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Asymptotic properties of randomized clinical trials designs

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Abstract

Nowadays, we are witnessing changes in the traditional clinical trial landscape: many methods have been proposed as a compromise between uncontrolled trials and randomized trials and a large number of adaptive randomization procedures have been developed for various studies, including multi-arm trials, dose-finding trials and platform trials. Adaptive designs often require time-consuming and computationally intensive Monte Carlo simulations to establish operating characteristics, particularly type I error probability and power. These statistical properties should be thoroughly investigated in order that the designs achieve regulatory approval. In particular, the estimated operating characteristics need to cover different scenarios, varying key parameters, such as enrollment rates and treatment effects. This makes routine applications of adaptive designs challenging. Also, at present new data sources are becoming available that can supplement data generated in standard randomized clinical trials. Externally-controlled clinical trials designs incorporate existing data about the control treatment available from external sources as external controls. So far, these designs have been evaluated mainly according to qualitative arguments or simulation studies.

In the first part of this PhD thesis, we focus on asymptotic properties of the designs of response-adaptive clinical trials, that is characteristics of these designs obtained under the assumption that the number of patients enrolled in the studies is large. Approximations of the operating characteristics, beyond simulations, leveraging asymptotic properties, could allow a fast comparison of designs across plausible scenarios.

In the second part of this PhD thesis, we investigate the statistical properties of externally-controlled randomized clinical trial designs, adopting a quantitative approach, and question whether these designs could shorten study length and benefit more patients being treated with a better treatment.

The aims of our research are threefold: to determine appropriate methodology that can be used in the assessment of asymptotic properties of the designs of response-adaptive clinical trials; to

develop a quantitative framework to compare externally-controlled randomized clinical trial designs to standard randomized clinical trial designs; and finally to examine the identified methods and verify our results via simulation studies, across a variety of scenarios and endpoints.

The key contributions of this work are:

- ▷ proposing a novel methodology to derive asymptotic results for the randomization probabilities and allocation proportions of patients to various arms in a broad class of Bayesian response-adaptive randomized clinical trials designs, by combining tools from the classical foundations of statistical inference and probability theory with mathematical techniques such as stochastic approximation.
- ▷ showing that asymptotic analyses of adaptive procedures simplify the design of clinical trials and reduce the need for time-consuming simulations to evaluate operating characteristics across potential trial scenarios.
- ▷ proving that externally-controlled clinical trials can increase power compared to randomized clinical trials by leveraging additional information from outside the trial rather than committing resources to an internal control.

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This thesis is dedicated to them.

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Outline of the thesis

This PhD thesis is organized as follows.
In Chapters 1 and 2, we study asymptotic characteristics of Bayesian Uncertainty directed trial Designs (BUDs), proposed by Ventz et al. [88]. These designs are an example of adaptive clinical trial designs using a Bayesian methodology. BUDs use information measure $u(\Sigma_t)$ - functions of the data Σ_t observed up to the t-th enrollment - to quantify accumulated informations on pivotal outcome summaries, such as the mean response to treatments. The goal is to minimize uncertainty at completion of the study.
In Chapter 3, we discuss the statistical properties of designs of clinical trials that use data from external studies to augment concurrent information generated during a standard clinical trial. We propose mixed effects models to account for the between-studies variability in the design of externally-controlled randomized clinical trials with different endpoints and we translate our findings to practical guidelines for the design of future clinical trials.
Supplementary insights are given in the Appendices at the end of these chapters.
Lastly, a discussion and a conclusion will deepen certain limits, perspectives and potential further research directions of our work.
A brief summary of the main chapters is provided below.

Chapter 1

Since the first work on the topic by Robbins and Monro [67], stochastic approximation has found applications in diverse areas, such as signal processing and finance, and new techniques have been developed for proofs of convergence and rate of convergence. However, the application of stochastic approximation methods in clinical trials is not common. In this chapter, after introducing BUDs in their general formulation, we bridge the stochastic approximation and the modern response-adaptive designs literatures to investigate asymptotic properties of BUDs. We assume that the distribution of patients' responses is in the natural exponential family with quadratic

variance function and that the information measure u is the sum of the (negative) posterior variance of the mean of the outcomes across different arms. We rewrite the updating rule of the randomization probabilities of a BUD as a classical recursive stochastic procedure and we study the properties of the ordinary differential equation associated with the stochastic approximation. This allows us to prove asymptotic normality of the randomization probabilities. Then, we derive a Central Limit Theorem type result for the allocation proportions by applying Delta method and Slutsky theorem. Finally, we illustrate through examples the accuracy of asymptotic approximations using Monte Carlo simulations and show that our analyses justify the use of asymptotic arguments for power calculations.

Chapter 2

Little research has been done on asymptotic characteristics of the design of response-adaptive randomized clinical trials with general endpoints: most studies present in literature focus on Bernoulli and Gaussian outcomes. In this chapter, we fill this gap by studying the asymptotic properties of BUDs when we relax the assumption made in Chapter 1 that the distribution of the outcomes is in the natural exponential family. We prove strong consistency of the allocation proportions and randomization probabilities under some mild requirements. Also, we derive the almost sure convergence of the allocation proportions when the information measure that characterize the BUD is the sum of the (negative) entropy of the posterior probability of the mean of the outcomes in the different arms. Numerical examples are provided.

Chapter 3

Recently, the idea of using external data to replace or complement data from current clinical trials is gaining attraction and researchers advocate the introduction of external controls in the design of clinical trials to augment the control arm. However, the statistical properties of externally-controlled randomized clinical trials have not been deepened. In this chapter, we address the following research question: "in testing the the null hypothesis of no treatment effect against the one-sided alternative of positive treatment effect, once the type I error is fixed at a certain nominal level, what is the most powerful option between designs of trials characterized by different randomization ratios and that could include external information on the control treatment from external studies?"

We derive closed-form expression of power of externally-controlled and standard randomized clinical studies and we provide a procedure to identify the optimal randomization ratio when responses

are Gaussian. For Bernoulli and time-to-event outcomes, instead, we propose an overall procedure based on simulation and bootstrap method to estimate power. We show that externally-controlled randomized clinical trials can increase power compared to standard randomized clinical trials by leveraging additional information from outside of the trial rather than committing resources to the internal control, provided that the between-studies variability is small.

Chapter 1

Asymptotic properties of Bayesian Uncertainty directed trial Designs

1.1 Introduction

Randomized clinical trials are essential to demonstrate the efficacy of novel experimental therapies [25]. The landscape of clinical studies has changed during the last decades, with an increasing number of trials that utilize adaptive designs, in some cases to evaluate several experimental treatments in biomarker-defined subpopulations [11, 87]. The primary aims vary across studies, ranging from dose optimization [31, 39] to the development of effective combination of synergistic therapeutics [81]. Adaptive designs are attractive to reduce the duration of the study and to allocate efficiently limited resources [16].

Most adaptive designs use data generated during the clinical trial for interim decisions [16], for example to vary the randomization probabilities during the study [11, 18, 87, 102] or to discontinue the evaluation of an experimental treatment [87]. In multi-arm studies adaptive randomization algorithms unbalance the randomization probabilities, in most cases, towards the most promising treatments. This can increase power compared to balanced randomization, or it can reduce the overall sample size necessary to test experimental treatments [95]. Adaptive randomization procedures have been developed for several designs, including multi-arm studies [18, 21], platform and basket studies [11, 87, 102].

The decision theoretic paradigm has been used to develop trial designs [15, 19, 30]. The study aims and costs are represented by a utility function $u(\cdot)$ of the data Σ generated during the trial and the study design d. Using a Bayesian joint model for patient profiles, outcomes and other key

variables, candidate designs d can be compared by computing their expected utility $E(u(\Sigma, d))$. The optimal design maximizes $E(u(\Sigma, d))$ among all candidate designs.

Several approximations of the described optimization have been proposed. For example, [88] discussed *Bayesian Uncertainty directed trial Designs* (BUDs), a class of approximate decision theoretic designs. The utility function u in BUDs coincides with an information metric. In different words, the goal is to minimize uncertainty at completion of the study. BUDs for dose-finding and basket trials have been discussed in [31] and [84]. Previous work, related to BUDs, proposed information-based sampling schemes [20, 59, 73].

There is a rich literature on large sample analyses of adaptive designs. For example [8, 96] studied the behavior of sequential urn schemes. See also [9, 36, 68, 100] for a summary on large sample results for urn schemes. The limiting behavior of adaptive biased coin designs have been investigated, among others, by [34, 43] and [44]. Relevant work connecting stochastic approximation with response-adaptive clinical trials include [12] and [52].

In this Chapter we focus on the asymptotic characteristics of BUDs. The design of adaptive clinical trials requires the estimation of several operating characteristics. In most cases these estimates are based on time consuming Monte Carlo simulations, conducted for different candidate designs and varying key parameters, including sample sizes, enrollment rates, and outcome distributions.

The need for computationally efficient approximations of design-specific operating characteristics motivates our study. We show the almost sure convergence and asymptotic normality of the relative allocation of patients to the experimental and control arms in BUDs. We first derive analytic results assuming that the arm-specific outcome distributions are within the natural exponential family [29], and later relax this assumption. In our analysis, we represent BUD randomization procedures as stochastic approximations (SAs). We study the ordinary differential equations associated with the resulting SAs and the stability of the stationary points, following the framework developed in [13] and using results of [51, 52]. We illustrate through examples the accuracy of asymptotic approximations by comparing asymptotic estimates of operating characteristics and Monte Carlo simulations. Our asymptotic results allow investigators to quickly approximate, for scenarios of interest, the distribution of the number of patients that will be assigned to each arm. Understanding the asymptotic behavior of BUD policies is useful to ascertain if the proportions of patients allocated to different arms converges to a nearly optimal limit. Additionally, our analyses justify the use of asymptotic arguments for power calculations.

1.2 Trial Design

We consider a clinical experiment that assigns n patients sequentially to K arms. We use $A_t \in \mathcal{A} = \{0, \cdots, K-1\}$ to indicate the assignment of individual $t = 1, \cdots, n$ to arm A_t, $Y_t \in \mathbb{R}$ is the response to treatment A_t, and the accumulated data up to enrollment t is summarized by $\Sigma_t = \{(A_\ell, Y_\ell)\,; \ell \leq t\}$. The BUD [88] is defined by first specifying a Bayesian model. Outcomes are conditionally independent $Y_t \mid A_t = a \sim f_{\theta_a}(y|a)$ and identically distributed within each arm a, $\theta_a \sim \pi(\theta_a)$ indicates the prior for the unknown parameter θ_a. The vector of parameters $\theta = (\theta_0, \ldots, \theta_{K-1})$ has joint distribution $\theta \sim \pi(\theta) = \prod_{a=0}^{K-1} \pi(\theta_a)$.
We quantify the information accrued by the experiment through the accumulated data Σ_t until stage t by considering an utility function $u(\Sigma_t)$. Large values of $u(\Sigma_t)$ correspond to low uncertainty levels. The function $\tilde{u}$ translates the posterior distribution $\pi(\theta \mid \Sigma_t)$ into an utility. In particular, we define $u(\Sigma_t) = \tilde{u}(\pi(\theta \mid \Sigma_t))$. The information metric $\tilde{u}$ is specified by a convex functional over the convex space of distributions of the parameters: $\tilde{u}\,(\omega\pi_1 + (1-w)\pi_2) \leq w\tilde{u}(\pi_1) + (1-\omega)\tilde{u}(\pi_2)$ for every pair of probability measures π_1 and π_2, when $\omega \in [0,1]$.
By Jensen's inequality, the information, on average, increases with each enrollment,

$$\Delta_t(a) := E\left(u(\Sigma_{t+1})|A_{t+1} = a, \Sigma_t\right) - u(\Sigma_t) \geq 0, \tag{1.1}$$

for every $a \in \mathcal{A}$. The myopic and deterministic policy $A_{t+1} = \arg\max_{a\in\mathcal{A}} \Delta_t(a)$, which is often inappropriate for clinical experiments [18] is relaxed in BUDs by a randomized version, with probabilities

$$p_{t,a} := p(A_{t+1} = a \mid \Sigma_t) \propto \Delta_t(a)^h. \tag{1.2}$$

where $h \geq 0$ is a tuning parameter. The randomization probabilities coincide with the myopic policy when $h \to \infty$, while with $h = 0$ the randomization probabilities become identical across arms.

Outcome distributions within the natural exponential family

We focus on outcome distributions f_{θ_a} in the natural exponential family (NEF) [14],

$$f_{\theta_a}(y|a) = f_{\psi_a}(y) \propto \exp\{y\psi_a - b(\psi_a)\}, \tag{1.3}$$

where $\psi_a \in \mathbb{R}$ is the canonical parameter and $b(\cdot)$ is the cumulant transform.
We indicate the mean and the variance of the responses to treatment a with $\theta_a = E_\psi(Y_t|A_t = a) = \int y f_{\psi_a}(y)dy = b'(\psi_a)$ and $\sigma_a^2 = \mathrm{Var}_\psi(Y_t|A_t = a) = \int y^2 f_{\psi_a}(y)dy - \left(\int y f_{\psi_a}(y)dy\right)^2 = b''(\psi_a)$, respectively. We use the equivalent parametrization f_{ψ_a} and f_{θ_a} interchangeably and we consider independent conjugate prior distributions [29] for ψ_a,

$$\pi(\psi_a \mid n_{0,a}, \mathbf{y}_{0,a}) \propto \exp\{n_{0,a}\tilde{y}_{0,a}\psi_a - n_{0,a}b(\psi_a)\}, \tag{1.4}$$

with hyper-parameters $n_{0,a} > 0$ and $\tilde{y}_{0,a} \in \mathbb{R}$. The posterior distribution for $\psi = (\psi_0, \cdots, \psi_{K-1})$ is $\pi(\psi \mid \Sigma_t) = \prod_{a=0}^{K-1} \pi(\psi_a \mid \Sigma_t)$, where $\pi(\psi_a \mid \Sigma_t)$ has the same form as (1.4) with updated parameters $n_{t,a} = n_{0,a} + t\hat{p}_{t,a}$ and $\tilde{y}_{t,a} = \left(n_{0,a}\tilde{y}_{0,a} + \sum_{s=1}^{t} Y_s 1(A_s = a)\right)/n_{t,a}$. Here $\hat{p}_{t,a}$ is the proportion of patients assigned to treatment a by time t and $1(A_s = a) = 1$ if patient s received treatment a and zero otherwise. Throughout Chapter 1, we consider

$$u(\Sigma_t) = -\sum_{a=0}^{K-1} \mathrm{Var}(\theta_a|\Sigma_t). \tag{1.5}$$

The expected information increment (1.1) becomes

$$\Delta_t(a) = \mathrm{Var}(\theta_a \mid \Sigma_t) - E\left(\mathrm{Var}(\theta_a \mid \Sigma_{t+1}) \mid A_{t+1} = a, \Sigma_t\right). \tag{1.6}$$

We recall a useful result from the literature on conjugate Bayesian models [14, 29], $\tilde{y}_{t,a} = E(\theta_a \mid \Sigma_t)$. Since A_{t+1} and θ_a are conditionally independent, given Σ_t, the information gain equals

$$\begin{aligned}
\Delta_t(a) &= \mathrm{Var}(E(\theta_a \mid \Sigma_{t+1}) \mid A_{t+1} = a, \Sigma_t) \\
&= \mathrm{Var}\left(\frac{n_{0,a} + \tilde{y}_{0,a} + \sum_{s=1}^{t+1} Y_s 1(A_s = a)}{n_{0,a} + t\hat{p}_{t,a} + 1} \mid A_{t+1} = a, \Sigma_t\right) \\
&= \mathrm{Var}\left(\frac{Y_{t+1}}{n_{0,a} + t\hat{p}_{t,a} + 1} \mid A_{t+1} = a, \Sigma_t\right),
\end{aligned}$$

where the first equality follows from the law of total variance and the second equality is a consequence of the properties of the natural exponential family. We can therefore write

$$\Delta_t(a) = \frac{\sigma_{t,a}^2}{(n_{0,a} + t\hat{p}_{t,a} + 1)^2},$$

where $\sigma_{t,a}^2 = \mathrm{Var}(Y_{t+1} \mid A_{t+1} = a, \Sigma_t)$.

1.3 Asymptotic properties

In this section, we discuss asymptotic properties of BUDs with sum of the (negative) posterior variances of $\theta_a, a = 0, \ldots, K-1$, as information measure $u(\Sigma_t)$.
In [88] a criterion is given for the allocation proportions to have a limit. Based on this result, we first prove convergence of allocation proportions and randomization probabilities under the assumption that the outcome distributions belong to the natural exponential family. We then investigate the rate of convergence of these quantities in the case $K = 2$.

1.3.1 Almost sure convergence of randomization probabilities and allocation proportions

Proposition 1 shows that the allocation proportion and randomization probability related to one of the two arms in two-arm BUDs converge almost surely to the same limit, which is proportional to a power of the variance of the outcomes related to that arm.

Proposition 1. *Consider a two-arm BUD, $K = 2$, with outcome distribution belonging to the NEF (1.3), conjugates prior (1.4) and information metric $u(\Sigma_t)$ in (1.5). Then, as $t \to \infty$,*
(i) the allocation of patients to treatments $a = 0, 1$ converges almost surely (a.s.),

$$\widehat{p}_{t,a} \longrightarrow \rho_a := \frac{\sigma_a^{\frac{2h}{2h+1}}}{\sigma_0^{\frac{2h}{2h+1}} + \sigma_1^{\frac{2h}{2h+1}}} \ a.s. \ \text{as} \ t \to \infty. \tag{1.7}$$

(ii) The randomization probability converges a.s. to the same limit as $t \to \infty$,

$$p_{t,a} \longrightarrow \rho_a \ a.s. \tag{1.8}$$

Proof. (Proposition 1) It is enough to prove (1.7) and (1.8) for $a = 1$. First, define

$$F_t = -\hat{p}_{t,1} + \frac{\left(\frac{\sigma_{t,1}^2}{(t_0+t\hat{p}_{t,1}+1)^2}\right)^h}{\left(\frac{\sigma_{t,0}^2}{(t_0+t\hat{p}_{t,0}+1)^2}\right)^h + \left(\frac{\sigma_{t,1}^2}{(t_0+t\hat{p}_{t,1}+1)^2}\right)^h}$$

and

$$\tilde{F}_t = -\hat{p}_{t,1} + \frac{\hat{p}_{t,1}^{-2h}\sigma_1^{2h}}{\hat{p}_{t,0}^{-2h}\sigma_0^{2h} + \hat{p}_{t,1}^{-2h}\sigma_1^{2h}}.$$

As a function of $\hat{p}_{t,1}$, $\tilde{F}_t$ is strictly decreasing.
The unique root of $\tilde{F}_t = 0$ is

$$\rho_1 := \frac{\sigma_1^{2h/(2h+1)}}{\sigma_0^{2h/(2h+1)} + \sigma_1^{2h/(2h+1)}} \tag{1.9}$$

Now, we show that $F_t - \tilde{F}_t$ converges to zero a.s. as $t \to \infty$.
The proof is based on the following elementary facts:

a If a_n, b_n, a'_n and b'_n are sequences of positive numbers, then

$$\left| \frac{a_n}{a_n + b_n} - \frac{a'_n}{a'_n + b'_n} \right| \leq \min \left(\left| \frac{a_n}{b_n} - \frac{a'_n}{b'_n} \right|, \left| \frac{b_n}{a_n} - \frac{b'_n}{a'_n} \right| \right).$$

