theta^\pi \left(\mathbb{T}(\mathbf{X}_{\bar{t}}) \geq \bar{c}(\zeta(\mathbf{X}_{\bar{t}})) \text{ or } \mathbb{T}(\mathbf{X}_{\bar{t}}) \leq \underline{c}(\zeta(\mathbf{X}_{\bar{t}})) \right) \leq \alpha.$$

Let $\text{SA}(\mathbf{x}_t) = (s(\mathbf{x}_t), n_C(\mathbf{x}_t))$ and $\text{S}(\mathbf{x}_t) = s(\mathbf{x}_t)$, according to [Corollary 3](#) the conditional test based on SA and S, the CX-SA and CX-S tests, are conditional exact tests under the assumptions of [Theorem 1](#), hence the nonparametric

null hypothesis in [Table 1](#). The next remark shows that [Corollary 3](#) recovers the result that FET is exact under the nonparametric null hypothesis and the CR NRA design ([Berger et al., 2021](#)).

Remark 2. *In the setting of [Remark 1](#), it follows from (9) that for all pairs $(s', n'_C) \in \mathcal{I}_0^2$ of successes and allocations, we have*

$$\underline{c}((s', n'_C)) = \max \left\{ c \in \bar{\mathbb{T}}(\mathcal{X}_{SA}((s', n'_C))) : \frac{\sum_{\mathbf{x}_{\bar{t}} \in \mathcal{X}_{SA}((s', n'_C)) : \mathbb{T}(\mathbf{x}_{\bar{t}}) \leq c} \binom{n_C(\mathbf{x}_{\bar{t}})}{s_C(\mathbf{x}_{\bar{t}})} \binom{n_D(\mathbf{x}_{\bar{t}})}{s_D(\mathbf{x}_{\bar{t}})}}{\sum_{\mathbf{x}_{\bar{t}} \in \mathcal{X}_{SA}((s', n'_C))} \binom{n_C(\mathbf{x}_{\bar{t}})}{s_C(\mathbf{x}_{\bar{t}})} \binom{n_D(\mathbf{x}_{\bar{t}})}{s_D(\mathbf{x}_{\bar{t}})}} \leq \underline{\alpha} \right\},$$

and $\bar{c}(\mathbf{X}_{\bar{t}})$ is defined similarly. Hence, letting $\bar{\alpha} = 0$, $\underline{\alpha} = \alpha$,

$$p_{FET}(\mathbf{x}_{\bar{t}}) = \binom{n_C(\mathbf{x}_{\bar{t}})}{s_C(\mathbf{x}_{\bar{t}})} \binom{n_D(\mathbf{x}_{\bar{t}})}{s_D(\mathbf{x}_{\bar{t}})} / \sum_{\mathbf{x}'_{\bar{t}} \in \mathcal{X}_{SA}((s(\mathbf{x}_{\bar{t}}), n_C(\mathbf{x}_{\bar{t}})))} \binom{n_C(\mathbf{x}'_{\bar{t}})}{s_C(\mathbf{x}'_{\bar{t}})} \binom{n_D(\mathbf{x}'_{\bar{t}})}{s_D(\mathbf{x}'_{\bar{t}})} \quad (12)$$

be the conditional probability of state $\mathbf{x}_{\bar{t}}$, and choosing the test statistic equal to the conditional probability of seeing a state more extreme than $\mathbf{x}_{\bar{t}}$ (in terms of p_{FET})

$$T_{FET}(\mathbf{x}_{\bar{t}}) = \sum_{\substack{\mathbf{x}'_{\bar{t}} \in \mathcal{X}_{SA}((s(\mathbf{x}_{\bar{t}}), n_C(\mathbf{x}_{\bar{t}}))) \\ p_{FET}(\mathbf{x}'_{\bar{t}}) \leq p_{FET}(\mathbf{x}_{\bar{t}})}} p_{FET}(\mathbf{x}'_{\bar{t}}) \quad (13)$$

we have that $\bar{c}((s(\mathbf{x}_{\bar{t}}), n_C(\mathbf{x}_{\bar{t}}))) = \infty$, $\underline{c}((s(\mathbf{x}_{\bar{t}}), n_C(\mathbf{x}_{\bar{t}}))) \in [0, \alpha]$, and the CX-SA corresponds to the two-sided FET given in [Agresti \(2002, Section 3.5.3\)](#).

3.4.2. Unconditional exact test

In this subsection we discuss an unconditional test for RA designs, generalizing Barnard's test ([Barnard, 1945](#)).

Definition 2 (Unconditional Test). *An unconditional test for test statistic function \mathbb{T} , RA procedure π , and significance level $0 < \alpha < 1$ rejects the null hypothesis when $\mathbb{T}(\mathbf{X}_{\bar{t}}) \geq \bar{c}$ or when $\mathbb{T}(\mathbf{X}_{\bar{t}}) \leq \underline{c}$ where, for $0 < \bar{\alpha}$, $\underline{\alpha} < 1$ such that $\bar{\alpha} + \underline{\alpha} = \alpha$, we have*

$$\bar{c} = \min \left\{ c \in \bar{\mathbb{T}}(\mathcal{X}_{\bar{t}}) : \max_{\substack{\theta \in [0,1]^2 \\ \theta_C = \theta_D}} \sum_{\mathbf{x}_{\bar{t}} \in \mathcal{X}_{\bar{t}} : \mathbb{T}(\mathbf{x}_{\bar{t}}) \geq c} g_{\bar{t}}^{\pi}(\mathbf{x}_{\bar{t}}) \prod_{a \in \{C,D\}} \theta_a^{s_a(\mathbf{x}_{\bar{t}})} (1 - \theta_a)^{n_a(\mathbf{x}_{\bar{t}}) - s_a(\mathbf{x}_{\bar{t}})} \leq \bar{\alpha} \right\},$$

$$\underline{c} = \max \left\{ c \in \bar{\mathbb{T}}(\mathcal{X}_{\bar{t}}) : \max_{\substack{\theta \in [0,1]^2 \\ \theta_C = \theta_D}} \sum_{\mathbf{x}_{\bar{t}} \in \mathcal{X}_{\bar{t}} : \mathbb{T}(\mathbf{x}_{\bar{t}}) \leq c} g_{\bar{t}}^{\pi}(\mathbf{x}_{\bar{t}}) \prod_{a \in \{C,D\}} \theta_a^{s_a(\mathbf{x}_{\bar{t}})} (1 - \theta_a)^{n_a(\mathbf{x}_{\bar{t}}) - s_a(\mathbf{x}_{\bar{t}})} \leq \bar{\alpha} \right\}.$$

The next result, for which the proof can be found in [Appendix A](#), states that the unconditional test is exact, i.e., is a UX test, when the assumptions of [Theorem 1](#) are met and μ is a probability measure. We note that this is a specific result for the null hypothesis H_0^{NP} , while in general, for different null hypotheses, the UX test is exact only under the parametric population model in [Table 1](#).

Corollary 2. *If the assumptions of [Theorem 1](#) hold with μ a probability measure, then under H_0^{NP} it holds that $\mathbb{P}_{\theta}^{\pi}(\mathbb{T}(\mathbf{X}_{\bar{t}}) \geq \bar{c} \text{ or } \mathbb{T}(\mathbf{X}_{\bar{t}}) \leq \underline{c}) \leq \alpha$, where \bar{c}, \underline{c} are as given in [Definition 2](#).*

No simple formula such as (10) exists for exact calculation of the critical values for a UX test, hence one needs to resort to computational techniques and bound the critical values from above or below respectively. We propose using [Algorithm 2](#) in [Appendix B](#) for this, which uses the Lipschitz property of the rejection rate function.

4. Analysis of randomized dynamic programming

This section evaluates the rejection rate for several tests under the *randomized dynamic programming* (RDP) RA procedure introduced in [Cheng and Berry \(2007\)](#) as a way to optimally balance statistical and participant benefit considerations. [Williamson et al. \(2017\)](#) suggested that a good balance is achieved by using the degree of randomization 0.9,

which however may still result in a large imbalance in the final allocations. The decision to declare a treatment was superior was implemented as a Bayesian decision rule in [Cheng and Berry \(2007\)](#) while [Williamson et al. \(2017\)](#) used the Fisher’s exact test. The Markov chain modelling the trial information necessary for statistical testing is the summary statistics Markov chain introduced in [Example 1](#).

In this section, we focus on the Wald statistic for the simple difference of the unknown parameters, as the Wald test was shown to be first-order efficient for specific RA designs and was furthermore shown to outperform other likelihood-based tests in RA designs with small samples ([Baldi Antognini et al., 2022](#)). We define the (adjusted) Wald statistic as

$$T_{\text{ws}}(\mathbf{X}_{\bar{i}}) = \frac{\hat{\theta}_{\text{D}}(\mathbf{X}_{\bar{i}}) - \hat{\theta}_{\text{C}}(\mathbf{X}_{\bar{i}})}{\sqrt{\hat{\theta}_{\text{C}}(\mathbf{X}_{\bar{i}})(1 - \hat{\theta}_{\text{C}}(\mathbf{X}_{\bar{i}}))/\tilde{n}_{\text{C}}(\mathbf{X}_{\bar{i}}) + \hat{\theta}_{\text{D}}(\mathbf{X}_{\bar{i}})(1 - \hat{\theta}_{\text{D}}(\mathbf{X}_{\bar{i}}))/\tilde{n}_{\text{D}}(\mathbf{X}_{\bar{i}})}}, \quad (14)$$

where $\hat{\theta}_a(\mathbf{X}_{\bar{i}}) = (s_a(\mathbf{X}_{\bar{i}}) + 1)/\tilde{n}_a(\mathbf{X}_{\bar{i}})$ and $\tilde{n}_a(\mathbf{X}_{\bar{i}}) = n_a(\mathbf{X}_{\bar{i}}) + 2$ for all $a \in \{\text{C}, \text{D}\}$. The adjustment of adding 2 observations (one success and one failure) to each treatment group to compute the Wald statistic induces that the statistic can be computed for all possible values of $S_{a,\bar{i}}, N_{a,\bar{i}}$ and was, e.g., suggested in ([Agresti, 2002](#), note 3.2). We consider RA designs where, after allocation with the RDP RA procedure, either a naive FET (i.e., ignoring the RA design) or the CX-S, CX-SA, UX, or asymptotic Wald tests are performed, where the asymptotic test assumes an asymptotic normal distribution for $T_{\text{ws}}(\mathbf{X}_{\bar{i}})$.

The maximum randomized allocation rate for RDP was set to 0.9. We illustrate the results for $\bar{i} \in \{60, 240, 960\}$ computed on a standard laptop (our memory-efficient code in Julia programming language allows one to consider trial sizes up to around 1,000 on a computer with 64 GB of RAM). For trial sizes $\bar{i} \in \{60, 240\}$ [Algorithm 2](#) in [Appendix B](#) was used to calculate the critical value for the UX test; for higher trial sizes, due to the increased computational complexity, the critical value is approximated by the smallest critical value for null success rates $\theta_{\text{C}} = \theta_{\text{D}} \in \{0.00, 0.01, \dots, 0.99, 1.00\}$. For the Wald tests, we set $\bar{\alpha} = \alpha = 0.025$ and for FET, we set $\underline{\alpha} = 0.050$ and $\bar{\alpha} = 0.0$ i.e., we reject if the outcomes data has low likelihood under the (naive) hypergeometric null distribution.

The subfigures on the left in [Figure 1](#) show the type I errors for the considered tests. The type I errors for the asymptotic Wald test lie above 0.05 for several values of $\theta_{\text{D}} = \theta_{\text{C}}$ for all values of \bar{i} , even for large values of \bar{i} . This behaviour is also indicated by the UX critical values, which are approximately 2.095, 2.103, and 2.100 for $\bar{i} = 60, 240, 960$ (in comparison to the usual asymptotic critical value around 1.960) for the Wald statistic respectively. While widely believed to be conservative, FET did not control type I error under RDP for large success rates under the null, and hence the critical value of FET was corrected to the minimum of 0.05 and the UX critical value. The corrected critical values for FET are approximately 0.050, 0.044, and 0.043 for $\bar{i} = 60, 240, 960$ respectively. Note that the corrected critical values for FET being below 5% indicates that FET (at the usual 5% level) would inflate type I error.

Subfigures A, C, and E show that the type I error of the CX-SA lies well below 0.05 for each value of $\theta_{\text{D}} = \theta_{\text{C}}$, reflecting the discreteness of this test. In principle, the rejection rate of this test can be increased in several ways to increase the power of the test, but in this case, the test would no longer be conditionally exact at level α . The type I error for the corrected FET is highest for high success rates for all considered trial sizes. Comparing the type I error of the CX and UX tests, the errors for the UX tests are less homogeneous over different values of the success rate, whereas the type I error for the CX-S test is almost constant and equal to 0.05 for $\bar{i} = 960$. Subfigures B, D, F in [Figure 1](#) show the difference in power (rejection rate when $\theta_{\text{D}} \neq \theta_{\text{C}}$) for the considered Wald tests compared to the corrected FET, where each curve corresponds to $\theta_{\text{C}} \in \{0.01, 0.3, 0.9\}$ and $\theta_{\text{D}} \geq \theta_{\text{C}}$, these three values of θ_{C} were chosen as they correspond to three different types of behaviour seen when considering all possible power difference curves. The power difference for the asymptotic test is omitted from Subfigures B, D, and F as this test did not control type I error in Subfigures A, C, and E.

The CX-SA Wald test often has lower power than the other tests, and only has higher power than the UX Wald and FET (corr.) tests for $\theta_{\text{C}} = 0.01$ and small values of θ_{D} . Both the UX and CX-S Wald test outperform (in terms of power) the corrected FET for all considered values of $\theta_{\text{C}} \leq 0.3$, while the corrected FET substantially outperforms the UX Wald test when $\theta_{\text{C}}, \theta_{\text{D}} \geq 0.9$. Comparing the performance of the UX and CX-S Wald tests, the CX-S Wald test often shows the highest power, where the difference is most notable for smaller trial sizes and $\theta_{\text{C}} \in \{0.01, 0.9\}$. The figure shows that CX-S is slightly outperformed by the corrected FET for certain values of θ_{D} when $\theta_{\text{C}} = 0.9$ and $\bar{i} = 960$. In [Appendix C](#), we present more results for the RDP procedure, as well as an analogous analysis for and comparison to an NRA design with equal allocation, i.e., when both treatment group sizes are (deterministically) equal to $\bar{i}/2$.

