Selective Randomization Inference for Adaptive Experiments

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Abstract

Adaptive experiments use preliminary analyses of the data to inform further course of action and are commonly used in many disciplines including medical and social sciences. Because the null hypothesis and experimental design are not pre-specified, it has long been recognized that statistical inference for adaptive experiments is not straightforward. Most existing methods only apply to specific adaptive designs and rely on strong assumptions. In this work, we propose selective randomization inference as a general framework for analyzing adaptive experiments. In a nutshell, our approach applies conditional post-selection inference to randomization tests. By using directed acyclic graphs to describe the data generating process, we derive a selective randomization p-value that controls the selective type-I error without requiring independent and identically distributed data or any other modelling assumptions. We show how rejection sampling and Markov Chain Monte Carlo can be used to compute the selective randomization p-values and construct confidence intervals for a homogeneous treatment effect. To mitigate the risk of disconnected confidence intervals, we propose the use of hold-out units. Lastly, we demonstrate our method and compare it with other randomization tests using synthetic and real-world data.

Keywords: Causal inference, enrichment design, randomization test, selection bias, selective inference, response-adaptive randomization

1 Introduction

In a talk in 1956 titled "Iterative Experimentation", the great statistician George Box suggested that we should keep in mind that scientific research is usually an iterative process. He wrote in the abstract:

The cycle: conjecture-design-experiment-analysis leads to a new cycle of conjecture-designexperiment-analysis and so on. [...] Although this cycle is repeated many times during an investigation, the experimental environment in which it is employed and the techniques appropriate for design and analysis tend to change as the investigation proceeds. (Box 1957)

John Tukey, another great statistician and Box's contemporary, acknowledged that Box's cycle "will serve excellently" if "an oversimple paradigm is to be selected", but he noted that "the point where the circle is to be broken can be freely chosen" and "there are short cuts and repeated steps as well as branchings and rejoinings" (Tukey 1963).

Thus, although the demarcation in Box's cycle is very useful to understand the role of statistical methodology in different phases of experimentation, scientific research in the real world does not always follow this linear process. Often, it is desirable to continuously revise the scientific hypothesis and design of the study as more data are gathered. This has motivated two long-standing themes of research in statistics: (i) *selective inference*, where valid inference is required on potential findings that are discovered after viewing the data, and (ii) *adaptive experimentation*, where data-adaptive designs are used to allow us to collect more relevant data, save time and resources, and/or assign more participants to a better treatment.



Figure 1: Schematic of a two-stage enrichment trial with two subgroups: low genetic risk score (green) and high genetic risk score (red).

As the scale of datasets grows and increasingly precise conclusions are sought, selective inference and adaptive experimentation have attracted much attention in the recent literature. However, there is strikingly little work on applying selective inference to adaptively collected data. In this article, we will attempt to fill this gap and develop a general method termed "selective randomization inference" that can be applied to a wide range of adaptive experiments. For the rest of this section, we will first introduce our proposal and then put it in the broader context set up by Box and Tukey.

1.1 Overview of the Selective Randomization Test

Let us first use a hypothetical two-stage enrichment trial as a running example to motivate the use of adaptive designs, illustrate the potential pitfalls, and introduce our proposal (see also Figure 1). This example is motivated by a post hoc analysis by Marston et al. (2020) of the FOURIER trial (Further Cardiovascular Outcomes Researh With PCSK9 Inhibition in Subjects With Elevated Risk). By partitioning patients into different groups according to their genetic risk scores for cardiovascular diseases, Marston et al. found that the new evolocumab therapy (PCSK9 inhibition) appear to benefit patients with high genetic risk much more than others. However, because of the post hoc nature of this subgroup analysis, further randomized studies may be required to confirm this conclusion.

Now consider a two-stage enrichment trial in which the patient population is divided at the beginning of the study into a low genetic risk group and a high genetic risk group. In the first stage of the trial, patients are recruited from both groups and randomly assigned the new therapy $(Z_{1i} = 1)$ or the placebo $(Z_{1i} = 0, \text{ where } i \text{ is the patient index})$. Based on a preliminary analysis of data from the first stage, we may wish to select one subgroup or both subgroups for further investigation in the second stage. For example, we may choose to only recruit people with high genetic risk score if they show more promising responses in the first stage and potentially assign the new therapy with higher probabilities as well. Let the treatment assignment in the second stage be denoted by Z_2 . We are interested in testing whether there is any treatment effect for the subgroup(s) selected at the end of the first stage, which is a categorical variable denoted by $S_1 \in S_1 = \{\text{only high, only low, both}\}.$

It has been recognized very early on that a naive analysis of such a sequential trial tends to overstate statistical significance (Anscombe 1963; Armitage 1960; Pocock 1977). To be more concrete, consider the following randomization p-value that ignores selection. Let $Z = (Z_1, Z_2)$ denote all the treatment assignments and W denote the recruitment decisions, covariates and potential outcomes of the patients. A randomization test conditions on W and only uses the randomness in the treatment assignment Z to calculate the following p-value

$$P_{\text{naive}} = \mathbb{P}(T(Z^*, W) \le T(Z, W) \mid Z, W),$$

where T(Z, W) is a test statistic that measures treatment efficacy and $Z^* = (Z_1^*, Z_2^*)$ has the same distribution of Z but is conditionally independent of Z given W. In this definition, conditioning on Z and W means that the probability is evaluated over the distribution of Z^* , an independent realization of the treatment assignment. Due to subgroup selection, P_{naive} is generally not a valid p-value in the sense that $\mathbb{P}(P_{\text{naive}} \leq \alpha)$ may be larger than the significance level $0 < \alpha < 1$. This is because even though the treatment assignment Z is randomized, the selection "changes" its distribution. Heuristically, suppose the high genetic risk group is selected at the end of stage 1 (so $S_1 = \text{only high}$), then the first stage data must have already shown promises for the new therapy in the high genetic risk group, and it is no longer appropriate to use the randomization distribution of Z_1 to calculate the p-value. In other words, it is "unfair" to compare Z_1 with Z_1^* generated from the original randomization distribution because Z_1 has gone through selection but Z_1^* does not.

A convenient solution to this problem is to discard the first stage, aka data splitting (Cox 1975). That is, we use the data of the first stage to choose the design and null hypothesis and the second stage for statistical inference. Mathematically, this is equivalent to conditioning on $Z_1^* = Z_1$, and in the context of randomization inference, this amounts to using

$$P_{\text{split}} = \mathbb{P}(T(Z^*, W) \le T(Z, W) \mid Z, W, Z_1^* = Z_1).$$

Obviously, this p-value is valid but uses the data in an inefficient way.

In a nutsell, our proposal is to condition on the exact amount of information used in the selection. This is inspired by the recent literature on conditional post-selection inference, as will be explained in Section 1.2. The key idea is that the selection in the first stage $S_1 = S_1(Z_1, W)$ is a function of the treatment assignment Z_1 and is thus a random variable. We argue that the appropriate way to adjust for selection is to condition on it, which leads to the definition of the *selective randomization p-value*:

$$P_{\text{sel}} = \mathbb{P}(T(Z^*, W) \le T(Z, W) \mid Z, W, S_1(Z_1^*, W) = S_1(Z_1, W)).$$

We will show that this p-value controls the selective type-I error in the sense that

$$\mathbb{P}(P_{\text{sel}} \le \alpha \mid W, S_1 = s_1) \le \alpha, \quad \text{for all } s_1 \in \mathcal{S}_1 \text{ and } 0 < \alpha < 1.$$
(1)

Thus, no matter which subgroup is selected at the end of the first stage, the false positive rate of this selective randomization test is controlled. Compared to data splitting, this test is expected to be more powerful because it uses the "left out" information in the first stage that is not used by the selection.

1.2 Related Work

Our proposal is related to a wide range of research that offers alternatives to the linear cycle of scientific research described by Box and discussed by Tukey. Next we will review the related literature and compare them with our proposal.

Adaptive designs can be traced back to the work of Thompson (1933) and are now frequently used in many fields of empirical research including medicine (Burnett et al. 2020), political science (Offer-Westort et al. 2021), and economics (Duflo et al. 2007; Kasy and Sautmann 2021). In many situations, the experiments have several designated stages, and within each stage the participants may be admitted on a rolling basis. Therefore, preliminary data from the initial participants are often available before the study concludes. This forms the basis for adapting the treatment allocation or recruitment in later stages of the experiment. For instance, it may be desirable to increase the assignment probability of more promising treatments or policies (this is called *response-adaptive randomization*, see e.g. Rosenberger et al. (2001) and Faseru et al. (2017)), discontinue certain arms of the study early (this is called *multi-arm multi-stage design*, see e.g. Magirr et al. (2012) and Sydes et al. (2009)), or focus on the subpopulation of participants that exhibit the best reactions (this is called *enrichment design*, see e.g. Magnusson and Turnbull (2013) and Ho et al. (2012)). Pallmann et al. (2018) provided an excellent review of adaptive designs in clinical trials from a practical perspective.

Logistical hurdles and statistical challenges have prevented a wider adoption of adaptive designs in clinical trials despite their ethical advantages (Robertson et al. 2023). In particular, because Box's linear process of "conjecture-design-experiment-analysis" no longer applies to adaptive experiments, most standard statistical methods exhibit selection bias (Rosenberger and Lachin 2015). For certain parametric models, the distribution of a test statistic in an adaptive study can be derived (Frieri et al. 2023; Lin et al. 2021; Spencer et al. 2016), or one can conduct hypothesis tests for the different stages of the trial separately and combine the resulting p-values (Müller and Schäfer 2001; Pocock 1982; Stallard 2023). However, these approaches are limited to just a few trial designs and heavily rely on modelling assumptions that are often difficult to justify. In the last decade, applications in online experiments of web services sparked renewed interest in adaptively collected data. A recent line of research uses adaptive weighting techniques to recover asymptotic normality (Deshpande et al. 2018; Hadad et al. 2021; Zhang et al. 2020, 2021). In another novel approach, Howard et al. (2021) use martingale concentration inequalities to construct any-time valid confidence intervals for the average treatment effect. These new methods usually require weaker assumptions but are often technically involved and only apply to simple response-adaptive designs.