Indeed

$$\begin{aligned} \left| \frac{a_n}{a_n + b_n} - \frac{a'_n}{a'_n + b'_n} \right| &= \left| \frac{1}{1 + b_n/a_n} - \frac{1}{1 + b'_n/a'_n} \right| \\ &= \left| \frac{b'_n/a'_n - b_n/a_n}{(1 + b_n/a_n)(1 + b'_n/a'_n)} \right| \\ &\leq \mid b'_n/a'_n - b_n/a_n \mid \end{aligned}$$

and

$$\begin{aligned} \left| \frac{a_n}{a_n + b_n} - \frac{a'_n}{a'_n + b'_n} \right| &= \left| 1 - \frac{a_n}{a_n + b_n} - 1 + \frac{a'_n}{a'_n + b'_n} \right| \\ &= \left| \frac{b_n}{a_n + b_n} - \frac{b'_n}{a'_n + b'_n} \right| \end{aligned}$$

b If a_n, b_n, a'_n and b'_n are bounded sequences of numbers such that $a_n - a'_n \to 0$ and $b_n - b'_n \to 0$, then $a_n b_n - a'_n b'_n \to 0$. Indeed,

$$\mid a_n b_n - a'_n b'_n \mid \leq \mid a_n b_n - a'_n b_n + a'_n b_n - a'_n b'_n \mid \leq \mid b_n \mid\mid a_n - a'_n \mid + \mid a'_n \mid\mid b_n - b'_n \mid$$

c If a_n and a'_n are bounded sequences such that $a_n - a'_n \to 0$ and r is a positive real number, then $a_n^r - a_n'^r \to 0$. The thesis is obvious if $r = 1$. If $r > 1$, and M is an upper bound for both sequences, then

$$\mid a_n^r - a_n'^r \mid \leq 2rM^{r-1} \mid a_n - a'_n \mid$$

If $r < 1$, then

$$\mid a_n^r - a_n'^r \mid \leq \mid a_n - a_n' \mid^r$$

Let us now prove that $F_t - \tilde{F}_t \to 0$ a.s.
By (a),

$$\mid F_t - \tilde{F}_t \mid \leq \min\left(\left|\frac{\sigma_{t,0}^{2h}((n_{0,1}+1)/t+\hat{p}_{t,1})^{2h}}{\sigma_{t,1}^{2h}((n_{0,0}+1)/t+\hat{p}_{t,0})^{2h}} - \frac{\sigma_0^{2h}\hat{p}_{t,1}^{2h}}{\sigma_1^{2h}\hat{p}_{t,0}^{2h}}\right|, \left|\frac{\sigma_{t,1}^{2h}((n_{0,0}+1)/t+\hat{p}_{t,0})^{2h}}{\sigma_{t,0}^{2h}((n_{0,1}+1)/t+\hat{p}_{t,1})^{2h}} - \frac{\sigma_1^{2h}\hat{p}_{t,0}^{2h}}{\sigma_0^{2h}\hat{p}_{t,1}^{2h}}\right|\right).$$

Hence

$$\begin{aligned}
\mid F_t - \tilde{F}_t \mid &\leq \left|\frac{\sigma_{t,0}^{2h}((n_{0,1}+1)/t+\hat{p}_{t,1})^{2h}}{\sigma_{t,1}^{2h}((n_{0,0}+1)/t+\hat{p}_{t,0})^{2h}} - \frac{\sigma_0^{2h}\hat{p}_{t,1}^{2h}}{\sigma_1^{2h}\hat{p}_{t,0}^{2h}}\right| 1_{(\hat{p}_{t,0}>1/2)} + \\
&+ \left|\frac{\sigma_{t,1}^{2h}((n_{0,0}+1)/t+\hat{p}_{t,0})^{2h}}{\sigma_{t,0}^{2h}((n_{0,1}+1)/t+\hat{p}_{t,1})^{2h}} - \frac{\sigma_1^{2h}\hat{p}_{t,0}^{2h}}{\sigma_0^{2h}\hat{p}_{t,1}^{2h}}\right| 1_{(\hat{p}_{t,0}\leq 1/2)} \\
&\leq \left|\frac{\sigma_{t,0}^{2h}\sigma_1^{2h}((n_{0,1}+1)/t+\hat{p}_{t,1})^{2h}\hat{p}_{t,0}^{2h} - \sigma_0^{2h}\sigma_{t,1}^{2h}((n_{0,0}+1)/t+\hat{p}_{t,0})^{2h}\hat{p}_{t,1}^{2h}}{\sigma_{t,1}^{2h}\sigma_1^{2h}((n_{0,0}+1)/t+\hat{p}_{t,0})^{2h}\hat{p}_{t,0}^{2h}}\right| 1_{(\hat{p}_{t,0}>1/2)} + \\
&+ \left|\frac{\sigma_{t,1}^{2h}\sigma_0^{2h}((n_{0,0}+1)/t+\hat{p}_{t,0})^{2h}\hat{p}_{t,1}^{2h} - \sigma_1^{2h}\sigma_{t,0}^{2h}((n_{0,1}+1)/t+\hat{p}_{t,1})^{2h}\hat{p}_{t,0}^{2h}}{\sigma_{t,0}^{2h}\sigma_0^{2h}((n_{0,1}+1)/t+\hat{p}_{t,1})^{2h}\hat{p}_{t,1}^{2h}}\right| 1_{(\hat{p}_{t,1}\geq 1/2)}.
\end{aligned}$$

Thus,

$$\begin{aligned}
\mid F_t - \tilde{F}_t \mid \leq \sigma_{t,1}^{-2h}\sigma_1^{-2h}2^{4h} \mid &\sigma_{t,0}^{2h}\sigma_1^{2h}((n_{0,1}+1)/t+\hat{p}_{t,1})^{2h}\hat{p}_{t,0}^{2h} - \\
&- \sigma_0^{2h}\sigma_{t,1}^{2h}((n_{0,0}+1)/t+\hat{p}_{t,0})^{2h}\hat{p}_{t,1}^{2h} \mid 1_{(\hat{p}_{t,0}>1/2)} + \\
+ \sigma_{t,0}^{-2h}\sigma_0^{-2h}2^{4h} \mid &\sigma_{t,1}^{2h}\sigma_0^{2h}((n_{0,0}+1)/t+\hat{p}_{t,0})^{2h}\hat{p}_{t,1}^{2h} - \\
&- \sigma_1^{2h}\sigma_{t,0}^{2h}((n_{0,1}+1)/t+\hat{p}_{t,1})^{2h}\hat{p}_{t,0}^{2h} \mid 1_{(\hat{p}_{t,1}\geq 1/2)}
\end{aligned}$$

By (c), for every $a = 0, 1$,

$$\left(\hat{p}_{t,a} + \frac{n_{0,a}+1}{t}\right)^{2h} - \hat{p}_{t,a}^{2h} \to 0$$

Now, if $\omega \in (A_t = 0 \ i.o.) \cap (A_t = 1 \ i.o)$, then $\sigma_{t,0}^2 \to \sigma_0^2$ and $\sigma_{t,1}^2 \to \sigma_1^2$ as $t \to \infty$. By (b), $F_t - \tilde{F}_t \to 0$.
On the other hand, if $\omega \in (A_t = 0 \ ultimately)$, then for t large enugh, $\sigma_{t,1} \to \sigma_1$, $\sigma_{t,0} \to \sigma_{T,0}$ for a finite stopping time T, $\hat{p}_{t,1} \to 0$ and $\hat{p}_{t,0} \to 1$.
Thus, $1_{(\hat{p}_{t,1}\geq 1/2)} \to 0$. Therefore, $F_t - \tilde{F}_t \to 0$. Analogously, if $\omega \in (A_t = 1 \ ultimately)$, then

$F_t - \tilde{F}_t \to 0$.

Now, let c be such that $\tilde{F}_t < -2c$ if $\hat{p}_{t,1} > \rho_1 + \epsilon$ and $\tilde{F}_t > 2c$ if $\hat{p}_{t,1} < \rho_1 - \epsilon$. Since $F_t - \tilde{F}_t \to 0$, there exists a random time T such that $\mid F_t - \tilde{F}_t \mid < c$ for all $t \geq T$. For every $t \geq T$, $F_t < -c$ if $\hat{p}_{t,1} > \rho_1 + \epsilon$ and $F_t > c$ if $\hat{p}_{t,1} < \rho_1 - \epsilon$. Based on basics of stochastic approximation (Lemma A.1 in the Appendix), it follows that $\hat{p}_{t,1} \to \rho_1$ almost surely.

Additionally, by definition of $p_{t,1}$, we have

$$p_{t,1} = \frac{1}{1 + \left(\frac{n_{0,1} + t\hat{p}_{t,1} + 1}{n_{0,0} + t(1 - \hat{p}_{t,1}) + 1}\right)^{2h} \frac{\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}}}. \tag{1.10}$$

Hence, applying continuous mapping theorem (Theorem 2.3 of [85]), we have

$$p_{t,1} \underset{t \to \infty}{\longrightarrow} \rho_1 \text{ a.s. } .$$

□

The extension of the result presented in Proposition 1 to multi-arm BUDs is formalized in Corollary 1.

Corollary 1. *Under the same assumptions of Proposition 1, if $K > 2$, then, as $t \to \infty$, the allocation of patients to treatments $(\widehat{p}_{t,0}, \ldots, \widehat{p}_{t,K-1})$ and the randomization probabilities $(p_{t,0}, \ldots, p_{t,K-1})$ converge a.s. to $(\rho_0, \ldots, \rho_{K-1})$, where*

$$\rho_a = \frac{\sigma_a^{\frac{2h}{2h+1}}}{\sum_{i=0}^{K-1} \sigma_i^{\frac{2h}{2h+1}}} \qquad \text{for } a \in \{0, \ldots, K-1\}. \tag{1.11}$$

Proof. (Corollary 1) First, we show that $A_t = a$ infinitely often for any $a = 0, \ldots, K-1$, that is for an infinite number of indices the assignment of patients to arm a holds true.

There exists a partition $\{\mathcal{B}_i\}_{i=0}^{K-1}$ of the sample space Ω such that in $\mathcal{B}_i$ arm i is visited i.o. Consider $i \in \{0, \ldots, K-1\}$, $j \in \{0, \ldots, K-1\} - \{i\}$ and reason iteratively as follows. Choose $\omega \in \mathcal{B}_j$. Then, define the sequences $T_{i_j}(\omega)$ of times where arm i or arm j is chosen in the multi-arm BUD. Given the sequence of BUD assignments of patients to arm i or j, the probability of

assigning a patient at time $T_{i_j}(\omega)$ to arm i is given by

$$p_{T_{i_j},i}(\omega) := P(A_{T_{i_j}(\omega)} = i \mid \{T_{i_j}\})(\omega)$$

that equals

$$p_{T_{i_j},i}(\omega) = \frac{\left(\frac{\sigma^2_{T_{i_j},i}}{(t_0+T_{i_j}\hat{p}_{T_{i_j},i}+1)^2}\right)^h}{\left(\frac{\sigma^2_{T_{i_j},i}}{(t_0+T_{i_j}\hat{p}_{T_{i_j},i}+1)^2}\right)^h + \left(\frac{\sigma^2_{T_{i_j},j}}{(t_0+T_{i_j}\hat{p}_{T_{i_j},j}+1)^2}\right)^h}.$$

Now we reason by contradiction: if arm i is visited a finite number of times, then $\widehat{p}_{T_{i_j},i}$ would converge to zero. But this implies that $p_{T_{i_j},i}(\omega)$ would converge to one and, indeed,

$$P(A_{T_{i_j}} = i \quad i.o. \mid \{T_{i_j}\})(\omega) \geq \limsup P(A_{T_{i_j}} = i \mid \{T_{i_j}\}) = 1.$$

This contradicts the assumption that arm i is visited a finite number of times.
As a consequence, arm i is visited i.o. $\forall \omega \in \mathcal{B}_j$.
Since this holds true for $\forall j \in \{0, \ldots, K-1\} - \{i\}$, we conclude that arm i is visited i.o. for $\forall \omega \in \Omega$. Since this holds true for $i \in \{0, \ldots, K-1\}$, we conclude that each arm is visited i.o. in all the sample space.
Therefore, for any pair of arms (a_1, a_2), we can consider the sequence $(T_k)_k$ of times for which the assignment of a patient falls on arm a_1 or arm a_2. The related subsequence of samples assigned to these two arms is equivalent to a two arm BUD.
Proposition 1 implies that almost surely

$$\frac{\widehat{p}_{T_k,a_1}}{\widehat{p}_{T_k,a_1} + \widehat{p}_{T_k,a_2}} \underset{k\to\infty}{\longrightarrow} \rho_{a_1,a_2} := \frac{\sigma_{a_1}^{\frac{2h}{2h+1}}}{\sigma_{a_1}^{\frac{2h}{2h+1}} + \sigma_{a_2}^{\frac{2h}{2h+1}}}$$

and, indeed, the general sequence $\dfrac{\widehat{p}_{t,a_1}}{\widehat{p}_{t,a_1} + \widehat{p}_{t,a_2}}$ converges to the same limit. Then, the allocation proportions $(\widehat{p}_{t,0}, \ldots, \widehat{p}_{t,K-1})$ converge to a limit $(\rho_0, \ldots, \rho_{K-1})$, which is the unique solution to

$$\sum_{a=0}^{K-1} \rho_a = 1 \quad \text{and} \quad \rho_{a_1} = \rho_{a_1,a_2}(\rho_{a_1} + \rho_{a_2}) \quad \text{for all } \{a_1, a_2\} \subset \{0, \ldots, K-1\}.$$

The solution of the above linear system is given by

$$\rho_a = \frac{\sigma_a^{\frac{2h}{2h+1}}}{\sum_{i=0}^{K-1} \sigma_i^{\frac{2h}{2h+1}}} \quad \text{for } a \in \{0, \ldots, K-1\} \tag{1.12}$$

Analogously, (1.12) defines the limit $(\rho_0, \ldots, \rho_{K-1})$ of the randomization probabilities of the BUD in the multi-arm setup. □

Notice that the asymptotic allocation of BUDs, is the target of well-known powered Neyman allocation, which reduces to standard Neyman allocation when $h \to \infty$. This allocation minimizes the sample size when power is fixed [6, 56]. Observe also that the limit of allocation proportions in BUDs is the same as the limit of randomization probabilities. This is a characteristic that is common to other adaptive designs. For instance, the asymptotic equivalence between allocation proportions and randomization probabilities of procedures based on generalized Polya urn models has been proven in [4, 5].

Before we state the main results for the rate of convergence and asymptotic distributions of the randomization probabilities and allocation proportions in BUDs, we recall that the NEFs with quadratic variance function consist of all NEFs such that the variance is a polynomial function of order 2 or lower of the mean , i.e.

$$\sigma_a^2 = v_0 + v_1\theta_a + v_2\theta_a^2$$

for some constants v_0, v_1, v_2. This class contains popular statistical models, such as the normal, Poisson, gamma, negative binomial and binomial distributions. We refer to Morris [57, 58] for a detailed study of this class of distributions.

1.3.2 Asymptotic normality of randomization probabilities and allocation proportions

Here, we prove asymptotic normality of the randomization probabilities $p_{t,a}$ and of the allocation proportions $\widehat{p}_{t,a}$ in two-arm BUDs characterized by the utility criteria $u(\Sigma_t) = -\sum_{a=0}^{1} \mathrm{Var}(\theta_a|\Sigma_t)$ when the statistical model f_{θ_a} is a NEF with quadratic variance.

First, for $a = 0, 1$, we define

$$\begin{aligned}\Delta\sigma^2_{t,a} &= \mathrm{Var}(Y_{t+2} \mid A_{t+2} = a, \Sigma_{t+1}) - \mathrm{Var}(Y_{t+1} \mid A_{t+1} = a, \Sigma_t),\\ v(\tilde{y}_{t,a}) &= \left(v_0 + v_1\tilde{y}_{t,a} + v_2\tilde{y}^2_{t,a}\right)^{\frac{1}{2}},\\ W_t &= [p_{t,1}, \tilde{y}_{t,1}, \tilde{y}_{t,0}]'\end{aligned}$$

and

$$k_a(W_t) = \left[1 + \left(\frac{p_{t,a}}{p_{t,1-a}}\right)^{\frac{1}{2h}} \frac{v(\tilde{y}_{t,1-a})}{v(\tilde{y}_{t,a})}\right],$$

where $p_{t,0}$ can be written as $1 - p_{t,1}$.
We also write $X(t) = \mathcal{O}_P(t^{-\alpha})$, where $\alpha > 0$, to intend that $\forall\, \epsilon > 0 \;\; \exists\, T, M > 0$ finite such that $P(|X(t)| > Mt^{-\alpha}) < \epsilon \,\forall t > T$.

Lemma 1 approximates, for $a \in \{0, 1\}$ the variables $\sigma_{t,a}$ and $\tilde{y}_{t+1,a}$ with functions of $(\tilde{y}_{t,a},\, p_{t,1})$ and (Y_{t+1}, A_{t+1}).

Lemma 1. *If the outcome distributions $f_{\psi_a}, a = 0, 1$ of a two-arm BUD belong to the NEF with quadratic variance function, then*

(i) $\sigma_{t,a} = v(\tilde{y}_{t,a}) + \mathcal{O}_P(t^{-1})$

(ii) $\tilde{y}_{t+1,a} = \tilde{y}_{t,a} + (Y_{t+1} - \tilde{y}_{t,a})\dfrac{1(A_{t+1} = a)}{t} k_a(W_t) + \mathcal{O}_P(t^{-2})$

(iii) $\Delta\sigma^2_{t,a} = (v_1 + 2v_2\tilde{y}_{t,a})(Y_{t+1} - \tilde{y}_{t,a})\dfrac{1(A_{t+1} = a)}{t} k_a(W_t) + \mathcal{O}_P(t^{-2})$.