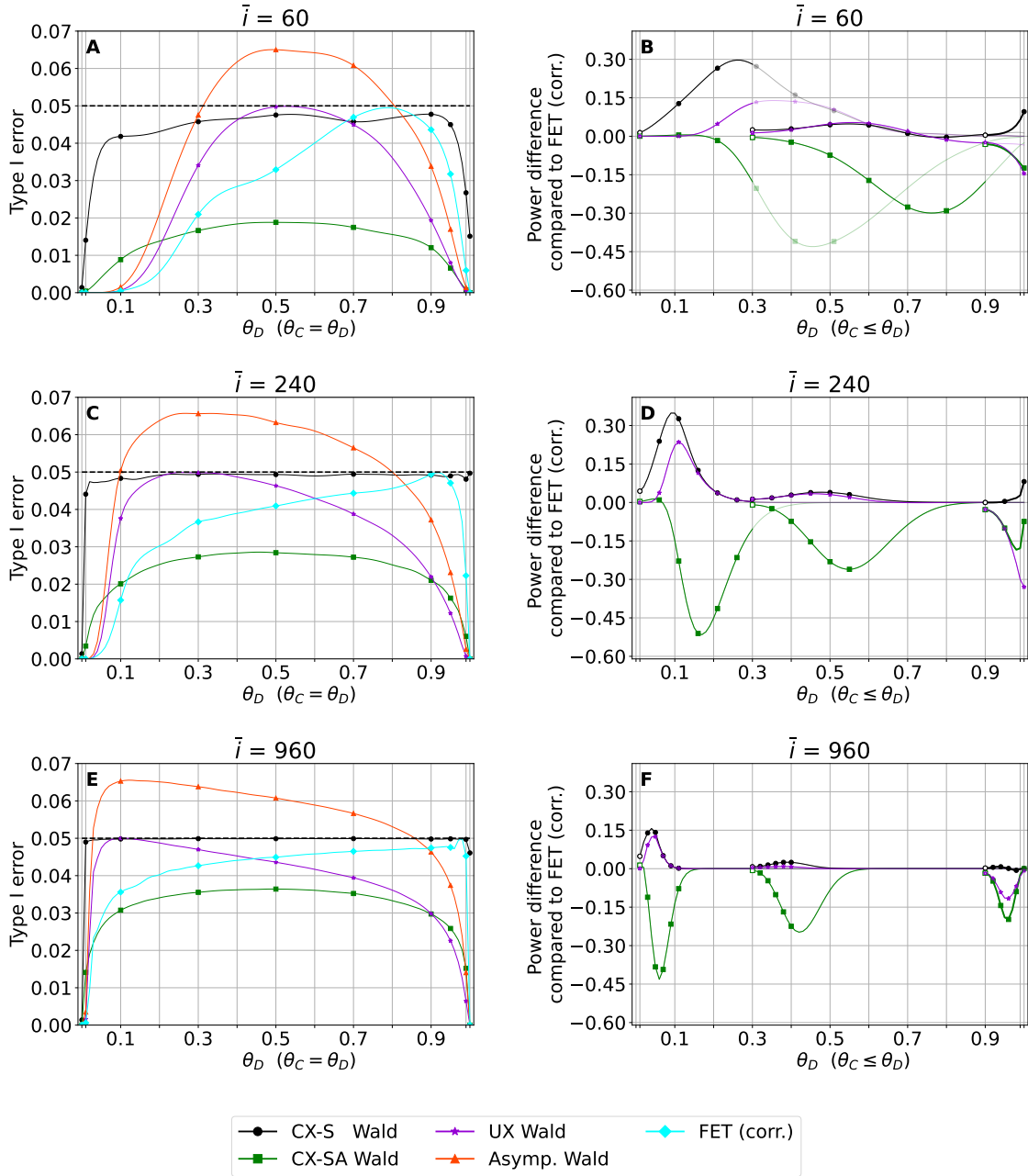


Figure 1: Subfigures A, C, E: Type I error under the RDP RAR procedure for the two-sided CX-S, CX-SA, UX, asymptotic Wald tests, and FET (corrected for type I error inflation). Subfigures B, D, F: Power difference under the RDP RAR procedure for the two-sided CX-S, CX-SA, and UX Wald tests (Asymptotic Wald test is omitted) compared to corrected FET, for $\theta_C \in \{0.1, 0.3, \dots, 0.9\}$ and $\theta_D \geq \theta_C$.

5. Application to real-world trial

In this section, we present results for a real-world trial that used a Bayesian RA design based on a modification of Thompson sampling (Thompson, 1933), and which required a tailored approach for its analysis, where we compare our proposed tests. We consider the *Advanced R²Eperfusion Strategies for Refractory Cardiac Arrest* (ARREST) trial (Yannopoulos et al., 2020), where *extracorporeal membrane oxygenation* (ECMO) facilitated resuscitation (developmental) was compared to standard advanced cardiac life support (control) in adults who experienced an out-of-hospital cardiac arrest and refractory ventricular fibrillation. We illustrate our approach by analyzing a recent clinical trial using a conventional RA design where the batched allocation and interim analyses (i.e., to allow for early stopping) make the RA design more difficult to analyze than a fully sequential and fixed sample size RA designs as that described in Example 1.

Another application to a DRA design based on a modified play-the-winner rule implemented in a different real-world trial (Reiertsen et al., 1993) is given in Appendix D. We chose to analyze this trial as it considered a moderate trial size, used a DRA procedure, and used a non-standard testing approach based on a log-rank test. Our results show again that the CX-S Wald test led to the highest power for this design, outperforming both the UX Wald and log-rank tests.

5.1. Design

In Yannopoulos et al. (2020), a success represented survival to hospital discharge. Participants were allocated to treatment in groups of 30 under a permuted block design, with allocation probability to control equal to the posterior probability (based on independent uniform priors) that the control treatment is superior, restricted between 0.25 and 0.75. While not explicitly stated in Yannopoulos et al. (2020), it is assumed for our calculations that all outcomes are available up to each interim analysis, i.e., there is no delay, possibly through truncation of the time to hospital discharge after a given amount of days. If at any of the interim analyses, the posterior probability of superiority for one of the treatments became higher than an *optional stopping threshold* (OST) of $\pi_C^* = 0.986$, the recommendation was made to stop the trial early. This OST controlled type I error at 0.05 based on a simulation study of 10,000 samples under the scenario $\theta_C = \theta_D = 0.12$. The target effect was a (survival) probability $\theta_D = 0.37$ of success for ECMO, which led to a power of 90% under a maximum trial size of 150 participants. The ARREST trial ended with a recommendation of the ECMO treatment after allocating the first group of 30 participants, with a posterior probability of superiority of 0.9861. Using the notation of Example 3, three different specifications of π_C^* , i.e., RA designs, are considered, the *simulation-based* (SB) OST $\pi_C^* = 0.986$ (Yannopoulos et al., 2020, pg. 6), a UX OST calculated as $\pi_C^* = 0.992$, and a CX-S OST with thresholds defined by (10) and (11) with $\alpha = \bar{\alpha} = 0.05/10$ (where division by 10 is due to the five two-sided tests) according to a Bonferroni correction.

5.2. Results

Given an OST π_C^* , the Markov chain in Example 3 is used for calculating the operating characteristics for the ARREST trial with $\tilde{\pi}_C(\mathbf{x}_t) = \mathbb{Q}(\theta_C > \theta_D \mid \mathbf{X}_t = \mathbf{x}_t)$, allocation probability $\pi_C = \min(0.75, \max(0.25, \tilde{\pi}_C(\mathbf{x}_t)))$ for $a \in \{C, D\}$, $\bar{i} = 150$ and block size $b_t = 30$ for all $t = \{1, 2, \dots, \bar{t}\}$ with $\bar{t} = 5$ update times. To calculate the UX OST, a separate Markov chain (see Subsection E.1) was used, where the state variable U_t was replaced by a state variable M_t denoting the highest value in a finite set \mathcal{M} that was crossed by $\tilde{\pi}_C(\mathbf{X}_{t'})$ for update time t' up to and including t , applying Algorithm 2 (see Appendix A) to the distribution of the Markov chain at update time \bar{t} when using M_t as the test statistic results in a UX OST for the ARREST trial. This approach was performed twice, first for $\mathcal{M}_1 = \{0.5, 0.6, \dots, 0.9, 0.95\} \cup 0.986 : 0.013/24 : 0.999$ and then for \mathcal{M}_2 consisting of value 0.5 and 29 equidistant points between the UX OST found in the first run and the highest value in \mathcal{M}_1 strictly below the UX OST, leading to a critical value of approximately 0.992. Note that $0.986 \in \mathcal{M}_1$ hence it is possible that the UX OST equals the SB OST. To have deterministic error guarantees and a deterministic critical value for the CX-S tests, values of $\tilde{\pi}_C(\mathbf{x}_t)$ were calculated as two-dimensional integrals using adaptive Gaussian quadrature (absolute tolerance 10^{-3}).

Figure 2 shows the type I error for the considered OSTs and difference in rejection rates. The SB OST controls type I error given that $\theta = \theta_C = \theta_D = 0.12$, when $\theta > 0.12$ the type I error grows to a value higher than 0.05, reaching a maximum of about 0.08 (Figure 2, Subfigure A). The type I error of the UX OST is close to 0.05 at its maximum. The power of all exact tests is below that of the SB OST (Figure 2, Subfigure B), where the UX OST performs best, while CX-S performs worst. Note that while the SB OST has highest power, it does not control type I error for values of $\theta_D = \theta_C$ that deviate even a slight bit from the assumed $\theta_C = 0.12$. The fact that CX-S performs worst in terms of power, could possibly be explained by the discreteness of the CX-S test for early updates. In Subsection E.2, we present

more results for the ARREST trial, such as the absolute power and expected proportion of allocations on the superior arm under all considered designs.

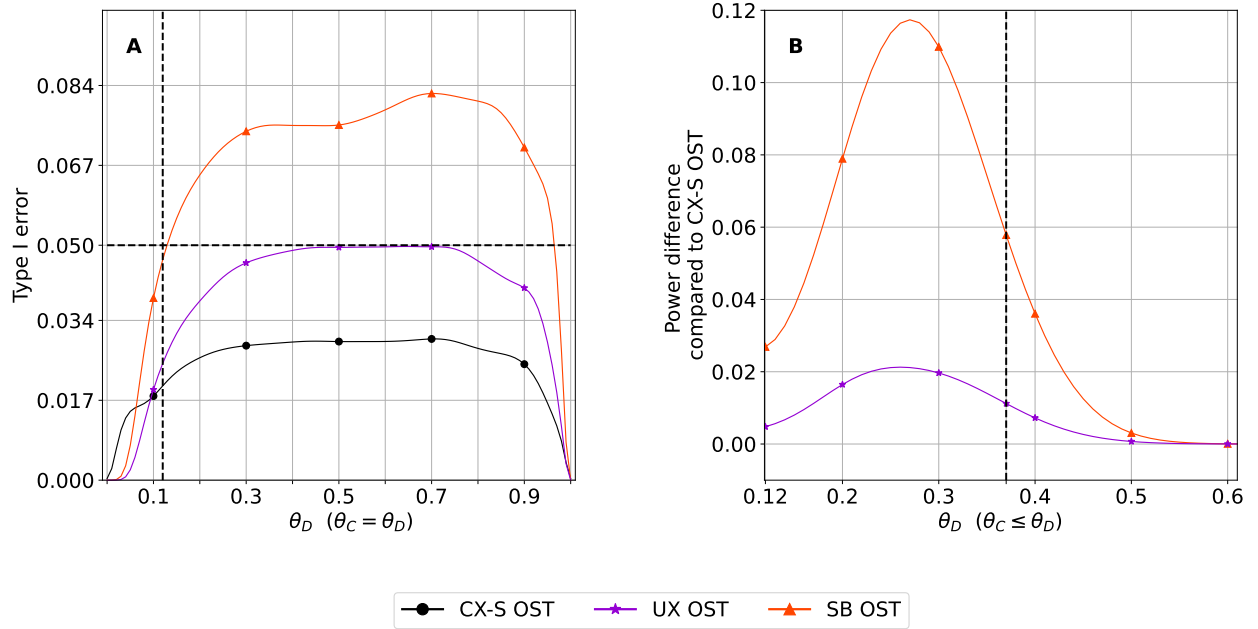


Figure 2: ARREST trial. Type I error under the SB, CX-S, and UX OST for $\theta_C = \theta_D$ (Subfigure A), the vertical line denotes $\theta_C = \theta_D = 0.12$. Power difference (Subfigure B) for the SB and UX OST compared to the CX-S OST, $\theta_C = 0.12$ and $\theta_D \geq \theta_C$, where the vertical line denotes $\theta_D = 0.37$. Both one-sided significance levels were set to 2.5%.

6. Discussion

We considered the theory and computation of exact tests for binary outcomes collected in a two-arm clinical trial using a *response-adaptive* (RA) procedure with possibly deterministic allocations. This approach allows for exact type I error control for RA designs in finite samples, even in cases where an asymptotic test does not yield type I error control which, as shown in the paper, can even occur in *non-response-adaptive* (NRA) designs with equal allocation and moderately large trial sizes. The Markov chain introduced in [Wei et al. \(1990\)](#) was generalized to allow for more elaborate designs and to construct exact conditional and unconditional tests for such designs.

The first key takeaway from our results is that, while the conditional exact test is often outperformed by the unconditional exact test in NRA designs with equal allocation, our results show that the opposite is true for several RA designs. This was seen for both the application to the randomized dynamic programming design and the modified play-the-winner design in [Appendix D](#), while the conservativeness of *conditional exact test based on total successes* (CX-S) for the real-life application in [Section 5](#) could be due to the use of a Bonferroni correction to account for possible type I error inflation from early stopping. This is in line with the findings in [Mehrotra et al. \(2003\)](#), where the conditional exact Wald test outperformed the unconditional exact Wald test in terms of power for NRA designs with unequal treatment group sizes, something likely to occur for more aggressive RA procedures. Out of the exact approaches considered, the conditional exact test often showed the highest power, is the most computationally tractable, and is exact when the outcomes are only assumed to be exchangeable. Lastly, the conservativeness of the unconditional and asymptotic tests close to the parameter space boundaries (i.e., for very low or very high success rates), both for RA and NRA designs, was not found for the CX-S test, which results in a significant advantage in terms of power by the CX-S test in such cases. This indicates that CX-S tests are a good candidate test for RA designs, as RA designs are often applied in cases with low or high success rates due to ethical reasons.

A second crucial lesson from our work is that, as seen in, e.g., our real-world application, the type I error inflation due to misspecification of the null success rate in simulation-based tests can be substantial. The proposed approach yields a

more robust test where type I error is under control no matter the null success rate, while, e.g., optimization over a subset of $[0, 1]$ for the unconditional threshold can result in an intermediate test with higher power (see, e.g., Yi (2013)).

Note that our results and conclusions are based on exact Wald tests for the null hypothesis of no treatment effect. In many situations, one could be interested in hypotheses that use a different estimand of interest (e.g. a log-odds ratio or a relative risk) and while our approach still applies, results may be different when changing the Wald test definition.

Future research is needed to extend the approach to more general settings, such as multiple trial phases (e.g., seamless phase II/III designs), multiple outcomes, multiple arms, other hypotheses (e.g., non-inferiority tests), random enrollment of participants, and possibly other adaptive procedures for clinical trials such as covariate-adjusted response-adaptive procedures. It would furthermore be interesting to consider whether results such as Theorem 1 could be extended to construct exact tests for other outcome types collected using a response-adaptive procedure, where a first next direction would be to consider categorical data. Most tests considered in this paper used the Wald statistic, and future research could focus on a comparison to other statistics, including randomization tests. Other topics in statistical inference such as estimation and providing reliable confidence intervals in response-adaptive designs are also important topics of future research.

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A. Proofs

In this section, we restate and give the proofs of the theorem and corollaries in the main paper.