Selective inference seeks valid inference on potential findings that are discovered after viewing the data (Benjamini 2020). Several notions of "validity" (or selective risks) have been considered. The notion with the longest history is familywise error, also known as simultaneous inference, dating back to the methods of Tukey (1949) and Scheffé (1959). Although simultaneous inference is often associated with multiple hypothesis testing, it can also be applied to post-model selection problems (Berk et al. 2013). A more lenient notion of risk is the average error rate over the selected; examples include the false discovery rate (Benjamini and Hochberg 1995) and the false coverage-statement rate (Benjamini and Yekutieli 2005). A third notion, which is the one we use in the proposed selective randomization test, is the conditional post-selection error (Fithian et al. 2017). Interest in this approach has surged recently after successful applications to the model selection problem (Lee et al. 2016); see Kuchibhotla et al. (2022) for a recent review.

Figure 2 illustrates how adaptive experiments and selective inference refine Box's linear process of conjecture-design-experiment-analysis (Figure 2a). In adaptive experiments, preliminary data from the experiment are used to modify the experimental design (Figure 2b) and conjecture (Figure 2c). In post-selection inference, preliminary analyses (e.g. a model selection procedure) are used to choose the conjecture (Figure 2d). As mentioned previously, the selective randomization test proposed here applies conditional post-selection inference to adaptive experiments (Figure 2e).

Two points merit a discussion at this point. First, among the different approaches to selective inference, we believe conditional inference is the most appropriate for adaptive clinical trials. This is because controlling the selective type-I error as in (1) allows us to *treat the selected hypothesis as given* when interpreting the results. This is crucial in objectively evaluating the evidence in a randomized experiment from a regulatory perspective. The familywise error rate is unnecessarily strict as we are often just interested in testing one hypothesis, and the more lenient notions such as the false discovery rate are more suitable for discovering promising hypotheses but not appropriate for confirmatory studies.

Second, compared to existing methods for inference after model selection, a distinguishing feature of the selective randomization test is that it is model-free. In particular, it does not require any parametric model on the outcome, not even that the data points are independent or identically distributed. Originally suggested by Fisher (1935) and elaborated by Pitman (1937), randomization inference is exactly based on the randomness introduced by the experimenter, or in Fisher's words, the "physical act of randomization" justifies the statistical inference. Although model-based inference is predominant in the analysis of randomized experiments, interest in randomization inference, especially for complex designs, has rekindled in



Figure 2: A schematic illustration of different modes of scientific research. Adaptive experimentation (Figure 2b and 2c) and post-selection inference (Figure 2d) break away from traditional statistical inference by inserting different "mini cycles" within each cycle of conjecture-design-experiment-analysis described by Box (1957).

recent years (Bugni et al. 2018; Ji et al. 2017; Offer-Westort et al. 2021; Rosenberger et al. 2019; Wang et al. 2020). Some previous works examined the use of randomization inference in adaptive experiments (Edwards 1999; Simon and Simon 2011), but the selective randomization test proposed here can be applied to a much wider class of adaptive designs.

1.3 Organization of the Article

In Section 2, we introduce our notation for the variables in a general adaptive study with multiple stages and describe their relationships using a directed acyclic graph. In Section 3, we formally define the selective randomization p-value and explain how it can be used to estimate and construct confidence intervals for a homogeneous treatment effect. In Section 4, we propose two Monte Carlo approximation strategies to compute the p-value: rejection sampling and Markov Chain Monte Carlo. In Sections 5 and 6, we illustrate the validity of our method using synthetic and real-world data. We conclude with a discussion on future research questions in Section 7. Proofs as well as further results and details about the simulation studies are deferred to the appendix.



Figure 3: Directed acyclic graph (DAG) of a two-stage adaptive trial, where Assumptions (A1^{*}) and (A2^{*}) hold. In addition, S_2 may directly depend on the observed data from the first stage: R_1, X_{R_1}, Z_1 and Y_{R_1} . For simplicity, these relationships are not depicted.

2 Adaptive Multi-stage Studies

We consider a adaptive study with K stages and L + 1 different treatments (e.g. drugs, dosages, policies, etc.) that are enumerated from 0 to $L \ge 1$. Denote $[K] := \{1, \ldots, K\}$, $[0] := \emptyset$, and we will use $k \in [K]$ to denote an arbitrary stage and $l \in \{0, \ldots, L\}$ an arbitrary treatment. At every stage, both the recruitment of participants and the treatment assignment mechanism may depend on the data observed in previous stages. Our assumptions can be visualized by the directed acyclic graph in Figure 3 for K = 2 stages. Next, we describe the setup more closely.

We assume participants are recruited from a pool of n units. For each candidate $i \in [n]$, we assume some covariate information X_i would become available if the candidate is recruited, and let us denote $X := (X_i)_{i \in [n]}$. Following the Neyman-Rubin causal model, the causal effect of a treatment l on a unit i is described using the potential outcome $Y_i(l)$. Let $Y_i(\cdot) := (Y_i(l))_{l \in \{0,...,L\}}$ denote all the potential outcomes of participant i, and let $Y(\cdot) := (Y_i(\cdot))_{i \in [n]}$. Here, we implicitly make the familiar assumption of "no interference", meaning the potential outcomes of one unit does not depend on the treatments received by the other units. Finally, for a subset $I \subseteq [n]$ of units, we use the notations $X_I := (X_i)_{i \in I}$ and $Y_I(\cdot) := (Y_i(\cdot))_{i \in I}$. We refer the reader to Imbens and Rubin (2015) for a comprehensive introduction to the Neyman-Rubin potential outcomes model.

The first distinguishing feature of our setup is that recruitment is modelled as a random event. In the clinical trials and causal inference literature, it is usually assumed (implicitly) that the recruited units are fixed. However, in adaptive experiments such as enrichment trials, recruitment decisions can depend on previously observed data. To incorporate this, we model the indices of units participating in each stage as the random sets $R_1, \ldots, R_K \subseteq [n]$. To simplify the problem, we do not consider longitudinal studies with patient follow-up over multiple time points in this work and assume that each unit can be included into the trial at most once, so R_1, \ldots, R_K are disjoint. This distinguishes our set-up from sequential multiple assignment randomized trials (SMART), where the same participants pass through multiple stages and receive interventions/treatments that can be adapted to their own past outcomes (Almirall et al. 2014). The covariates and potential outcomes of participants at stage k are denoted by

 X_{R_k} and $Y_{R_k}(\cdot)$, respectively. Denote $R = \bigcup_k R_k$, $R_{[k]} = \bigcup_{j=1}^k R_k$ and $R^C = [n] \setminus R$. At stage k, a total of $|R_k|$ units are recruited; let their administered treatments be denoted as $Z_k \in \mathcal{Z}_k \subseteq$ $\{0, \ldots, L\}^{|R_k|}$. The treatment assignment determines which of the potential outcomes is actually realized: the observed values of the outcome variable are denoted by Y_{R_k} . We assume consistency between the potential outcomes and factual outcomes, that is, $Y_{R_k} = Y_{R_k}(Z_k)$. In the following, we use the short-hand notations $Z = (Z_k)_{k \in [K]}$, $\mathcal{Z} = \bigotimes_{k=1}^K \mathcal{Z}_k$ and $Y_R = (Y_{R_k})_{k \in [K]}$. Further, we denote $W_k = (R_k, X_{R_k}, Y_{R_k}(\cdot))$ and $W = (W_k)_k \in \mathcal{W}$.

In adaptive experiments, Z_k is randomized by the experimenter and may depend on the covariates of the recruited participants X_{R_k} and observed data from previous stages. We can formalize these conditions as the following conditional independence relationship:

$$Z_{k} \perp Y_{R_{[k]}}(\cdot) \mid R_{[k]}, X_{R_{[k]}}, Y_{R_{[k-1]}}, Z_{[k-1]}, \qquad \forall k \in [K].$$
(A1)

Assumption (A1) is similar to the ignorability or no unmeasured confounders conditions in causal inference that says that the treatment assignment is (conditionally) independent of the potential outcomes. It is satisfied if the treatment assignment in stage k is indeed randomized, and the randomization distribution is allowed to depend on all the data observed before that time point.

The second characteristic feature of our setting is the selection statistics S_1, \ldots, S_K which describe the adaptive nature of the experiment. After administering the treatment and recording the response in stage k, the experimenter is allowed to give a preliminary analysis of the data from stages 1 through kand summarize their findings by a statistic S_k , which then determines the design of the next stage of the experiment. In other words, the recruitment and treatment assignment in stage k + 1 are allowed to depend on S_k ; in Figure 3, this corresponds to the directed edges $S_1 \to R_2$ and $S_1 \to Z_2$. Note that S_k is a deterministic function of the previously observed data $R_{[k]}, X_{R_{[k]}}, Y_{R_{[k]}}$ and $Z_{[k]}$. After completing the trial, the researchers choose a null hypothesis that may depend on the observed data of all stages of the trial. Hence, we model it as the final selection statistic S_K . We set $S := (S_1, \ldots, S_K) \in \mathcal{S} = \mathcal{S}_{-K} \times \mathcal{S}_K$. To emphasize the dependence of S on Z, we often write it as S(Z). Moreover, we use the convention $S_0 := \emptyset.$

For the methodological development below, it is important to assume that the selection statistic S_{k-1} captures all the information in previously observed data that impacts the design of the stage k. This can be formalized as follows:

$$R_k, X_{R_k}, Y_{R_k}(\cdot) \perp Z_{[k-1]} \mid W_{[k-1]}, S_{k-1}, \qquad \forall k \in [K].$$
(A2)

Assumption (A2) stipulates that the recruitment as well as the covariates and potential outcomes of the recruited units in stage k depend on the treatments assigned in earlier stages $Z_{[k-1]}$ only through earlier recruitment decisions, covariates and potential outcomes as well as the statistic S_{k-1} .