Proof. (Lemma 1) We make use of the following properties of $\mathcal{O}_P(\cdot)$

$$\begin{aligned}\mathcal{O}_P(a(t))\mathcal{O}_P(b(t)) &= \mathcal{O}_P(a(t)b(t))\\ \mathcal{O}_P(a(t)) + \mathcal{O}_P(a(t)) &= \mathcal{O}_P(a(t)),\end{aligned} \tag{1.13}$$

for any sets of constants $a(t), b(t)$ indexed by t.
Moreover, we invoke the following properties that are peculiar characteristics of the members of

the NEF class of distributions (see [29])

$$\begin{aligned} E_{\psi_a}(Y_i) &= b'(\psi_a) \\ \mathrm{Var}_{\psi_a}(Y_i) &= b''(\psi_a) \\ E(b'(\psi_a) \mid \Sigma_t) &= \tilde{y}_{t,a} \end{aligned} \tag{1.14}$$

for $i \in \mathbb{N}, a \in \{0,1\}$.
From the law of total variance and the characterization of the distributions in the NEF with quadratic variance function, we have

$$\begin{aligned} \sigma^2_{t,a} &= E(\mathrm{Var}_{\psi_a}(Y_{t+1}) \mid \Sigma_t) + \mathrm{Var}(E_{\psi_a}(Y_{t+1}) \mid \Sigma_t) \\ &= E(v_0 + v_1 b'(\psi_a) + v_2 b'(\psi_a)^2 \mid \Sigma_t) + \mathrm{Var}(b'(\psi_a) \mid \Sigma_t) \\ &= v_0 + v_1 \tilde{y}_{t,a} + (v_2+1) E(b'(\psi_a)^2 \mid \Sigma_t) - E(b'(\psi_a) \mid \Sigma_t)^2 \\ &= v_0 + v_1 \tilde{y}_{t,a} + (v_2+1)(E(b'(\psi_a)^2 \mid \Sigma_t) - E(b'(\psi_a) \mid \Sigma_t)^2) + v_2 \tilde{y}^2_{t,a} \end{aligned} \tag{1.15}$$

for $a \in \{0,1\}$.
Now, from Theorem 5.3 of Morris [58], it holds that

$$E(b'(\psi_a)^2 \mid \Sigma_t) - E(b'(\psi_a) \mid \Sigma_t)^2 = \frac{1}{n_{0,a} + t\hat{p}_{t,a} - v_2}(v_0 + v_1 \tilde{y}_{t,a} + v_2 \tilde{y}^2_{t,a}) \tag{1.16}$$

and (1.15) becomes

$$\sigma^2_{t,a} = v_0 + v_1 \tilde{y}_{t,a} + v_2 \tilde{y}^2_{t,a} + \mathcal{O}_P(t^{-1}). \tag{1.17}$$

Equation (1.17) is a consequence of the convergence of $\hat{p}_{t,a}$ and of the properties (1.13).
By taking the square root of (1.17), (i) follows. Also, by inverting (1.10), we obtain

$$\begin{aligned} \hat{p}_{t,1} &= \frac{1}{1 + \left(\frac{p_{t,1}}{1-p_{t,1}}\right)^{\frac{1}{2h}} \frac{\sigma_{t,0}}{\sigma_{t,1}}} + \frac{1}{t} \frac{(n_{0,0}+1)\left(\frac{1-p_{t,1}}{p_{t,1}}\right)^{\frac{1}{2h}} \frac{\sigma_{t,1}}{\sigma_{t,0}} - (n_{0,1}+1)}{1 + \left(\frac{1-p_{t,1}}{p_{t,1}}\right)^{\frac{1}{2h}} \frac{\sigma_{t,1}}{\sigma_{t,0}}} \\ &= \frac{1}{1 + \left(\frac{p_{t,1}}{1-p_{t,1}}\right)^{\frac{1}{2h}} \frac{\sigma_{t,0}}{\sigma_{t,1}}} + \mathcal{O}_P(t^{-1}). \end{aligned} \tag{1.18}$$

Therefore,

$$\hat{p}_{t,1}^{-1} = 1 + \left(\frac{p_{t,1}}{1-p_{t,1}}\right)^{\frac{1}{2h}} \frac{\sigma_{t,0}}{\sigma_{t,1}} + \mathcal{O}_P(t^{-1}). \tag{1.19}$$

We have

$$\begin{aligned}
\tilde{y}_{t+1,1} &= A_{t+1}\left(\tilde{y}_{t,1} + \frac{Y_{t+1} - \tilde{y}_{t,1}}{t\hat{p}_{t,1} + 1}\right) + (1 - A_{t+1})\tilde{y}_{t,1} \\
&= \tilde{y}_{t,1} + A_{t+1}\frac{Y_{t+1} - \tilde{y}_{t,1}}{t\hat{p}_{t,1}} + \mathcal{O}_P(t^{-2}) && (1.20) \\
&= \tilde{y}_{t,1} + A_{t+1}\frac{(Y_{t+1} - \tilde{y}_{t,1})}{t}\left[1 + \left(\frac{p_{t,1}}{1-p_{t,1}}\right)^{\frac{1}{2h}} \frac{\sigma_{t,0}}{\sigma_{t,1}}\right] + \mathcal{O}_P(t^{-2}) && (1.21) \\
&= \tilde{y}_{t,1} + A_{t+1}\frac{(Y_{t+1} - \tilde{y}_{t,1})}{t}\left[1 + \left(\frac{p_{t,1}}{1-p_{t,1}}\right)^{\frac{1}{2h}} \frac{v(\tilde{y}_{t,0})}{v(\tilde{y}_{t,1})}\right] + \mathcal{O}_P(t^{-2}). && (1.22)
\end{aligned}$$

Equation (1.21) is obtained by plugging (1.19) into (1.20); instead, equation (1.22) is a consequence of (i).
So, the generalization of equation (1.22) to arm $a \in \{0, 1\}$ is given by

$$y_{t+1,a} = \tilde{y}_{t,a} + 1(A_{t+1} = a)\frac{(Y_{t+1} - \tilde{y}_{t,a})}{t}\left[1 + \left(\frac{p_{t,a}}{p_{t,1-a}}\right)^{\frac{1}{2h}} \frac{v(\tilde{y}_{t,1-a})}{v(\tilde{y}_{t,a})}\right] + \mathcal{O}_P(t^{-2}) \tag{1.23}$$

and this proves (ii).
Finally, by using (ii), we get

$$\begin{aligned}
\Delta\sigma_{t,1}^2 &= v_0 + v_1\tilde{y}_{t+1,1} + v_2\tilde{y}_{t+1,1}^2 - (v_0 + v_1\tilde{y}_{t,1} + v_2\tilde{y}_{t,1}^2) \\
&= (v_1 + 2v_2\tilde{y}_{t,1})A_{t+1}\frac{(Y_{t+1} - \tilde{y}_{t,1})}{t}\left[1 + \left(\frac{p_{t,1}}{1-p_{t,1}}\right)^{\frac{1}{2h}} \frac{v(\tilde{y}_{t,0})}{v(\tilde{y}_{t,1})}\right] + \mathcal{O}_P(t^{-2}) && (1.24)
\end{aligned}$$

and, analogously,

$$\Delta\sigma_{t,0}^2 = (v_1 + 2v_2\tilde{y}_{t,0})(1 - A_{t+1})\frac{(Y_{t+1} - \tilde{y}_{t,0})}{t}\left[1 + \left(\frac{1-p_{t,1}}{p_{t,1}}\right)^{\frac{1}{2h}} \frac{v(\tilde{y}_{t,1})}{v(\tilde{y}_{t,0})}\right] + \mathcal{O}_P(t^{-2}). \tag{1.25}$$

This completes the proof of (iii).

□

The next lemma is similar in spirit to the previous result and illustrates that $p_{t+1,1}$ can be ap-

proximated by a function of W_t, Y_{t+1}, A_{t+1} with an $\mathcal{O}_P(t^{-2})$ error term.

Lemma 2. *Let the outcome distributions $f_{\psi_a}, a = 0, 1$ of a two-arm BUD belong to the NEF with quadratic variance function. For the sequence of randomization probability $p_{t,1}, t \geq 1$ it holds that*

$$p_{t+1,1} = p_{t,1} + hp_{t,1}(1-p_{t,1})\Bigg\{ \left[\frac{(v_1 + 2v_2\tilde{y}_{t,1})(Y_{t+1} - \tilde{y}_{t,1})}{v(\tilde{y}_{t,1})^2} - 2\right] \frac{A_{t+1}}{t} k_1(W_t) + \left[2 - \frac{(v_1 + 2v_2\tilde{y}_{t,0})(Y_{t+1} - \tilde{y}_{t,0})}{v(\tilde{y}_{t,0})^2}\right] \frac{(1-A_{t+1})}{t} k_0(W_t) \Bigg\} + \mathcal{O}_P(t^{-2}). \tag{1.26}$$

Proof. (Lemma 2) Throughout this proof, we consider a first-order approximation of $p_{t+1} - p_t$. First, by definition of the randomization probabilities of the BUD in terms of the information increments, we have

$$\begin{aligned} p_{t+1,1} - p_{t,1} &= \frac{\left[\frac{\sigma^2_{t+1,1}}{(n_{0,1} + (t+1)\hat{p}_{t+1,1} + 1)^2}\right]^h}{\left[\frac{\sigma^2_{t+1,0}}{(n_{0,0} + (t+1)\hat{p}_{t+1,0} + 1)^2}\right]^h + \left[\frac{\sigma^2_{t+1,1}}{(n_{0,1} + (t+1)\hat{p}_{t+1,1} + 1)^2}\right]^h} - \\ &\quad - \frac{\left[\frac{\sigma^2_{t,1}}{(n_{0,0} + t\hat{p}_{t,0} + 1)^2}\right]^h}{\left[\frac{\sigma^2_{t,0}}{(n_{0,0} + t\hat{p}_{t,0} + 1)^2}\right]^h + \left[\frac{\sigma^2_{t,1}}{(n_{0,1} + t\hat{p}_{t,1} + 1)^2}\right]^h} \\ &= \frac{1}{1 + \frac{\sigma^{2h}_{t+1,0}}{\sigma^{2h}_{t+1,1}} \left(\frac{n_{0,1} + 1 + t\hat{p}_{t,1} + A_{t+1}}{n_{0,0} + 1 + t(1-\hat{p}_{t,1}) + 1 - A_{t+1}}\right)^{2h}} - \\ &\quad - \frac{1}{1 + \frac{\sigma^{2h}_{t,0}}{\sigma^{2h}_{t,1}} \left(\frac{n_{0,1} + 1 + t\hat{p}_{t,1}}{n_{0,0} + 1 + t(1-\hat{p}_{t,1})}\right)^{2h}} \end{aligned} \tag{1.27}$$

$$= \left\{ \frac{\frac{\sigma^{2h}_{t,0}}{\sigma^{2h}_{t,1}} \left(\frac{n_{0,1} + 1 + t\hat{p}_{t,1}}{n_{0,0} + 1 + t(1-\hat{p}_{t,1})}\right)^{2h}}{1 + \frac{\sigma^{2h}_{t,0}}{\sigma^{2h}_{t,1}} \left(\frac{n_{0,1} + 1 + t\hat{p}_{t,1}}{n_{0,0} + 1 + t(1-\hat{p}_{t,1})}\right)^{2h}} - \right. \tag{1.28}$$

$$
\left.
-\frac{\frac{\sigma_{t+1,0}^{2h}}{\sigma_{t+1,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}+A_{t+1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})+1-A_{t+1}}\right)^{2h}}{1+\frac{\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})}\right)^{2h}}
\right\}\times
$$

$$
\times\left[1+\frac{\sigma_{t+1,0}^{2h}}{\sigma_{t+1,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}+A_{t+1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})+1-A_{t+1}}\right)^{2h}\right]^{-1} \tag{1.29}
$$

$$
=\left\{\frac{\frac{\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})}\right)^{2h}}{\left[1+\frac{\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})}\right)^{2h}\right]^2}-\right.
$$

$$
\left.-\frac{\frac{\sigma_{t+1,0}^{2h}}{\sigma_{t+1,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}+A_{t+1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})+1-A_{t+1}}\right)^{2h}}{\left[1+\frac{\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})}\right)^{2h}\right]^2}\right\}\left(1+\mathcal{O}_P(t^{-1})\right). \tag{1.30}
$$

To obtain (1.30) we have noticed that the two factors of the denominator in the right-hand-side of (1.29) share the same asymptotic behavior. Thus, we have isolated the principal part of the denominator in (1.29) and we have identified a remainder term which appears as $\mathcal{O}_P(t^{-1})$ since, due to Proposition 1, $\hat{p}_{t,1}$ converges almost surely to a limit which is different from 0 and 1 and $\sigma_{t,a}^2$ converges to a finite limit different from 0 almost surely for $a \in \{0,1\}$.

Now, we split the right-hand-side of (1.30) into two parts, referring to the possible assignements of treatment $(t+1)$ and using the fact that A_{t+1} takes value 1 when treatment $(t+1)$ is assigned to arm 1 and 0 otherwise. So, when the response Y_{t+1} comes from arm 1, $\sigma_{t+1,0}^2 = \sigma_{t,0}^2$ and, instead, when the $(t+1)^{th}$ treatment is assigned to arm 0, $\sigma_{t+1,1}^2 = \sigma_{t,1}^2$.

We get

$$
p_{t+1,1}-p_{t,1}=\left\{A_{t+1}\frac{\left[\frac{\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})}\right)^{2h}-\frac{\sigma_{t,0}^{2h}}{\sigma_{t+1,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}+A_{t+1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})}\right)^{2h}\right]}{\left[1+\frac{\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})}\right)^{2h}\right]^2}+\right. \tag{1.31}
$$

$$+(1-A_{t+1})\frac{\left[\frac{\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})}\right)^{2h}-\frac{\sigma_{t+1,0}^{2h}}{\sigma_{t,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})+1-A_{t+1}}\right)^{2h}\right]}{\left[1+\frac{\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})}\right)^{2h}\right]^2}\Bigg\}\times$$

$$\times\left(1+\mathcal{O}_P(t^{-1})\right). \tag{1.32}$$

Next, we invoke the following result, stated as a separate Lemma, whose proof is given in the Appendix at the end of this Chapter.

Lemma A.1. *Under the assumptions of Lemma 2, we have*

$$A_{t+1}\left[\frac{\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})}\right)^{2h}-\frac{\sigma_{t,0}^{2h}}{\sigma_{t+1,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}+A_{t+1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})}\right)^{2h}\right]$$
$$=A_{t+1}h\frac{\sigma_{t,0}^{2h}\hat{p}_{t,1}^{2h}}{\sigma_{t,1}^{2h}(1-\hat{p}_{t,1})^{2h}}\left[\frac{\Delta\sigma_{t,1}^2}{\sigma_{t,1}^2}-\frac{2}{t\hat{p}_{t,1}}\right]+\mathcal{O}_P(t^{-2}) \tag{1.33}$$

and

$$(1-A_{t+1})\left[\frac{\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})}\right)^{2h}-\frac{\sigma_{t+1,0}^{2h}}{\sigma_{t,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})+1-A_{t+1}}\right)^{2h}\right]$$
$$=(1-A_{t+1})\frac{\hat{p}_{t,1}^{2h}\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}(1-\hat{p}_{t,1})^{2h}}h\left[-\frac{\Delta\sigma_{t,0}^2}{\sigma_{t,0}^2}+\frac{2}{t(1-\hat{p}_{t,1})}\right]+\mathcal{O}_P(t^{-2}). \tag{1.34}$$

Thus, we replace the numerators of the two addenda in (1.32) with the right-hand-side of equations (1.33) and (1.34) and we write

$$p_{t+1,1}-p_{t,1}=\frac{h\frac{\hat{p}_{t,1}^{2h}\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}(1-\hat{p}_{t,1})^{2h}}}{\left[1+\frac{\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})}\right)^{2h}\right]^2}\left[A_{t+1}\left(\frac{\Delta\sigma_{t,1}^2}{\sigma_{t,1}^2}-\frac{2}{t\hat{p}_{t,1}}\right)+\right.$$
$$\left.+(1-A_{t+1})\left(-\frac{\Delta\sigma_{t,0}^2}{\sigma_{t,0}^2}+\frac{2}{t(1-\hat{p}_{t,1})}\right)+\mathcal{O}_P(t^{-2})\right]\left(1+\mathcal{O}_P(t^{-1})\right). \tag{1.35}$$

Retaining the dominant part of the denominator in equation (1.35), it follows that

$$p_{t+1,1} - p_{t,1} = \frac{h\frac{\hat{p}_{t,1}^{2h}\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}(1-\hat{p}_{t,1})^{2h}}}{\left(1+\frac{\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}}\left(\frac{\hat{p}_{t,1}}{1-\hat{p}_{t,1}}\right)^{2h}\right)^2}\left[A_{t+1}\left(\frac{\Delta\sigma_{t,1}^2}{\sigma_{t,1}^2}-\frac{2}{t\hat{p}_{t,1}}\right)+\right.$$

$$\left.+(1-A_{t+1})\left(-\frac{\Delta\sigma_{t,0}^2}{\sigma_{t,0}^2}+\frac{2}{t(1-\hat{p}_{t,1})}\right)+\mathcal{O}_P(t^{-2})\right]\left(1+\mathcal{O}_P(t^{-1})\right). \tag{1.36}$$

Furthermore, noting that

$$\left(\frac{1-p_{t,1}}{p_{t,1}}\right)^{\frac{1}{2h}}\frac{\sigma_{t,1}}{\sigma_{t,0}} = \frac{n_{0,1}+1+t\hat{p}_{t,1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})}, \tag{1.37}$$

it holds that

$$\begin{aligned}\left(\frac{1-p_{t,1}}{p_{t,1}}\right)^{\frac{1}{2h}}\frac{\sigma_{t,1}}{\sigma_{t,0}} &= \frac{\hat{p}_{t,1}}{1-\hat{p}_{t,1}}+\frac{n_{0,1}+1}{n_{0,0}+1+t(1-\hat{p}_{t,1})}-\frac{\hat{p}_{t,1}(n_{0,0}+1)}{(t(1-\hat{p}_{t,1})+n_{0,0}+1)(1-\hat{p}_{t,1})}\\ &= \frac{\hat{p}_{t,1}}{1-\hat{p}_{t,1}}+\mathcal{O}_P(t^{-1})\end{aligned} \tag{1.38}$$

and

$$\begin{aligned}\left(\frac{\hat{p}_{t,1}}{1-\hat{p}_{t,1}}\right)^{2h} &= \left[\left(\frac{1-p_{t,1}}{p_{t,1}}\right)^{\frac{1}{2h}}\frac{\sigma_{t,1}}{\sigma_{t,0}}+\mathcal{O}_P(t^{-1})\right]^{2h}\\ &= \frac{1-p_{t,1}}{p_{t,1}}\frac{\sigma_{t,1}^{2h}}{\sigma_{t,0}^{2h}}+\mathcal{O}_P(t^{-1}).\end{aligned} \tag{1.39}$$

Plugging (1.39) and (1.18) into (1.36) yield to

$$\begin{aligned}p_{t+1,1}-p_{t,1} = \left(hp_{t,1}(1-p_{t,1})+\mathcal{O}_P(t^{-1})\right)&\left\{A_{t+1}\left[\frac{\Delta\sigma_{t,1}^2}{\sigma_{t,1}^2}-\frac{2}{t}\left(\left(\frac{p_{t,1}}{1-p_{t,1}}\right)^{\frac{1}{2h}}\frac{\sigma_{t,0}}{\sigma_{t,1}}+1\right)\right]\right.\\ &\left.+(1-A_{t+1})\left[-\frac{\Delta\sigma_{t,0}^2}{\sigma_{t,0}^2}+\frac{2}{t}\left(\left(\frac{1-p_{t,1}}{p_{t,1}}\right)^{\frac{1}{2h}}\frac{\sigma_{t,1}}{\sigma_{t,0}}+1\right)\right]+\mathcal{O}_P(t^{-2})\right\}\left(1+\mathcal{O}_P(t^{-1})\right).\end{aligned} \tag{1.40}$$

In order to derive equation (1.40) we have used the following equations

$$\frac{h\dfrac{\hat{p}_{t,1}^{2h}\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}(1-\hat{p}_{t,1})^{2h}}}{\left(1+\dfrac{\hat{p}_{t,1}^{2h}\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}(1-\hat{p}_{t,1})^{2h}}\right)^2} = hp_{t,1}(1-p_{t,1}) + \mathcal{O}_P(t^{-1}),$$

$$\hat{p}_{t,1}^{-1} = 1 + \left(\frac{p_{t,1}}{1-p_{t,1}}\right)^{\frac{1}{2h}} \frac{\sigma_{t,0}}{\sigma_{t,1}} + \mathcal{O}_P(t^{-1}) \tag{1.41}$$

and

$$(1-\hat{p}_{t,1})^{-1} = 1 + \left(\frac{1-p_{t,1}}{p_{t,1}}\right)^{\frac{1}{2h}} \frac{\sigma_{t,1}}{\sigma_{t,0}} + \mathcal{O}_P(t^{-1}).$$

Indeed, by properties (1.13), (1.40) becomes

$$\begin{aligned}
p_{t+1,1} - p_{t,1} &= hp_{t,1}(1-p_{t,1})\left\{A_{t+1}\left[\frac{\Delta\sigma_{t,1}^2}{\sigma_{t,1}^2} - \frac{2}{t}\left(\left(\frac{p_{t,1}}{1-p_{t,1}}\right)^{\frac{1}{2h}}\frac{\sigma_{t,0}}{\sigma_{t,1}} + 1\right)\right]\right. \\
&\left. +(1-A_{t+1})\left[-\frac{\Delta\sigma_{t,0}^2}{\sigma_{t,0}^2} + \frac{2}{t}\left(\left(\frac{1-p_{t,1}}{p_{t,1}}\right)^{\frac{1}{2h}}\frac{\sigma_{t,1}}{\sigma_{t,0}} + 1\right)\right]\right\} + \mathcal{O}_P(t^{-2}) \\
&= hp_{t,1}(1-p_{t,1})\left\{\left[\frac{\Delta\sigma_{t,1}^2}{\sigma_{t,1}^2} - \frac{2A_{t+1}}{t}\left(\left(\frac{p_{t,1}}{1-p_{t,1}}\right)^{\frac{1}{2h}}\frac{\sigma_{t,0}}{\sigma_{t,1}} + 1\right)\right]\right. \\
&\left. + \left[\frac{2(1-A_{t+1})}{t}\left(\left(\frac{1-p_{t,1}}{p_{t,1}}\right)^{\frac{1}{2h}}\frac{\sigma_{t,1}}{\sigma_{t,0}} + 1\right) - \frac{\Delta\sigma_{t,0}^2}{\sigma_{t,0}^2}\right]\right\} + \mathcal{O}_P(t^{-2}) \qquad (1.42) \\
&= hp_{t,1}(1-p_{t,1})\left\{\left[\frac{\Delta\sigma_{t,1}^2}{\sigma_{t,1}^2} - \frac{2A_{t+1}}{t}\left(\left(\frac{p_{t,1}}{1-p_{t,1}}\right)^{\frac{1}{2h}}\frac{v(\tilde{y}_{t,0})}{v(\tilde{y}_{t,1})} + 1\right)\right]\right. \\
&\left. + \left[\frac{2(1-A_{t+1})}{t}\left(\left(\frac{1-p_{t,1}}{p_{t,1}}\right)^{\frac{1}{2h}}\frac{v(\tilde{y}_{t,1})}{v(\tilde{y}_{t,0})} + 1\right) - \frac{\Delta\sigma_{t,0}^2}{\sigma_{t,0}^2}\right]\right\} + \mathcal{O}_P(t^{-2}), \qquad (1.43)
\end{aligned}$$

where (1.42) follows from $A_{t+1}\Delta\sigma_{t,1}^2 = \Delta\sigma_{t,1}^2$ and $(1-A_{t+1})\Delta\sigma_{t,0}^2 = \Delta\sigma_{t,0}^2$ and (1.43) is a consequence of (i) of Lemma 1.