Theorem 1. Assume there is a signed measure μ on $([0, 1]^2, \mathcal{B}([0, 1]^2))$ such that for all $\mathbf{y}_C, \mathbf{y}_D \in \{0, 1\}^{\bar{i}}$

$$\mathbb{P}(\mathbf{Y}_a = \mathbf{y}_a \quad \forall a \in \{C, D\}) = \int_{[0,1]^2} \prod_{a \in \{C, D\}} \theta_a^{\sum_{i=1}^{\bar{i}} y_{a,i}} (1 - \theta_a)^{\sum_{i=1}^{\bar{i}} (1 - y_{a,i})} \mu(d\theta) \quad (15)$$

and the process $(\mathbf{X}_t)_t$ has transition structure (1) with the factor $p_{\theta}(\partial \mathbf{s}(\mathbf{x}_t, \mathbf{x}_{t+1}) \mid \partial \mathbf{n}(\mathbf{x}_t, \mathbf{x}_{t+1}))$ replaced by $p(\partial \mathbf{s}(\mathbf{x}_t, \mathbf{x}_{t+1}) \mid \partial \mathbf{n}(\mathbf{x}_t, \mathbf{x}_{t+1}), \mathbf{n}(\mathbf{x}_t), \mathbf{s}(\mathbf{x}_t))$ where

$$p(\partial \mathbf{s}' \mid \partial \mathbf{n}', \mathbf{n}', \mathbf{s}') = \mathbb{P} \left(\sum_{i=n'_a+1}^{n'_a+\partial n'_a} Y_{a,i} = \partial s'_a \quad \forall a \in \{C, D\} \mid \sum_{i=1}^{n'_a} Y_{a,i} = s'_a \quad \forall a \in \{C, D\} \right) \quad (16)$$

for all $\mathbf{n}', \mathbf{s}' \in \mathcal{I}_0^2, \partial \mathbf{s}', \partial \mathbf{n}' \in \mathcal{D}^2$, then

$$\mathbb{P}^{\pi}(\mathbf{X}_t = \mathbf{x}_t) = g_t^{\pi}(\mathbf{x}_t) \int_{[0,1]^2} \prod_{a \in \{C, D\}} \theta_a^{s_a(\mathbf{x}_t)} (1 - \theta_a)^{n_a(\mathbf{x}_t) - s_a(\mathbf{x}_t)} \mu(d\theta) \quad \forall \mathbf{x}_t \in \mathcal{X}_t, \quad (17)$$

where, letting $\binom{n}{k}$ denote the binomial coefficient for natural numbers n, k , for all $t, \mathbf{x}_t \in \mathcal{X}_t$

$$g_0^{\pi}(\mathbf{x}_0) = 1, g_t^{\pi}(\mathbf{x}_t) = \sum_{\mathbf{x}_{t-1} \in \mathcal{X}_{t-1}} \left(\prod_{a \in \{C, D\}} \binom{\partial n_a(\mathbf{x}_{t-1}, \mathbf{x}_t)}{\partial s_a(\mathbf{x}_{t-1}, \mathbf{x}_t)} \right) g_{t-1}^{\pi}(\mathbf{x}_{t-1}) q^{\pi}(\mathbf{x}_{t-1}, \mathbf{x}_t).$$

Proof. Examining (16) and summing over paths that contain s'_a successes in the first n'_a observations and $\partial s'_a$ in the next $\partial n'_a$ gives for all $\mathbf{n}', \mathbf{s}' \in \mathcal{I}_0^2, \partial \mathbf{s}', \partial \mathbf{n}' \in \mathcal{D}^2$

$$p(\partial \mathbf{s}' \mid \partial \mathbf{n}', \mathbf{n}', \mathbf{s}') = \frac{\int_{[0,1]^2} \prod_{a \in \{C, D\}} \binom{n'_a}{s'_a} \binom{\partial n'_a}{\partial s'_a} \theta_a^{s'_a + \partial s'_a} (1 - \theta_a)^{(n'_a + \partial n'_a - s'_a - \partial s'_a)} \mu(d\theta)}{\int_{[0,1]^2} \prod_{a \in \{C, D\}} \binom{n'_a}{s'_a} \theta_a^{s'_a} (1 - \theta_a)^{(n'_a - s'_a)} \mu(d\theta)}.$$

The statement of the theorem is shown by induction, with (trivial) base case $t = 0$ as $S_{a,0} = N_{a,0} = 0$. Assume the statement holds up to and including $t - 1$, then by (1),

$$\begin{aligned} \mathbb{P}^{\pi}(\mathbf{X}_t = \mathbf{x}_t) &= \sum_{\mathbf{x}_{t-1} \in \mathcal{X}_{t-1}} \mathbb{P}^{\pi}(\mathbf{X}_{t-1} = \mathbf{x}_{t-1}) q^{\pi}(\mathbf{x}_{t-1}, \mathbf{x}_t) \cdot p(\partial \mathbf{s}(\mathbf{x}_{t-1}, \mathbf{x}_t) \mid \partial \mathbf{n}(\mathbf{x}_{t-1}, \mathbf{x}_t), \mathbf{n}(\mathbf{x}_{t-1}), \mathbf{s}(\mathbf{x}_{t-1})) \\ &\stackrel{(\text{Ind. Hyp})}{=} \sum_{\mathbf{x}_{t-1} \in \mathcal{X}_{t-1}} g_{t-1}^{\pi}(\mathbf{x}_{t-1}) q^{\pi}(\mathbf{x}_{t-1}, \mathbf{x}_t) \int_{[0,1]^2} \prod_a \binom{\partial n_a(\mathbf{x}_{t-1}, \mathbf{x}_t)}{\partial s_a(\mathbf{x}_{t-1}, \mathbf{x}_t)} \theta_a^{s_a(\mathbf{x}_t)} (1 - \theta_a)^{(n_a(\mathbf{x}_t) - s_a(\mathbf{x}_t))} \mu(d\theta) \\ &= \left(\sum_{\mathbf{x}_{t-1} \in \mathcal{X}_{t-1}} \left(\prod_a \binom{\partial n_a(\mathbf{x}_{t-1}, \mathbf{x}_t)}{\partial s_a(\mathbf{x}_{t-1}, \mathbf{x}_t)} \right) g_{t-1}^{\pi}(\mathbf{x}_{t-1}) q^{\pi}(\mathbf{x}_{t-1}, \mathbf{x}_t) \right) \\ &\quad \cdot \left(\int_{[0,1]^2} \prod_{a \in \{C, D\}} \theta_a^{s_a(\mathbf{x}_t)} (1 - \theta_a)^{(n_a(\mathbf{x}_t) - s_a(\mathbf{x}_t))} \mu(d\theta) \right) \\ &= g_t^{\pi}(\mathbf{x}_t) \int_{[0,1]^2} \prod_{a \in \{C, D\}} \theta_a^{s_a(\mathbf{x}_t)} (1 - \theta_a)^{(n_a(\mathbf{x}_t) - s_a(\mathbf{x}_t))} \mu(d\theta) \quad \forall \mathbf{x}_t \in \mathcal{X}_t. \end{aligned}$$

Hence, the statement follows by mathematical induction. \square

Corollary 3. If $\zeta : \mathcal{X}_{\bar{t}} \mapsto \mathcal{Z}$, $s(\mathbf{X}_{\bar{t}}) = \tilde{s}(\zeta(\mathbf{X}_{\bar{t}}))$ for a function $\tilde{s} : \mathcal{Z} \mapsto \mathcal{I}_0$ and the assumptions of [Theorem 1](#) hold then under the nonparametric null hypothesis H_0^{NP} in [Table 1](#) we have

$$\mathbb{P}_{\theta}^{\pi} \left(\mathbb{T}(\mathbf{X}_{\bar{t}}) \geq \bar{c}(\zeta(\mathbf{X}_{\bar{t}})) \text{ or } \mathbb{T}(\mathbf{X}_{\bar{t}}) \leq \underline{c}(\zeta(\mathbf{X}_{\bar{t}})) \right) \leq \alpha.$$

Proof. Using the convention $0/0 = 1$, following [Theorem 1](#) we have that for all $z \in \mathcal{Z}$ for which $\mathbb{P}^\pi(\zeta(\mathbf{X}_{\bar{i}}) = z) > 0$:

$$\begin{aligned}
& \mathbb{P}^\pi(\mathsf{T}(\mathbf{X}_{\bar{i}}) \geq \bar{c}(\zeta(\mathbf{X}_{\bar{i}})) \mid \zeta(\mathbf{X}_{\bar{i}}) = z) = \mathbb{P}^\pi(\mathsf{T}(\mathbf{X}_{\bar{i}}) \geq \bar{c}(z) \mid \zeta(\mathbf{X}_{\bar{i}}) = z) \\
& \stackrel{\text{(Theorem 1)}}{=} \frac{\sum_{\mathbf{x}_{\bar{i}} \in \mathcal{X}_\zeta(z) : \mathsf{T}(\mathbf{x}_{\bar{i}}) \geq \bar{c}(z)} g_{\bar{i}}^\pi(\mathbf{x}_{\bar{i}}) \int_{[0,1]^2} \prod_{a \in \{C,D\}} \theta_a^{s_a(\mathbf{x}_{\bar{i}})} (1 - \theta_a)^{n_a(\mathbf{x}_{\bar{i}}) - s_a(\mathbf{x}_{\bar{i}})} \mu(d\boldsymbol{\theta})}{\sum_{\mathbf{x}_{\bar{i}} \in \mathcal{X}_\zeta(z)} g_{\bar{i}}^\pi(\mathbf{x}_{\bar{i}}) \int_{[0,1]^2} \prod_{a \in \{C,D\}} \theta_a^{s_a(\mathbf{x}_{\bar{i}})} (1 - \theta_a)^{n_a(\mathbf{x}_{\bar{i}}) - s_a(\mathbf{x}_{\bar{i}})} \mu(d\boldsymbol{\theta})} \\
& = \frac{\sum_{\mathbf{x}_{\bar{i}} \in \mathcal{X}_\zeta(z) : \mathsf{T}(\mathbf{x}_{\bar{i}}) \geq \bar{c}(z)} g_{\bar{i}}^\pi(\mathbf{x}_{\bar{i}}) \int_{\{\boldsymbol{\theta} \in [0,1]^2 : \theta_C = \theta_D\}} \theta_C^{s(\mathbf{x}_{\bar{i}})} (1 - \theta_C)^{\bar{i} - s(\mathbf{x}_{\bar{i}})} \mu(d\boldsymbol{\theta})}{\sum_{\mathbf{x}_{\bar{i}} \in \mathcal{X}_\zeta(z)} g_{\bar{i}}^\pi(\mathbf{x}_{\bar{i}}) \int_{\{\boldsymbol{\theta} \in [0,1]^2 : \theta_C = \theta_D\}} \theta_C^{s(\mathbf{x}_{\bar{i}})} (1 - \theta_C)^{\bar{i} - s(\mathbf{x}_{\bar{i}})} \mu(d\boldsymbol{\theta})} \\
& = \frac{\int_{\{\boldsymbol{\theta} \in [0,1]^2 : \theta_C = \theta_D\}} \theta_C^{\bar{s}(z)} (1 - \theta_C)^{\bar{i} - \bar{s}(z)} \mu(d\boldsymbol{\theta}) \cdot \sum_{\mathbf{x}_{\bar{i}} \in \mathcal{X}_\zeta(z) : \mathsf{T}(\mathbf{x}_{\bar{i}}) \geq \bar{c}(z)} g_{\bar{i}}^\pi(\mathbf{x}_{\bar{i}})}{\int_{\{\boldsymbol{\theta} \in [0,1]^2 : \theta_C = \theta_D\}} \theta_C^{\bar{s}(z)} (1 - \theta_C)^{\bar{i} - \bar{s}(z)} \mu(d\boldsymbol{\theta}) \cdot \sum_{\mathbf{x}_{\bar{i}} \in \mathcal{X}_\zeta(z)} g_{\bar{i}}^\pi(\mathbf{x}_{\bar{i}})} \\
& = \frac{\sum_{\mathbf{x}_{\bar{i}} \in \mathcal{X}_\zeta(z) : \mathsf{T}(\mathbf{x}_{\bar{i}}) \geq \bar{c}(z)} g_{\bar{i}}^\pi(\mathbf{x}_{\bar{i}})}{\sum_{\mathbf{x}_{\bar{i}} \in \mathcal{X}_\zeta(z)} g_{\bar{i}}^\pi(\mathbf{x}_{\bar{i}})} \stackrel{(11)}{\leq} \bar{\alpha}.
\end{aligned}$$

Similarly $\mathbb{P}^\pi(\mathsf{T}(\mathbf{X}_{\bar{i}}) \leq \underline{c}(\zeta(\mathbf{X}_{\bar{i}})) \mid \zeta(\mathbf{X}_{\bar{i}}) = z) \leq \alpha$, and hence the statement of the theorem is proven by the law of total expectation. \square

Corollary 4. *If the assumptions of [Theorem 1](#) hold with μ a probability measure, then under H_0^{NP} it holds that $\mathbb{P}_\theta^\pi(\mathsf{T}(\mathbf{X}_{\bar{i}}) \geq \bar{c} \text{ or } \mathsf{T}(\mathbf{X}_{\bar{i}}) \leq \underline{c}) \leq \alpha$, where \bar{c}, \underline{c} are as given in [Definition 2](#).*

Proof. By [Theorem 1](#), we have

$$\begin{aligned}
\mathbb{P}^\pi(\mathsf{T}(\mathbf{X}_{\bar{i}}) \geq \bar{c}) &= \int_{[0,1]^2} \mathbb{P}_\theta^\pi(\mathsf{T}(\mathbf{X}_{\bar{i}}) \geq \bar{c}) \mu(d\boldsymbol{\theta}) \\
&= \int_{\{\boldsymbol{\theta} \in [0,1]^2 : \theta_C = \theta_D\}} \mathbb{P}_\theta^\pi(\mathsf{T}(\mathbf{X}_{\bar{i}}) \geq \bar{c}) \mu(d\boldsymbol{\theta}) \leq \max_{\boldsymbol{\theta} \in [0,1]^2 : \theta_C = \theta_D} \mathbb{P}_\theta^\pi(\mathsf{T}(\mathbf{X}_{\bar{i}}) \geq \bar{c}) \leq \bar{\alpha}.
\end{aligned}$$

Where the penultimate inequality follows by taking the maximum inside the integral and as μ is a probability measure. Similarly $\mathbb{P}^\pi(\mathsf{T}(\mathbf{X}_{\bar{i}}) \leq \underline{c}) \leq \alpha$, proving the statement. \square

B. Algorithms and computation time results

B.1. Algorithm for calculating an upper bound for unconditional critical values

This section provides an algorithm to compute a (tight) upper bound for a UX upper critical value \bar{c} , based on [Theorem 1](#). Often, due to symmetry, it suffices to only compute \bar{c} , otherwise, the computational procedure has to be adjusted in a straightforward manner. Hence, we focus on the computation of a (tight) upper bound for \bar{c} . In order to determine a numerical procedure for calculating an upper bound of \bar{c} the following result, bounding the difference between the rejection rate at different parameter values, is of use.