Assumptions (A1) and (A2) are the minimal conditions which we require in this article. They allow for highly adaptive recruitment decisions and treatment assignment distributions. In practice, however, many designs fulfill stronger conditional independence relationships that are easier to verify. For instance, (A1) can be strengthened as follows

$$Z_{k} \perp Z_{[k-1]}, W_{[k-1]}, Y_{R_{k}}(\cdot) \mid R_{k}, X_{R_{k}}, S_{k-1}, \qquad \forall k \in [K].$$
(A1*)

This assumption states that the treatments Z_k depend on (observed and counterfactual) data from previous stages only through the recruitment and covariates in stage k and the selection statistic S_{k-1} . One notable feature of designs which satisfy $(A1^*)$ is that they allow to parallelize the computation of the selective randomization, see Proposition 3.2. Moreover, we can strengthen Assumption (A2) by additionally requiring that the recruitment in stage k depends on data from previous stages only through S_{k-1} . We can express this stronger condition as the following two conditional independence relationships

$$R_k \perp Z_{[k-1]}, W_{[k-1]} \mid S_{k-1}, \qquad \forall k \in [K], \qquad (A2^*-1)$$

$$X_{R_k}, Y_{R_k}(\cdot) \perp Z_{[k-1]} \mid R_k, W_{[k-1]}, S_{k-1}, \qquad \forall k \in [K].$$
(A2*-2)

Note that (A2) is implied by the two assumptions above via the rules of weak union and contraction for conditional independence (Dawid 1979; Pearl 1988). From here on, we collectively refer to Assumptions (A2*-1) and (A2*-2) as (A2*).

We visualize the relationships between the different variables via a directed acyclic graph (DAG), see Figure 3 for a study with two stages. All the assumptions (for k = 1, 2) can be read off from the DAG by applying the d-separation criterion (Pearl 1988). Note that the DAG in Figure 3 does not depict the most general case and thus implies more conditional independence relationships than needed.

3 Selective Randomization Inference

This section applies ideas from the literature on conditional post-selection inference to randomization tests in adaptive experiments. We will formally define the selective randomization p-value and discuss how to estimate and construct confidence intervals for the treatment effect.

3.1 Selective Randomization Distribution

Randomization inference leverages the fact that the conditional distribution of the treatment assignments Z is specified by the experimenter and is thus known. In order to avoid imposing any modelling assumptions on the potential outcomes $Y(\cdot)$ and covariates X that may be unrealistic, we condition the distribution of Z on these quantities. In most settings, the choice of units to include into the study is fixed and therefore not explicitly pointed out. In adaptive studies, however, the recruitment of participants R may depend on the treatment assignments Z. Since we do not observe any of the potential outcomes of non-recruited units and may not even know their covariates, we cannot conduct inference for them. To restrict our analysis to recruited units, we additionally condition on R. This yields the randomization distribution

$$\mathbb{P}(Z = \cdot \mid W) = \mathbb{P}(Z = \cdot \mid R, X_R, Y_R(\cdot)).$$

As explained in Section 1.1, this distribution can be used to conduct naive randomization inference. Yet, such an approach does generally not provide statistical guarantees, like type-I error control, because the data-dependent choices of recruitment, treatment assignment and null hypothesis carry information about the validity of the null hypothesis. To remove any such information, a general solution is to additionally condition on the selection statistics $S = (S_1, \ldots, S_K)$ (Fithian et al. 2017). This solves two problems. First, there are two sources of randomness of Z_{R_k} : the recruitment R_k , which is modelled as a random event, and the randomized treatment assignment given R_k , which is the basis of randomization inference. Thus, it is essential that we condition on the recruitment R_k , whose distribution depends on S_{k-1} due to the adaptive nature of the design. Second, the null hypothesis, represented by the statistic S_K , is also generally data-dependent in an adaptive experiment. It is critical to condition on S_K to ensure type-I error control for the selected hypothesis. The resulting selective randomization distribution by

$$\mathbb{P}(Z = \cdot \mid W, S(Z)) = \mathbb{P}(Z = \cdot \mid R, X_R, Y_R(\cdot), S(Z)).$$

3.2 Hypothesis Testing

In order to analyse the effectiveness of the studied treatments, we compare the corresponding potential outcomes. Since we observe only one potential outcome for every recruited participant, the null hypothesis typically relates (a subset of) the realized to the unobserved potential outcomes. Thus, we can impute (a subset of) $Y_R(\cdot)$ from Y_R . A common hypothesis in randomization inference is Fisher's sharp null that states there is no treatment effect whatsoever:

$$H_0: Y_i(l) = Y_i(l'), \text{ for all } l, l' \in \{0, \dots, L\}, i \in R.$$

Under this hypothesis, all potential outcomes can be imputed from the observed outcomes, i.e. W is known, and we can directly use the selective randomization distribution to conduct inference. To this end, we

choose a test statistic T(Z, W) and compare its observed value to its selective randomization distribution under the null.

Yet, in many adaptive studies the null hypothesis of interest only allows to impute a subset of the potential outcomes $Y_R(\cdot)$ from the Y_R . Zhang and Zhao (2023) call such a null hypothesis *partially sharp*. In this case, we usually need to restrict the support of the selective randomization distribution by conditioning on an additional statistic G(Z) := G(Z, W).

Example 1. We may want to test the effect of the treatments only in a specific subgroup, e.g.

 $H_0: Y_i(l) = Y_i(l'), \text{ for all } l, l' \in \{0, \dots, L\}, i \in R: X_i \ge 0.$

Since the null hypothesis only applies to a certain subset of participants, we discard the data from other units in the hypothesis test. Mathematically, this can be achieved by conditioning the selective randomization distribution on $G(Z) = (Z_{k,i}: X_{k,i} < 0)_{k,i}$.

Example 2. We may only be interested in comparing a subset of treatments, e.g. $L \geq 2$ and

$$H_0: Y_i(0) = Y_i(1), \text{ for all } i \in \mathbb{R}$$

In this case, we only consider units who received the treatments 0 or 1 in the original study and discard data from other participants. Moreover, we need to restrict the treatment assignment for the remaining units to 0 and 1 as only the corresponding potential outcomes can be imputed. This is can be accomplished by conditioning on $G(Z) = (Z_{k,i} \in \{0,1\})_{k,i}$.

In summary, conditioning on S accounts for the selection of design and null hypothesis, and conditioning on G accommodates partially sharp null hypothesis. Based on the selective randomization distribution of the test statistic T given by

$$\mathbb{P}(T(Z,W) = \cdot \mid W, S(Z), G(Z)),$$

we define the selective randomization p-value as follows.

Definition 1. In the setting above, let Z^* have the same distribution as Z and fulfill $Z \perp Z^* \mid W$. Then, the *selective randomization p-value* is given by

$$P_{\rm sel} := \mathbb{P}\Big(T(Z^*, W) \le T(Z, W) \ \middle| \ W, Z, S(Z^*) = S(Z), G(Z^*) = G(Z)\Big).$$
(3)

Note that the selective randomization p-value is a specific instance of the conditional randomization p-value of Zhang and Zhao (2023). Therefore, the selective type-I error control follows immediately.

Proposition 3.1. Let $\alpha \in [0, 1]$. The selective randomization *p*-value as given in Definition 1 stochastically dominates the uniform distribution on [0, 1]:

$$\mathbb{P}(P_{\text{sel}} \le \alpha \,|\, W, S(Z) = s, G(Z) = g) \le \alpha, \quad \forall \, s \in \mathcal{S}, g \in \mathcal{G}.$$

Consequently, a test which rejects the selected null hypothesis when $P_{sel} \leq \alpha$ controls the selective type-I error, that is

 $\mathbb{P}(P_{\text{sel}} \leq \alpha \mid W, S(Z) = s) \leq \alpha, \quad \forall s \in \mathcal{S}.$

Proof. See Zhang and Zhao (2023, Thm. 1), where the partition of the treatment assignment space \mathcal{Z} is given by the preimages of (S, G), cf. Zhang and Zhao (2023, Prop. 1).

Remark 1. Simon and Simon (2011) consider experiments where the recruitment scheme and null hypothesis are fixed, but the treatment assignment distribution may depend on data from previous stages. They implicitly assume ignorability, cf. Assumption (A1), and prove that – under a condition akin to Assumption (A2) – the usual/naive randomization p-value is valid. Their result follows as a special case of Proposition 3.1: The indices of the recruited people are deterministic R = [n]; moreover, their assumptions imply that S can only be function of W but not Z and can consequently be dropped as W is already conditioned on.

When randomization inference is applied in practice, S is stipulated by the experimenters before executing the trial, whereas G and the test statistic T are chosen by the statisticians analysing the trial after its completion. If the selected null hypothesis is partially sharp, only a subset of the potential outcomes $Y_R(\cdot)$ of the recruited participants can be imputed from the observed outcomes Y_R . Since the selective randomization p-value generally depends on all potential outcomes, this raises the question whether it can actually be computed. To ensure this, statisticians need to choose the test statistic T and the function G such that for all $z^* \in \mathbb{Z}$ satisfying $S(z^*) = S(Z)$ and $G(z^*) = G(Z)$ the value of the test statistic $T(z^*, W)$ depends only on the potential outcomes that can be imputed under the null hypothesis chosen by $S_K(Z)$. Accordingly, such a test statistic is called *imputable*; for a more detailed discussion, we refer to Zhang and Zhao (2023). Likewise, the treatment assignment distribution in stage k may depend on previously realized outcomes $Y_{R_{[k-1]}}(Z_{[k-1]})$. Therefore, G also has to restrict the support of \mathbb{Z} such that $Y_{R_{[k]}}(z^*_{[k]})$ can be imputed for all $z^* \in \mathbb{Z}$ that fulfill $S(z^*) = S(Z)$ and $G(z^*) = G(Z)$. We then call the treatment assignments *imputable*.