Finally, the statement of Lemma 2 is obtained by plugging the expression for $\sigma_{t,1}^2, \Delta\sigma_{t,1}^2, \sigma_{t,0}^2$ and $\Delta\sigma_{t,0}^2$ given in Lemma 1 into (1.43) and by invoking properties (1.13).

□

Lemmas 1 and 2 suggest how to approximate $\tilde{y}_{t+1,a} - \tilde{y}_{t,a}$ for $a \in \{0,1\}$ and $p_{t+1,1} - p_{t,1}$.

Therefore, we are able to determine the random vector $\tilde{G}_{t+1} = [G_{t+1}, G_{t+1,1}, G_{t+1,0}]'$, whose components are approximations of $t(p_{t+1,1} - p_{t,1})$ and $t(\tilde{y}_{t+1,a} - \tilde{y}_{t,a})$, respectively.
Let

$$G_{t+1} := hp_{t,1}(1-p_{t,1})\Bigg\{\left[\frac{(v_1+2v_2\tilde{y}_{t,1})(Y_{t+1}-\tilde{y}_{t,1})}{v(\tilde{y}_{t,1})^2}-2\right]A_{t+1}k_1(W_t)+ \\ +\left[2-\frac{(v_1+2v_2\tilde{y}_{t,0})(Y_{t+1}-\tilde{y}_{t,0})}{v(\tilde{y}_{t,0})^2}\right](1-A_{t+1})k_0(W_t)\Bigg\},$$

and $G_{t+1,a} := 1(A_{t+1}=a)(Y_{t+1}-\tilde{y}_{t,a})k_a(W_t)$ for $a = 0, 1$.
By computing the conditional expectations $\tilde{g}(W_t) = -E_\psi(\tilde{G}_{t+1} \mid \Sigma_t)$, we define the map $\tilde{g}(\cdot) = [g(\cdot), g_1(\cdot), g_0(\cdot)]'$, whose components are

$$\begin{aligned} g(W_t) :=& -2h\frac{v(\tilde{y}_{t,1})}{v(\tilde{y}_{t,0})}\frac{(1-p_{t,1})^{\frac{2h+1}{2h}}}{p_{t,1}^{\frac{1-2h}{2h}}}k_1(W_t)^2\left(\frac{1}{k_1(W_t)}-p_{t,1}\right)- \\ &-\Bigg[p_{t,1}\frac{(v_1+2v_2\tilde{y}_{t,1})(b'(\psi_1)-\tilde{y}_{t,1})}{v(\tilde{y}_{t,1})^2}k_1(W_t)- \\ &-(1-p_{t,1})\frac{(v_1+2v_2\tilde{y}_{t,0})(b'(\psi_0)-\tilde{y}_{t,0})}{v(\tilde{y}_{t,0})^2}k_0(W_t)\Bigg]hp_{t,1}(1-p_{t,1}), \\ g_a(W_t) :=& -p_{t,a}(b'(\psi_a)-\tilde{y}_{t,a})k_a(W_t) \quad \text{for } a\in\{0,1\}. \end{aligned}$$

In Proposition 2 we rewrite $t(W_{t+1} - W_t)$ as the sum of (i) a function of W_t, (ii) a Σ_t-martingale-difference sequence $\Delta\tilde{M}_{t+1}$ and (iii) a Σ_{t+1}-measurable sequence of remainder terms. In particular, $\Delta\tilde{M}_{t+1} = [\Delta M_{t+1}, \Delta M_{t+1,1}, \Delta M_{t+1,0}]'$ is defined by $\tilde{G}_{t+1} + \tilde{g}(W_t)$.

Proposition 2. *Let the outcome distributions $f_{\psi_a}, a = 0, 1$, of a two-arm BUD belong to the NEF with quadratic variance function. Then, we have*

$$W_{t+1} = W_t - \frac{1}{t}\tilde{g}(W_t) + \frac{1}{t}(\Delta\tilde{M}_{t+1} + \tilde{r}_{t+1}), \tag{1.44}$$

where the reminder terms $\tilde{r}_{t+1} := [r_{t+1}, r_{t+1,1}, r_{t+1,0}]$ are three $\mathcal{O}_P(t^{-1})$ sequences.

Proof. (Proposition 2) In Lemma 2 we have simplified the expression for $p_{t+1,1} - p_{t,1}$, highlighting its principal part. Relying on this result, we verify that the updating rule for the randomization

probabilities of a BUD can be written as a stochastic approximation of the following form

$$\begin{aligned} p_{t+1,1} &= p_{t,1} + \frac{1}{t}(G_{t+1} + r_{t+1}) \\ &= p_{t,1} - \frac{1}{t} g(p_{t,1}, \tilde{y}_{t,1}, \tilde{y}_{t,0}) + \frac{1}{t}(\Delta M_{t+1} + r_{t+1}), \end{aligned} \tag{1.45}$$

for a specific process G_{t+1}, where $g(p_{t,1}, \tilde{y}_{t,1}, \tilde{y}_{t,0}) = -E_\psi\left(G_{t+1} \mid \Sigma_t\right)$, $r_{t+1} = \mathcal{O}_P(t^{-1})$ and ΔM_{t+1} is a Σ_t-martingale difference sequence.
In particular, Lemma 2 suggests us to define G_{t+1} as

$$\begin{aligned} G_{t+1} :=& h p_{t,1}(1-p_{t,1}) \left\{ \left[\frac{(v_1 + 2v_2\tilde{y}_{t,1})(Y_{t+1} - \tilde{y}_{t,1})}{v(\tilde{y}_{t,1})^2} - 2 \right] A_{t+1} \left[1 + \left(\frac{p_{t,1}}{1-p_{t,1}} \right)^{\frac{1}{2h}} \frac{v(\tilde{y}_{t,0})}{v(\tilde{y}_{t,1})} \right] \right. \\ &+ \left. \left[2 - \frac{(v_1 + 2v_2\tilde{y}_{t,0})(Y_{t+1} - \tilde{y}_{t,0})}{v(\tilde{y}_{t,0})^2} \right] (1 - A_{t+1}) \left[1 + \left(\frac{1-p_{t,1}}{p_{t,1}} \right)^{\frac{1}{2h}} \frac{v(\tilde{y}_{t,1})}{v(\tilde{y}_{t,0})} \right] \right\}. \end{aligned} \tag{1.46}$$

With this definition of G_{t+1}, the randomization probabilities of a BUD meet the above properties of the stochastic approximation (1.45).
Now, $g(p_{t,1}, \tilde{y}_{t,1}, \tilde{y}_{t,0}) = -E_\psi\left(G_{t+1} \mid \Sigma_t\right)$ implies that

$$\begin{aligned} g(p_{t,1}, \tilde{y}_{t,1}, \tilde{y}_{t,0}) =& -h p_{t,1}(1-p_{t,1}) \left\{ -2p_{t,1} \left[1 + \left(\frac{p_{t,1}}{1-p_{t,1}} \right)^{1/(2h)} \frac{v(\tilde{y}_{t,0})}{v(\tilde{y}_{t,1})} \right] + \right. \\ &\left. + 2(1-p_{t,1}) \left[1 + \left(\frac{1-p_{t,1}}{p_{t,1}} \right)^{1/(2h)} \frac{v(\tilde{y}_{t,1})}{v(\tilde{y}_{t,0})} \right] \right\} - \\ &- h p_{t,1}(1-p_{t,1}) \left\{ p_{t,1} \frac{(v_1 + 2v_2\tilde{y}_{t,1})(b'(\psi_1) - \tilde{y}_{t,1})}{v(\tilde{y}_{t,1})^2} \left[1 + \left(\frac{p_{t,1}}{1-p_{t,1}} \right)^{\frac{1}{2h}} \frac{v(\tilde{y}_{t,0})}{v(\tilde{y}_{t,1})} \right] - \right. \end{aligned} \tag{1.47}$$

$$\left. - (1-p_{t,1}) \frac{(v_1 + 2v_2\tilde{y}_{t,0})(b'(\psi_0) - \tilde{y}_{t,0})}{v(\tilde{y}_{t,0})^2} \left[1 + \left(\frac{1-p_{t,1}}{p_{t,1}} \right)^{\frac{1}{2h}} \frac{v(\tilde{y}_{t,1})}{v(\tilde{y}_{t,0})} \right] \right\}. \tag{1.48}$$

Rearranging the right-hand-side of (1.48), it follows that

$$\begin{aligned} g(p_{t,1}, \tilde{y}_{t,1}, \tilde{y}_{t,0}) =& -2h \frac{v(\tilde{y}_{t,1})}{v(\tilde{y}_{t,0})} (1-p_{t,1})^{\frac{2h+1}{2h}} p_{t,1}^{\frac{2h-1}{2h}} \left[1 + \left(\frac{p_{t,1}}{1-p_{t,1}} \right)^{\frac{1}{2h}} \frac{v(\tilde{y}_{t,0})}{v(\tilde{y}_{t,1})} \right]^2 \times \\ &\times \left\{ \left[1 + \left(\frac{p_{t,1}}{1-p_{t,1}} \right)^{\frac{1}{2h}} \frac{v(\tilde{y}_{t,0})}{v(\tilde{y}_{t,1})} \right]^{-1} - p_{t,1} \right\} - \end{aligned} \tag{1.49}$$

$$- hp_{t,1}(1-p_{t,1})\left\{p_{t,1}\frac{(v_1+2v_2\tilde{y}_{t,1})(b'(\psi_1)-\tilde{y}_{t,1})}{v(\tilde{y}_{t,1})^2}\left[1+\left(\frac{p_{t,1}}{1-p_{t,1}}\right)^{\frac{1}{2h}}\frac{v(\tilde{y}_{t,0})}{v(\tilde{y}_{t,1})}\right]- \tag{1.50}$$

$$- (1-p_{t,1})\frac{(v_1+2v_2\tilde{y}_{t,0})(b'(\psi_0)-\tilde{y}_{t,0})}{v(\tilde{y}_{t,0})^2}\left[1+\left(\frac{1-p_{t,1}}{p_{t,1}}\right)^{\frac{1}{2h}}\frac{v(\tilde{y}_{t,1})}{v(\tilde{y}_{t,0})}\right]\right\}. \tag{1.51}$$

Nonetheless, ΔM_{t+1}, defined as

$$\Delta M_{t+1} := G_{t+1} + g(p_{t,1}, \tilde{y}_{t,1}, \tilde{y}_{t,0}), \tag{1.52}$$

is a Σ_t-martingale difference sequence, since, by construction, its expectation with respect to Σ_t is zero.

Additionally, $t^{-1}r_{t+1}$, defined as $(p_{t+1,1}-p_{t,1}) - t^{-1}G_{t+1}$, determined from (1.26) and (1.46), is $\mathcal{O}_P(t^{-2})$, due to Lemma 2. As a consequence, $r_{t+1} = \mathcal{O}_P(t^{-1})$.

Analogously, we derive the stochastic approximation for $\tilde{y}_{t+1,a}$ for $a \in \{0,1\}$: equation (ii) of Lemma 1 suggests us to define

$$G_{t+1,a} := 1(A_{t+1}=a)(Y_{t+1}-\tilde{y}_{t,a})\left[1+\left(\frac{p_{t,a}}{p_{t,1-a}}\right)^{\frac{1}{2h}}\frac{v(\tilde{y}_{t,1-a})}{v(\tilde{y}_{t,a})}\right] \tag{1.53}$$

and

$$g_a(p_{t,1}, \tilde{y}_{t,1}, \tilde{y}_{t,0}) := -E_\psi(G_{t+1,a} \mid \Sigma_t) = -p_{t,a}(b'(\psi_a)-\tilde{y}_{t,a})\left[1+\left(\frac{p_{t,a}}{p_{t,1-a}}\right)^{\frac{1}{2h}}\frac{v(\tilde{y}_{t,1-a})}{v(\tilde{y}_{t,a})}\right],$$

so that $\tilde{y}_{t+1,a}$ satisfies the following recursive rule

$$\begin{aligned}\tilde{y}_{t+1,a} &= \tilde{y}_{t,a} + \frac{1}{t}(G_{t+1,a} + r_{t+1,a}) \\ &= \tilde{y}_{t,a} - \frac{1}{t}g_a(p_{t,1}, \tilde{y}_{t,1}, \tilde{y}_{t,0}) + \frac{1}{t}(\Delta M_{t+1,a} + r_{t+1,a}),\end{aligned} \tag{1.54}$$

where $\Delta M_{t+1,a} = G_{t+1,a} + g_a(p_{t,1}, \tilde{y}_{t,1}, \tilde{y}_{t,0})$ is a Σ_t-martingale difference sequence and $r_{t+1,a}$, defined as $t(\tilde{y}_{t+1,a}-\tilde{y}_{t,a}) - G_{t+1,a}$ from (1.23) and (1.53), is $\mathcal{O}_P(t^{-1})$.

Indeed, joining the above results, we get the stochastic approximation for the vector $[p_{t,1}, \tilde{y}_{t,1}, \tilde{y}_{t,0}]'$ presented in Proposition 2.

□

Using Proposition 2 we leverage the theory of stochastic approximation [13, 51, 63] and tackle

the convergence analysis of W_t within this framework. This is done by relating equation (1.44) with an ordinary differential equation (ODE) of the following form

$$\frac{dW_t}{dt} = -\tilde{g}(W_t), \tag{1.55}$$

where $t \in (0, +\infty)$ denotes continuous time. The ODE has arbitrary initial conditions.
Note that if we ignore the residual term $\tilde{r}_{t+1}$, the difference $W_{t+1} - W_t$ in (1.44) is equal to $-\frac{1}{t}\tilde{g}(W_t)$ plus a Σ_t-martingale-difference sequence.

We describe the distribution of W_t for large values of t, by analyzing the asymptotic behaviour of the ODE (1.55). By identifying the stationary point $[\rho_1, b'(\psi_1), b'(\psi_0)]$ of the ODE, assessing its stability and some regularity conditions on $\Delta\tilde{M}_{t+1}$ and $\tilde{r}_{t+1}$, we prove a Central Limit type result for W_t.
In particular, Theorem 1 indicates the asymptotic normality of the randomization probability $p_{t,1}$.

Theorem 1. *Under the same assumptions of Proposition 2, we have*

$$t^{1/2}(p_{t,1} - \rho_1) \to \mathcal{N}\Big(0, \frac{\Gamma}{1+4h}\Big),$$

where

$$\Gamma = h^2\rho_1^2(1-\rho_1)^2\left[\frac{(v_1 + 2v_2b'(\psi_1))^2}{\rho_1\sigma_1^2} + \frac{(v_1 + 2v_2b'(\psi_0))^2}{(1-\rho_1)\sigma_0^2} + \frac{4}{\rho_1} + \frac{4}{1-\rho_1}\right]. \tag{1.56}$$

Proof. (Theorem 1) The ordinary differential equation associated to the stochastic approximation of Proposition 2 has the following form

$$\begin{cases} \frac{dp}{dt} = -g(p, \tilde{y}_1, \tilde{y}_0) \\ \frac{d\tilde{y}_1}{dt} = -g_1(p, \tilde{y}_1, \tilde{y}_0) \\ \frac{d\tilde{y}_0}{dt} = -g_0(p, \tilde{y}_1, \tilde{y}_0) \end{cases} \tag{1.57}$$

with initial condition

$$\begin{cases} p(0) = p_0 \\ \tilde{y}_1(0) = \tilde{y}_{01} \\ \tilde{y}_0(0) = \tilde{y}_{00} \end{cases} \tag{1.58}$$

where $[p_0, \tilde{y}_{01}, \tilde{y}_{00}] \in (0,1) \times \mathbb{R}^2$ and $\tilde{g} = [g, g_1, g_0]'$ is defined in the main text. Refer to [13] and

[51] for a presentation of the mathematical results and theory on stochastic approximation.
Thus, the result of Theorem 1 follows from Theorem on asymptotics of stochastic approximation by Laruelle and Pagès in [52] (see Theorem A.2 in the Appendix at the end of this Chapter), once we have proven that the required hypotheses of the Theorem are satisfied by the stochastic approximation given in Proposition 2.
The assumptions are the following:

A1) the point $[\rho_1, b'(\psi_1), b'(\psi_0)]$ is a stationary point of the ordinary differential equation (1.57);

A2) $\tilde{g}$ is differentiable and $\Lambda := \mathrm{Re}(\lambda_{min}) > \frac{1}{2}$, where λ_{min} denotes the eigenvalue of of $D\tilde{g}(\rho_1, b'(\psi_1), b'(\psi_0))$ with the lowest real part;

A3) $E_\psi(\Delta\tilde{M}_{t+1}\Delta\tilde{M}'_{t+1} \mid \Sigma_t)$ converges a.s. to a symmetric and definite positive matrix $\tilde{\Gamma}$ and, in particular, $\mathrm{Var}_\psi(G_{t+1} \mid \Sigma_t) = E_\psi(\Delta M^2_{t+1} \mid \Sigma_t) \underset{t\to\infty}{\longrightarrow} \Gamma = \tilde{\Gamma}_{1,1}$ a.s.;

A4) for some $\delta > 0$, $\sup_t E_\psi\left(\|\Delta\tilde{M}_{t+1}\|^{2+\delta} \mid \Sigma_t\right) < \infty$;

A5) for an $\epsilon > 0$, $(t+1)E_\psi\left(\|\tilde{r}_{t+1}\|^2 \mathbf{1}_{\{\|[p_{t,1}, \tilde{y}_{t,1}, \tilde{y}_{t,0}] - [\rho_1, b'(\psi_1), b'(\psi_0)]\| < \epsilon\}}\right) \underset{t\to\infty}{\longrightarrow} 0$.

Then, we can conclude that

$$t^{1/2} \begin{bmatrix} p_{t,1} - \rho_1 \\ \tilde{y}_{t,1} - b'(\psi_1) \\ \tilde{y}_{t,0} - b'(\psi_0) \end{bmatrix} \underset{t\to\infty}{\longrightarrow} \mathcal{N}(0, \frac{1}{2\Lambda - 1}\tilde{\Sigma}), \tag{1.59}$$

where

$$\tilde{\Sigma} := \int_0^\infty \left(e^{-(D\tilde{g}(\rho_1, b'(\psi_1), b'(\psi_0)) - \frac{I_3}{2})u}\right)' \tilde{\Gamma} e^{-(D\tilde{g}(\rho_1, b'(\psi_1), b'(\psi_0)) - \frac{I_3}{2})u} \mathrm{d}u. \tag{1.60}$$

In the following steps we verify that assumptions A1)-A5) are satisfied, we apply the above Theorem and we compute the asymptotic variance of $p_{t,1}$.