Lemma 1. *Let $r_c(\boldsymbol{\theta}) = \mathbb{P}_{(\boldsymbol{\theta}, \boldsymbol{\theta})}^\pi(\mathsf{T}(\mathbf{X}_{\bar{i}}) \geq c)$ for all $\boldsymbol{\theta} \in [0, 1]$. Then, for $\theta_1, \theta_2 \in [0, 1]$ where $\theta_1 \leq \theta_2$ we have*

$$r_c(\theta_3) - r_c(\theta_1) \leq k_c(\theta_1, \theta_2)(\theta_3 - \theta_1) \forall \theta_3 \in [\theta_1, \theta_2],$$

where

$$\begin{aligned}
k_c(\theta_1, \theta_2) &= \sum_{\mathbf{x}_{\bar{i}} \in \mathcal{X}_{\bar{i}} : \mathsf{T}(\mathbf{x}_{\bar{i}}) \geq c} g_{\bar{i}}^\pi(\mathbf{x}_{\bar{i}}) h^*(\mathbf{x}_{\bar{i}}, \theta_1, \theta_2) \\
h^*(\mathbf{x}_{\bar{i}}, \theta_1, \theta_2) &= \max(\{h(\mathbf{x}_{\bar{i}}, \theta_1), h(\mathbf{x}_{\bar{i}}, \theta_2), h(\mathbf{x}_{\bar{i}}, \text{Proj}_{[\theta_1, \theta_2]}(\theta_-^*(\mathbf{x}_{\bar{i}}))), h(\mathbf{x}_{\bar{i}}, \text{Proj}_{[\theta_1, \theta_2]}(\theta_+^*(\mathbf{x}_{\bar{i}})))\}) \\
h(\mathbf{x}_{\bar{i}}, \theta) &= (s(\mathbf{x}_{\bar{i}}) - \bar{i} \cdot \theta) \theta^{s(\mathbf{x}_{\bar{i}}) - 1} (1 - \theta)^{\bar{i} - s(\mathbf{x}_{\bar{i}}) - 1},
\end{aligned}$$

$\text{Proj}_{[\theta_1, \theta_2]}(x) = \min(\theta_1, \max(\theta_2, x))$, and

$$\theta_\pm^*(\mathbf{x}_{\bar{i}}) = \frac{2s(\mathbf{x}_{\bar{i}})(\bar{i} - 1) \pm \sqrt{4s(\mathbf{x}_{\bar{i}})^2(\bar{i} - 1)^2 - 4\bar{i}(\bar{i} - 1)s(\mathbf{x}_{\bar{i}})(s(\mathbf{x}_{\bar{i}}) - 1)}}{2\bar{i}(\bar{i} - 1)}.$$

Proof. From (8) we have $r_c(\theta) = \sum_{\mathbf{x}_{\bar{i}} \in \mathcal{X}_{\bar{i}}: T(\mathbf{x}_{\bar{i}}) \geq c} g_{\bar{i}}^{\pi}(\mathbf{x}_{\bar{i}}) \cdot \theta^{s(\mathbf{x}_{\bar{i}})} (1 - \theta)^{\bar{i} - s(\mathbf{x}_{\bar{i}})}$ hence

$$r'_c(\theta) = \sum_{\mathbf{x}_{\bar{i}} \in \mathcal{X}_{\bar{i}}: T(\mathbf{x}_{\bar{i}}) \geq c} g_{\bar{i}}^{\pi}(\mathbf{x}_{\bar{i}}) h(\mathbf{x}_{\bar{i}}, \theta), r''_c(\theta) = \sum_{\mathbf{x}_{\bar{i}} \in \mathcal{X}_{\bar{i}}: T(\mathbf{x}_{\bar{i}}) \geq c} g_{\bar{i}}^{\pi}(\mathbf{x}_{\bar{i}}) h'(\mathbf{x}_{\bar{i}}, \theta)$$

where

$$h'(\mathbf{x}_{\bar{i}}, \theta) = (\bar{i}(\bar{i} - 1)\theta^2 - 2s(\mathbf{x}_{\bar{i}})(\bar{i} - 1)\theta + s(\mathbf{x}_{\bar{i}})(s(\mathbf{x}_{\bar{i}}) - 1))\theta^{s(\mathbf{x}_{\bar{i}}) - 2} (1 - \theta)^{\bar{i} - s(\mathbf{x}_{\bar{i}}) - 2}.$$

Note that $h'(\mathbf{x}_{\bar{i}}, \theta) = 0$ and hence the extreme values of h occur at $\theta_{\pm}^*(\mathbf{x}_{\bar{i}})$ and $\{0, 1\}$. By the mean value theorem, we have for all points $\theta_3 \in [\theta_1, \theta_2]$ that $r_c(\theta_1) - r_c(\theta_2) = r'_c(\theta_3)(\theta_1 - \theta_2)$. The bound now follows as we can bound $r'_c(\theta_3)$ by maximizing each function $h(\mathbf{x}_{\bar{i}}, \theta_3)$ for $\theta_3 \in [\theta_1, \theta_2]$, making use of the fact that the maximum occurs either at θ_1, θ_2 or at the zeroes $\theta_{\pm}^*(\mathbf{x}_{\bar{i}})$ of h' whenever they fall in $[\theta_1, \theta_2]$. \square

From [Lemma 1](#), for $0 < \epsilon < 1$, if $\theta_1 - \theta_2 \leq \epsilon/k_c(\theta_1, \theta_2)$ then $r_c(\theta_1) - r_c(\theta_3) \leq \epsilon$ for all $\theta_3 \in [\theta_1, \theta_2]$. Hence, if we have a sequence of points $0 = \theta_0 < \theta_1 < \dots < \theta_m = 1$ such that the bound $\theta_\ell - \theta_{\ell+1} \leq \epsilon/k_c(\theta_\ell, \theta_{\ell+1})$ holds and $r_c(\theta_\ell) \leq \bar{\alpha} - \epsilon$ for all ℓ then $r_c(\theta) \leq \bar{\alpha}$ for all $\theta \in [0, 1]$ hence $c \geq \bar{c}$. This is the idea behind [Algorithm 2](#) for calculating an upper bound for \bar{c} , which first determines the constants $k_c(\theta_1, \theta_2)$ for a coarse grid, and then refines the grid such that the distance between consecutive points is less than $\epsilon/k_c(\theta_1, \theta_2)$, using the fact that $k_c(\theta_1, \theta_2)$ is decreasing in the difference between θ_1 and θ_2 and in c . Finally, the algorithm calculates c such that $r_c(\theta) \leq \bar{\alpha} - \epsilon$ for all values of θ in the grid, where certain values can be skipped depending on the difference between the current rejection rate and $\bar{\alpha} - \epsilon$. A similar approach was introduced in [Suissa and Shuster \(1985\)](#).

B.2. Considerations regarding computation time

[Algorithm 1](#) until [Algorithm 4](#) form the most important algorithms for generating the results of this paper, and can be used to calculate the operating characteristics, critical values, and the p-values under FET. From [Algorithm 3](#) it can be seen that the complexity of calculating the OCs in the state space size is $O(|\mathcal{X}_{\bar{i}}|)$ (coming from the for-loop), while [Algorithm 1](#) with $|v| = |\mathcal{X}_{\bar{i}}|$, due to the sorting step, will have complexity $O(|\mathcal{X}_{\bar{i}}| \log(|\mathcal{X}_{\bar{i}}|))$. As [Algorithm 2](#) also uses [Algorithm 1](#) to determine the critical value for values in a grid the complexity in terms of the state space size is also $O(|\mathcal{X}_{\bar{i}}| \log(|\mathcal{X}_{\bar{i}}|))$. Lastly, [Algorithm 4](#) has complexity $O(|\mathcal{X}_{\bar{i}}| \cdot \max_{s', n'_c} |\mathcal{X}_{SA}(s', n'_c)|)$ due to the for-loop over $\mathcal{X}_{SA}(s', n'_c)$ including the sum over a vector of size $\mathcal{X}_{SA}(s', n'_c)$. In case of the Markov chain in [Example 1](#), we will have that $|\mathcal{X}_{\bar{i}}| \in O(\bar{i}^3)$ (see, e.g., [Jacko \(2019\)](#)), hence the complexities in \bar{i} become $O(\bar{i}^3)$, $O(\bar{i}^3 \cdot \log(\bar{i}))$, and $O(\bar{i}^4)$, as for [Example 1](#) we have $|\mathcal{X}_{SA}(s', n'_c)| = \min(s', n'_c) \leq \bar{i}$. [Figure 3](#) is in agreement with these theoretical results, where it is shown that a linear regression (found using ordinary least squares) on the above theoretical orders including intercept results in a good fit for [Algorithm 1](#), [Algorithm 3](#), and [Algorithm 4](#).

Algorithm 1 Algorithm for calculating upper critical values of v for significance level α and probability weight vector w

- 1: **Inputs:**
 v, w, α ;
 - 2: Sort v and permute w accordingly;
 - 3: Set $i = 1$;
 - 4: **while** $\sum_{i'=1}^i w_{i'} < 1 - \alpha$ **do**
 - 5: $i := i + 1$;
 - 6: **end while**
 - 7: **if** $\sum_{i': v_{i'} \geq v_i} w_{i'} > \alpha$ **then** *(this happens in case of ties in v)*
 - 8: Set $i := \min\{i' \geq i : v_{i'} > v_i\}$;
 - 9: **end if**
 - 10: **Outputs:** v_i .
-

Algorithm 2 Algorithm for calculating an upper bound for UX critical value \bar{c}

```

1: Inputs:
    $0 < \epsilon, \bar{\alpha}, \theta_0 < 1, m \in \{1, 2, \dots\}$ ;
2: Initialize:
   Set  $\mathbf{v} = ()$  and  $\bar{c} = \min\{c \in \bar{\mathbb{T}}(\mathcal{X}_{\bar{t}}) : r_c(\theta_0) \leq \bar{\alpha} - \epsilon\}$  using Algorithm 1;
3: for  $\ell \in \{1, \dots, m\}$  do
4:   if  $\epsilon/k_{\bar{c}}((\ell - 1)/m, \ell/m) \in (0, 1/m)$  then
5:     Set  $d\theta = \epsilon/k_{\bar{c}}((\ell - 1)/m, \ell/m)$ ;
6:   else
7:     Set  $d\theta = 1/m$ ;
8:   end if
9:   Update  $\mathbf{v} := \mathbf{v} \frown (\ell - 1)/m : d\theta : \ell/m$ ; ( $\frown$  denotes concatenation)
10: end for
11: Set  $k = 1$ ;
12: while  $k \leq |\mathbf{v}|$  do
13:   Set  $\bar{c}' = \min\{c \in \bar{\mathbb{T}}(\mathcal{X}_{\bar{t}}) : r_c(v_k) \leq \bar{\alpha} - \epsilon\}$  using Algorithm 1;
14:   Update  $\bar{c} := \max(\bar{c}', \bar{c})$ ;
15:   Update  $k := k + \max(1, \lfloor (\bar{\alpha} - r_{\bar{c}}(v_k))/\epsilon \rfloor)$ ;
16: end while
17: Outputs:  $\bar{c}$ 

```

Algorithm 3 Algorithm for calculating operating characteristics $\mathbb{E}_{\theta}^{\pi}[f(\mathbf{X}_{\bar{t}})]$ where i is an index mapping function for $\mathcal{X}_{\bar{t}}$.

```

1: Inputs:
    $i, f, g_{\bar{t}}^{\pi}, \theta$ ;
2: Set  $\mathbf{p}, \mathbf{g}, \mathbf{v} = \mathbf{0}_{|\mathcal{X}_{\bar{t}}|}$ ;
3: for  $\mathbf{x}_{\bar{t}} \in \mathcal{X}_{\bar{t}}$  do
4:   Set  $p_{i(\mathbf{x}_{\bar{t}})} = \prod_{a \in \{C, D\}} \theta_a^{s_a(\mathbf{x}_{\bar{t}})} (1 - \theta_a)^{n_a(\mathbf{x}_{\bar{t}}) - s_a(\mathbf{x}_{\bar{t}})}$ ;
5:   Set  $g_{i(\mathbf{x}_{\bar{t}})} = g_{\bar{t}}^{\pi}(\mathbf{x}_{\bar{t}})$  and  $v_{i(\mathbf{x}_{\bar{t}})} = f(\mathbf{x}_{\bar{t}})$ ;
6: end for
7: Outputs:  $\mathbf{p}^{\top}(\mathbf{g} \circ \mathbf{v})$  (where  $\top$  means transpose and  $\circ$  the Hadamard product)

```

Algorithm 4 Algorithm for calculating \mathbb{T}_{FET} for every state as a vector \mathbf{v}_{T} .

```

1: Inputs:
   index mapping function  $i$  for  $\mathcal{X}_{\bar{t}}$ ;
2: Set  $\mathbf{p}', \mathbf{v}_{\text{T}} = \mathbf{0}_{|\mathcal{X}_{\bar{t}}|}$ ;
3: for  $s', n'_C \in \mathcal{I}_0$  do
4:   Set  $\mathcal{P} = \emptyset$ ;
5:   for  $\mathbf{x}_{\bar{t}} \in \mathcal{X}_{\text{SA}}((s', n'_C))$  do
6:     Set  $p'_{i(\mathbf{x}_{\bar{t}})} = p_{\text{FET}}(\mathbf{x}_{\bar{t}})$  with  $p_{\text{FET}}$  as defined in (12);
7:     Update  $\mathcal{P} := \mathcal{P} \cup \{p'_{i(\mathbf{x}_{\bar{t}})}\}$ ;
8:   end for
9:   for  $\mathbf{x}_{\bar{t}} \in \mathcal{X}_{\text{SA}}((s', n'_C))$  do
10:    Set  $v_{\text{T}, i(\mathbf{x}_{\bar{t}})} = \sum_{p'' \in \mathcal{P} : p'' \leq p'_{i(\mathbf{x}_{\bar{t}})}} p''$ ;
11:   end for
12: end for
13: Outputs:  $\mathbf{v}_{\text{T}}$ 

```

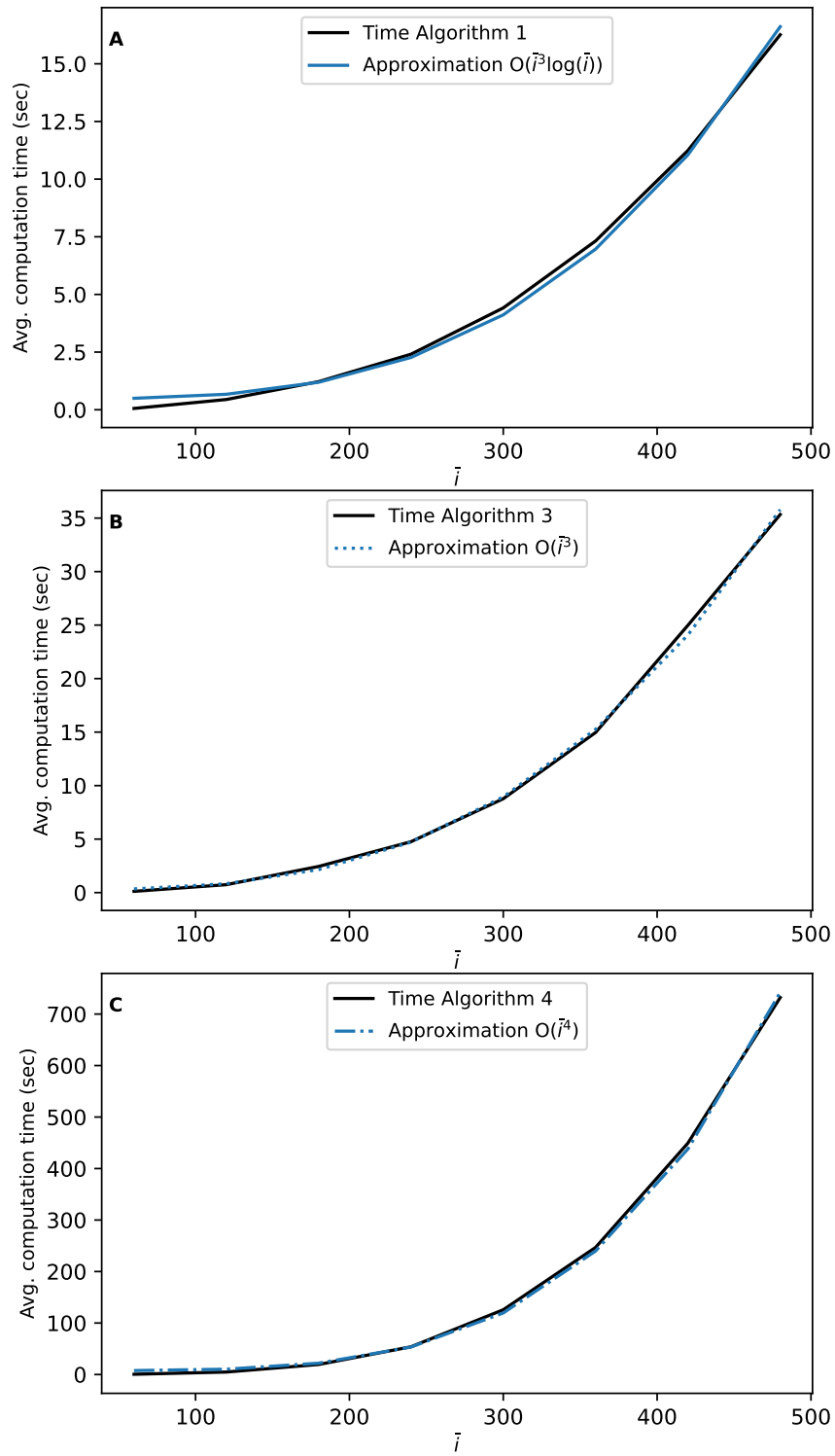


Figure 3: Average computation times (25 runs) vs. linear regressions on the time complexities for Algorithm 1 (Subfigure A), Algorithm 3 (Subfigure B) and Algorithm 4 (Subfigure C).