Proposition 3.2. Let $z \in \mathbb{Z}, w = (r, x, y) \in \mathcal{W}, s \in S$ and $g \in \mathcal{G}$. Under Assumptions (A1) and (A2),

$$\mathbb{P}(Z = z \mid W = w, S(Z) = s, G(Z) = g) = \frac{q(z \mid w, s, g)}{\sum_{z' \in \mathcal{Z}} q(z' \mid w, s, g)},$$
(4)

where q is defined as

$$q(z \mid w, s, g) = \mathbf{1} \{ G(z) = g, S(z) = s \} \cdot \prod_{k=1}^{K} \mathbb{P}(Z_k = z_k \mid R_{[k]} = r_{[k]}, X_{R_{[k]}} = x_{R_{[k]}}, Y_{R_{[k-1]}}(z_{k-1}) = y_{R_{[k]}}, Z_{[k-1]} = z_{[k-1]}).$$

If additionally Assumption (A1^{*}) holds, this simplifies to

$$q(z \mid w, s, g) = \mathbf{1}\{G(z) = g, S(z) = s\} \cdot \prod_{k=1}^{K} \mathbb{P}(Z_k = z_k \mid R_k = r_k, X_{R_k} = x_{R_k}, S_{k-1} = s_{k-1}).$$

Assume that the test statistic T and the treatment assignments are imputable. Then, the selective randomization p-value can be computed as follows:

$$P_{\rm sel} = \frac{\sum_{z^* \in \mathcal{Z}} \mathbf{1} \{ T(z^*, W) \le T(Z, W) \} q(z^* \mid W, S(Z), G(Z))}{\sum_{z^* \in \mathcal{Z}} q(z^* \mid W, S(Z), G(Z))}.$$

Proof Sketch. The left-hand side of (4) is proportional to $\mathbb{P}(Z = z, W = w, S(Z) = s, G(Z) = g)$ for any given (w, s, g). The key idea of the proof is constructing a factorization of this probability according to the topological ordering of the DAG (or equivalently the progress of time in the experiment):

$$\dots \rightarrow R_k \rightarrow X_{R_k}, Y_{R_k}(\cdot) \rightarrow Z_k \rightarrow S_k \rightarrow \dots$$

At each stage k, we obtain four terms: the conditional probability of R_k given all data from previous stages, then the conditional probability of $X_{R_k}, Y_{R_k}(\cdot)$ given previous data and R_k and so on. Multiplying the terms from all stages yields the factorization of $\mathbb{P}(Z = z, W, S(Z) = s, G(Z) = g)$. Assumptions (A1) and (A2) help us to simplify the resulting expression. Thus, we derive (4).

Then, the formula for the selective randomization p-value directly follows from its definition, the conditional independence $Z^* \perp Z \mid W$ and normalizing the probabilities q. The details can be found in Appendix A.

The formula above provides a straightforward way of computing (or approximating) the selective randomization p-value: If the probabilities $q(z^* | S(Z), G(Z))$ are known analytically, we can directly compute P_{sel} ; otherwise, we can generate samples from the treatment assignment distribution and use a Monte Carlo approximation, see Section 4. If Assumption (A1*) holds, we can even parallelize the sampling for the different stages as the distribution of each Z_k^* depends on data from previous stages only through S_{k-1} which is conditioned on.

3.3 Confidence Intervals and Estimation

Thus far, we have focused on hypothesis tests. Yet, our proposed selective randomization p-value can also be used to construct confidence intervals and estimators for a homogeneous treatment effect τ . This effect is usually defined as the differences between the potential outcomes under two treatments l and l' in a subset of the recruited units I. The associated null hypothesis is given by

$$\mathrm{H}_{0}^{\tau}$$
: $Y_{i}(l) - Y_{i}(l') = \tau \quad \forall i \in I \subseteq R$

and the corresponding selective randomization p-value is denoted by $P_{sel}(\tau)$. (Note that we can equally define the homogeneous treatment effect τ across more than two treatments.) To emphasize the dependence of the selection statistic on τ , we use the notation $S(Z;\tau)$.

Due to the duality of hypothesis testing and confidence sets, we can simply invert the selective hypothesis tests for different values of τ to construct the confidence set

$$C_{1-\alpha} := \{ \tau \in \mathbb{R} \colon P_{\text{sel}}(\tau) > \alpha \}.$$
(5)

Lemma 3.1. Let $\alpha \in [0,1]$. If there exists a τ_0 such that the hypothesis $H_0^{\tau_0}$ is true, then $C_{1-\alpha}$ is a selective $1-\alpha$ confidence set, that is

$$\mathbb{P}(\tau_0 \in C_{1-\alpha} \mid W, S(Z; \tau_0) = s) \ge 1 - \alpha \quad \forall s \in \mathcal{S}.$$

Proof. By definition of the confidence set and Proposition 3.1, we obtain

$$\mathbb{P}(\tau_0 \notin C_{1-\alpha} \mid W, S(Z;\tau_0) = s) = \mathbb{P}(P_{\text{sel}}(\tau_0) \le \alpha \mid W, S(Z;\tau_0) = s) \le \alpha \quad \forall s \in \mathcal{S}.$$

Applying a similar reasoning, we can estimate the homogeneous effect as the τ -value that achieves a selective randomization p-value of 1/2, i.e. $\hat{\tau} = \tau$ such that $P_{sel}(\tau) = 1/2$. Since it may be impossible to find a value of τ that fulfills this condition exactly, the Hodges-Lehmann (HL) estimator (Hodges and Lehmann 1963; Rosenbaum 1993) is defined as follows

$$\hat{\tau} = \frac{\sup\{\tau \colon P_{\text{sel}}(\tau) < 1/2\} + \inf\{\tau \colon P_{\text{sel}}(\tau) > 1/2\}}{2}.$$

When the p-value $P_{sel}(\tau)$ is monotonically increasing in τ , the curve $\tau \mapsto P_{sel}(\tau)$ crosses every level exactly once. Consequently, the proposed confidence set and estimator are "well-behaved": $C_{1-\alpha}$ as defined in (5) is an *interval* and the HL estimator is the most intuitively right definition of a point estimator. For unconditional randomization inference, Caughey et al. (2023) provide conditions under which the corresponding p-value is indeed monotone.

Yet, when we condition on the selection event, the p-value curve is generally not monotone; even under Caughey et al.'s conditions. Heuristically, if we test increasingly extreme values of τ , there are usually fewer and fewer alternative treatment assignments Z^* that lead to the same selective choices as in the original trial, i.e. $S(Z^*;\tau) = S(Z;\tau)$. Therefore, the p-value curve becomes increasingly jagged. Hence, the confidence set defined via inversion of tests may be disconnected and the p-value curve may cross the level 1/2 multiple times complicating the definition of a sensible point estimator. We demonstrate this phenomenon with the two-stage trial example from the introduction. More details on this simulation study can be found in Section 5 and Appendix B. When the selection of the null hypothesis depends on data from the first and second stage, the first panel of Figure 4 shows that the p-value curve may be far from monotone. For instance, it crosses the level 1/2 six times yielding six potential point estimates.

To our knowledge, the problem of non-monotone p-value curves has not been studied before and cannot be completely circumvented. However, we can mitigate the risk of a jagged p-value curve and the resulting complications in interpreting the inference results by using *hold-out units*. These units are not taken into account when making selective choices; for example, the experimenters may decide on the null hypothesis before gathering data from the participants in the last stage of the study. Since S does not depend on the



Figure 4: Smoothing effect of hold-out units. In the first panel, the p-value curve (green) is plotted for a selection rule that uses stage I and II units; in the second panel, only stage I units are used for selection; in the third panel, only stage I units are used for selection but inference is based on the second stage randomization p-value, cf. data splitting. The true treatment effect equals 1 in this simulation.

treatments assigned to hold-out units, the number of alternative treatments Z^* cannot sink below a certain threshold – even for extreme values of τ . In the second panel of Figure 4, we plot the p-value curve when only the first stage data is used for selection of the null hypothesis and the second stage participants serve as hold-out units. The curve is not monotone but clearly smoother and yields a unique point estimate and 90% confidence interval.

4 Computation

The feasible treatment assignment space is denoted as $Z = X_k Z_k$, and we use $Z_{s,g} := \{Z \in Z : S(Z) = s, G(Z) = g\}$ to denote the subset of treatments yielding S(Z) = s and G(Z) = g. In Section 4.1, we display the computational challenges, primarily stemming from conditioning on S(Z) and G(Z). In Section 4.2, we describe two approaches for computing a single conditional randomization test p-value: the standard rejection sampling and a Markov Chain Monte Carlo algorithm. In Section 4.3, we employ the inversion of a series of conditional randomization tests to construct confidence intervals.

4.1 Computational Challenges

For tests based on randomization or permutation, it is typically infeasible to enumerate all possible treatment configurations whose number grows exponentially regarding the sample size. As an approximation, one could draw M Monte Carlo samples $Z^{(t)}$, t = 1, ..., M, satisfying $Z^{(t)} | W$ and Z | W being equal in distribution, and compute

$$\hat{P}_M := \frac{1 + \sum_{t=1}^M \mathbf{1}\{T(Z^{(t)}, W) \le T(Z, W)\}}{1 + M}.$$

Here the additional one is added to the denominator and numerator to ensure the validity of the p-value.

In this section, we focus on the additional challenges induced by the conditioning event, namely, the process of generating random samples belonging to $Z_{s,g}$. First, the probability of the conditional event might be exceedingly small. For example, when one conditions on a continuous statistic attaining a specific value, or when the potential outcomes are imputed under some pre-defined null that is at odds with the observed data, it becomes difficult to generate samples that yield the observed selection, cf. Section 3.3. Second, the feasible treatment space Z typically has a simple topology and convenient to sample from,

Table 1: Summary of approaches for computing a single conditional randomization test p-value. We recommend rejection sampling when the success probability is not exceptionally low, and the Markov Chain Monte Carlo algorithm otherwise.