STEP 1: Assumptions A1)-A2), ODE, stationarity and stability
The unique stationary point of the ODE (1.57) is $[\rho_1, b'(\psi_1), b'(\psi_0)]$, since

$$\tilde{g}(p_{t,1}, \tilde{y}_{t,1}, \tilde{y}_{t,0}) = 0 \quad \text{if and only if} \quad [p_{t,1}, \tilde{y}_{t,1}, \tilde{y}_{t,0}] = [\rho_1, b'(\psi_1), b'(\psi_0)]. \tag{1.61}$$

Moreover, standard computations show that the differential of $\tilde{g}$ evaluated at the equilibrium

point takes value

$$D\tilde{g}(\rho_1, b'(\psi_1), b'(\psi_0)) = \begin{bmatrix} 1+2h & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}. \tag{1.62}$$

Thus all the eigenvalues of $D\tilde{g}(\rho_1, b'(\psi_1), b'(\psi_0))$ are real and the minimum eigenvalue is $\Lambda = 1 > \frac{1}{2}$.

STEP 2: Assumption A3), finiteness of the limiting variance

In order to prove that the matrix $\tilde{\Gamma} = \lim_{t\to\infty} E_\psi(\Delta\tilde{M}_{t+1}\Delta\tilde{M}'_{t+1} \mid \Sigma_t)$ is positive definite it is sufficient to show that the diagonal elements of the matrix obtained by the triangularization of $\tilde{\Gamma}$ are positive. In fact, by Sylvester's criterion, $\tilde{\Gamma}$ is positive definite if and only if all the k^{th} leading principal minor of the matrix are positive for $k = 1, 2, 3$.

Now, by using elementary row operations, this matrix can be reduced to an upper triangular matrix and, since the k^{th} leading principal minor of a triangular matrix is the product of its diagonal elements up to row k, Sylvester's criterion is equivalent to checking whether its diagonal elements are all positive.

The components of the matrix $\tilde{\Gamma}$ can be determined combining the explicit expression of the conditional expectation of the pairwise products of the components of $\Delta\tilde{M}_{t+1}$, which are functions of $\tilde{G}_{t+1}$ and $\tilde{g}$, and the following remarks:

a) $E_{\psi_1}(A_{t+1}(Y_{t+1} - \tilde{y}_{t,1}) \mid \Sigma_t) \underset{t\to\infty}{\longrightarrow} 0$ and $E_{\psi_0}((1 - A_{t+1})(Y_{t+1} - \tilde{y}_{t,0}) \mid \Sigma_t) \underset{t\to\infty}{\longrightarrow} 0$ since $\tilde{y}_{t,a} = \dfrac{\sum_{s=1}^{t} Y_s 1(A_s = a)}{t\hat{p}_{t,a}} + \mathcal{O}_P(t^{-1})$ for $a \in \{0, 1\}$ and the law of large numbers can be applied to the outcomes of the two arms;

b) $E_{\psi_1}(b'(\psi_1) - \tilde{y}_{t,1} \mid \Sigma_t) \underset{t\to\infty}{\longrightarrow} 0$ and $E_{\psi_0}(b'(\psi_0) - \tilde{y}_{t,0} \mid \Sigma_t) \underset{t\to\infty}{\longrightarrow} 0$ due to a similar reasoning as above;

c) the conditional expectation of products containing A_{t+1} and $(1 - A_{t+1})$ as factors vanishes;

d) $p_{t,1}, \tilde{y}_{t,1}, \tilde{y}_{t,0}$ converge.

Thus,

$$\begin{aligned} \tilde{\Gamma}_{1,1} = \Gamma &= \lim_{t\to\infty} \mathrm{Var}_\psi(G_{t+1} \mid \Sigma_t) \\ &= h^2\rho_1^2(1-\rho_1)^2 \left[\frac{(v_1 + 2v_2 b'(\psi_1))^2}{\rho_1\sigma_1^2} + \frac{(v_1 + 2v_2 b'(\psi_0))^2}{(1-\rho_1)\sigma_0^2} + \frac{4}{\rho_1} + \frac{4}{1-\rho_1} \right], \end{aligned} \tag{1.63}$$

$$\begin{aligned}
\tilde{\Gamma}_{2,2} &= \lim_{t\to\infty} \mathrm{Var}_\psi(G_{t+1,1} \mid \Sigma_t) \\
&= \frac{\sigma_1^2}{\rho_1}, \qquad (1.64) \\
\tilde{\Gamma}_{3,3} &= \lim_{t\to\infty} \mathrm{Var}_\psi(G_{t+1,0} \mid \Sigma_t) \\
&= \frac{\sigma_0^2}{1-\rho_1}, \qquad (1.65) \\
\tilde{\Gamma}_{1,2} &= \tilde{\Gamma}_{2,1} = \lim_{t\to\infty} E_\psi(\Delta M_{t+1}\Delta M_{t+1,1} \mid \Sigma_t) \\
&= h(1-\rho_1)(v_1 + 2v_2 b'(\psi_1)), \\
\tilde{\Gamma}_{1,3} &= \tilde{\Gamma}_{3,1} = \lim_{t\to\infty} E_\psi(\Delta M_{t+1}\Delta M_{t+1,0} \mid \Sigma_t) \\
&= -h\rho_1(v_1 + 2v_2 b'(\psi_0)), \\
\tilde{\Gamma}_{2,3} &= \tilde{\Gamma}_{3,2} = \lim_{t\to\infty} E_\psi(\Delta M_{t+1,1}\Delta M_{t+1,0} \mid \Sigma_t) \\
&= 0. \qquad (1.66)
\end{aligned}$$

To triangularize $\tilde{\Gamma}$, it is sufficient to substitute the first row by a linear combination of the second and third rows, so that the elements (1,2) and (1,3) of the matrix vanish. In particular the entry $(1,1)$ becomes

$$\begin{aligned}
\tilde{\Gamma}_{3,3}(\tilde{\Gamma}_{2,2}\tilde{\Gamma}_{1,1} - \tilde{\Gamma}_{1,2}^2) - \tilde{\Gamma}_{1,3}^2\tilde{\Gamma}_{2,2} &= 4h^2\sigma_0^2\sigma_1^2 \\
&> 0. \qquad (1.67)
\end{aligned}$$

Since the above inequality holds and $\tilde{\Gamma}_{2,2} > 0, \tilde{\Gamma}_{3,3} > 0$, we can conclude that the matrix $\tilde{\Gamma}$ is positive definite.

STEP 3: Assumption A4), finiteness of $(2+\delta)^{th}$-moment

To prove A4) it is sufficient to prove the finiteness of $\sup_t E_\psi(\Delta M_{t+1}^{2+\delta} \mid \Sigma_t), \sup_t E_\psi(\Delta M_{t+1,1}^{2+\delta} \mid \Sigma_t)$ and $\sup_t E_\psi(\Delta M_{t+1,0}^{2+\delta} \mid \Sigma_t)$ separately. But this follows from the convergence of $[p_{t,1}, \tilde{y}_{t,1}, \tilde{y}_{t,0}]$ and the finiteness of the moments of distributions in the natural exponential family with quadratic variance function.

STEP 4: Assumption A5), remainder term

Assumption A5) is a consequence of the construction of the remainder term $\tilde{r}_{t+1}$.

Recall that $r_{t+1}, r_{t+1,1}$ and $r_{t+1,0}$ are $\mathcal{O}_P(t^{-1})$ as stated in Proposition 2 and they have been ob-

tained by isolating the dominant terms in the expression for $t(p_{t+1,1}-p_{t,1}), t(\tilde{y}_{t,1}-b'(\psi_1)), t(\tilde{y}_{t,0}-b'(\psi_0))$ and subtracting the components of $\tilde{G}_{t+1}$, respectively.
Thus, if $\|[p_{t,1},\tilde{y}_{t,1},\tilde{y}_{t,0}]-[\rho_1,b'(\psi_1),b'(\psi_0)]\| < \epsilon$ for some $\epsilon > 0$, then also $\mid \sigma^2_{t,1}-\sigma^2_1 \mid < \delta_1$, $\mid \sigma^2_{t,0}-\sigma^2_0 \mid < \delta_2$ for some δ_1,δ_2 and $\hat{p}_{t,1} \in K$, where K is a compact subset of $(0,1)$, since it can be computed as in (1.18). Under this conditions, for $\forall w$, $t^2\|\tilde{r}_{t+1}\|^2$ is, by construction, an algebraic function of random variables that have small variability around their limits, which are different from zero and are finite, and, therefore, it is bounded. This implies that

$$(t+1)E_\psi\left(\|\tilde{r}_{t+1}\|^2\mathbf{1}_{\{\|[p_{t,1},\tilde{y}_{t,1},\tilde{y}_{t,0}]-[\rho_1,b'(\psi_1),b'(\psi_0)]\|<\epsilon\}}\right) \underset{t\to\infty}{\longrightarrow} 0. \tag{1.68}$$

STEP 5: SA theorem
From the above steps, we have shown that Theorem A.2 on asymptotics of stochastic approximation by Laruelle and Pagès in [52] holds: it follows that $t^{1/2}(p_{t,1}-\rho_1) \underset{t\to\infty}{\longrightarrow} \mathcal{N}(0,\Sigma)$, where Σ is the entry $(1,1)$ of the matrix $\tilde{\Sigma}$, defined in (1.60). Thus, we have

$$\tilde{\Sigma} = \int_0^\infty \sum_{k=0}^\infty \frac{1}{k!}\left(\left(-D\tilde{g}(\rho_1,b'(\psi_1),b'(\psi_0))+\frac{I_3}{2}\right)^k\right)' u^k\tilde{\Gamma}\sum_{j=0}^\infty\frac{1}{j!}\left(-D\tilde{g}(\rho_1,b'(\psi_1),b'(\psi_0))+\frac{I_3}{2}\right)^j u^j \mathrm{d}u. \tag{1.69}$$

and, in particular, the entry (1,1) equals $\Sigma = \dfrac{\Gamma}{1+4h}$, where Γ has been computed in (1.63).
Therefore we obtain the multivariate Central Limit type result (1.59) for $[p_{t,1},\tilde{y}_{t,1},\tilde{y}_{t,0}]'$, where the asymptotic variance-covariance matrix given in (1.60) becomes (1.69). This completes the proof of the Theorem.

□

The idea of fitting the evolution of treatment allocation proportions or probabilities of adaptive procedures into a Stochastic Approximation rule, in order to derive their asymptotic normality, has been already adopted in [3, 52]. However, it is not possible to infer Theorem 1 directly from the asymptotic results presented in these works, since they apply to adaptive procedures based on the generalized Friedman urn model or to adaptive procedures where the probability of assigning a patient to arm a, based on data accumulated up to time t, is a function of $\hat{p}_{t,a}$ and not also of history of outcomes of patients enrolled in the study previously to that time.

The following corollary illustrates asymptotic normality of the allocation proportion $\hat{p}_{t,1}$ of a two-arm BUD. This result is a consequence of Theorem 1, Delta method and Slutsky Theorem.

Corollary 2. *Under the assumptions of Theorem 1, it holds that*

$$t^{1/2}(\hat{p}_{t,1}-\rho_1) \longrightarrow \mathcal{N}\Big(0, \frac{\Gamma}{4h^2(1+4h)}+\frac{\rho_1(1-\rho_1)^2}{4\sigma_1^2}(v_1+2v_2b'(\psi_1))^2+\frac{\rho_1^2(1-\rho_1)}{4\sigma_0^2}(v_1+2v_2b'(\psi_0))^2\Big).$$

Proof. (Corollary 2) First, by inverting the definitory equation

$$p_{t,1} = \frac{1}{1+\frac{\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}}\left(\frac{t_{0,1}+1+t\hat{p}_{t,1}}{t_{0,0}+1+t(1-\hat{p}_{t,1})}\right)^{2h}}, \tag{1.70}$$

and by (i) of Lemma 1, we have

$$\hat{p}_{t,1} = \frac{1}{1+\left(\frac{p_{t,1}}{1-p_{t,1}}\right)^{\frac{1}{2h}}\frac{v(\tilde{y}_{t,0})}{v(\tilde{y}_{t,1})}} + \mathcal{O}_P(t^{-1}). \tag{1.71}$$

Second, starting from the asymptotic result (1.59) with (1.69), we can apply a multivariate Delta Method and Slutsky Theorem (see 5.5.17 and 5.5.24 of [23]) to deduce the asymptotic normality of the allocation proportion of a BUD.
In particular, we use the principal part of (1.71), that is the function f that maps $(p_{t,1}, \tilde{y}_{t,1}, \tilde{y}_{t,0})$ into $\left[1+\left(\frac{p_{t,1}}{1-p_{t,1}}\right)^{\frac{1}{2h}}\frac{v(\tilde{y}_{t,0})}{v(\tilde{y}_{t,1})}\right]^{-1}$, to conclude that

$$t^{1/2}(f(p_{t,1},\tilde{y}_{t,1},\tilde{y}_{t,0})-f(\rho_1,b'(\psi_1),b'(\psi_0))) \underset{t\to\infty}{\longrightarrow} \mathcal{N}(0, \nabla f(\rho_1,b'(\psi_1),b'(\psi_0))'\tilde{\Sigma}\nabla f(\rho_1,b'(\psi_1),b'(\psi_0))),$$

where $\tilde{\Sigma}$ is the matrix given computed by (1.69).
Standard calculations show that $f(\rho_1, b'(\psi_1), b'(\psi_0))) = \rho_1$ and that

$$\nabla f(\rho_1,b'(\psi_1),b'(\psi_0))' = \left[\frac{1}{2h}, \frac{\rho_1(1-\rho_1)}{2\sigma_1^2}(v_1+2v_2b'(\psi_1)), -\frac{\rho_1(1-\rho_1)}{2\sigma_0^2}(v_1+2v_2b'(\psi_0))\right].$$

Thus, the asymptotic variance of the allocation proportion $\hat{p}_{t,1}$ is equal to

$$\frac{\Gamma}{4h^2(1+4h)} + \frac{\rho_1(1-\rho_1)^2}{4\sigma_1^2}(v_1+2v_2b'(\psi_1))^2 + \frac{\rho_1^2(1-\rho_1)}{4\sigma_0^2}(v_1+2v_2b'(\psi_0))^2,$$

that can be re-written as $\frac{\rho_1^2(1-\rho_1)^2}{4}\left[\left(\frac{(v_1+2v_2b'(\psi_1))^2}{\rho_1\sigma_1^2}+\frac{(v_1+2v_2b'(\psi_0))^2}{(1-\rho_1)\sigma_0^2}\right)\left(1+\frac{1}{1+4h}\right)+\right.$
$\left.+\frac{4}{\rho_1(1+4h)}+\frac{4}{(1-\rho_1)(1+4h)}\right]$.

□

1.4 Applications and examples

We apply the results presented in Section 1.3 to the design of clinical trials. We consider three common outcomes, binary, time-to-event and continuous.

Binary outcomes. For $Y_t \in \{0,1\}$, we use the Bernoulli model $f_{\psi_a}(1) = 1 - f_{\psi_a}(0) = \theta_a$, $\theta_a = 1/(1+e^{-\psi_a})$, and conjugated prior $\theta_a \sim \text{Beta}(\alpha_{0,a}, \beta_{0,a})$. The outcome variance σ_a^2 in expression (1.7) is $\theta_a(1-\theta_a)$, and the parameters of the quadratic variance function in (1.56) are $v_1 = 1$ and $v_2 = -1$. Therefore, $t^{1/2}(\hat{p}_{t,1} - \rho_1)$ converges in distribution to a mean zero Gaussian variable with variance

$$\frac{\rho_1^2(1-\rho_1)^2}{4}\left[\left(\frac{(1-2\theta_1)^2}{\rho_1\sigma_1^2}+\frac{(1-2\theta_0)^2}{(1-\rho_1)\sigma_0^2}\right)\left(1+\frac{1}{1+4h}\right)+\frac{4}{\rho_1(1+4h)}+\frac{4}{(1-\rho_1)(1+4h)}\right].$$

The top panel of the second column of Figure 1.1 shows a trajectory $\hat{p}_{t,1}, t = 1, \cdots, 10,000$ for a single simulated two-arm BUD trial (black curve). The response probabilities (θ_0, θ_1) are set equal to 0.2 and 0.4. We used $\alpha_{0,a} = \beta_{0,a} = 2$ and $h = 5$. The shaded area shows (point-wise at each t) upper and lower 2.5% quantiles of the distribution of $\hat{p}_{t,1}$ across 1,000 simulations. The second row, illustrates the distribution of $t^{1/2}(\hat{p}_{t,1} - \rho_1)$ across 1000 simulations of the two-arm BUD trial. The empirical distribution of $t^{1/2}(\hat{p}_{t,1} - \rho_1)$ has been smoothed with a kernel density estimator. The panel compares the $\mathcal{N}(0, 0.097)$ density (asymptotic approximation) to the empirical distribution of $t^{1/2}(\hat{p}_{t,1} - \rho_1)$ across simulations, when $t = 100, 1000$ and $10,000$. The last row compares the empirical distribution distribution of $t^{1/2}(p_{t,1} - \rho_1)$ to the $\mathcal{N}\left(0, \frac{\Gamma}{1+4h}\right)$ density.

Time-to-event outcomes. We consider an exponential model $f_{\psi_a}(y) = \exp\{-y\psi_a\}\psi_a, y \geq 0$ with mean $\theta_0 = 1/\psi_a$, and we use the conjugated gamma prior $\psi_a \sim \text{Gamma}(\alpha_{0,a}, \beta_{0,a})$. The outcome variance σ_a^2 in expression (1.7) is $1/\psi_a^2$, the parameters of the quadratic variance function in (1.56) are $v_1 = 0$ and $v_2 = 1$ and the parameter h is equal to 5. Therefore, the asymptotic variance of

$t^{1/2}(\hat{p}_{t,1} - \rho_1)$ is

$$\rho_1^2(1-\rho_1)^2\left(\frac{1}{\rho_1}+\frac{1}{1-\rho_1}\right)\left(\frac{2}{1+4h}+1\right).$$

The third Column of Figure 1.1 compares, as we discussed the Binary model, the asymptotic and empirical distributions of $t^{1/2}(\hat{p}_{t,1}-\rho_1)$ and $t^{1/2}(p_{t,1}-\rho_1)$, based on 1000 simulations of the BUD trial. In this example $(\theta_0, \theta_1) = (5, 7)$.

Continuous outcomes. We consider a normal outcome model $\mathcal{N}(\theta_a, \sigma_a^2)$ with known variance σ_a^2. We use a conjugated prior $\theta_a \sim \mathcal{N}(0, v_{0,a}^2)$. In this case $v_1 = v_2 = 0$, $h = 5$, and

$$t^{1/2}(\hat{p}_{t,1} - \rho_1) \underset{t\to\infty}{\longrightarrow} \mathcal{N}(0, \frac{\rho_1(1-\rho_1)}{1+4h}). \tag{1.72}$$

Column 1 of Figure 1.1 illustrates the empirical distribution of $t^{1/2}(\hat{p}_{t,1} - \rho_1)$, $t = 100, 1000$ or 10000, and the normal approximation.

Power analysis and sample size selection. We explore the application of the results in Section 1.3 to select the sample size of BUD studies accordingly to the targeted type I and II error rates α and β. We approximate the power function of the BUD under several scenarios leveraging on Theorem 1 and Corollary 2. We assume that the primary aim is to test the null hypothesis $H_0 : \theta_{0,1} = \theta_{0,0}$. The alternative hypothesis is $H_1 : \theta_{0,1} > \theta_{0,0}$. We verified (Appendix) that the maximum-likelihood estimates $\widehat{\theta}_{t,a}$ of the unknown true mean response to treatment $a = 0, 1$ within the NEF of outcome models, under the sequential BUD design, have the same limiting distribution as the maximum-likelihood estimator of a study design with fixed and matched arm-specific sample sizes,

$$t^{1/2}\begin{bmatrix}\hat{\theta}_{t,0}-\theta_{0,0}\\ \hat{\theta}_{t,1}-\theta_{0,1}\end{bmatrix} \underset{t\to\infty}{\longrightarrow} \mathcal{N}\left(\mathbf{0}, Diag(\eta_{0,0}, \eta_{0,1})\right), \tag{1.73}$$

where $\eta_{0,a} := \left(\rho_a I_{\theta_{0,a}}\right)^{-1}$ and $I_{\theta_{0,a}}$ is the Fisher information.