C. Additional results for randomized dynamic programming and equal allocation design

Table 2 until Table 4 show the rejection rates for the RDP RAR procedure under several parameter configurations, tests, and trial sizes 60, 240 and 960 participants, where $\bar{\alpha} = \alpha = 2.5\%$. The rows of the table where $\theta_C \in \{0.01, 0.3, 0.9\}$ correspond to the markers in the right subfigures of Figure 1. In the tables, bold (red) indicates type I error inflation for the column corresponding to the asymptotic Wald test, (bold) green indicates highest power for the other columns. The asymptotic Wald test is excluded from consideration in the power comparison as it does not control type I error.

The tables show that the CX-S test often has highest power, and in cases where it is outperformed the power differences are less than 1%. For very small and very high control success rates the increase in power for the CX-S test over other tests is quite substantial, e.g., for $\theta_C = 0.0$, power differences around 20 – 30% are seen for all values of \bar{i} . Something that also stands out is that the rejection rate at the points $\theta_C = \theta_D \in \{0, 1\}$ for the CX-S test is higher than 0, and even around 5% for $\bar{i} = 960$ and $\theta_C = \theta_D = 1.0$. This is because, while the treatment outcomes are deterministic in such cases, the allocations are still a source of randomness. The rejection rate is zero for the CX-SA test in such cases as we remove the only source of randomness when conditioning on the allocations as well. The rejection rate for the UX Wald test and FET (corr.) is zero because null success rates 0 and 1 induce significantly less variance in the test statistic in comparison to the parameter configuration where type I error is highest. As also seen in Figure 1, the type I error inflation under the asymptotic test does not reduce for large trial sizes.

Figure 4 shows the comparison made in Figure 1 of the paper when both treatment group sizes are (deterministically) equal to $\bar{i}/2$, i.e. in case of an NRA design with *equal allocation* (EA), such as a design with truncated binomial allocation or 1:1 permuted block allocation. As FET controls the type I error under EA, FET does not need to be corrected. As there is a one-to-one relation between the test statistic outcome and the number of successes in an arm when both allocations and total successes are fixed, the rejection rates of the FET, CX-S, and CX-SA Wald test coincide.

Figure 4 shows that the UX Wald test often has the highest power, where the maximum difference in power decreases with \bar{i} . The asymptotic Wald test does not control type I error for each value of the null success rate, even under an NRA design. However, the maximum type I error becomes closer to α when \bar{i} increases. The UX critical values \bar{c} also indicate this behavior, with values 2.066, 1.978, and 1.970 for $\bar{i} = 60, 240, 960$ respectively, in comparison to the asymptotic critical value around 1.960 (see Table 8). Similar curves can be found in, e.g., Shan (2016, pg. 18).

Table 5 until Table 7 show the (absolute) rejection rates under all tests for EA for $\bar{i} = 60, 240$ and 960. The rows of the table for $\theta_C = 0.01, 0.3$ and 0.9 correspond to the markers in Figure 4, while each vertical line in the figure corresponds to a row in the tables where $\theta_C = \theta_D$. First, the tables indicate that the type I error inflation occurring under EA is easily missed, as there is only one case (for $\bar{i} = 60$) where type I error inflation occurs. Second, the tables show that the UX Wald test uniformly has highest power out of the considered tests and parameter values, as the asymptotic Wald test is not considered in the power comparison as it does not yield type I error control. Third, a thing of note is that the rejection rate of the CX-S test at $\theta_C = \theta_D \in \{0, 1\}$ is 0, as EA is a fixed design.

Table 2: Rejection rates (%) for the RDP RAR procedure under several parameter configurations, tests, and trial size $\bar{i} = 60$. Red indicates type I error inflation, green indicates highest power (excluding asymptotic test).

\bar{i}	θ_C	θ_D	CX-S Wald	CX-SA Wald	UX Wald	Asymp. Wald	FET (corr.)	
60	0.0	0.0	0.14	0.00	0.00	0.00	0.00	
		0.1	13.64	0.49	0.17	0.40	0.15	
		0.2	32.39	2.69	8.40	13.64	4.09	
		0.3	57.80	8.04	41.51	51.78	27.42	
		0.4	79.73	19.85	76.16	82.16	62.08	
		0.5	91.83	38.95	92.29	94.37	81.57	
		0.01	0.01	1.40	0.04	0.00	0.00	0.00
			0.11	12.95	0.69	0.26	0.58	0.21
			0.21	31.19	2.98	9.46	14.92	4.65
			0.31	55.96	8.42	42.03	51.54	28.76
			0.41	77.33	20.26	74.72	80.43	61.22
		0.51	90.10	39.11	90.62	93.01	80.14	
		0.05	0.05	3.83	0.41	0.00	0.01	0.00
			0.15	10.98	1.37	0.93	1.81	0.50
			0.25	27.37	3.79	13.38	19.00	7.52
			0.35	49.49	9.66	42.59	49.83	31.86
			0.45	69.72	21.64	69.41	74.81	57.13
		0.55	84.63	39.59	85.23	88.45	76.05	
		0.1	0.1	4.18	0.88	0.06	0.15	0.05
			0.2	9.63	1.82	2.45	4.10	1.17
			0.3	23.95	4.49	16.79	21.65	11.18
			0.4	43.44	10.93	41.30	47.43	31.87
			0.5	63.63	22.87	64.22	69.79	53.08
		0.6	80.21	40.14	80.60	84.31	73.81	
		0.3	0.3	4.57	1.66	3.41	4.75	2.10
	0.4		7.97	2.78	7.62	9.85	5.09	
	0.5		18.36	6.49	18.69	22.66	13.88	
	0.6		35.54	13.97	36.22	41.36	31.20	
	0.7		55.89	27.18	56.75	62.17	54.79	
	0.8	75.88	47.21	74.90	78.96	76.26		
	0.5	0.5	4.75	1.88	4.97	6.50	3.29	
		0.6	8.03	3.15	8.34	10.48	6.77	
		0.7	18.96	8.00	19.25	23.20	18.82	
		0.8	39.92	19.26	37.99	43.42	41.04	
		0.9	68.02	42.33	60.18	66.98	67.86	
	1.0	95.77	83.40	80.02	85.71	91.33		
	0.7	0.7	4.58	1.75	4.50	6.08	4.69	
		0.8	9.44	3.67	8.14	10.60	9.97	
		0.9	30.16	13.73	21.85	28.10	30.12	
		1.0	81.20	53.68	48.85	59.06	72.11	
	0.9	0.9	4.78	1.21	1.93	3.38	4.36	
		1.0	30.58	8.58	6.45	10.77	20.99	
	0.95	0.95	4.50	0.66	0.80	1.70	3.17	
		0.96	4.64	0.64	0.73	1.57	3.11	
		0.97	5.29	0.72	0.73	1.59	3.36	
		0.98	6.61	0.92	0.81	1.75	3.96	
		0.99	8.81	1.26	0.96	2.03	4.99	
	1.0	12.24	1.78	1.19	2.44	6.51		
	0.99	0.99	2.67	0.08	0.05	0.14	0.60	
		1.0	2.57	0.06	0.03	0.08	0.45	
	1.0	1.0	1.51	0.00	0.00	0.00	0.00	

Table 3: Rejection rates (%) for the RDP RAR procedure under several parameter configurations, tests, and trial size $\bar{i} = 240$. Red indicates type I error inflation, green indicates highest power (excluding asymptotic test).

\bar{i}	θ_C	θ_D	CX-S Wald	CX-SA Wald	UX Wald	Asymp. Wald	FET (corr.)
240	0.0	0.0	0.14	0.00	0.00	0.00	0.00
		0.05	31.22	2.46	3.51	6.35	1.48
		0.1	75.72	8.44	60.05	69.84	30.52
		0.15	97.89	24.88	96.73	98.11	83.91
		0.2	99.92	55.10	99.90	99.95	98.38
		0.25	100.00	82.16	100.00	100.00	99.88
0.01	0.01	0.01	4.41	0.34	0.00	0.00	0.00
		0.06	25.94	3.07	5.82	9.48	2.08
		0.11	64.62	9.12	55.51	63.18	31.98
		0.16	88.55	24.94	87.54	90.60	76.03
		0.21	97.16	52.07	97.09	98.02	93.43
		0.26	99.44	76.94	99.45	99.66	98.43
0.05	0.05	0.05	4.74	1.53	0.57	1.09	0.18
		0.1	15.71	3.92	11.88	15.20	5.58
		0.15	40.80	10.52	39.12	44.89	28.45
		0.2	67.94	23.73	67.51	72.72	56.55
		0.25	86.18	43.10	86.23	89.32	78.67
		0.3	95.04	63.84	95.10	96.47	91.79
0.1	0.1	0.1	4.83	2.01	3.76	5.04	1.57
		0.15	11.68	4.28	11.04	13.76	7.08
		0.2	30.64	10.71	30.28	35.36	22.53
		0.25	54.90	21.66	54.95	60.71	45.49
		0.3	75.51	37.24	75.71	80.16	68.84
		0.35	88.85	55.23	88.94	91.49	84.99
0.3	0.3	0.3	4.94	2.73	4.98	6.56	3.67
		0.35	8.65	4.48	8.68	11.05	6.87
		0.4	19.93	9.70	19.81	24.01	17.04
		0.45	37.72	18.50	37.26	43.09	33.87
		0.5	57.90	30.93	57.07	62.98	54.01
		0.55	75.49	46.33	74.45	79.12	72.40
0.5	0.5	0.5	4.93	2.84	4.63	6.32	4.09
		0.55	8.35	4.56	7.75	10.24	7.28
		0.6	19.25	10.13	17.80	22.32	17.62
		0.65	37.40	20.09	34.73	41.09	35.30
		0.7	58.86	34.62	55.19	61.81	56.79
		0.75	77.60	52.98	73.91	79.19	76.15
0.7	0.7	0.7	4.94	2.72	3.88	5.65	4.43
		0.75	9.53	5.11	7.49	10.32	8.77
		0.8	25.10	13.61	20.35	25.73	23.87
		0.85	50.73	30.48	42.80	50.02	49.89
		0.9	77.00	56.02	68.15	74.74	77.36
		0.95	93.89	83.90	87.72	91.28	94.44
0.9	0.9	0.9	4.92	2.10	2.19	3.72	4.94
		0.95	20.47	10.05	9.80	14.24	20.05
		1.0	90.11	74.57	49.01	60.72	81.96
0.95	0.95	0.95	4.90	1.63	1.22	2.31	4.71
		0.96	5.94	1.97	1.43	2.64	5.54
		0.97	9.70	3.46	2.41	4.23	8.76
		0.98	17.88	7.05	4.58	7.69	15.77
		0.99	34.54	15.26	8.78	14.59	29.38
		1.0	67.60	35.61	17.49	27.09	51.69
0.99	0.99	0.99	4.81	0.60	0.07	0.26	2.23
		1.0	11.42	1.50	0.13	0.39	3.18
1.0	1.0	4.97	0.00	0.00	0.00	0.00	

Table 4: Rejection rates (%) for the RDP RAR procedure under several parameter configurations, tests, and trial size $\bar{i} = 960$. Red indicates type I error inflation, green indicates highest power (excluding asymptotic test).

\bar{i}	θ_C	θ_D	CX-S Wald	CX-SA Wald	UX Wald	Asymp. Wald	FET (corr.)
960	0.0	0.0	0.14	0.00	0.00	0.00	0.00
		0.02	56.83	5.17	26.51	36.39	11.55
		0.04	99.14	20.41	98.34	99.21	92.75
		0.06	100.00	62.98	100.00	100.00	99.96
		0.08	100.00	95.50	100.00	100.00	100.00
		0.1	100.00	99.88	100.00	100.00	100.00
	0.01	0.01	4.90	1.41	0.16	0.35	0.06
		0.03	31.44	6.38	26.70	31.62	17.52
		0.05	72.93	20.49	71.27	76.25	58.79
		0.07	93.51	49.13	93.34	95.10	88.43
		0.09	98.94	76.21	98.94	99.30	97.82
		0.11	99.87	91.90	99.88	99.93	99.70
	0.05	0.05	4.97	2.62	4.74	6.11	2.83
		0.07	14.01	6.23	13.87	16.96	10.01
		0.09	37.75	15.45	37.77	43.15	31.06
		0.11	64.81	29.63	64.88	70.10	57.73
		0.13	84.24	48.01	84.29	87.56	79.30
		0.15	94.28	66.94	94.29	95.79	91.77
	0.1	0.1	4.98	3.08	5.00	6.53	3.56
		0.12	10.26	5.58	10.29	12.89	7.98
0.14		25.50	12.39	25.50	30.17	21.35	
0.16		47.10	22.73	46.99	52.74	41.78	
0.18		68.10	36.30	67.90	72.99	63.35	
0.2		83.57	52.02	83.35	86.82	80.17	
0.3	0.3	4.99	3.55	4.70	6.38	4.26	
	0.32	7.50	4.95	7.07	9.32	6.59	
	0.34	15.20	9.06	14.41	18.06	13.76	
	0.36	27.91	15.72	26.67	31.85	25.85	
	0.38	43.94	24.63	42.34	48.42	41.48	
	0.4	60.40	35.47	58.70	64.63	57.93	
0.5	0.5	4.99	3.64	4.36	6.08	4.49	
	0.52	7.21	4.91	6.35	8.57	6.59	
	0.54	14.12	8.79	12.66	16.19	13.17	
	0.56	25.83	15.28	23.56	28.69	24.47	
	0.58	41.14	24.19	38.20	44.44	39.50	
	0.6	57.50	35.18	54.34	60.68	55.86	
0.7	0.7	4.99	3.52	3.94	5.67	4.65	
	0.72	7.78	5.13	6.28	8.63	7.32	
	0.74	16.71	10.23	13.97	18.00	15.93	
	0.76	31.84	19.07	27.60	33.50	30.76	
	0.78	50.77	31.41	45.61	52.40	49.63	
	0.8	69.18	46.52	64.22	70.37	68.28	
0.9	0.9	4.98	2.97	2.98	4.63	4.74	
	0.92	12.63	7.26	8.27	11.57	12.10	
	0.94	38.49	23.38	28.55	35.44	37.75	
	0.96	73.10	53.23	61.37	68.71	73.00	
	0.98	94.95	86.63	88.79	92.22	95.59	
	1.0	99.99	99.96	99.22	99.79	99.96	
0.95	0.95	4.98	2.59	2.26	3.74	4.76	
	0.96	8.80	4.56	4.28	6.60	8.30	
	0.97	22.51	12.42	12.44	17.35	21.85	
	0.98	47.75	30.07	30.07	38.13	48.07	
	0.99	77.22	60.23	56.15	64.92	78.15	
	1.0	98.86	96.75	82.42	91.43	97.50	
0.99	0.99	4.97	1.52	0.64	1.40	4.52	
	1.0	58.01	23.29	10.46	19.43	41.61	
1.0	1.0	4.61	0.00	0.00	0.00	0.00	