	Rejection sampling	Markov Chain Monte Carlo (MCMC)
Algorithm	Algorithm 1	Algorithm 2
Treatment assignment scheme	Arbitrary	Arbitrary
Conditioning event	Arbitrary	Arbitrary
Small prob. conditioning event	Slow	Efficient
Hyper-parameter tuning	Tuning-free	Window-size, burn-in etc.

for instance, when each Z_k is associated with a completely randomized trial or a Bernoulli trial. However, the additional constraint S(Z) = s, G(Z) = g typically disrupts this helpful structure. Third, since Z is a discrete random vector, gradient-based sampling methods are typically not suitable.

4.2 Testing a Single Hypothesis

In Section 4.2.1, we discuss the rejection sampling method, which is practically convenient but may consume exceedingly high computation time when the probability of the event conditioned on is small. Markov chain Monte Carlo (MCMC) algorithms could potentially be much more efficient but require the construction of a suitable Markov Chain and careful tuning. Table 1 provides a summary of the two computation methods.

4.2.1 Rejection Sampling

Rejection sampling starts with the random selection of a treatment vector Z^* from \mathcal{Z} following the actual randomization mechanism without any conditioning. If $Z^* \in \mathcal{Z}_{s,g}$, the generated treatment Z^* is accepted; otherwise, Z^* is rejected. This process continues until the desired number of samples is reached. The algorithm is summarized in Algorithm 1.

Suppose the success probability $\mathbb{P}(Z^* \in \mathcal{Z}_{s,g})$ equals q, then the expected number of draws required to obtain one acceptable treatment is 1/q. When q is extremely small, potentially scaling exponentially with the number of randomized units, the expected number of Z^* attempted can be considerably high. This computational challenge is illustrated through simulations in Section 5: In the trials where only one subgroup is selected, the conditional randomization test with rejection sampling takes around 150 times of the computation time compared to the randomization test without conditioning; in other words, roughly only one out of 150 proposals is accepted.

4.2.2 Random Walk Metropolis-Hastings Algorithm

We describe a general random walk Metropolis-Hastings algorithm (Metropolis et al. 1953) to compute the p-value. The algorithm can be significantly simplified for treatment assignments where at each stage a completely randomized design or a Bernoulli trial is conducted given the selection in the previous stages, see Example 3 and Example 4 below.

We initialize the random walk Metropolis-Hastings (RWM) algorithm at the observed treatment assignment Z and repeat the following iteration M times. In the t-th iteration, we select with probability $\rho(\mathcal{A})$ a subset $\mathcal{A} \subseteq R$ of entries of $Z^{(t-1)}$ for updating their values. Here ρ can be any probability measure defined on the power set of R. Let π denote the joint distribution of the realized treatment assignment mechanism. Provided with \mathcal{A} , we fix the treatment assignment of units not in \mathcal{A} , and generate the treatment of units in \mathcal{A} following the conditional probability $\pi(Z^*_{\mathcal{A}} \mid Z^*_{\mathcal{A}^c} = Z^{(t)}_{\mathcal{A}^c})$. Upon obtaining a new proposal Z^* , we set

Algorithm 1 Rejection sampling

Input: data Z, W (observed or imputed); selection statistic functions $S(\cdot)$, $G(\cdot)$, selected test statistic $T(\cdot)$; realized treatment assignment mechanism π ; number of samples M. Initialization: the current number of accepted treatments t = 0. while t < M do Generate a treatment assignment Z^* following the distribution π if $Z^* \in \mathcal{Z}_{S(Z),G(Z)}$ then Accept Z^* and let $Z^{(t)} \leftarrow Z^*$, $t \leftarrow t + 1$. else Reject Z^* and continue. end if end while Compute $\hat{P}_M = \left(1 + \sum_{t=1}^M \mathbf{1}\{T(Z^{(t)}, W) \leq T_{S,G}(Z, W)\}\right)/(1 + M)$. Output: \hat{P}_M .

 $Z^{(t)} = Z^*$ if $Z^* \in \mathcal{Z}_{s,g}$ and reject Z^* and use $Z^{(t)} = Z^{(t-1)}$, otherwise. The details are summarized in Algorithm 2.

Example 3 (Completely randomized design). A completely randomized design randomly assigns prefixed numbers of units to the different arms of the study with uniform probability. Suppose that at each stage a completely randomized design is conducted independently, and let $Z_k^{(t)}$ be the treatment assignment of stage k in $Z^{(t)}$. Then, for each stage k, we can choose a window-size $h_k \in \mathbb{N}$, and randomly select h_k entries from $Z_k^{(t)}$ and shuffle these h_k values to generate a new Z_k^* . This is equivalent to setting ρ as the uniform measure supported on all subsets consisting of exactly h_k units from stage k.

Example 4 (Bernoulli trial). In a Bernoulli trial, each unit *i* is independently assigned to the treatment with probability p_i , where the probability p_i may depend on their covariates. Suppose at each stage an independent Bernoulli trial is conducted, where the probability parameter may depend on the selection made in prior stages and a unit's covariates. Similar to Example 3, in each iteration, we randomly select $2 \leq h_k \in \mathbb{N}$ entries from $Z_k^{(t)}$ and replace them by independent Bernoulli random variables with the same probability parameter.

Markov Chain Monte Carlo algorithms, like the RWM algorithm, generate samples from the treatment assignment distribution by traversing the space \mathcal{Z} . As the conditioning event of the selective randomization p-value may be complex, the selective randomization distribution may have disconnected support. Therefore, the RWM sampler may not be able "reach" every feasible treatment assignment. This phenomenon is described by the notion of *communication*: For a Markov chain, we say that $z \in \mathcal{Z}$ and $z' \in \mathcal{Z}$ communicate if and only if z can be reached from z' in finitely many steps with positive probability and vice versa. Hence, communication defines an equivalence relation and partitions \mathcal{Z} into communication classes. For the RWM algorithm, a larger window-size h is associated with larger and fewer communication classes, typically more powerful tests, but also higher computational complexity.

Since a Markov chain is always confined to the states that communicate with the starting value $Z^{(0)}$, we cannot always approximate the selective randomization p-value as defined in (3). Instead, we additionally condition it on the communication class and denote the resulting p-value \tilde{P}_{sel} . Importantly, this p-value inherits the selective type-I error control – more details in Appendix C.1 – and can be approximated by the RWM sampler.

Proposition 4.1. For the Monte Carlo approximation in Algorithm 2, there exists $\sigma^2 < \infty$ such that

$$\sqrt{M}(\hat{P}_M - \tilde{P}_{sel}) \mid Z, W \xrightarrow{d} \mathcal{N}(0, \sigma^2), \quad as \ M \to \infty.$$

This result establishes the asymptotic distribution of the p-value calculated with Algorithm 2 under general treatment designs including Bernoulli and completely randomized trials. We can directly read off

Algorithm 2 Random walk Metropolis-Hastings algorithm

Input: data Z, W (observed or imputed); selection statistic functions $S(\cdot)$, $G(\cdot)$, selected test statistic $T(\cdot)$; realized treatment assignment mechanism π ; a probability measure ρ on the power set of all entries in Z^{*}; number of samples M; burn-in size b. Initialization: Set $Z^{(0)} = Z$ (observed value). for t = 1 : M do Select a subset \mathcal{A} of entries with probability $\rho(\mathcal{A})$, and generate a new proposal Z^{*} following the conditional distribution $\pi(\cdot | Z^*_{\mathcal{A}_c} = Z^{(t-1)}_{\mathcal{A}_c})$. if $Z^* \in \mathcal{Z}_{S(Z),G(Z)}$ then $Z^{(t)} \leftarrow Z^*$. else $Z^{(t)} \leftarrow Z^{(t-1)}$. end if end for Compute $\hat{P}_M = \left(1 + \sum_{t=b+1}^M \mathbf{1}\{T(Z^{(t)}, W) \leq T(Z, W)\}\right) / (1 + (M - b))$. Output: \hat{P}_M .

that the convergence rate is of order $\mathcal{O}_p(M^{-1/2})$. The proof of Proposition 4.1 relies on the observation that the proposed chain in Algorithm 2 is self-reflexive, i.e. $\pi(Z^* = Z^{(t)} \mid Z^*_{\mathcal{A}^c} = Z^{(t)}_{\mathcal{A}^c}) > 0$, with the stationary distribution being the desired treatment assignment mechanism. Details are summarized in Appendix C.2.

To conclude this subsection, we discuss hyper-parameter selection. We choose the window size to maximize the empirical efficiency metric Mean Squared Euclidean Jump Distance (MSEJD) defined as

$$S^{2} = \frac{1}{M-1} \sum_{t=1}^{M-1} \|Z^{(t+1)} - Z^{(t)}\|_{2}^{2}.$$

MSEJD is equivalent to a weighted sum of the lag-1 auto-correlation for stationary chains with finite posterior variance (Sherlock et al. 2010), and a higher MSEJD value indicates greater efficiency. We remark that for binary treatments, S^2 is equivalent to the average Hamming distance between adjacent samples $Z^{(t)}$ and $Z^{(t+1)}$, $t \in \{1, \ldots, M-1\}$. Compared to the rejection probability of a new proposal, the significance of MSEJD lies in its ability to not only account for the frequency of acceptance but also capture the magnitude of the differences $Z^* - Z^{(t)}$ among accepted proposals Z^* .

4.3 Constructing Confidence Set

We discuss computation details of constructing confidence sets as outlined in (5). Let \mathcal{I} denote a userspecified set of potential constant treatment and suppose \mathcal{I} is of finite-length. For arbitrary selective hypothesis test p-values, possibly non-monotone, one can discretize \mathcal{I} into bins of width $\varepsilon > 0$, and evaluate the p-value at the representative value of each bin. The confidence set shall comprise all bins associated with p-values above the significant level. The testing of different representative values of τ can be computed independently, allowing the entire procedure to be accelerated through parallel computing. If the p-values are monotone, the confidence set is an interval. In this case, the Robbins-Monro algorithm and the bisection method can be employed to efficiently compute the lower and upper limits of this interval (Garthwaite 1996; Wang et al. 2020).