We use a standard Wald-statistics, $Z_a = \dfrac{\sqrt{t}\times(\hat{\theta}_{t,1}-\hat{\theta}_{t,0})}{\sqrt{\widehat{\eta}_{t,a}+\widehat{\eta}_{t,1}}}$, where $\widehat{\eta}_{t,a} = 1/(\widehat{\rho}_a \times I_{\widehat{\theta}_{t,a}})$, and the maximum-likelihood estimates $\widehat{\sigma}_a^2$ for $\widehat{\rho}_a = \rho_a(\widehat{\sigma}_a^2)$ in (1.7) to test $H_{0,a}$. The power function is approximated by $\Phi\Big(z_{1-\alpha} - \dfrac{\sqrt{t}(\theta_{0,1}-\theta_{0,0})}{\sqrt{\eta_{0,1}+\eta_{0,0}}}\Big)$ where $\Phi(\cdot)$ is the cumulative distribution function of a standard normal random variable and $\Phi(z_{1-\alpha}) = 1-\alpha$. Therefore $\widehat{t}_{1-\alpha,1-\beta} =$

$\frac{(z_{1-\alpha} - z_{1-\beta})^2(\eta_{0,0} + \eta_{0,1})}{(\theta_{0,1} - \theta_{0,0})^2}$ approximates the sample size of the BUD study to achieve a power equal to 1-β.

Figure 1.2 compares, for three BUD designs (binary, continuous and time to event outcomes), power estimates based on asymptotic approximations (blue dotted lines) and on standard Monte Carlo simulations (1000 simulated trials, blue solid lines).

The computational time for the simulation-based calculations is orders of magnitude larger.

We also show the targeted type I error rate ($\alpha = 0.05$, brown dotted lines) of the outlined testing procedure, which leverage asymptotic results, and empirical estimates of the type I error rates obtained with Monte Carlo simulations (brown solid lines). For the normal outcome model, $\sigma_0^2 = 1, \sigma_1^2 = 3$, and $\theta_0 = \theta_1 = 0$ (null scenario, brown dotted line) or $(\theta_1, \theta_2) = (0, 1)$ (positive treatment effect, blue lines). Similarly, for the Bernoulli and Exponential models the parameter values θ that defined null (brown lines) and alternative scenarios (blue lines) are indicated in the panels of Figure 1.2 .

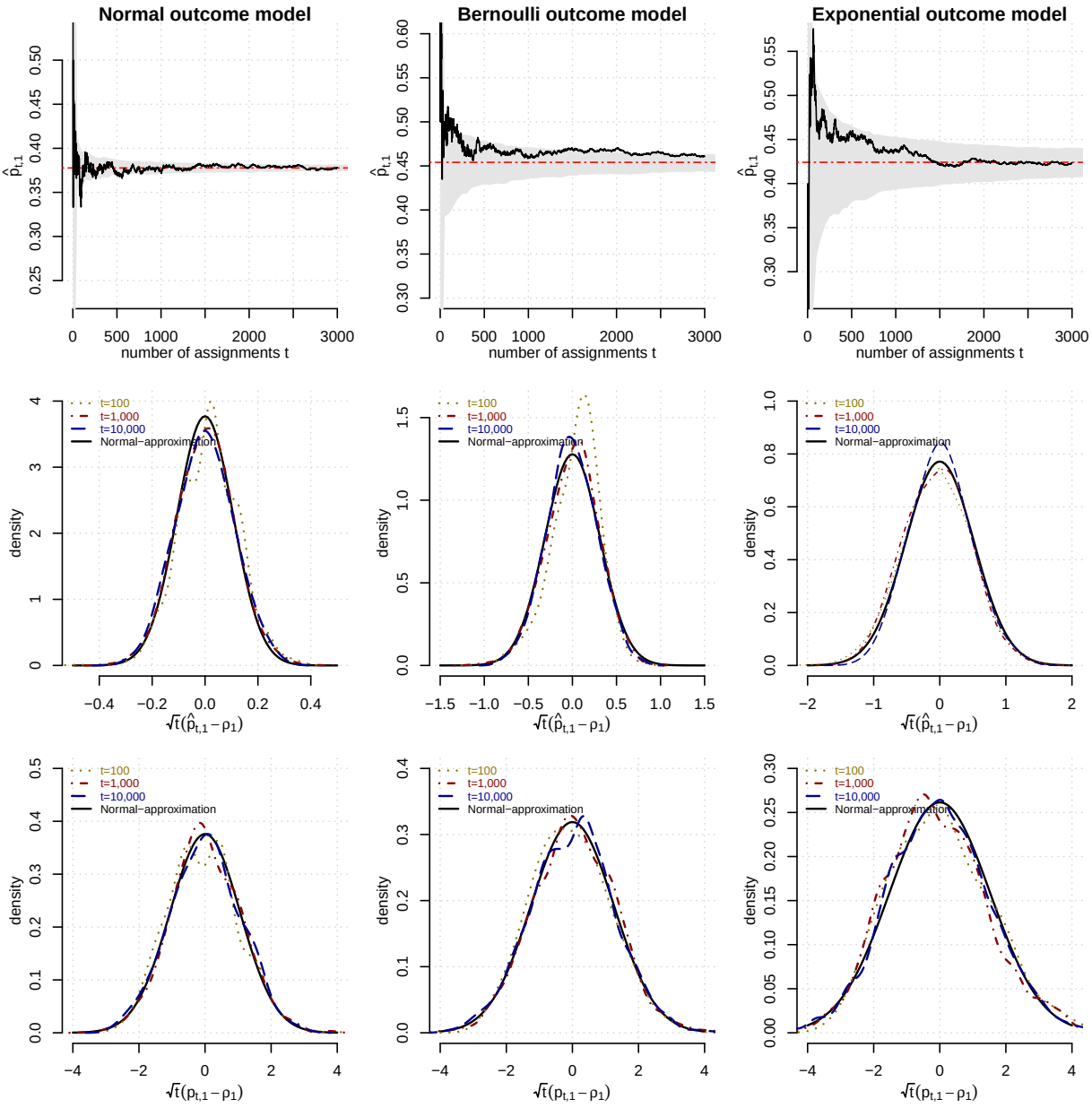

Figure 1.1: The panels in the first row compare $\hat{p}_{t,1}$ with the limit ρ_1 (red line) in each of the three examples (binary, continuous and time to event outcomes). The other panels compare asymptotic and empirical distributions of randomization probabilities $p_{t,1}$ and allocation proportions $\hat{p}_{t,1}$. The empirical distributions in each of the three examples (binary, continuous and time to event outcomes) are based on 1000 simulations of the two-arm BUD trial.

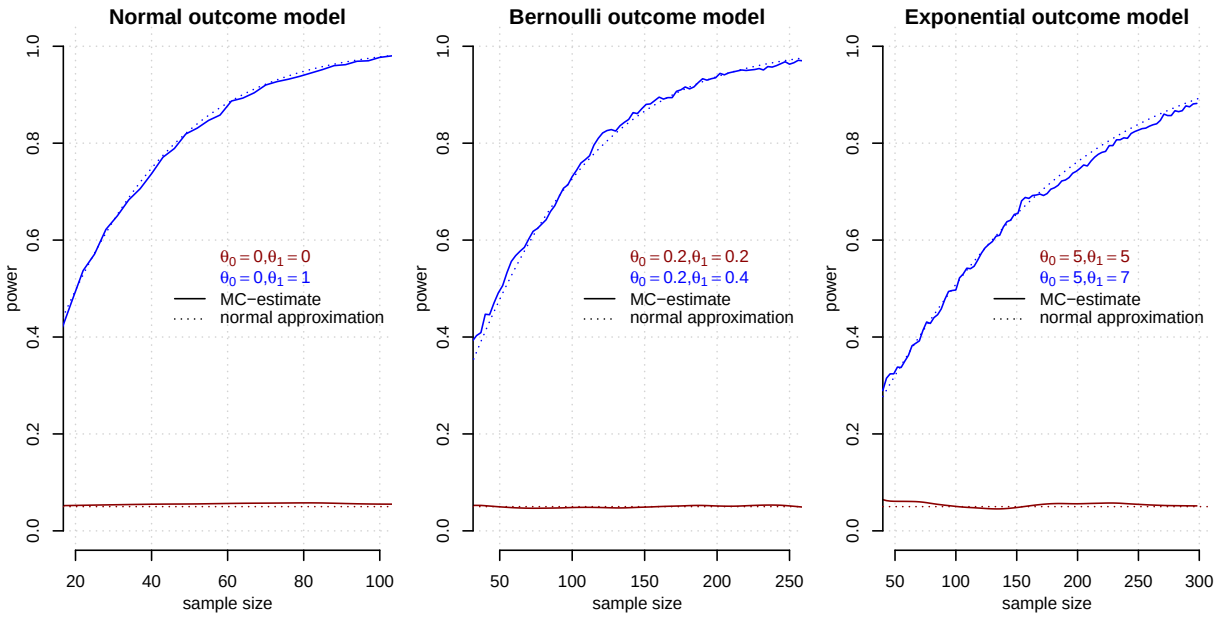

Figure 1.2: Power (blue lines) and type I error (red lines): comparison of estimates based on asymptotic approximations (dotted lines) and standard Monte Carlo simulations (1000 simulated trials, solid lines), for binary, continuous and time-to-event outcomes.

Reference Bonsaglio, M., Fortini, S., Ventz, S., Trippa, L. (2021+), *Approximating the Operating Characteristics of Bayesian Uncertainty Directed Trial Designs*, http://arxiv.org/abs/2105.11177

Appendix A

Supplement to Chapter 1

A.1 Additional results and proofs

In this section we provide statement and proofs complementary to the content of Chapter 1.

Proof of Lemma A.1

Proof. (Lemma A.1) We have

$$
\begin{aligned}
A_{t+1}\left[\frac{\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})}\right)^{2h}-\frac{\sigma_{t,0}^{2h}}{\sigma_{t+1,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}+A_{t+1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})}\right)^{2h}\right] \\
&= A_{t+1}\frac{\sigma_{t,0}^{2h}}{(n_{0,0}+1+t(1-\hat{p}_{t,1}))^{2h}}\left[\frac{(n_{0,1}+1+t\hat{p}_{t,1})^{2h}}{\sigma_{t,1}^{2h}}-\frac{(n_{0,1}+1+t\hat{p}_{t,1}+1)^{2h}}{\sigma_{t+1,1}^{2h}}\right] \\
&= A_{t+1}\frac{\sigma_{t,0}^{2h}t^{2h}\hat{p}_{t,1}^{2h}}{(n_{0,0}+1+t(1-\hat{p}_{t,1}))^{2h}}\left[\frac{\left(1+\frac{n_{0,1}+1}{t\hat{p}_{t,1}}\right)^{2h}}{\sigma_{t,1}^{2h}}-\frac{\left(1+\frac{n_{0,1}+2}{t\hat{p}_{t,1}}\right)^{2h}}{\sigma_{t+1,1}^{2h}}\right] \qquad \text{(A.1)} \\
&= A_{t+1}\frac{\sigma_{t,0}^{2h}\hat{p}_{t,1}^{2h}}{(1-\hat{p}_{t,1})^{2h}}\left[\frac{\left(1+\frac{n_{0,1}+1}{t\hat{p}_{t,1}}\right)^{2h}}{\sigma_{t,1}^{2h}}-\frac{\left(1+\frac{n_{0,1}+2}{t\hat{p}_{t,1}}\right)^{2h}}{\sigma_{t+1,1}^{2h}}\right]\left(1+\mathcal{O}_P(t^{-1})\right) \qquad \text{(A.2)} \\
&= A_{t+1}\frac{\sigma_{t,0}^{2h}\hat{p}_{t,1}^{2h}}{(1-\hat{p}_{t,1})^{2h}}\left[\frac{\sigma_{t+1,1}^{2h}-\sigma_{t,1}^{2h}+2h\frac{n_{0,1}+1}{t\hat{p}_{t,1}}\sigma_{t+1,1}^{2h}-2h\frac{n_{0,1}+2}{t\hat{p}_{t,1}}\sigma_{t,1}^{2h}}{\sigma_{t,1}^{2h}\sigma_{t+1,1}^{2h}}+\mathcal{O}_P(t^{-2})\right]\times \\
&\quad\times\left(1+\mathcal{O}_P(t^{-1})\right) \qquad \text{(A.3)}
\end{aligned}
$$

$$= A_{t+1}\frac{\sigma_{t,0}^{2h}\hat{p}_{t,1}^{2h}}{\sigma_{t+1,1}^{2h}\sigma_{t,1}^{2h}(1-\hat{p}_{t,1})^{2h}}\left[\left(1+2h\frac{n_{0,1}+1}{t\hat{p}_{t,1}}\right)\left(\sigma_{t+1,1}^{2h}-\sigma_{t,1}^{2h}\right)-\right.$$
$$\left.-\frac{2h}{t\hat{p}_{t,1}}\sigma_{t,1}^{2h}+\mathcal{O}_P(t^{-2})\right]\times\left(1+\mathcal{O}_P(t^{-1})\right) \tag{A.4}$$
$$= A_{t+1}\frac{\sigma_{t,0}^{2h}\hat{p}_{t,1}^{2h}}{\sigma_{t+1,1}^{2h}\sigma_{t,1}^{2h}(1-\hat{p}_{t,1})^{2h}}\left[\left(\sigma_{t+1,1}^{2h}-\sigma_{t,1}^{2h}\right)-\frac{2h}{t\hat{p}_{t,1}}\sigma_{t,1}^{2h}\right]+\mathcal{O}_P(t^{-2}) \tag{A.5}$$
$$= A_{t+1}\frac{\sigma_{t,0}^{2h}\hat{p}_{t,1}^{2h}}{\sigma_{t+1,1}^{2h}\sigma_{t,1}^{2h}(1-\hat{p}_{t,1})^{2h}}\left[\left(\sigma_{t,1}^{2}+\Delta\sigma_{t,1}^{2}\right)^{h}-\sigma_{t,1}^{2h}-\frac{2h}{t\hat{p}_{t,1}}\sigma_{t,1}^{2h}\right]+\mathcal{O}_P(t^{-2}) \tag{A.6}$$
$$= A_{t+1}\frac{\sigma_{t,0}^{2h}\hat{p}_{t,1}^{2h}}{\sigma_{t+1,1}^{2h}(1-\hat{p}_{t,1})^{2h}}\left[\left(1+\frac{\Delta\sigma_{t,1}^{2}}{\sigma_{t,1}^{2}}\right)^{h}-1-\frac{2h}{t\hat{p}_{t,1}}\right]+\mathcal{O}_P(t^{-2}) \tag{A.7}$$
$$= A_{t+1}h\frac{\sigma_{t,0}^{2h}\hat{p}_{t,1}^{2h}}{\sigma_{t,1}^{2h}(1-\hat{p}_{t,1})^{2h}}\left[\frac{\Delta\sigma_{t,1}^{2}}{\sigma_{t,1}^{2}}-\frac{2}{t\hat{p}_{t,1}}\right]+\mathcal{O}_P(t^{-2}). \tag{A.8}$$

The first equality is obtained leveraging the fact that the left-hand-side doesn't vanishes only when $A_{t+1}=1$. In (A.1) we collect the term $t^{2h}\hat{p}_{t,1}^{2h}$ and we retain the dominant part to obtain (A.2). The remainder term appears as $\mathcal{O}_P(t^{-1})$ since $\sigma_{t,a}^2$ converges to a finite limit different from 0 almost surely for $a\in\{0,1\}$ and, due to Proposition 1, $\hat{p}_{t,1}$ and $(1-\hat{p}_{t,1})$ converge almost surely to a limit which is different from 0: indeed, we can bound $(1-\hat{p}_{t,1})$ in a compact set which doesn't contain 0 with arbitrarily high probability. The terms $\left(1+\frac{n_{0,1}+1}{t\hat{p}_{t,1}}\right)^{2h}$ and $\left(1+\frac{n_{0,1}+2}{t\hat{p}_{t,1}}\right)^{2h}$ in the left-hand-side of equation (A.2) can be approximated by Tailor expansion:

$$\left(1+\frac{n_{0,1}+1}{t\hat{p}_{t,1}}\right)^{2h}=1+2h\frac{n_{0,1}+1}{t\hat{p}_{t,1}}+\mathcal{O}_P(t^{-2})$$

and

$$\left(1+\frac{n_{0,1}+2}{t\hat{p}_{t,1}}\right)^{2h}=1+2h\frac{n_{0,1}+2}{t\hat{p}_{t,1}}+\mathcal{O}_P(t^{-2}).$$

Therefore (A.2) equals (A.3). The $\mathcal{O}_P(t^{-2})$ in (A.4) is justified by invoking Lemma 1 and noting that $\Delta\sigma_{t,a}^2=\mathcal{O}_P(t^{-1})$ for $a\in\{0,1\}$. The term $2h\frac{n_{0,1}+1}{t\hat{p}_{t,1}}\left(\sigma_{t+1,1}^{2h}-\sigma_{t,1}^{2h}\right)$ in (A.4) enters the remainder term in (A.5). In (A.6) we have rewritten $\sigma_{t+1,1}^2$ as $\sigma_{t,1}^2+\Delta\sigma_{t,1}^2$. The equality in (A.7) follows from a Taylor expansion of $\left(1+\frac{\Delta\sigma_{t,1}^2}{\sigma_{t,1}^2}\right)^h$.