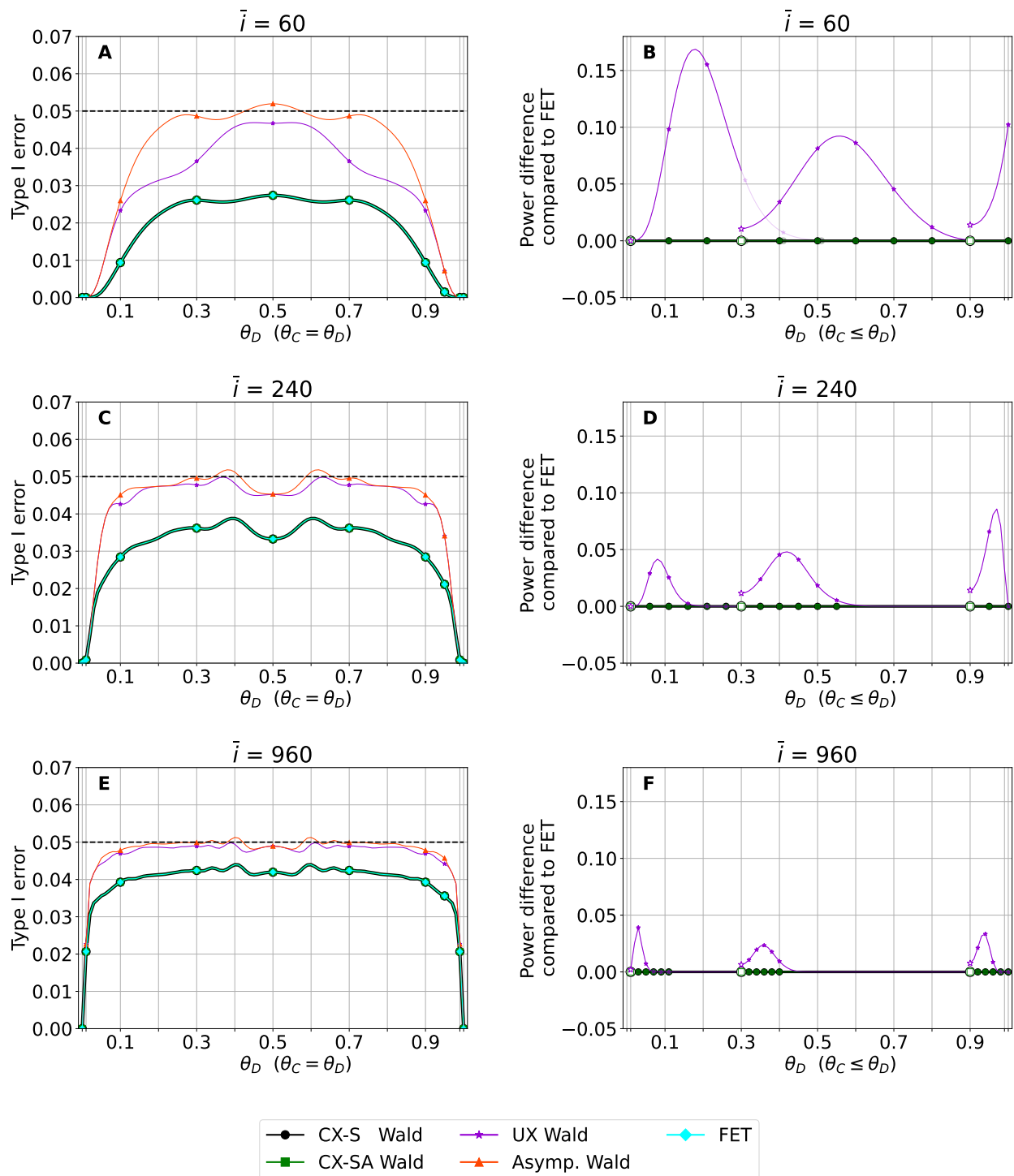


Figure 4: Subfigures A, B, C: Type I error under the equal allocation (EA) NRA procedure of CX-S, CX-SA, UX, asymptotic Wald tests, and FET (one-sided significance level 2.5%). Subfigures B, D, F: Power difference under the EA NRA procedure of two-sided CX-S, CX-SA, and UX Wald tests (Asymptotic Wald test is omitted) compared to FET, for $\theta_C \in \{0.1, 0.3, \dots, 0.9\}$ and $\theta_D \geq \theta_C$.

Table 5: Rejection rates (%) for the EA NRA procedure under several parameter configurations, tests, and trial size 60. All columns except the last one consider the Wald statistic. Red indicates type I error inflation, green indicates highest power (excluding asymptotic test).

\bar{i}	θ_C	θ_D	CX-S Wald	CX-SA Wald	UX Wald	Asymp. Wald	FET	
60	0.0	0.0	0.00	0.00	0.00	0.00	0.00	
		0.1	7.32	7.32	17.55	17.55	7.32	
		0.2	57.25	57.25	74.48	74.48	57.25	
		0.3	92.34	92.34	96.98	96.98	92.34	
		0.4	99.43	99.43	99.85	99.85	99.43	
		0.5	99.98	99.98	100.00	100.00	99.98	
	0.01	0.01	0.00	0.00	0.00	0.00	0.00	0.00
		0.11	8.08	8.08	17.90	17.94	8.08	
		0.21	53.15	53.15	68.67	69.08	53.15	
		0.31	88.51	88.51	93.85	94.32	88.51	
		0.41	98.58	98.58	99.32	99.46	98.58	
		0.51	99.92	99.92	99.96	99.98	99.92	
	0.05	0.05	0.15	0.15	0.15	0.71	0.71	0.15
		0.15	9.34	9.34	16.24	17.33	9.34	
		0.25	43.62	43.62	52.66	57.06	43.62	
		0.35	78.82	78.82	83.29	86.72	78.82	
		0.45	95.33	95.33	96.50	97.59	95.33	
		0.55	99.45	99.45	99.60	99.77	99.45	
	0.1	0.1	0.94	0.94	0.94	2.33	2.60	0.94
		0.2	9.57	9.57	13.34	16.23	9.57	
0.3		37.16	37.16	42.55	48.69	37.16		
0.4		70.51	70.51	74.31	79.44	70.51		
0.5		91.35	91.35	93.04	94.89	91.35		
0.6		98.53	98.53	99.04	99.27	98.53		
0.3	0.3	2.61	2.61	2.61	3.65	4.86	2.61	
	0.4	7.82	7.82	11.22	12.31	7.82		
	0.5	25.94	25.94	34.06	35.11	25.94		
	0.6	56.08	56.08	64.70	66.31	56.08		
	0.7	83.83	83.83	88.37	89.59	83.83		
	0.8	97.14	97.14	98.34	98.53	97.14		
0.5	0.5	2.74	2.74	2.74	4.67	5.19	2.74	
	0.6	7.67	7.67	11.55	12.33	7.67		
	0.7	25.94	25.94	34.06	35.11	25.94		
	0.8	59.64	59.64	67.08	69.24	59.64		
	0.9	91.35	91.35	93.04	94.89	91.35		
	1.0	99.98	99.98	100.00	100.00	99.98		
0.7	0.7	2.61	2.61	2.61	3.65	4.86	2.61	
	0.8	8.90	8.90	10.80	14.14	8.90		
	0.9	37.16	37.16	42.55	48.69	37.16		
	1.0	92.34	92.34	96.98	96.98	92.34		
0.9	0.9	0.94	0.94	0.94	2.33	2.60	0.94	
	1.0	7.32	7.32	17.55	17.55	7.32		
0.95	0.95	0.15	0.15	0.15	0.71	0.71	0.15	
	0.96	0.12	0.12	0.62	0.62	0.12		
	0.97	0.14	0.14	0.69	0.69	0.14		
	0.98	0.18	0.18	0.88	0.88	0.18		
	0.99	0.24	0.24	1.17	1.17	0.24		
	1.0	0.33	0.33	1.56	1.56	0.33		
0.99	0.99	0.00	0.00	0.00	0.00	0.00	0.00	
	1.0	0.00	0.00	0.00	0.00	0.00		
1.0	1.0	0.00	0.00	0.00	0.00	0.00		

Table 6: Rejection rates (%) for the EA NRA procedure under several parameter configurations, tests, and trial size 240. All columns except the last one consider the Wald statistic. Red indicates type I error inflation, green indicates highest power (excluding asymptotic test).

\bar{i}	θ_C	θ_D	CX-S Wald	CX-SA Wald	UX Wald	Asymp. Wald	FET	
240	0.0	0.0	0.00	0.00	0.00	0.00	0.00	
		0.05	55.85	55.85	55.85	55.85	55.85	
		0.1	98.40	98.40	98.40	98.40	98.40	
		0.15	99.99	99.99	99.99	99.99	99.99	
		0.2	100.00	100.00	100.00	100.00	100.00	
		0.25	100.00	100.00	100.00	100.00	100.00	
	0.01	0.01	0.09	0.09	0.09	0.09	0.09	0.09
		0.06	42.19	42.19	45.09	45.09	42.19	
		0.11	90.94	90.94	93.48	93.48	90.94	
		0.16	99.48	99.48	99.72	99.72	99.48	
		0.21	99.99	99.99	99.99	99.99	99.99	
		0.26	100.00	100.00	100.00	100.00	100.00	
	0.05	0.05	2.11	2.11	3.41	3.41	2.11	
		0.1	22.22	22.22	28.80	28.90	22.22	
		0.15	67.43	67.43	73.40	74.06	67.43	
		0.2	93.47	93.47	95.14	95.49	93.47	
		0.25	99.33	99.33	99.56	99.59	99.33	
		0.3	99.96	99.96	99.98	99.98	99.96	
	0.1	0.1	2.85	2.85	4.26	4.51	2.85	
		0.15	16.08	16.08	19.84	20.69	16.08	
		0.2	51.60	51.60	57.63	58.06	51.60	
		0.25	83.67	83.67	87.20	87.25	83.67	
		0.3	96.90	96.90	97.82	97.82	96.90	
		0.35	99.67	99.67	99.79	99.79	99.67	
	0.3	0.3	3.62	3.62	4.77	4.96	3.62	
0.35		10.34	10.34	12.71	12.97	10.34		
0.4		32.14	32.14	36.69	37.03	32.14		
0.45		63.19	63.19	67.31	67.90	63.19		
0.5		86.90	86.90	88.74	89.24	86.90		
0.55		97.05	97.05	97.59	97.72	97.05		
0.5	0.5	3.33	3.33	4.52	4.53	3.33		
	0.55	9.04	9.04	11.22	11.29	9.04		
	0.6	29.09	29.09	32.76	33.20	29.09		
	0.65	60.82	60.82	64.13	65.02	60.82		
	0.7	86.90	86.90	88.74	89.24	86.90		
	0.75	97.66	97.66	98.23	98.29	97.66		
0.7	0.7	3.62	3.62	4.77	4.96	3.62		
	0.75	11.11	11.11	13.55	13.80	11.11		
	0.8	37.91	37.91	42.56	42.70	37.91		
	0.85	75.89	75.89	79.76	79.77	75.89		
	0.9	96.90	96.90	97.82	97.82	96.90		
	0.95	99.96	99.96	99.98	99.98	99.96		
0.9	0.9	2.85	2.85	4.26	4.51	2.85		
	0.95	22.22	22.22	28.80	28.90	22.22		
	1.0	98.40	98.40	98.40	98.40	98.40		
0.95	0.95	2.11	2.11	3.41	3.41	2.11		
	0.96	2.86	2.86	4.25	4.25	2.86		
	0.97	5.87	5.87	7.81	7.81	5.87		
	0.98	12.96	12.96	15.36	15.36	12.96		
	0.99	27.76	27.76	29.47	29.47	27.76		
	1.0	55.85	55.85	55.85	55.85	55.85		
0.99	0.99	0.09	0.09	0.09	0.09	0.09		
	1.0	0.14	0.14	0.14	0.14	0.14		
1.0	1.0	0.00	0.00	0.00	0.00	0.00		

Table 7: Rejection rates (%) for the EA NRA procedure under several parameter configurations, tests, and trial size 960. All columns except the last one consider the Wald statistic. Red indicates type I error inflation, green indicates highest power (excluding asymptotic test).

\bar{i}	θ_C	θ_D	CX-S Wald	CX-SA Wald	UX Wald	Asymp. Wald	FET
960	0.0	0.0	0.00	0.00	0.00	0.00	0.00
		0.02	91.83	91.83	91.83	91.83	91.83
		0.04	99.99	99.99	99.99	99.99	99.99
		0.06	100.00	100.00	100.00	100.00	100.00
		0.08	100.00	100.00	100.00	100.00	100.00
		0.1	100.00	100.00	100.00	100.00	100.00
0.01	0.01	0.01	2.07	2.07	2.27	2.27	2.07
		0.03	53.88	53.88	57.78	57.78	53.88
		0.05	95.96	95.96	96.68	96.68	95.96
		0.07	99.90	99.90	99.92	99.92	99.90
		0.09	100.00	100.00	100.00	100.00	100.00
		0.11	100.00	100.00	100.00	100.00	100.00
0.05	0.05	0.05	3.56	3.56	4.42	4.57	3.56
		0.07	21.44	21.44	24.16	24.64	21.44
		0.09	64.05	64.05	67.30	67.80	64.05
		0.11	91.99	91.99	93.21	93.36	91.99
		0.13	99.11	99.11	99.30	99.31	99.11
		0.15	99.95	99.95	99.96	99.96	99.95
0.1	0.1	0.1	3.93	3.93	4.69	4.78	3.93
		0.12	14.44	14.44	16.03	16.36	14.44
		0.14	44.37	44.37	46.96	47.52	44.37
		0.16	76.63	76.63	78.69	79.06	76.63
		0.18	93.99	93.99	94.81	94.91	93.99
		0.2	99.06	99.06	99.23	99.24	99.06
0.3	0.3	0.3	4.24	4.24	4.89	4.99	4.24
		0.32	9.02	9.02	10.07	10.22	9.02
		0.34	24.18	24.18	26.13	26.36	24.18
		0.36	48.09	48.09	50.43	50.79	48.09
		0.38	72.48	72.48	74.25	74.67	72.48
		0.4	89.09	89.09	90.03	90.28	89.09
0.5	0.5	0.5	4.20	4.20	4.89	4.89	4.20
		0.52	8.26	8.26	9.33	9.33	8.26
		0.54	21.38	21.38	23.32	23.32	21.38
		0.56	43.09	43.09	45.65	45.65	43.09
		0.58	67.35	67.35	69.63	69.65	67.35
		0.6	85.96	85.96	87.31	87.36	85.96
0.7	0.7	0.7	4.24	4.24	4.89	4.99	4.24
		0.72	9.23	9.23	10.32	10.48	9.23
		0.74	25.79	25.79	27.81	28.11	25.79
		0.76	52.57	52.57	54.98	55.37	52.57
		0.78	78.82	78.82	80.56	80.83	78.82
		0.8	94.06	94.06	94.76	94.87	94.06
0.9	0.9	0.9	3.93	3.93	4.69	4.78	3.93
		0.92	16.26	16.26	18.38	18.48	16.26
		0.94	58.66	58.66	62.00	62.35	58.66
		0.96	94.93	94.93	95.79	95.91	94.93
		0.98	99.98	99.98	99.98	99.98	99.98
		1.0	100.00	100.00	100.00	100.00	100.00
0.95	0.95	0.95	3.56	3.56	4.42	4.57	3.56
		0.96	8.88	8.88	10.49	10.63	8.88
		0.97	29.84	29.84	33.19	33.26	29.84
		0.98	67.55	67.55	70.81	70.81	67.55
		0.99	95.96	95.96	96.68	96.68	95.96
		1.0	100.00	100.00	100.00	100.00	100.00
0.99	0.99	0.99	2.07	2.07	2.27	2.27	2.07
		1.0	34.88	34.88	34.88	34.88	34.88
1.0	1.0	0.00	0.00	0.00	0.00	0.00	

Table 8 shows the critical values of the unconditional Wald test and FET for both the RDP and EA designs for several trial sizes. The UX FET under an EA design is a special case of Boschloo’s test (Boschloo, 1970). Even for $\bar{i} = 960$, the critical values for the Wald test and FET are off from their respective asymptotic values 1.96 and 5% for both designs, where the critical value for the Wald test under the EA NRA design is closest to 1.96. Note that the asymptotic Wald test inflates type I error under the EA design for $\bar{i} = 960$ as the UX critical value is above 1.96. As FET is a CX-S (or CX-SA) test for the EA design, the UX critical value is always above 5% so that the UX test corrects for type I error deflation. In Figure 1, the critical value for FET (corr.) under the RDP design was set to the minimum of 5% and the value reported in Table 8 to make sure to only correct for type I error inflation, while in Figure 4, the critical value for FET under the EA design was 5% in accordance to the usual FET. Note that for the critical values under $\bar{i} = 960$, an approximation was made where we only consider $\theta_C = \theta_D \in 0 : 0.01 : 1$.