5 Simulation Study

To verify our proposed methods empirically, we use the two-stage enrichment trial example introduced in Section 1. We use the following notations and data-generating mechanism.

The population of interest is subdivided into two groups with low and high genetic risk score, respectively; this is captured in the covariate $X_i \in \{\text{low}, \text{high}\}$, where *i* is the patient index. Every participant is assigned to the new drug $(Z_i = 1)$ or the placebo $(Z_i = 0)$. In both stages, of the trial we use a completely randomized treatment assignment mechanism. That is, we assign half of the units to the new drug and half of the units to the placebo with equal probability. The outcome variable of interest Y_i is continuous, e.g. LDL cholesterol level. In this simulation study, we generate the potential outcomes $Y_i(1) = Y_i(0)$ as i.i.d. standard normals. Hence, there is no treatment effect in neither group and the sharp null hypothesis holds true. In the first stage, we simulate $n_1 = 100$ recruited patients, 50 with low and high genetic risk score, respectively. To select the group(s) to recruit from in the second stage, we compare the standardized average treatment effects Δ_r in the first stage, which are defined as

$$\Delta_r = \frac{\bar{Y}_{r,1} - \bar{Y}_{r,0}}{\sqrt{\hat{\sigma}_{r,1}^2 + \hat{\sigma}_{r,0}^2}}, \qquad \hat{\sigma}_{r,t}^2 = \frac{\sum_{i:X_i=r,Z_i=t}^{n} (Y_i - \bar{Y}_{r,t})^2}{\sum_{i=1}^{n_1} \mathbb{1}_{\{X_i=r,Z_i=t\}}}, \qquad r \in \{\text{low, high}\}, t \in \{0,1\},$$
(6)

where $\bar{Y}_{r,t}$ denotes the average outcome in group r under treatment t. We define the selection statistic S in terms of the scaled difference ATE difference $\Delta = (\Delta_{\text{high}} - \Delta_{\text{low}})/\sqrt{2}$ as follows

$$S = \begin{cases} \text{only low,} & \Delta < \Phi^{-1}(0.2), & \text{recruit 40 from group } X_i = \text{low,} \\ \text{only high,} & \Delta > \Phi^{-1}(0.8), & \text{recruit 40 from group } X_i = \text{high,} \\ \text{both,} & \text{otherwise,} & \text{recruit 20 from group } X_i = \text{low and } X_i = \text{high each.} \end{cases}$$
(7)

Here $\Phi(\cdot)$ denotes the cdf of a standard normal distribution. This selection rule is motivated by a traditional model: If the distribution of the outcomes is the same under placebo and drug for both groups and the data points are i.i.d., Δ approximately follows a standard normal distribution. Note that these assumptions are only used to design the experiment but not to analyse the resulting data.

In the following, we compare three types of randomization inference: the standard randomization test (RT), the randomization test of the second stage (RT 2nd) and the proposed selection randomization test (SRT). For the latter, we experiment with two implementations: rejection sampling and the RWM sampler with window size of 5. Appendix D contains additional results on the RWM sampler.

For the test statistic T, we use the standardized ATE (6) applied to the selected group(s) with data from both stages. A larger value of the test statistic T indicates a stronger treatment effect. We perform inference on the null hypothesis across a range of treatment effects $\tau \in \{-1, -0.8, \ldots, 0.8, 1\}$. Null hypotheses corresponding to smaller treatment effects should have a higher probability of being rejected. Additionally, the probability of rejecting the null hypothesis with $\tau = 0$ should not exceed the target significance level. We repeat from the generation of potential outcomes and covariates 400 times and report the rejection probabilities for each null hypothesis. We also display the rejection probabilities among trials with a specific stage 1 subgroup selection: subgroup $X_i = \text{low}$, or subgroup $X_i = \text{high}$, or both subgroups. In addition, we compare the computation time of RT, RT 2nd, SRT with rejection sampling, and SRT with RWM sampling. The source code is available on Github.

5.1 Hypothesis Testing

As demonstrated in Figure 5, RT does not control the type I error (the null with zero effect, i.e., $\tau = 0$), especially in cases where the selection bias is severe: selecting subgroup X_i = high or selecting subgroup X_i = low). SRT and RT 2nd both control the unconditional and unconditional type I errors. SRT exhibits



(b) Computation time

Figure 5: Comparison of randomization tests regarding computation time and rejection probabilities for testing a sequence of nulls of constant treatment effect τ . The potential outcomes satisfy $\tau = 0$.

greater power than RT 2nd when both subgroups are selected due to the randomness recycled from the first stage. The power curves do not significantly differ across rejection sampling and MCMC.

In terms of the computation time, RT and RT 2nd are the most efficient, followed by RWM. Rejection sampling is significantly slower, especially when one of the subgroups is selected and the hypothesis being tested is extreme. In this scenario the success probability of the rejection sampling is very low, leading to a prohibitive computational burden.

5.2 Confidence Intervals

According to the discussion of the monotonicity of the selective randomization p-value, we proceed to construct confidence intervals by inverting randomization tests using the baseline discretization method. In particular, we construct one-sided confidence intervals and use binary search to determine the left boundary value $\underline{\tau}$. We evaluate the coverage of the confidence intervals and also compute the average value of $\underline{\tau}$, where a greater value of $\underline{\tau}$ indicates higher power.

According to Table 2, RT fails to produce the right coverage when only one of the subgroups is selected. SRT and RT 2nd yield reasonably good coverage. Figure 6 suggests that the lower boundary of SRT is in general larger than that of RT 2nd, suggesting that SRT is more powerful. The results are consistent with those in Section 5.1.

6 Real Data Analysis

We create hypothetical two-stage enrichment trials from the data of a one-stage randomized experiment and compare the RT, SRT, and RT 2nd adopted in the simulation section on the hypothetical data.

The hypothetical dataset is generated from the Systolic blood pressure intervention trial (SPRINT) (Gao et al. 2021; National Heart, Lung, and Blood Institute (NHLBI) 2016) which aims to study whether

Table 2: Comparison of randomization tests regarding coverage probability (significance level 0.1). We report the conditional coverage given the subgroup(s) selected, and the unconditional coverage marginalizing over the selection.

	SRT MCMC	RS	RT 2nd	RT
Unconditional	0.910	0.920	0.910	0.858
Subgroup $X_i = \text{high}$	0.861	0.873	0.873	0.722
Subgroup $X_i = \text{low}$	0.921	0.934	0.949	0.795
Both subgroups	0.909	0.918	0.909	0.922



Figure 6: Comparison of randomization tests regarding lower boundary of the confidence interval.

a new treatment program targeting reducing systolic blood pressure will reduce cardiovascular disease (CVD) risk. The outcome is whether a major CVD event happens to the subject. There are 20 features: 3 demographic features including age, race; 6 medical history features including daily Aspirin use, history of CVD; 11 lab measurements including body mass index (BMI), SBP. We classify the subjects into four age subgroups: no older than 59, 60 to 69, 70 to 79, no younger than 80. In the first stage, we randomly sample 2000 units without replacement, compute the relative risk ($\mathbb{P}(\text{CVD event} \mid \text{treatment arm})/\mathbb{P}(\text{CVD event} \mid \text{control arm})$) for each age group, and select the age group with the minimal relative risk, i.e. the most significant improvement. In the second stage, we randomly sample an additional 200 units without replacement of the selected age group from the units not chosen by the first stage. The hypothetical dataset is summarized in Table 3.

We test the sharp null that there is no treatment effect. We use the relative risk as the test statistic and approximate the p-value using 1000 Monte Carlo samples. For the selective randomization test, we adopt the rejection sampling algorithm. As shown in Table 3, SRT exhibits significantly higher statistical power than RT 2nd due to the randomness in the first stage left after the selection. In this scenario, SRT is comparable to RT regarding power, but the RT is not guaranteed to control the type-I error.

In Appendix E, we repeat the above power comparison from constructing the hypothetical real dataset via subsampling multiple times. The distribution of the p-value from the SRT is stochastically dominated by that of the RT 2nd. We also perform a placebo analysis evaluating the type-I error. In particular, we subsample from the control group of the original SPRINT trial and generate artificial treatment assignments following independent Bernoulli(0.5) multiple times. All the units in the constructed dataset did not receive the treatment, and the null hypothesis that the artificial treatment has no treatment effect is true. In the placebo analysis, the RT fails to control the type-I error while SRT does.

The source code for generating and analysing this hypothetical clinical trial is available on Github.

Sta	ge	Stage 1 ($N_1 = 2000$)		Stage 2 ($N_2 = 200$)		
Age group		≤ 60	[60, 69]	[70, 79]	≥ 80	≥ 80
Control	Y = 1	8	17	22	19	17
	Y = 0	187	349	275	123	87
Treated	Y = 1	12	13	22	7	13
	Y = 0	201	331	289	125	83

Table 3: Comparison of randomization tests on a hypothetical dataset generated from the SPRINT dataset.

	SRT	RT 2nd	RT
P-value	0.048	0.314	0.027

7 Discussion and Outlook

To analyse data from adaptive studies, we use the paradigm of randomization inference as it has two major benefits. First, randomization inference does not require any modelling assumptions on the distribution of the covariates and outcomes or the ubiquitous condition of i.i.d. data points. Therefore, it is an ideal default tool for conducting inference that can stand on its own or complement a model-based analysis. Second, randomization inference naturally lends itself to handle selective choices. Recent model-based proposals typically involve considerable technical difficulties and can only be used for specific types of adaptive studies. On the other hand, our proposed selective randomization p-value can accommodate all kinds of selective choices. The reason for this flexibility stems from the following insight: In standard randomization inference, we compare the realized treatment assignment Z to all alternative assignments Z^* ; in adaptive studies, however, it is only fair to compare to Z^* that lead to the same choices as in the original trial. Hence, conditioning on the information expressed in the selection, i.e. conditioning on $S(Z^*) = S(Z)$, suffices to provide valid inference. This holds true regardless of the type of selective choice.