With similar arguments we can prove (1.34). We have

$$
\begin{aligned}
&(1-A_{t+1})\left[\frac{\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})}\right)^{2h}-\frac{\sigma_{t+1,0}^{2h}}{\sigma_{t,1}^{2h}}\left(\frac{n_{0,1}+1+t\hat{p}_{t,1}}{n_{0,0}+1+t(1-\hat{p}_{t,1})+1-A_{t+1}}\right)^{2h}\right]\\
&\quad=(1-A_{t+1})\frac{(n_{0,1}+1+t\hat{p}_{t,1})^{2h}}{\sigma_{t,1}^{2h}}\left[\frac{\sigma_{t,0}^{2h}}{(n_{0,0}+1+t(1-\hat{p}_{t,1}))^{2h}}-\right.\\
&\qquad\left.-\frac{\sigma_{t+1,0}^{2h}}{(n_{0,0}+1+t(1-\hat{p}_{t,1})+1)^{2h}}\right]\\
&\quad=(1-A_{t+1})\frac{(n_{0,1}+1+t\hat{p}_{t,1})^{2h}}{\sigma_{t,1}^{2h}t^{2h}(1-\hat{p}_{t,1})^{2h}}\left[\frac{\sigma_{t,0}^{2h}}{\left(1+\frac{n_{0,0}+1}{t(1-\hat{p}_{t,1})}\right)^{2h}}-\frac{\sigma_{t+1,0}^{2h}}{\left(1+\frac{n_{0,0}+2}{t(1-\hat{p}_{t,1})}\right)^{2h}}\right]\\
&\quad=(1-A_{t+1})\frac{\hat{p}_{t,1}^{2h}}{\sigma_{t,1}^{2h}(1-\hat{p}_{t,1})^{2h}}\left[\frac{\sigma_{t,0}^{2h}}{\left(1+\frac{n_{0,0}+1}{t(1-\hat{p}_{t,1})}\right)^{2h}}-\frac{\sigma_{t+1,0}^{2h}}{\left(1+\frac{n_{0,0}+2}{t(1-\hat{p}_{t,1})}\right)^{2h}}\right]\left(1+\mathcal{O}_P(t^{-1})\right)\\
&\quad=(1-A_{t+1})\frac{\hat{p}_{t,1}^{2h}}{\sigma_{t,1}^{2h}(1-\hat{p}_{t,1})^{2h}}\left[\left(\sigma_{t,0}^{2h}-\sigma_{t+1,0}^{2h}\right)+\frac{2h(n_{0,0}+2)}{t(1-\hat{p}_{t,1})}\sigma_{t,0}^{2h}-\right.\\
&\qquad\left.-\frac{2h(n_{0,0}+1)}{t(1-\hat{p}_{t,1})}\sigma_{t+1,0}^{2h}+\mathcal{O}_P(t^{-2})\right]\left(1+\mathcal{O}_P(t^{-1})\right)\\
&\quad=(1-A_{t+1})\frac{\hat{p}_{t,1}^{2h}}{\sigma_{t,1}^{2h}(1-\hat{p}_{t,1})^{2h}}\left[\left(\sigma_{t,0}^{2h}-\sigma_{t+1,0}^{2h}\right)+\frac{2h}{t(1-\hat{p}_{t,1})}\sigma_{t,0}^{2h}\right]+\mathcal{O}_P(t^{-2})\\
&\quad=(1-A_{t+1})\frac{\hat{p}_{t,1}^{2h}\sigma_{t,0}^{2h}}{\sigma_{t,1}^{2h}(1-\hat{p}_{t,1})^{2h}}h\left[-\frac{\Delta\sigma_{t,0}^2}{\sigma_{t,0}^2}+\frac{2}{t(1-\hat{p}_{t,1})}\right]+\mathcal{O}_P(t^{-2}).
\end{aligned}
\tag{A.9}
$$

This concludes the proof of this auxiliary Lemma. □

Supplementary Result

Lemma A.2. *Consider a two-arm BUD where patients are assigned to arms $\mathcal{A}=\{0,1\}$ and the information metric is $u(\cdot)$. Define $F_t=-\hat{p}_{t,0}+\dfrac{\Delta_t(0)^h}{\Delta_t(0)^h+\Delta_t(1)^h}$, where $\Delta_t(a)=E(u(\Sigma_{t+1})\mid A_{t+1}=a,\Sigma_t)-u(\Sigma_t)$ for $a\in\{0,1\}$. If on a set of probability 1, for any $\epsilon>0$, there is a random time T and number $c>0$ such that $F_t<-c$ wherever $\hat{p}_{t,0}>\rho_0+\epsilon$, and $F_t>c$ wherever $\hat{p}_{t,0}<\rho_0-\epsilon$ for all $t>T$, then $\hat{p}_{t,a}\underset{t\to\infty}{\longrightarrow}\rho_a$ a.s.*

Proof. (Lemma A.2) We show that for any $\epsilon > 0$, the process of allocation proportions $\hat{p}_{t,0}$ visit the interval $[\rho_0+\epsilon, 1]$ finitely often. A symmetric argument can be applied to intervals lying below ρ_0. Define $S_t = \hat{p}_{t,0} - \sum_{i=1}^{t} E(\hat{p}_{i,0} - \hat{p}_{i-1,0} \mid \Sigma_{i-1})$. This is a martingale. Since $S_{t+1} - S_t \leq \mathcal{O}_p(t^{-1})$, then $S_t \to S_\infty < \infty$ a.s. Furthermore, it holds that

$$E(\hat{p}_{t+1,0} - \hat{p}_{t,0} \mid \Sigma_t) = -\frac{\hat{p}_{t,0}}{t+1} + \frac{1}{t+1}\frac{\Delta_t^h(0)}{\Delta_t^h(0) + \Delta_t^h(1)} = \frac{F_t}{t+1}.$$

In order to prove that $\hat{p}_{t,0} = S_t + \sum_{i=1}^{t} E(\hat{p}_{i,0} - \hat{p}_{i-1,0} \mid \Sigma_{i-1})$ only visits $[\rho_0+\epsilon, 1]$ finitely often we use the convergence of the first term and the fact that the summands in the second term define a drift toward ρ_0 for large values of i. On a set of probability 1, there is a number N such that for any $t > N$, $\mid S_t - S_\infty \mid > \frac{\epsilon}{4}$ and $F_t < -c < 0$ when $\hat{p}_{t,0} \in [\rho_0 + \frac{\epsilon}{2}, 1]$. Therefore, the trajectory $(\hat{p}_{N+k,0})_{k\geq 1}$ cannot increase more than $\frac{\epsilon}{4}$ while staying in $[\rho_0 + \frac{\epsilon}{2}, 1]$. As $\sum_{t=1}^{\infty}(t+1)^{-1} = \infty$, every time the process enters this interval, it will eventually exit below $\rho_0 + \frac{\epsilon}{2}$. Finally, $\mid F_t \mid \leq 2$ and thus $\mid \frac{F_t}{t+1} \mid \to 0$. So, for t large enough, the process cannot reenter the interval $[\rho_0 + \frac{\epsilon}{2}, 1]$ above $\rho_0 + \frac{3\epsilon}{4}$, but it can only enter $[\rho_0 + \epsilon, 1]$ finitely often. □

Behavior of the MLE of θ_a in BUD

The maximum-likelihood estimates $\widehat{\theta}_{t,a}$ of the unknown true mean response to treatment $a = 0, 1$ within the NEF of outcome models, derived under the sequential BUD design at time t, have the same limiting distribution as the maximum-likelihood estimator of a study design with fixed sample size. Whilst we are considering a response-adaptive procedure, a version of the central limit theorem for the maximum-likelihood estimator arising in the classical setting of independent and identically distributed random variables is preserved. For the proof of this result we refer to [42] that presents and proves it in a more general framework (see Theorem 3.1).

A.2 Tools of Stochastic Approximation

In this section we give some of the most important results on the convergence of stochastic approximation algorithms present in literature.
In general terms, we consider the following recursive procedure defined on a filtered probability space $(\Omega, \mathcal{A}, (\mathcal{F}_t)_{t\geq 0}, P)$

$$\forall t \geq t_0, \quad \gamma_{t+1} = \gamma_t - \frac{1}{t} g(\gamma_t) + \frac{1}{t}(\Delta M_{t+1} + r_{t+1}), \tag{A.10}$$

where $g : \mathbb{R}^d \to \mathbb{R}^d$ is a locally Lipschitz continuous function (for every x in $\mathbb{R}^d$ there exists a neighborhood U of x and a real constant $K_U \geq 0$ such that, for all x_1 and x_2 in U, $\|g(x_1) - g(x_2)\| \leq K_U \|x_1 - x_2\|$) and γ_{t_0} is an $\mathcal{F}_{t_0}$-measurable finite random vector.
Also, for every $t \geq t_0$, (ΔM_t) is a sequence of $(\mathcal{F}_t)$-martingale increment and (r_t) is an $(\mathcal{F}_t)$-adapted sequence of remainder terms.
Theorem A.1 is a statement on the almost sure convergence of γ_t.

Theorem A.1. *Assume that g is locally Lipschitz, that*

$$r_t \to 0 \ \ a.s. \ as \ \ t \to \infty \ \ and \ \ \sup_{t \geq t_0} E(\|\Delta M_{t+1}\|^2 \mid \mathcal{F}_t) < \infty \ \ a.s.$$

Then the set Γ^∞ of its limiting values as $t \to \infty$ is a.s. a compact connected set, stable by the flow of the ordinary differential equation (ODE)

$$\dot{\gamma} = -g(\gamma). \tag{A.11}$$

Furthermore, if $\gamma^* \in \Gamma^\infty$ is a uniformly stable equilibrium on Γ^∞ of this ODE, then

$$\gamma_t \to \gamma^* \ \ a.s. \ as \ \ t \to \infty.$$

Notice that by uniformly stable we mean that

$$\sup_{\gamma \in \Gamma^\infty} |\gamma(\gamma_0, t) - \gamma^*| \to 0 \ \text{as} \, t \to \infty$$

where $\gamma(\gamma_0, t)_{\gamma_0 \in \Gamma^\infty, t \in \mathbb{R}^+}$ is the flow of the ODE (A.11) on Γ^∞. Now, the vector field g is η-

differentiable at γ^* if

$$g(\gamma) = g(\gamma^*) + Dg(\gamma^*)(\gamma - \gamma^*) + o(\|\gamma - \gamma^*\|^{1+\eta}) \quad as\, \gamma \to \gamma^* \ \text{ for some } \eta > 0. \tag{A.12}$$

Theorem A.2 assesses the rate of convergence of γ_t to γ^*.

Theorem A.2. *Let γ^* be an equilibrium point of $\{g = 0\}$. Assume that the function g is differentiable at γ^* and all the eigenvalues of $Dg(\gamma^*)$ have positive real parts. Assume that for some $\delta > 0$,*

$$\sup_{t \geq t_0} E(\|\Delta M_{t+1}\|^{2+\delta} \mid \mathcal{F}_t) < \infty \quad a.s., \quad E(\Delta M_{t+1} \Delta M'_{t+1} \mid \mathcal{F}_t) \to \tilde{\Gamma} \ \ a.s.\ as\ t \to \infty, \tag{A.13}$$

where $\tilde{\Gamma}$ is a deterministic symmetric definite positive matrix. Suppose also that for an $\epsilon > 0$,

$$(t+1) v_t E(\|r_{t+1}\|^2 1(\{\|\gamma_t - \gamma^*\| \leq \epsilon\})) \to 0 \ \ as\, t \to \infty, \tag{A.14}$$

where v_t is a positive sequence.
(a) If $\Lambda := Re(\lambda_{min}) > \frac{1}{2}$, where λ_{min} denotes the eigenvalue of $Dg(\gamma^*)$ with the lowest real part and (A.14) holds with $v_t = 1, t \geq 1$, then, the above a.s. convergence is ruled on the convergence set $\{\gamma_t \to \gamma^*\}$ by the following Central Limit Theorem

$$t^{\frac{1}{2}}(\gamma_t - \gamma^*) \to N(0, \frac{1}{2\Lambda - 1}\Sigma) \ \ as\, t \to \infty \quad with\ \ \Sigma := \int_0^\infty e^{-(Dg(\gamma^*)' - \frac{I_d}{2})u} \tilde{\Gamma} e^{-(Dg(\gamma^*) - \frac{I_d}{2})u} du. \tag{A.15}$$

(b) If $Re(\lambda_{min}) = \frac{1}{2}$, g is η-differentiable at γ^* with diagonalizable $Dg(\gamma^*)$ and (A.14) holds with $v_t = \log t, t \geq 2$, then

$$\left(\frac{t}{\log t}\right)^{\frac{1}{2}} (\gamma_t - \gamma^*) \to N(0, \Sigma) \ \ as\, t \to \infty$$

with

$$\Sigma := \lim_{T \to \infty} \frac{1}{T} \int_0^T e^{-(Dg(\gamma^*)' - \frac{I_d}{2})u} \tilde{\Gamma} e^{-(Dg(\gamma^*) - \frac{I_d}{2})u} du.$$

(c) If $\lambda_{min} \in (0, \frac{1}{2})$, $Dg(\gamma^*)$ is as above and (A.14) holds with $v_t = t^{2\lambda_{min} - 1 + \epsilon}, t \geq 1$, for some $\epsilon > 0$, then $t^{\lambda_{min}}(\gamma_t - \gamma^*)$ converges almost surely as $t \to \infty$ towards a finite random variable.

A.3 Literature review: asymptotic analysis of adaptive clinical trials designs

Adaptive procedures in clinical trials use the cumulative information of ongoing trials to adjust treatment assignments to coming patients. Much of the past literature on adaptive designs has focused on proposing new designs and evaluating properties of these designs. In particular, the behavior of patients' allocation proportions and randomization probabilities is of interest. Different response adaptive randomization procedures can be directly evaluated in terms of power and they can be compared by studying their asymptotic distributions, especially their asymptotic variabilities. In fact, the variability of allocations affects power. This has been demonstrated by simulation studies in [54, 70] and theoretically in [41], where the relationship between the power of a test and the variability of the randomization procedure for a given allocation proportion is assed: the average power of a randomization procedure is a decreasing function of the variability of the procedure.
We present below the existing literature about asymptotic analysis of adaptive designs in clinical trials.

In adaptive designs based on randomized urn models, each patient's treatment assignment is determined by drawing a ball from an urn containing different types of balls, and the urn composition is updated by adding/dropping a number of balls of the same type and/or of the opposite type, often according to patients' responses. Results on strong consistency and asymptotic normality of the treatment allocation proportions (proportions of balls of each type drawn) and randomization probabilities (proportions of balls of each type in the urn) of many designs based on urn models have been determined under certain assumptions on the drawing rule, mainly depending on the eigenstructure of the limiting generating matrices, which determine how balls are added to the urn. The first theoretical analysis of randomized urn models can be traced back to the work of Athereya and Karlin [5] and other early works on the topic includes [8] and [80] about Generalized Pólya Urn models.

Early studies of urn models have a number of drawbacks: they are usually proposed for binary or multinomial outcomes, the urn process usually has higher variability than other types of procedures [41] and thus it is less powerful in statistical inferences. Also, the formulation of the asymptotic variability is usually quite complex and it is difficult to derive a reasonable estimate.

Finally, the models are designed mainly for the comparison of two treatments, so there is a shortage of methodology to handle cases with multiple treatments.

Later, alternative urn designs have been developed to overcome the aforementioned drawbacks and their asymptotic properties have been studied intensively: law of large numbers and central limit theorems for the number of sampled balls of these models have been estabilished. Relevant examples consist of the works of Ivanova [46] on drop-the-loser model, Zhang, Hu et al. [101] on immigrated urn model and Ghiglietti, Vidyashankar and Rosenberger [36] on an adaptive randomly reinforced urn model. Asymptotic properties of this type of designs are mainly studied by using theory of stochastic processes, often invoking martingale arguments. Alternatively, a similar technique to that used in Chapter 1 - based on stochastic approximation - could be employed to derive asymptotic characteristics of urn models. Laruelle and Pagès [52] outlined the link between stochastic approximation and response-adaptive clinical trials in the case of binary responses with randomization procedure based on the Generalized Friedman Urn; instead, L.X. Zhang [100], inspired by stochastic approximation techniques, estabilished the asymptotic properties of the same model under weaker conditions.

Other important contributions to the literature about adaptive randomized designs, have focused on target driven randomization procedures. These designs are constructed in such a way that the sample allocation proportion converges to a target allocation proportion defined as a function of the unknown parameters of the response model, often identified due to some optimality property. The ensuing optimal allocation depends in general on the unknown model parameters and, therefore, these designs are based on the sequential estimation of unknown parameters in order to allocate sequentially subjects to treatments. In literature, a number of asymptotic results for these designs is reported: Melfi and Page [55] studied the sequential maximum likelihood approach, Hu, Zhang and He [44] investigated the efficient response adaptive randomization design and earlier Eisele and Woodroofe [34] and later Hu and Zhang [43] examined the doubly adaptive coin design. More recently, Baldi Antognini and Zagoraiou [2, 3] proved results on the almost sure convergence and asymptotic normality of a vast class of adaptive allocation procedures based on randomization functions. Although the large majority of the literature is focused on the estimation of the treatment effects, recent efforts has been directed in developing multipurpose design methodology which maximizes the power of statistical tests to detect correct conclusions about the treatment effects under a suitable ethical constraint reflecting the effectiveness of the

treatments [10].

Finally, there is a considerable literature on Bayesian adaptive designs, whose allocation rules combine prior knowledge with the information provided by accumulating patient responses through Bayesian principles. Advantages of Bayesian designs over classical designs of clinical trials include the ability to incorporate prior information regarding treatment efficacy into the analysis; the ability to make multiple interim analysis of accumulating data without increasing the error rate of the study; the ability to calculate the probability that one treatment is more effective than another; and the ability to deal with missing data with great flexibility, using predictive probabilities. Nevertheless, from the statistical point of view, the frequentist paradigm has dominated the field of clinical trials over the past sixty years. Two major barriers have prevented Bayesian methods from becoming popular: the inherent computational demands and the use of subjective information [47]. Asymptotic properties of Bayesian adaptive designs are often derived through simulation studies. In fact, it is a state of affairs that in general there is no sounder way to analyse and evaluate the performance of Bayesian designs other than by simulations. As far as we know, few researchers have derived analytic results on the asymptotic properties of these designs. We mention the work on Bayesian doubly adaptive randomization [98].

Emerging new designs such as Bayesian platform trials [75] and basket designs [87] have great potential to accelerate the development of new drugs, assigning more patients to promising arms relative to many traditional randomized designs [17]. While the use of Bayesian designs becomes more frequent [37], there also appears to be a trend in the literature towards more complex designs. This trend toward adaptive designs that become increasingly complex and tailored to end points and clinical hypotheses might have positive effects in terms of statistical efficiency, time, and resources to develop new treatments, but it also poses the challenge to establish procedures that are appropriate for quantifying power and other operating characteristics of relatively simple designs, such as controlled balanced designs, but inappropriate for these modern adaptive designs. All the more reason, asymptotic properties of these adaptive designs could be derived exclusively through simulation studies.

Chapter 2

Asymptotic properties of Bayesian Uncertainty directed trial Designs for general outcomes and utilities

A variety of response-adaptive randomization procedures have been proposed in literature assuming Bernoulli and Gaussian outcomes. Literature on asymptotic properties of these procedures is quite well developed, refer to [68, 99] for summary results. On the other hand, the list is not so long when the distribution of the outcomes is not in the natural exponential family.

In this Chapter we extend the result presented in Proposition 1 about the strong consistency of allocation proportions and randomization probabilities of a BUD to outcomes distributions outside the natural exponential family. Also, we study some asymptotic properties of BUD based on utilities different than (1.5).

2.1 Almost sure convergence of randomization probabilities and allocation proportions: beyond natural exponential family

We first exhibit in Lemma 3 approximations of the information increment (1.1) of BUDs with sum of the (negative) posterior variances of the parameters $\theta_a, a = 0, 1$, as information measure when the outcomes distributions are not restricted to be in the natural exponential family. Throughout this section θ_a is not necessary required to be the mean of the outcomes as in Chapter 1. We write $X(t) = o_P(a(t))$ to intend that $X(t)/a(t)$ converges to zero in probability as $t \to +\infty$.

Lemma 3. *Let us consider two-arm BUDs with information metric $u(\Sigma_t)$ in (1.5). Assume that the parameter space $\Theta \subset \mathbb{R}$ is a bounded open interval, that the true value of the parameter $\theta_{0,a}$ is an interior point of Θ for $a \in \{0,1\}$ and that the prior is the uniform distribution on Θ. If*

(i) $\inf_{y,\theta_a} f_{\theta_a}(y) > 0$

(ii) $\sup_{y,\theta_a} f_{\theta_a}(y) < \infty$

(iii) $\sup_{y,\theta_a} \left| \frac{\partial^k f_{\theta_a}(y)}{\partial \theta_a^k} \right| < \infty$ *for* $k = 1, 2, 3,$

then

$$\Delta_t(a) = I_{\theta_{0,a}}^{-1} \times (t\hat{p}_{t,a})^{-2} + o_P((t\hat{p}_{t,a})^{-2}), \tag{2.1}$$

where $I_{\theta_{0,a}}$ is the Fisher information.

Note that (i) implies that the space of observations is bounded. Regularity conditions of Lemma 3 are more restrictive than what is necessary to prove (2.1), but they are simpler. We provide below a less stringent set of conditions under which the approximation of the information gain (2.1) holds and, by leveraging on an additional Lemma 4, we prove Lemma 3 in this setup.

Regularity conditions (Lemma 3)

For simplicity, we consider responsess $Y_1, \ldots, Y_n$ observed in a single arm. Let us denote by $\mathcal{F}_n$ the sigma algebra generated by them.

Assume that the parameter space $\Theta \subset \mathbb{R}$ is a bounded open interval, that the true value of the parameter θ_0 is an interior point of Θ and that the prior is the uniform distribution on Θ. Let $f(y,\theta)$ and $l(y,\theta)$ denote the density function and the log-likelihood of the observations, respectively. Denote by

$$\dot{f}(y,\theta) = \frac{\partial}{\partial\theta} f(y,\theta), \quad \ddot{f}(y,\theta) = \frac{\partial^2}{\partial\theta^2} f(y,\theta)$$

and by $\hat{\theta}_n$ the MLE based on a sample of size n. Also, let

$$f(y,\theta,\rho) = \sup_{|\theta-\theta'|\leq\rho} f(y,\theta'), \qquad Q(y,r) = \sup_{|\theta|>r} f(y,\theta)$$

for $\rho, r > 0$.