Table 8: Upper critical values for the unconditional exact test for different trial sizes, statistics, and RA procedures. The one-sided significance level is set to 2.5% in each setting. Note: critical values for $\bar{i} = 960$ found by restricting the null set $[0, 1]$ to $0.00 : 0.01 : 1.00$.

\bar{i}	UX FET RDP	Wald RDP	UX FET EA	Wald EA
10	0.1	1.7272595098492414	0.13333333333333333	1.959965156484713
20	0.08668730650154799	1.9215378456610455	0.14035087719298245	1.853047161780774
30	0.06666666666666667	2.0359633906020442	0.10811407483071651	1.9329712334408418
40	0.056160926432242395	2.082478408222474	0.09480249480249481	1.9625514979929637
50	0.05384897107006595	2.077347117755887	0.08450068146047536	1.9970918228698624
60	0.050815732062114774	2.0953869552983915	0.06977998727279189	2.06568306450296
70	0.05111272283085849	2.0980279891303883	0.08221013616964479	1.967736176247307
80	0.04984354552541328	2.096976978695872	0.07211385187049967	2.0160645150967422
90	0.049230363163264006	2.0944721097402654	0.07937738341030817	1.9592844056604022
100	0.04629884007947289	2.1014769412666388	0.07040879622570355	2.0046321754009315
120	0.045915383653536694	2.1027665720396795	0.06709588404416586	2.0099557916716355
150	0.04508205644330902	2.10273332962542	0.06898224231605116	1.9787001382948695
180	0.04403334678418491	2.1061977615142933	0.06816766165704137	1.979735020132453
210	0.04423613894350655	2.103763815417522	0.066778869568174	1.9696196403913138
240	0.043880073891202416	2.103157864866603	0.06528413110170263	1.9711384650967143
960	0.0425576537814003	2.0995182034464555	0.05681751737279753	1.9694556533734013

D. Application: play-the-winner designed trial

We investigate the results in Reiertsen et al. (1993), who analyzed the safety of administering Enoxaparin (developmental) versus Dextran-70 (control) during digestive surgery. We illustrate the advantages of our approach using this trial as it considered a moderate trial size, used a *modified play-the-winner* (M-PTW) DRA procedure, and used a non-standard testing approach based on a log-rank test. The next section first justifies the use of the log-rank test.

D.1. Design

We describe the design proposed in Reiertsen et al. (1993). In this trial, a success represented the absence of any of a set of adverse events in the first week after surgery. The trial considered $\bar{i} = 327$ participants and was designed based on a modification of the play-the-winner (PTW) procedure. The PTW procedure allocates the next participant to current “winning” treatment $W_i \in \{C, D\}$, i.e., $A_{i+1} = W_i$, where W_0 is chosen uniformly at random prior to assigning the first participant (corresponding to clinical equipoise) and $W_i \neq W_{i-1}$ when the allocation A_i results in a failure. In M-PTW, W_i furthermore switches when the same treatment is allocated 15 times in a row (denoted a cut-off), i.e., $W_{i+1} \neq W_i$ when $L_i = 15$ where we define $L_0 = 1$, $L_i = L_{i-1} \cdot \mathbb{I}(W_i = W_{i-1}) + 1$ for $i \geq 1$ to be the amount of subsequent allocations up to and including participant $i + 1$ (note that this is a function of \mathbf{H}_i). The modification of PTW described above results in a more balanced allocation to both treatments than under PTW. As the follow-up time was one week, a new M-PTW sequence as described above was started whenever a participant arrived and all current M-PTW sequences were awaiting a new outcome (see, e.g., Reiertsen et al., 1993, Fig. 2). Under the model of Section 3 these sequences can be modeled by concatenating all M-PTW sequences, forcing $L_i = 1$ and resampling W_i uniformly at

random for certain participant indices i in the setting above, corresponding to a M-PTW sequence reaching its end at participant $i - 1$.

Let $L'_1 = \min\{i \geq 1 : L_i = 1\}$ and

$$L'_{k+1} = \min\{i \geq 1 : L_{i+\sum_{k'=1}^k L'_{k'}} = 1 \text{ or } \sum_{k'=1}^k L'_{k'} + i = \bar{i}\}$$

be the treatment allocation sequence lengths and $W'_k = W_{\sum_{k'=1}^k L'_{k'}-1}$ be the treatment allocation indicators, i.e., the treatment being administered, during treatment allocation sequence k . After the trial was completed, a test from survival analysis, which we assumed to be the log-rank test was performed on $(\ell', \mathbf{w}', \delta)$, where ℓ' , \mathbf{w}' are the realizations of L' , W' (resp.) and δ_k are the censoring indicators denoting whether treatment allocation sequence k was right-censored due to cut-off, switching the winner by misclassification of a success as a failure, or reaching the end of a M-PTW sequence. The log-rank test resulted in a P-value of 0.05, while the success rates were estimated at 0.830 and 0.748 for Enoxaparin and Dextran-70 respectively. In this chapter, the design of [Reiertsen et al. \(1993\)](#) is compared to RA designs using the CX-S and UX Wald tests under the same, M-PTW, RA procedure.

D.1.1. Justification of log-rank test

This section justifies the use of the log-rank test in the design of [Reiertsen et al. \(1993\)](#). Let $(\tilde{L}_k)_{k=1}^\infty$, be an independent sequence of positive real-valued event times (random variables) and $W_k \in \{C, D\}$ be a set of treatment indicators such that each $\tilde{L}_k \mid W_k = a$ has the same cumulative distribution function F_a for all $k \in \{1, 2, \dots\}$, $a \in \{C, D\}$. Let δ_k be an (observed) set of positive real-valued censoring times and $L'_k = \min(\delta_k, \tilde{L}_k)$ be the observed times for $k \in \{1, \dots, \kappa\}$. It is assumed that the censoring times are independent of the event times and treatment indicators. Following [Lee and Wenyuwang \(2003\)](#), under these assumptions, the log-rank test, taking as input a realisation ℓ' , \mathbf{w}' of L' , W' , as well as the censoring times δ , is an asymptotic test for testing $F_C(\ell) = F_D(\ell)$ for all $\ell \leq \max_k \ell'_k$ versus $\exists \ell \leq \max_k \ell'_k$ such that $F_C(\ell) \neq F_D(\ell)$.

Under the M-PTW design and the i.i.d. Bernoulli outcomes model, the treatment sequence lengths L'_k can be considered as observed times corresponding to geometric event times, i.e., we have $F_a(\ell) = 1 - \theta_a^{\lfloor \ell \rfloor}$. When the censoring times are independent of the event times, the theoretical guarantees of the log-rank test hold. Censoring the multiple M-PTW sequences at the end of the M-PTW sequences may however induce length time bias, as there is a higher probability that extraordinarily long trial sequences are occurring at the end of the M-PTW sequence. When increasing the trial size to infinity, the effect of this will vanish.

D.1.2. Markov chain formulation

We now describe the Markov chain used to model the design in [Reiertsen et al. \(1993\)](#). The Markov chain modeling the M-PTW DRA procedure is the Markov chain described in [Example 1](#), augmented with W_i and L_i . The length of the M-PTW sequences were not reported in [Reiertsen et al. \(1993\)](#) and hence an assumption needs to be made on this part of the data. In order to analyze the power of the trial, it is assumed that the length of the concurrent sequences are roughly the same as the lengths reported in [Reiertsen et al. \(1993, Figure 2\)](#), scaled such that it matches the actual sample size. In practice, the lengths of the M-PTW sequences could be derived from a surgery schedule. [Table 9](#) presents the assumed M-PTW sequence lengths.

Table 9: Assumed M-PTW sequence lengths.

M-PTW sequence	1	2	3	4	5	6
Monday	18	15	15	15	10	-
Tuesday	16	16	10	8	-	-
Wednesday	19	16	16	13	10	8
Thursday	18	15	15	12	-	-
Friday	19	16	13	9	5	-

The multiple independent M-PTW sequences started in the trial are modeled by restarting the M-PTW procedure (keeping the successes and allocations per arm) whenever the length of the current M-PTW sequence reaches a value in [Table 9](#), i.e., letting $\ell_1, \ell_2, \dots, \ell_m$ be the length of the trial sequences (e.g., 18, 15, 15, \dots , 16, 16, 10, \dots , 9, 5), we define $\mathcal{L} = \{\ell_1, \ell_1 + \ell_2, \dots, \sum_{k=1}^{|\mathcal{L}|-1} \ell_k\}$ to be the decision epochs where M-PTW restarts.

We introduce a Markov chain describing the evolution of the collected data under the M-PTW design. To accurately describe the behavior under M-PTW, we take $i_t = t$ (hence we can use i and t interchangeably) and augment the state for the Markov chain described in Example 1 with W_t and L_t , i.e., $\mathbf{X}_t = (\mathbf{S}_t, \mathbf{N}_t, W_t, L_t)$. The process \mathbf{X} is a Markov chain with initial state

$$\mathbf{X}_0 = \begin{cases} ((0, 0), (0, 0), \mathbf{C}, 1), & \text{with probability } 1/2, \\ ((0, 0), (0, 0), \mathbf{D}, 1), & \text{with probability } 1/2, \end{cases}$$

state space $\mathcal{X} = \cup_t \mathcal{X}_t$ with

$$\mathcal{X}_t = \{((s'_C, s'_D), (n'_C, n'_D), w, \ell) : ((s'_C, s'_D), (n'_C, n'_D)) \in \mathcal{X}_t^{\text{SS}}, w \in \{\mathbf{C}, \mathbf{D}\}, \ell \in \mathcal{I}_{15}\},$$

and transition dynamics according to (1) where, letting w, ℓ be functions such that $w(\mathbf{X}_t) = W_t$, and $\ell(\mathbf{X}_t) = L_t$, we have that $q^\pi(\mathbf{x}_t, \mathbf{x}_{t+1}) = 1$ when we have $t+1 \notin \mathcal{L}$, $n_{w(\mathbf{x}_t)}(\mathbf{x}_{t+1}) = n_{w(\mathbf{x}_t)}(\mathbf{x}_t) + 1$, $\sum_{a \in \{\mathbf{C}, \mathbf{D}\}} |\partial n_a(\mathbf{x}_t, \mathbf{x}_{t+1})| = 1$, and either

- (a) $\ell(\mathbf{x}_{t+1}) = \ell(\mathbf{x}_t) + 1$, $\partial s_{w(\mathbf{x}_t)}(\mathbf{x}_t, \mathbf{x}_{t+1}) = 1$, $w(\mathbf{x}_{t+1}) = w(\mathbf{x}_t)$,
- (b) $\ell(\mathbf{x}_{t+1}) = 1$, $\ell(\mathbf{x}_t) = 15$, $w(\mathbf{x}_{t+1}) \neq w(\mathbf{x}_t)$,
- (c) $\ell(\mathbf{x}_{t+1}) = 1$, $\partial s_{w(\mathbf{x}_t)}(\mathbf{x}_t, \mathbf{x}_{t+1}) = 0$, $w(\mathbf{x}_{t+1}) \neq w(\mathbf{x}_t)$.

Furthermore, $q^\pi(\mathbf{x}_t, \mathbf{x}_{t+1}) = 1/2$ when $t+1 \in \mathcal{L}$, $\sum_{a \in \{\mathbf{C}, \mathbf{D}\}} |\partial n_a(\mathbf{x}_t, \mathbf{x}_{t+1})| = 1$, $\ell(\mathbf{x}_{t+1}) = 1$, $\partial n_{w(\mathbf{x}_t)}(\mathbf{x}_t, \mathbf{x}_{t+1}) = 1$, and $\partial s_{w(\mathbf{x}_t)}(\mathbf{x}_t, \mathbf{x}_{t+1}) = y$ for $y \in \{0, 1\}$.

Misclassification of the outcomes as a zero occurred rarely (Reiertsen et al., 1993), out of 327 outcomes only 2 successes were misclassified ($p_{\text{miscl}} \approx 0.612\%$). Hence, the choice is made not to take misclassification into account in the Markov chain, although (assuming independence and that the probability of misclassification is constant over time) this could be done by, e.g., the introduction of a randomization probability for the allocations, i.e., by changing case (a) above to

$$q^\pi(\mathbf{x}_t, \mathbf{x}_{t+1}) = \begin{cases} p_{\text{miscl}}, & \text{if } \ell(\mathbf{x}_{t+1}) = 1, \\ & \partial s_{w(\mathbf{x}_t)}(\mathbf{x}_t, \mathbf{x}_{t+1}) = 1, \\ & \text{and } w(\mathbf{x}_{t+1}) \neq w(\mathbf{x}_t), \\ 1 - p_{\text{miscl}}, & \text{if } \ell(\mathbf{x}_{t+1}) = \ell(\mathbf{x}_t) + 1, \\ & \partial s_{w(\mathbf{x}_t)}(\mathbf{x}_t, \mathbf{x}_{t+1}) = 1, \\ & \text{and } w(\mathbf{x}_{t+1}) = w(\mathbf{x}_t). \end{cases}$$

D.2. Results

Using Theorem 1, we can calculate coefficients g_t^π based on this Markov chain, and hence the exact OCs for the M-PTW RA design based on any test that depends on the summary statistics $\mathbf{S}_t, \mathbf{N}_t$ at the end of the trial. The UX critical value of the Wald statistic (given in the caption of Table 10) was approximately equal to 1.96, and hence close to the well-known asymptotic value under designs with equal allocation.

Figure 5 shows the type I error for the log-rank test (based on 100,000 simulations, with 95% confidence interval (CI) based on a normal approximation), UX Wald test and CX-S Wald test, as well as the difference in power for the UX Wald test and log-rank test over the CX-S Wald test for $\theta_C = 0.748$ and $\theta_D \geq \theta_C$ based on the M-PTW procedure. Results for the CX-S and the UX Wald test are presented, as these tests showed highest power in Section 4 of the paper. We evaluate the log-rank test by simulation, and not direct computation, as the log-rank statistic depends on the joint distribution of the treatment lengths, treatment values, and censoring indicators, hence directly calculating the distribution of the log-rank statistic is outside the scope of this paper.

The type I error is bounded by 0.05 for the CX-S and UX Wald tests, while the estimated type I error for the log-rank test is often close to 0.05 (Figure 5, Subfigure A). Empirically, for 28.4% of the considered values of $\theta = \theta_C = \theta_D$ the lower bound for the 95% CI of the rejection rate was higher than 0.05, indicating that the log-rank test, being an asymptotic test, does not control type I error, although simulations indicate that the type I error is close to 5% for all parameter values under the null.