While this article is mainly concerned with introducing selective randomization inference and exploring some immediate questions like constructing confidence intervals or computing the p-value, there are many conceivable extensions.

First, this work focuses on developing a general theoretical framework to *analyse* data from adaptive experiments. In turn, the developed methodology also has implications on the design of such adaptive studies: The preliminary data analyses between stages, the treatment assignments and the recruitment decisions must obey Assumptions (A1) and (A2) or their stronger versions (A1^{*}) and (A2^{*}). This touches on the subtle question at which point(s) in the study the experimenters can use which type of data to make adaptive choices. We save a detailed investigation of this issue for future, more application-oriented work.

Second, we only consider the classical case of a (partially) sharp null hypothesis in this work. This implies testing that the treatment effect is the same for every (or a subgroup of) individual in the study. Since such null hypotheses are sometimes criticized as overly restrictive and therefore of little interest to practitioners, many recent articles focus on relaxing the sharp null. Caughey et al. (2023) propose to test one-sided null hypotheses; another line of research considers weak null hypotheses that concern the average treatment effect among the participants (Cohen and Fogarty 2022; Ding 2017; Wu and Ding 2021). Moreover, standard treatment assignment mechanisms, e.g. completely randomized or Bernoulli trials, may lead to covariate imbalance between different arms of the study. To remedy this issue, rerandomization tests (Morgan and Rubin 2012; Wang and Li 2022) condition the distribution of Z on a balance criterion. Integrating these recent developments into our selective randomization inference framework, would greatly add to its flexibility and appeal.

Third, this work is mainly targeted to adaptive studies that use a selection statistic S that takes

discrete values. Conceptually, there is no obstacle to apply our method to continuous selection rules. However, the selective randomization p-value may reduce to the data splitting p-value. Consider our running example of a two-stage enrichment trial: In the extreme case that each first-stage treatment assignment leads to a different value of the selection statistic $S(Z_1)$, conditioning on $S(Z_1^*) = S(Z_1)$ is equivalent to conditioning on $Z_1^* = Z_1$. Even when there are a few first-stage treatment assignments yielding the same value of a continuous selection statistic, it is computationally hard to identify them, especially when rejection sampling is used. These characteristics seem to be unfavourable for analysing a common type of enrichment trial where a continuous biomarker is used as selection criterion. Researchers typically use the first stage data to determine a threshold and recruit in the second stage only participants whose biomarker passes this hurdle (Friede et al. 2012; Lai et al. 2019; Rosenblum et al. 2016; Stallard 2023; Stallard et al. 2014). However, if we make additional assumptions such as a monotone relationship between the biomarker and treatment effect, some of the "first-stage randomness" can be retained and used for conducting inference.

Fourth, drop-out units, which are commonly observed in clinical trials, pose challenges for drawing valid inference. The particular difficulty of conducting randomization tests lies in the inability to impute the missing outcomes of drop-out units. Solutions to this problem include model-based or non-informative outcome imputation and reweighting the treatment assignments probabilities among the subjects with observed outcomes based on the outcome missingness probabilities (Edgington and Onghena 2007; Heussen et al. 2023; Ivanova et al. 2022; Rosenberger et al. 2019). If the missingness is independent of the outcomes but possibly influenced by the treatment administered (analogous to the missing at random mechanism), we can extend our proposal to incorporate the missingness following the path of reweighting. The resulting p-values will be valid for finite samples if the mechanism of missingness is known, or valid asymptotically if the missing mechanism can be consistently estimated.

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A Proof of Proposition 3.2

Proof. First, we derive the factorization of the selective randomization distribution. To this end, let $z \in \mathcal{Z}, w \in \mathcal{W}, s \in \mathcal{S}$ and $g \in \mathcal{G}$. We repeatedly use the definition of conditional independence to construct a factorization where each random variable/vector is only conditioned on variables that predate it in the topological ordering of the DAG (and in time):

$$\mathbb{P}(Z = z \mid W = w, S = s, G = g) = \frac{\mathbb{P}(Z = z, W = w, S = s, G = g)}{\mathbb{P}(W = w, S = s, G = g)} \\ \propto \mathbb{P}(S_K = s_K, G = g \mid Z = z, W = w, S_{[k-1]} = s_{[K-1]}) \cdot \\ \prod_{k=1}^{K} \mathbb{P}(R_k = r_k \mid W_{[k-1]} = w_{[k-1]}, Z_{[k-1]} = z_{[k-1]}, S_{[k-1]} = s_{[k-1]}) \cdot \\ \mathbb{P}(X_{R_k} = x_{R_k}, Y_k(\cdot) = y_k(\cdot) \mid R_k = r_k, W_{[k-1]} = w_{[k-1]}, Z_{[k-1]} = z_{[k-1]}, S_{[k-1]} = s_{[k-1]}) \cdot \\ \mathbb{P}(Z_k = z_k \mid W_{[k]} = w_{[k]}, Z_{[k-1]} = z_{[k-1]}, S_{[k-1]} = s_{[k-1]}) \cdot \\ \mathbb{P}(S_k = s_k \mid W_{[k]} = w_{[k]}, Z_{[k]} = z_{[k]}, S_{[k-1]} = s_{[k-1]})$$

To simplify this expression, we apply Assumptions (A1) and (A2). Moreover, we use the fact that G is a deterministic function of Z and W and S_k is a deterministic function of $R_{[k]}, X_{R_{[k]}}, Y_{R_{[k]}}$ and $Z_{[k]}$, where $k \in [K]$; this is denoted by (D). We obtain

$$\mathbb{P}(Z = z \mid W = w, S = s, G = g)$$

$$(D)$$

$$\propto \mathbf{1}\{G(z,w) = g, S_K(z,w) = s_K\} \cdot \tag{D}$$

$$\prod_{k=1} \mathbb{P}(R_k = r_k \mid S_{k-1} = s_{k-1}) \cdot \tag{A2}$$

$$\mathbb{P}(X_{R_k} = x_{R_k}, Y_k(\cdot) = y_k(\cdot) \mid R_k = r_k, W_{[k-1]} = w_{[k-1]}, S_{k-1} = s_{k-1}).$$
(A2)

$$\mathbb{P}(Z_k = z_k \mid R_{[k]} = r_{[k]}, X_{R_{[k]}} = x_{R_{[k]}}, Y_{R_{[k-1]}}(z_{[k-1]}) = y_{R_{[k-1]}}, Z_{[k-1]} = z_{[k-1]}) \cdot$$
(A1)

$$\mathbf{1}\{S_k(w_{[k]}, z_{[k]}) = s_k\}$$
(D)

$$\begin{aligned} &\propto \mathbf{1}\{G(z,w) = g, S(z,w) = s\} \\ &\qquad \mathbb{P}(Z_k = z_k \mid R_{[k]} = r_{[k]}, X_{R_{[k]}} = x_{R_{[k]}}, Y_{R_{[k-1]}}(z_{[k-1]}) = y_{R_{[k-1]}}, Z_{[k-1]} = z_{[k-1]}) \\ &\propto q(z \mid s, g) \end{aligned}$$

If additionally Assumption (A1*) holds, the expression above simplifies further:

$$\mathbb{P}(Z = z \mid W = w, S = s, G = g)$$

$$\propto \mathbf{1}\{G(z, w) = g, S(z, w) = s\} \prod_{k=1}^{K} \mathbb{P}(Z_k = z_k \mid R_k = r_k, X_{R_k} = x_{R_k}, S_{k-1} = s_{k-1}).$$

Next, we consider the selective randomization distribution of Z^* conditional on Z; let $z^* \in \mathcal{Z}$. Using the fact that S and G are deterministic functions of W and Z^* or W and Z, respectively, and applying the conditional independence $Z^* \perp Z \mid W$, we find

$$\begin{split} \mathbb{P}(Z^* = z^* \mid W = w, Z = z, S(z^*) = S(z), G(z^*) = G(z)) \\ &= \mathbf{1}\{S(z^*) = S(z), G(z^*) = G(z)\} \cdot \mathbb{P}(Z^* = z^* \mid W = w, Z = z) \\ &= \mathbb{P}(Z^* = z^* \mid W = w, S(z^*) = S(z), G(z^*) = G(z)). \end{split}$$

The result now follows from expanding the formula of the selective randomization p-value, applying the equation above as well as (4):

$$P_{sel} = \sum_{z^* \in \mathcal{Z}} \mathbf{1} \{ T(z^*, W) \le T(Z, W) \} \cdot \mathbb{P}(Z^* = z^* \mid W, S(z^*) = S(Z), G(z^*) = G(Z) \}$$
$$= \frac{\sum_{z^* \in \mathcal{Z}} \mathbf{1} \{ T(z^*, W) \le T(Z, W) \} q(z^* \mid S(Z), G(Z))}{\sum_{z^* \in \mathcal{Z}} q(z^* \mid S(Z), G(Z))}$$

This expression can be computed because the test statistic and the treatment assignment are assumed to be imputable. Under the stronger condition (A1^{*}), we can simplify the formula of the conditional probabilities $q(z^* | S(Z), G(Z))$.

B Details of the Simulation Study on Hold-out Units

We use the data-generating mechanism of the two-stage enrichment trial as described in Section 5 and modify it as follows.

First, we consider the common scenario that there is treatment effect heterogeneity between groups, cf. Marston et al. (2020). To this end, we generate the potential outcomes as $Y_i(1) = Y_i(0) + 1$ for participants with high genetic risk and as $Y_i(1) = Y_i(0)$ for participants with low genetic risk; $Y_i(0)$ are i.i.d. draws from a standard normal distribution. Hence, the treatment effect in the former group is 1 and 0 in the latter.

Second, we lower the number of recruited patients to 16 in the first and second stage each. This allows us to precisely compute the p-values for different treatment effects τ without the need for a Monte Carlo approximation. Therefore, we can exclude numerical errors as a cause of our findings.