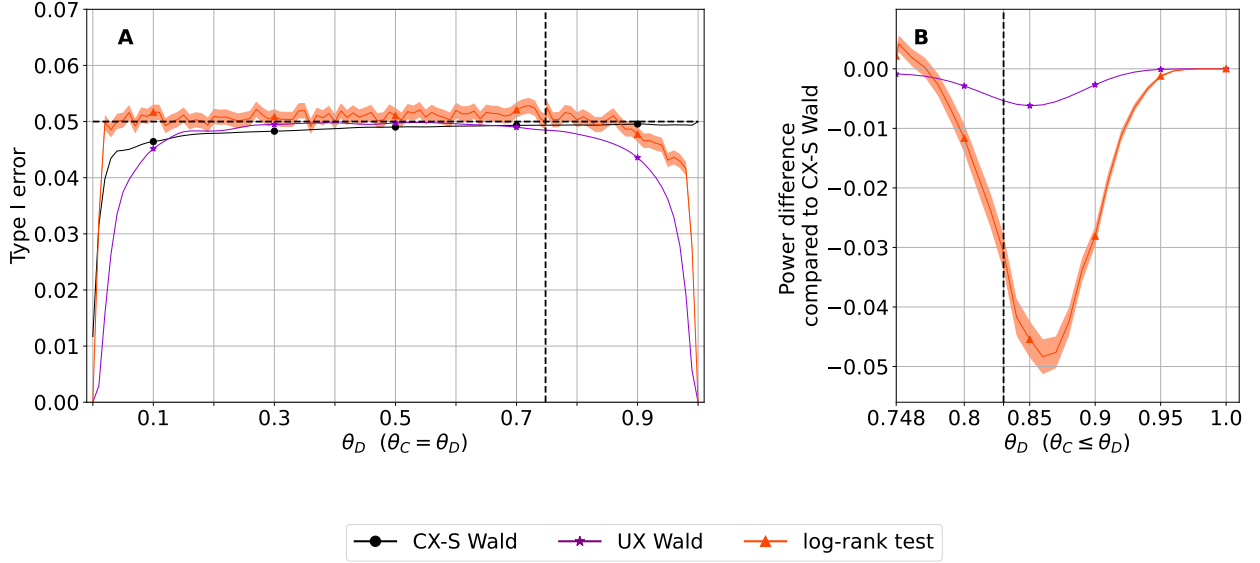


Figure 5: M-PTW design. Subfigure A: type I error for the CX-S and UX Wald tests, as well as the log-rank test (with 95% simulation-based CI). The vertical line denotes $\theta_C = \theta_D = 0.748$. Subfigure B: Power difference for control success rate $\theta_C = 0.748$ and $\theta_D \geq \theta_C$ of the UX Wald and log-rank compared to the CX-S Wald test. The vertical line denotes $\theta_D = 0.830$. Each one-sided significance level equals 2.5%.

The power of the log-rank test is lower than the power of both the exact tests for M-PTW (Figure 5, Subfigure B), except for values θ_D close to $\theta_C = 0.748$ (up to around 0.77, which might not be considered clinically relevant). Under the success rates $\theta_C = 0.830$ (Enoxaparin) and $\theta_D = 0.748$ (Dextran-70) found in Reiertsen et al. (1993), the difference in power for the log-rank test over the CX-S Wald test is about -0.03 , while for the UX Wald test it is about -0.005 ; hence for both exact tests, the power is higher at the estimated value of θ . The absolute rejection rates for M-PTW under the considered tests are given in Table 10, where it is shown that the power of the considered tests is actually around 40% for the reported success rates.

Table 10: Rejection rates (in percentage points) for the CX-S Wald, UX Wald, and log-rank test (upper and lower significance level equal to 2.5%) for $\theta_C = 0.748$, $\theta_D \geq \theta_C$ under the M-PTW design. The 95% confidence radius shown for the log-rank test is based on a normal approximation. The critical value for the UX Wald test was 1.9626231638655138.

θ_C	θ_D ($\theta_C \leq \theta_D$)	CX-S Wald	UX Wald	log-rank test
0.748	0.748	4.93	4.85	5.15 +/- 0.14
	0.80	19.82	19.53	18.65 +/- 0.24
	0.83	43.53	43.00	40.45 +/- 0.3
	0.85	62.61	61.99	58.06 +/- 0.31
	0.90	95.17	94.90	92.36 +/- 0.16
	0.95	99.96	99.95	99.83 +/- 0.03
	1.00	100.00	100.00	100.00 +/- 0.0

E. Further computational details and results for the ARREST trial application

E.1. Markov chain formulation for determining UX stopping threshold

In this section, the Markov chain used to derive the UX OST for the ARREST trial is described. Let $\mathbf{X}_t = (S_t, N_t, M_t)$ where $M_t = \text{Proj}_{\mathcal{M}}(\max_{t' \leq t} \tilde{\pi}_C(\mathbf{X}_{t'}))$, and we define $\text{Proj}_E(x) = \max\{y \in E : y \leq x\}$ for $x \in [0, 1]$, $E \subset [0, 1]$,

and $\{0.5\} \subseteq \mathcal{M} \subset [0.5, 1]$ with $|\mathcal{M}| < \infty$. The state variable M_t denotes the highest value in \mathcal{M} that was crossed by the posterior probability $\tilde{\pi}_C(\mathbf{X}_{t'})$ that treatment C is optimal based on $\mathbf{X}_{t'}$, for time t' up to and including t . Assume that the assignment in blocks is done using PBD. Then, letting $i_0 = 0$ and $i_t = \sum_{u=1}^t b_u$ where $(b_t)_t$ is the sequence of block sizes and m be a function such that $m(\mathbf{X}_t) = M_t$, the process \mathbf{X} is a Markov chain with state space $\mathcal{X} = \cup_t \mathcal{X}_t$ with $\mathcal{X}_t = \{((s'_C, s'_D), (n'_C, n'_D), m) : ((s'_C, s'_D), (n'_C, n'_D)) \in \mathcal{X}_{i_t}^{SS}, m \in \mathcal{M}\}$, initial state $\mathbf{X}_0 = ((0, 0), (0, 0), 0.5)$ and transition structure (1) with $q^\pi(\mathbf{x}_t, \mathbf{x}_{t+1})$ equal to

$$\begin{cases} p_C(\mathbf{x}_t)b_t - \lfloor p_C(\mathbf{x}_t)b_t \rfloor, & \text{if } \partial \mathbf{n}(\mathbf{x}_t, \mathbf{x}_{t+1}) = (\lceil p_C(\mathbf{x}_t)b_t \rceil, b_t - \lceil p_C(\mathbf{x}_t)b_t \rceil) \\ & \text{and } \max(m(\mathbf{x}_t), \text{Proj}_{\mathcal{M}}(\tilde{\pi}_C(\mathbf{x}_{t+1}))) = m(\mathbf{x}_{t+1}) \\ \lfloor p_C(\mathbf{x}_t)b_t \rfloor - p_C(\mathbf{x}_t)b_t, & \text{if } \partial \mathbf{n}(\mathbf{x}_t, \mathbf{x}_{t+1}) = (\lfloor p_C(\mathbf{x}_t)b_t \rfloor, b_t - \lfloor p_C(\mathbf{x}_t)b_t \rfloor) \\ & \text{and } \max(m(\mathbf{x}_t), \text{Proj}_{\mathcal{M}}(\tilde{\pi}_C(\mathbf{x}_{t+1}))) = m(\mathbf{x}_{t+1}) \\ 0, & \text{else,} \end{cases} \quad (18)$$

for all $\mathbf{x}_t \in \mathcal{X}_t, \mathbf{x}_{t+1} \in \mathcal{X}_{t+1}$, where $\lfloor \delta \rfloor = \lceil \delta \rceil - 1$ for all $\delta \in \mathcal{D}$. When calculating the UX OST, symmetry was used to calculate the two-sided critical value as, given $\theta_C = \theta_D$,

$$\begin{aligned} & \arg \min\{p^* \in \mathcal{M} : \mathbb{P}_{\theta}^\pi(\max_{t \leq \bar{i}} \max\{\Pi(\theta_D \geq \theta_C | \mathbf{X}_t), \Pi(\theta_C \geq \theta_D | \mathbf{X}_t)\} \geq p^*) \leq \alpha\} \\ & = \arg \min\{p^* \in \mathcal{M} : \mathbb{P}_{\theta}^\pi(m(\mathbf{X}_t) \geq p^*) \leq \alpha/2\}. \end{aligned}$$

Note that the critical value calculated in this manner really controls type I error, but it can be too conservative if \mathcal{M} is too discrete.

E.2. Additional results

Figure 6 shows, in addition to the results in Figure 2 of the paper, the expected participant outcomes, and expected trial size $\mathbb{E}_{\theta}^\pi[i_{u(\mathbf{X}_{\bar{i}})}]$ for the SB and UX OSTs versus the CX-S OST. The *expected proportion of allocations on the superior arm* (EPASA), assuming that after early stopping due to superiority of treatment D, all remaining participants are allocated the developmental treatment, is defined as

$$(N_{D, i_{u(\mathbf{X}_{\bar{i}})} + (\bar{i} - i_{u(\mathbf{X}_{\bar{i}})})\mathbb{I}(\text{Optional stopping in favor of D})/\bar{i}.$$

In terms of expected trial size and EPASA, the SB OST is best (i.e., shows higher expected treatment outcomes and smaller expected trial sizes), while the UX OST performs best out of the exact tests. The UX OST results in a decrease of about 1% in EPASA and an expected trial size of around 8 participants more than when compared to SB OST. Table 11 shows the operating characteristics, together with EPASA up to optional stopping, where this OC is highest for CX-S as optional stopping occurs at later time points.

Table 11: ARREST trial: Operating characteristics (in percentage points) for the SB, CX-S, and UX optional stopping thresholds for $\theta_C = 0.12, \theta_D \geq \theta_C$. The expected amount of participants allocated to the superior arm excluding optional stopping (EPASA, excl. OS) is defined as $N_{D, i_{u(\mathbf{X}_{\bar{i}})}/\bar{i}$. The UX OST was 0.9918742236024845. Both the upper and lower significance level was set to 2.5%.

OST	Measure	θ_C	θ_D							
		0.12	0.2	0.3	0.37	0.5	0.7	0.9	1.0	
CX-S OST	EPASA	75.00	93.76	107.90	115.50	125.61	132.41	134.78	135.00	
	EPASA (excl. OS)	75.00	89.25	83.20	68.45	42.36	22.74	15.67	15.00	
	RR	2.01	12.65	56.64	84.68	99.48	100.00	100.00	100.00	
	Trial size	149.30	145.46	125.30	102.94	66.75	40.33	30.89	30.00	
UX OST	EPASA	75.00	94.41	110.05	118.50	128.58	133.87	134.97	135.00	
	EPASA (excl. OS)	75.00	87.23	76.77	59.44	33.46	18.37	15.09	15.00	
	RR	2.49	14.29	58.60	85.80	99.55	100.00	100.00	100.00	
	Trial size	148.69	142.73	116.71	90.94	54.89	34.50	30.11	30.00	
SB OST	EPASA	75.00	95.39	112.31	120.76	129.76	134.07	134.97	135.00	
	EPASA (excl. OS)	75.00	84.18	69.95	52.65	29.92	17.77	15.08	15.00	
	RR	4.69	20.54	67.62	90.46	99.78	100.00	100.00	100.00	
	Trial size	147.27	138.58	107.62	81.89	50.16	33.69	30.11	30.00	

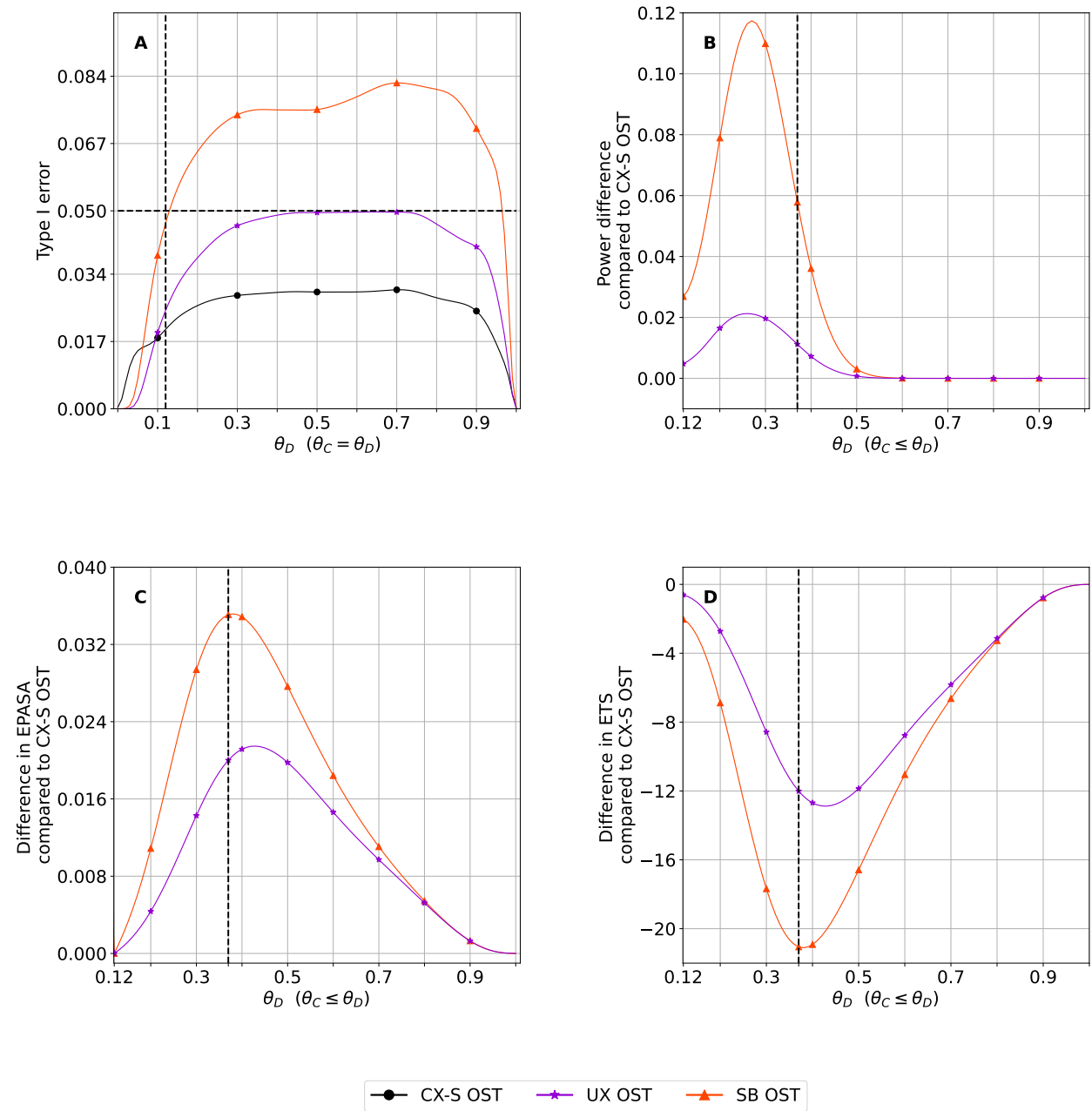


Figure 6: ARREST trial. Type I error under the SB, CX-S, and UX OST for $\theta_C = \theta_D$ (Subfigure A), the vertical line denotes $\theta_C = \theta_D = 0.12$. Power difference (Subfigure B), expected amount of participants allocated to the superior arm (EPASA, Subfigure C), and trial size $\mathbb{E}_{\theta}^{\pi}[i_u(\mathbf{x}_{\bar{i}})]$ (ETS, Subfigure D) for the SB and UX OST compared to CX-S OST, $\theta_C = 0.12$ and $\theta_D \geq \theta_C$, where the vertical line denotes $\theta_D = 0.37$. The upper and lower significance levels both equal 2.5%.