Third, we employ two different selection rules. For the study with hold-out units, we decide after the first stage for which group(s) we test the (partially) sharp null hypothesis. Hence, we use S as defined in (7) with data from the first stage. Thus, the selection depends on Z_1 but not Z_2 . For the study without hold-out units, we choose the null hypothesis only after completing the second stage. Hence, we use S (7) with data from both stages. Consequently, S depends on Z_1 and Z_2 in this scenario.

We simulate 10 different datasets. Since the true treatment effect in the group with high genetic risk is larger, we observe that the selection rules choose this group in the majority of cases. Since we employ two different rules, they may disagree, however. In order to make a fair comparison between the two adaptive designs, we only consider scenarios where both rules choose to test the null hypothesis for the group with high genetic risk. Among the remaining datasets, we compute the p-value curve via discretizing the interval [-2, 3]. Figure 4 depicts the most jagged p-value curve we found.

The source code of this simulation study is available on Github.

C Details on Random Walk Metropolis-Hastings Algorithm

C.1 Communication Class

Recall that for a Markov chain we say that $z \in \mathbb{Z}$ and $z' \in \mathbb{Z}$ communicate if and only if $z \in \mathbb{Z}$ can be reached from z' in finitely many steps of the Markov chain with positive probability and vice versa. We denote the resulting equivalence relation \equiv_C and define the communication class of a state $z \in \mathbb{Z}$ as follows

 $C_{s,q}(z) := \{ z' \in \mathcal{Z} \colon S(z') = s, G(z') = g, z \equiv_C z' \}, \quad \text{for } s \in \mathcal{S}, g \in \mathcal{G}.$

Analogously to Definition 1, we can define the selective randomization p-value that additionally conditions on the communication class of the starting point of a Markov chain **Definition 2.** In the setting above, let Z^* have the same distribution as Z and fulfill $Z^* \perp Z \mid W$. Then, the selective randomization p-value conditional on the communication class is given by

$$\tilde{P}_{sel} := \mathbb{P}\Big(T_{S,G}(Z^*, W) \le T_{S,G}(Z, W) \, \Big| \, W, Z, S(Z^*) = S(Z), G(Z^*) = G(Z), Z^* \in C_{S,G}(Z)\Big).$$

Moreover, the modified selective randomization p-value preserves the type-I error control.

Proposition C.1. Let $\alpha \in [0,1]$. The selective randomization *p*-value as given in Definition 2 stochastically dominates the uniform distribution on [0,1]:

$$\mathbb{P}(P_{sel} \le \alpha \,|\, W, S(Z) = s, G(Z) = g, Z^* \in C_{S,G}(Z)) \le \alpha \quad \forall \, s \in \mathcal{S}, g \in \mathcal{G}.$$

Consequently, a test which rejects the selected null hypothesis when $\tilde{P}_{sel} \leq \alpha$ controls the selective type-I error, that is

$$\mathbb{P}(\tilde{P}_{sel} \le \alpha \mid W, S(Z) = s) \le \alpha \quad \forall s \in \mathcal{S}.$$

Proof. See Zhang and Zhao (2023, Thm. 1), where the partition of the treatment assignment space \mathcal{Z} is given by the preimages of (S, G) and the equivalence relation \equiv_C , cf. Zhang and Zhao (2023, Prop. 1). \Box

C.2 Approximation of P-value

Here, we state and prove a more rigorous version of Proposition 4.1. We consider the Markov chain defined by the random walk Metropolis-Hastings Algorithm 2.

Proposition C.2. For fixed Z, the Markov Chain restricted to the communicating class $C_{s,g}(Z)$ is aperiodic, irreducible, and reversible at equilibrium with the stationary distribution $\pi(\cdot)$ restricted to $C_{s,g}(Z)$. In addition, suppose $Z^{(0)} = Z$, then there exists $\sigma^2(Z, W) < \infty$ such that

$$\sqrt{M}\left(\hat{P}_M - \tilde{P}_{sel}(Z, W)\right) \mid Z, W \stackrel{d}{\to} \mathcal{N}\left(0, \sigma^2(Z, W)\right), \quad M \to \infty.$$

Proof. For any acceptable z, the probability of reaching itself is positive, and thus the Markov Chain is aperiodic. Moreover, it is irreducible since we restrict it to one communication class.

If the transition probability is reversible at equilibrium with the stationary distribution $\pi(\cdot)$ restricted to $C_{s,g}(Z)$, then $\pi(\cdot)$ restricted to $C_{s,g}(Z)$ is the stationary distribution. By Levin and Peres (2017, Thm. 4.9), the Markov Chain is then geometrically ergodic on $C_{s,g}(Z)$. Since any geometrically ergodic reversible Markov chain satisfies a central limit theorem for all functions with a finite second moment with respect to the stationary distribution (Gilks et al. 1996) and that the indicator function $\mathbf{1}\{T(z, W) \leq T(Z, W)\}$ is bounded, we obtain the desired central limit theorem like convergence result.

Hence, it is left to show that the transition probability is reversible at equilibrium with the stationary distribution $\pi(\cdot)$ restricted to $C_{s,g}(Z)$. Let $\Sigma(z)$ be the set of operations $\sigma = \kappa \circ s$, where s denotes the operation of randomly picking h_k entries of z_k , $k \in \{1, \ldots, K\}$, and κ denotes randomly shuffling the h_k entries. Note that $|\Sigma(z)|$ does not depend on z. Let $\Sigma(z \to z^*) := \{\sigma \in \Sigma(z) : \sigma(z) = z^*\}$ be the set of operations in $\Sigma(z)$ transitioning z to z^* . Note that if $\kappa \circ s(z) = z^*$, then $\kappa^{-1} \circ s(z^*) = z$. This implies there is an injection mapping from $\Sigma(z \to z^*)$ to $\Sigma(z^* \to z)$. By symmetry, the mapping is a bijection, and we obtain $|\Sigma(z \to z^*)| = |\Sigma(z^* \to z)|$.

Note that the proposal distribution of the Markov chain is given by

$$p(z^* \mid z) = \frac{|\Sigma(z \to z^*)|}{|\Sigma(z)|}, \quad z^* \in \mathcal{Z},$$

which satisfies

$$p(z \mid z^*) = \frac{|\Sigma(z \to z^*)|}{|\Sigma(z)|} = \frac{|\Sigma(z^* \to z)|}{|\Sigma(z^*)|} = p(z^* \mid z).$$

Recall the acceptance probability is $\alpha(z^*|z) = \mathbf{1}\{z^* \in C_{s,g}(z)\}$, then the probability of the new proposal being accepted is given by

$$\alpha(z) = \sum_{z^* \in C_{s,g}(z)} \frac{|\Sigma(z \to z^*)|}{|\Sigma(z)|}.$$

The transition probability matrix takes the form

$$P(z, z^*) = p(z^* \mid z) \mathbf{1}\{z^* \in C_{s,g}(z)\} + (1 - \alpha(z)) \mathbf{1}\{z^* = z\}.$$

Note that $\pi(\cdot)$ restricted to $C_{s,g}(z)$ in this case is the uniform distribution $\mathcal{U}(C_{s,g}(z))$. For $z^* \in C_{s,g}(z)$, $z^* \neq z$,

$$\pi(z) \mathbf{P}(z, z^*) = \pi(z) p(z^* \mid z) = \pi(z^*) p(z \mid z^*) = \pi(z^*) \mathbf{P}(z^*, z),$$

which yields the desired reversibility.

D Additional Results on the RWM Sampler

We vary the window size of the RWM sampler in $\{2, 5, 10, 15\}$ and demonstrate the computation time as well as the rejection probability at different null hypotheses, see Figure 7.

As the window size increases, the running time largely remains the same (or increases only mildly). This is because, regardless if the proposal is accepted or not, the RWM sampler will proceed to the next iteration, in contrast to the rejection sampling algorithm. The RWM sampler is slower than RT 2nd and RT due to the extra step verifying whether the proposal is acceptable.

The rejection probability remains relatively consistent across window sizes, possibly because the communicating classes associated with a small window size h = 2 is already sufficiently large. The power comparison of SRT, RT 2nd, and RT is similar to that in Section 5.



Figure 7: Comparison of computation time and rejection probability of the RWM sampler with different window sizes. We follow the simulation setting in Section 5 and vary the window size in $\{2, 5, 10, 15\}$.



Figure 8: Hypothetical two-stage enrichment trials generated from the SPRINT dataset.

E Additional Real Data Analysis

We perform a placebo analysis evaluating the type-I error. To this end, we generate artificial treatment assignments following independent Bernoulli(0.5) multiple times for the control group. As in Section 6, in the first stage, we randomly sample 2000 units without replacement but only from the original control group, compute the relative risk for each age group based on the artificial treatment assignment, and select the age group with the minimal relative risk (the most significant improvement). In the second stage, we randomly sample an additional 200 units without replacement of the selected age group, originally under control, and not recruited in the first stage. We repeat from generating artificial treatments multiple times and, as in Section 6, focus on the trials where the age group "no younger than 80" is selected. All the units in the constructed dataset did not receive the treatment, and the null hypothesis that the artificial treatment has no treatment effect is true. As indicated by the CDF curves of the p-values in Figure 8a, which are based on 1000 trials with the target selection, the RT fails to control the type I error while SRT and RT 2nd do.

We repeat the power comparison in Section 6 from constructing the hypothetical real dataset via subsampling multiple times. We focus on the trials where the age group "no younger than 80" is selected. As indicated by the CDF curves of the p-values in Figure 8b, the p-value from the SRT is stochastically dominated by that of the RT 2nd. An analysis of the treatment effect in the age group "no younger than 80" based on the original SPRINT trial rejects the null of no treatment effect, and the p-value CDFs indicate that the SRT is more powerful than RT 2nd. In particular, the rejection probability at the significance level 0.05 is 35.3% for SRT but only 25.8% for RT 2nd.