We require regularity conditions of Johnson in [49] to hold:

a) f is three times continuously differentiable with respect to θ.
b) For every $\theta \in \bar{\Theta}$ and $\rho, r > 0$, $f(y, \theta, \rho)$ and $Q(y, r)$ are measurable functions of y and for sufficiently small ρ and sufficiently large r,

$$E_{\theta_0} \left[\log f(Y, \theta, \rho)\right]^+ < \infty, \qquad E_{\theta_0} \left[\log Q(Y, r)\right]^+ < \infty.$$

c) There exists G_k for $k = 1, 2$ satisfying $\mid \frac{\partial^k}{\partial \theta^k} l(y, \theta) \mid \leq G_k(y)$ for θ in a neighborhood of θ_0 and $E_{\theta_0} G_k(Y) < \infty$.
In addition to assumptions a)-c) we assume that the following conditions are satisfied:
d) There exists G_3 such that $\sup_{|\theta - \hat{\theta}_n| < \delta} |\frac{\partial^3}{\partial \theta^3} l(y, \theta)| \leq G_3(y)$ and $E_{\theta_0} G_3(Y) < \infty$.
e) For some $\delta > 0$

$$\int \sup_{|\theta - \hat{\theta}_n| < \delta} |\ddot{f}(y, \theta)| dy = O_P(1), \tag{2.2}$$

$$\int \sup_{|\theta - \hat{\theta}_n| < \delta} |\ddot{f}(y, \theta)| \frac{|\dot{f}(y, \hat{\theta}_n)|}{f(y, \hat{\theta}_n)} dy = O_P(1), \tag{2.3}$$

$$\int \sup_{|\theta - \hat{\theta}_n| < \delta} \frac{\ddot{f}(y, \theta)^2}{f(y, \hat{\theta}_n)} dy = O_P(1), \tag{2.4}$$

$$\int \sup_{|\theta_1 - \hat{\theta}_n| < \delta, |\theta_2 - \hat{\theta}_n| < \delta} \frac{|\dot{f}(y, \theta_1)|}{f(y, \theta_2)} f(y, \hat{\theta}_n) dy = O_P(1), \tag{2.5}$$

$$\int \sup_{|\theta_1 - \hat{\theta}_n| < \delta, |\theta_2 - \hat{\theta}_n| < \delta, |\theta_3 - \hat{\theta}_n| < \delta} \frac{\dot{f}(y, \theta_1)^2 |\dot{f}(y, \theta_2)|}{f(y, \theta_3) f(y, \hat{\theta}_n)} dy = O_P(1). \tag{2.6}$$

Additional Lemma (complementary to the proof of Lemma 3)

Lemma 4. *Let $Y_1, Y_2, \ldots$ be a sequence of random variables satisfying the regularity conditions of the previous section. For every n, let $\mathcal{F}_n$ be the sigma algebra generated by $Y_1, \ldots, Y_n$. Then, $\Delta_n := Var(\theta \mid \mathcal{F}_n) - E(Var(\theta \mid \mathcal{F}_{n+1}) \mid \mathcal{F}_n) = I_{\theta_0}^{-1} n^{-2} + o_P(n^{-2})$.*

Before proving Lemma 4, let us introduce some further notation and preliminary results.
First, notice that, for every θ,

$$\int \dot{f}(y, \theta) dy = 0. \tag{2.7}$$

Let

$$a_{k,n}(\theta) = \frac{1}{n} \sum_{i=1}^{n} \frac{\partial^k}{\partial \theta^k} \log f(Y_i, \theta).$$

By definition $a_{1,n}(\hat{\theta}_n) = 0$.
Moreover

$$a_{2,n}(\hat{\theta}_n) \to -I_{\theta_0} \quad a.s.$$

as $n \to \infty$, where $I_\theta = E_\theta(\frac{\partial}{\partial\theta} \log f(Y,\theta))^2 = -E_\theta(\frac{\partial^2}{\partial\theta^2} \log f(Y,\theta)))$. Also,

$$\prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} = \exp(\frac{1}{2} n a_{2,n}(\hat{\theta}_n)\phi^2 + \frac{1}{6} n a_{3,n}(\theta_n^*)\phi^3),$$

for some $\theta_n^* = \theta_n^*(\phi)$ that satisfies $|\theta_n^* - \hat{\theta}_n| < \phi$.
By the change of variable $u = \sqrt{n}\phi$, we obtain

$$\prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + u/\sqrt{n})}{f(Y_i, \hat{\theta}_n)} = \exp(a_{2,n}(\hat{\theta}_n)u^2/2 + a_{3,n}(\theta_n^*)u^3/(6\sqrt{n})),$$

for some $\theta_n^* = \theta_n^*(u)$ that satisfies $|\theta_n^* - \hat{\theta}_n| < u/\sqrt{n}$.
Let $C_n(u) = a_{2,n}(\hat{\theta}_n)u^2/2 + a_{3,n}(\theta_n^*)u^3/(6\sqrt{n})$, then

$$\prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + u/\sqrt{n})}{f(Y_i, \hat{\theta}_n)} = e^{C_n(u)}. \tag{2.8}$$

By Lemma 2.2, Lemma 2.3 and (2.5) in [49] there exist ϵ, δ and N_0 such that, P-a.s.,

$$\prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} \le \exp(-\phi^2/12) \quad \text{for } |\phi| \le \delta \text{ and } n \ge N_0 \tag{2.9}$$

and

$$\prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} \le \exp(-n\epsilon) \quad \text{for } |\phi| > \delta \text{ and } n \ge N_0. \tag{2.10}$$

By the change of variable $u = \sqrt{n}\phi$, we obtain

$$\prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + u/\sqrt{n})}{f(Y_i, \hat{\theta}_n)} \le \exp(-u^2/(12n)) \quad \text{for } |u| \le \delta\sqrt{n} \text{ and } n \ge N_0 \quad \text{a.s.} \tag{2.11}$$

and

$$\prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + u/\sqrt{n})}{f(Y_i, \hat{\theta}_n)} \le \exp(-n\epsilon) \quad \text{for } |u| > \delta\sqrt{n} \text{ and } n \ge N_0 \quad \text{a.s..} \tag{2.12}$$

The first inequality can be rewritten as

$$e^{C_n(u)} \leq \exp(-u^2/(12n)) \quad \text{for } |u| \leq \delta\sqrt{n} \text{ and } n \geq N_0 \quad \text{a.s.} \tag{2.13}$$

Proof. (Lemma 4) First, in STEP 1, we show that

$$\Delta_n = \frac{1}{\int \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi} \left[\int \frac{\left(\int \phi f(y,\hat{\theta}_n+\phi) \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi \right)^2}{\int f(y,\hat{\theta}_n+\phi) \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi} dy - \right.$$
$$\left. - \frac{\left(\int \phi \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi \right)^2}{\int \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi} \right].$$

Then, we provide a useful approximation of Δ_n: let δ be defined such that inequalities (2.11) and (2.12) hold, and let

$$\tilde{\Delta}_n = \frac{1}{\int_{-\delta}^{\delta} \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi} \left[\int \frac{\left(\int_{-\delta}^{\delta} \phi f(y,\hat{\theta}_n+\phi) \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi \right)^2}{\int_{-\delta}^{\delta} f(y,\hat{\theta}_n+\phi) \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi} dy - \right.$$
$$\left. - \frac{\left(\int_{-\delta}^{\delta} \phi \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi \right)^2}{\int_{-\delta}^{\delta} \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi} \right].$$

The proof proceeds by proving in STEP 2 that $\tilde{\Delta}_n = I_{\theta_0}^{-1} n^{-2} + o_P(n^{-2})$ and then in STEP 3 that

$$\Delta_n = \tilde{\Delta}_n + o_P(n^{-2}). \tag{2.14}$$

By extending the above approximation of the information increment to the two arm setting, we conclude the proof of Lemma 4.

STEP 1: Expression of Δ_n

Since

$$\mathrm{Var}(\theta \mid \mathcal{F}_{n+1}) = E(\theta^2 \mid \mathcal{F}_{n+1}) - E(\theta \mid \mathcal{F}_{n+1})^2,$$

then

$$E(\mathrm{Var}(\theta \mid \mathcal{F}_{n+1}) \mid \mathcal{F}_n) = E(\theta^2 \mid \mathcal{F}_n) - E(E(\theta \mid \mathcal{F}_{n+1})^2 \mid \mathcal{F}_n).$$

Thus,

$$\begin{aligned}\Delta_n &= E(E(\theta \mid \mathcal{F}_{n+1})^2 \mid \mathcal{F}_n) - E(\theta \mid \mathcal{F}_n)^2 \\ &= E(E(\theta - \hat{\theta}_n \mid \mathcal{F}_{n+1})^2 \mid \mathcal{F}_n) - E(\theta - \hat{\theta}_n \mid \mathcal{F}_n)^2.\end{aligned}$$

It holds

$$\begin{aligned}\Delta_n &= \int \frac{\left(\int \phi f(y,\hat{\theta}_n+\phi)\prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi\right)^2}{\left(\int f(y,\hat{\theta}_n+\phi)\prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi\right)^2}\frac{\int f(y,\hat{\theta}_n+\phi)\prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi}{\int \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi}dy- \\ &- \frac{\left(\int \phi \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi\right)^2}{\left(\int \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi\right)^2} \\ &= \int \frac{\left(\int \phi f(y,\hat{\theta}_n+\phi)\prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi\right)^2}{\int f(y,\hat{\theta}_n+\phi)\prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi \int \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi}dy - \frac{\left(\int \phi \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi\right)^2}{\left(\int \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi\right)^2} \\ &= \frac{1}{\int \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi}\left[\int \frac{\left(\int \phi f(y,\hat{\theta}_n+\phi)\prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi\right)^2}{\int f(y,\hat{\theta}_n+\phi)\prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi}dy- \right. \\ &\left. - \frac{\left(\int \phi \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi\right)^2}{\int \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi}\right]\end{aligned}$$

STEP 2: $\tilde{\Delta}_n = I_{\theta_0}^{-1} n^{-2} + o_P(n^{-2})$

We have

$$\begin{aligned}\tilde{\Delta}_n &= \frac{1}{\int_{-\delta}^{\delta} \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi}\left[\int \frac{\left(\int_{-\delta}^{\delta} \phi f(y,\hat{\theta}_n+\phi)\prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi\right)^2}{\int_{-\delta}^{\delta} f(y,\hat{\theta}_n+\phi)\prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi}dy- \right. \\ &\left. - \frac{\left(\int_{-\delta}^{\delta} \phi \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi\right)^2}{\int_{-\delta}^{\delta} \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi}\right]\end{aligned} \tag{2.15}$$

$$= \frac{1}{n}\frac{1}{\int_{-\delta\sqrt{n}}^{\delta\sqrt{n}} e^{C_n(u)}du}\left[\int \frac{\left(\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} uf(y,\hat{\theta}_n + u/\sqrt{n})e^{C_n(u)}du\right)^2}{\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} f(y,\hat{\theta}_n + u/\sqrt{n})e^{C_n(u)}du}dy - \right.$$
$$\left. - \frac{\left(\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} ue^{C_n(u)}du\right)^2}{\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} e^{C_n(u)}du}\right], \tag{2.16}$$

where (2.15) is the definition of $\tilde{\Delta}_n$ and (2.16) is a consequence of the change of variable $u = \sqrt{n}\phi$ and (2.8).

Thus,

$$\tilde{\Delta}_n = \frac{1}{n}\frac{1}{\int_{-\delta\sqrt{n}}^{\delta\sqrt{n}} e^{C_n(u)}du}\left[\int \frac{\left(\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} uf(y,\hat{\theta}_n + u/\sqrt{n})e^{C_n(u)}du\right)^2}{\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} f(y,\hat{\theta}_n + u/\sqrt{n})e^{C_n(u)}du}dy - \right.$$
$$\left. - \frac{\left(\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} uf(y,\hat{\theta}_n)e^{C_n(u)}du\right)^2}{\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} f(y,\hat{\theta}_n)e^{C_n(u)}du}\right]$$
$$= \frac{1}{n}\frac{1}{\int_{-\delta\sqrt{n}}^{\delta\sqrt{n}} e^{C_n(u)}du}\int\left(\frac{A_n'(y)^2}{B_n'(y)} - \frac{A_n(y)^2}{B_n(y)}\right)dy, \tag{2.17}$$

where

$$A_n'(y) = \int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} uf(y,\hat{\theta}_n + u/\sqrt{n})e^{C_n(u)}du$$
$$B_n'(y) = \int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} f(y,\hat{\theta}_n + u/\sqrt{n})e^{C_n(u)}du$$
$$A_n(y) = \int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} uf(y,\hat{\theta}_n)e^{C_n(u)}du$$
$$B_n(y) = \int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} f(y,\hat{\theta}_n)e^{C_n(u)}du.$$

Therefore, we can rewrite (2.17) as follows

$$\tilde{\Delta}_n = \frac{1}{n}\left(\frac{1}{\int_{-\delta\sqrt{n}}^{\delta\sqrt{n}} e^{C_n(u)}du}\right)^2\left[2\int\frac{A_n(y)(A_n'(y) - A_n(y))}{f(y,\hat{\theta}_n)}dy + \int\frac{(A_n'(y) - A_n(y))^2}{f(y,\hat{\theta}_n)}dy - \right.$$
$$\left. - \int\frac{A_n'(y)^2}{B_n'(y)}\frac{B_n'(y) - B_n(y)}{f(y,\hat{\theta}_n)}dy\right]$$

We will show that $\tilde{\Delta}_n = I_{\theta_0}^{-1} n^{-2} + o_P(n^{-2})$, by showing that:

1. $\int \frac{A_n(y)(A_n'(y)-A_n(y))}{f(y,\hat{\theta}_n)} dy = o_P(\frac{1}{n})$

2. $\int \frac{(A_n'(y)-A_n(y))^2}{f(y,\hat{\theta}_n)} dy = \frac{1}{n} 2\pi I_{\theta_0}^{-2\cdot} + o_P(\frac{1}{n})$

3. $\int \frac{A'(y)^2}{B'(y)} \frac{B(y)-B'(y)}{f(y,\hat{\theta}_n)} dy = o_P(\frac{1}{n})$.

4. $\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} e^{C_n(u)} du = (2\pi)^{1/2} I_{\theta_0}^{-1/2} + o_P(1)$.

1. Let us show that $\int \frac{A_n(y)(A_n'(y)-A_n(y))}{f(y,\hat{\theta}_n)} dy = o_P(\frac{1}{n})$.
There exists $\theta_n^{(1)}$ such that $|\theta_n^{(1)} - \hat{\theta}_n| < \delta$ and

$$\begin{aligned}
&\int \frac{A_n(y)(A_n'(y) - A_n(y))}{f(y,\hat{\theta}_n)} dy \\
&= \int \left[\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} u e^{C_n(u)} du \int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} u \left(\dot{f}(y,\hat{\theta}_n) \frac{u}{\sqrt{n}} + \ddot{f}(y,\theta_n^{(1)}) \frac{u^2}{n} \right] e^{C_n(u)} du \right) dy \\
&= \int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} u e^{C_n(u)} du \int \int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} \ddot{f}(y,\theta_n^{(1)}) \frac{u^3}{n} e^{C_n(u)} du dy \qquad (2.18) \\
&\leq \frac{1}{n} \sup_\theta \int |\ddot{f}(y,\theta)| dy \int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} u e^{C_n(u)} du \int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} u^3 e^{C_n(u)} du, \qquad (2.19)
\end{aligned}$$

where in (2.18) we have used (2.7) and the fact that $\int u^2 e^{C_n(u)} du < \infty$.
Furthermore,

$$\begin{aligned}
\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} u e^{C_n(u)} du &= \int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} u e^{a_{2,n}(\hat{\theta}_n)u^2/2 + a_{3,n}(\theta_n^*)u^3/(6\sqrt{n})} du \\
&= \int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} u e^{a_{2,n}(\hat{\theta}_n)u^2/2} \left(1 + (e^{a_{3,n}(\theta_n^*)u^3/(6\sqrt{n})} - 1) \right) du \\
&= \int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} u e^{a_{2,n}(\hat{\theta}_n)u^2/2} (e^{a_{3,n}(\theta_n^*)u^3/(6\sqrt{n})} - 1) du \\
&\leq \int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} \frac{u^4}{6\sqrt{n}} |a_{3,n}(\theta_n^*)| e^{a_{2,n}(\hat{\theta}_n)u^2/2 + a_{3,n}(\theta_n^*)u^3/(6\sqrt{n})} du \qquad (2.20) \\
&\leq \frac{1}{\sqrt{n}} \int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} \frac{u^4}{6} |a_{3,n}(\theta_n^*)| e^{C_n(u)} du
\end{aligned}$$

$$\leq \left(\frac{1}{n}\sum_{i=1}^{n} G_3(Y_i)\right)\frac{1}{\sqrt{n}}\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}\frac{u^4}{6}e^{C_n(u)}du$$
$$= O_P\left(\frac{1}{\sqrt{n}}\right), \tag{2.21}$$

where (2.20) follows from $e^x - 1 \leq xe^x$ for any $x \in \mathbb{R}$ and equation (2.21) is a consequence of assumption d), equation (2.13) and dominated convergence theorem.
On the other hand, by (2.13),

$$\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} |u|^3 e^{C_n(u)}du < \infty. \tag{2.22}$$

Thus, combining (2.19) and (2.22) with (2.2), we get

$$\int \frac{A_n(y)(A'_n(y) - A_n(y))}{f(y,\hat{\theta}_n)}dy = O_P(\frac{1}{n\sqrt{n}}).$$

2. Let us show that $\int \frac{(A'_n(y) - A_n(y))^2}{f(y,\hat{\theta}_n)}dy = \frac{1}{n}2\pi I_{\theta_0}^{-2} + o_P(\frac{1}{n})$.
There exists $\theta_n^{(2)}$ such that $|\theta_n^{(2)} - \hat{\theta}_n| < \delta$ and

$$\int \frac{(A'_n(y) - A_n(y))^2}{f(y,\hat{\theta}_n)}dx = \int \left(\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} u\left(\dot{f}(y,\hat{\theta}_n)\frac{u}{\sqrt{n}} + \ddot{f}(y,\theta_n^{(2)})\frac{u^2}{2n}\right)e^{C_n(u)}du\right)^2 \frac{1}{f(y,\hat{\theta}_n)}dy$$
$$= \frac{1}{n}\int \frac{\dot{f}(y,\hat{\theta}_n)^2}{f(y,\hat{\theta}_n)^2}f(y,\hat{\theta}_n)dy\left(\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} u^2 e^{C_n(u)}du\right)^2$$
$$+ \frac{1}{4n^2}\int \left(\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} \ddot{f}(\theta_n^{(2)})u^3 e^{C_n(u)}du\right)^2 \frac{1}{f(y,\hat{\theta}_n)}du + R_n$$

with

$$|R_n| \leq \frac{1}{n\sqrt{n}}\int \sup_{|\theta-\hat{\theta}_n|<\delta} |\ddot{f}(y,\theta)|\frac{|\dot{f}(y,\hat{\theta}_n)|}{f(y,\hat{\theta}_n)}dy\left(\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} u^4 e^{C_n(u)}du\right)^2$$
$$= O_P(\frac{1}{n\sqrt{n}}),$$

by (2.3) and (2.13).

On the other hand,

$$\frac{1}{n}\int \frac{\dot{f}(y,\hat{\theta}_n)^2}{f(y,\hat{\theta}_n)^2} f(y,\hat{\theta}_n)dy \left(\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} u^2 e^{C_n(u)du}\right)^2 \sim \frac{1}{n} E_{\hat{\theta}_n}\left(\frac{\dot{f}(Y,\hat{\theta}_n)^2}{f(Y,\hat{\theta}_n)^2}\right) I_{\theta_0}^{-2}\frac{2\pi}{I_{\theta_0}} \sim \frac{1}{n} 2\pi I_{\theta_0}^{-2}.$$

Furthermore,

$$\begin{aligned}
&\frac{1}{n^2}\int \left(\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} \ddot{f}(\theta_n^{(2)})u^3 e^{C_n(u)}du\right)^2 \frac{1}{f(y,\hat{\theta}_n)}dy \\
&\quad \le \frac{1}{n^2}\left(\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} u^3 e^{C_n(u)}du\right)^2 \int \sup_{|\theta-\hat{\theta}_n|<\delta} \ddot{f}(x,\theta)^2 \frac{1}{f(y,\hat{\theta}_n)}dy \\
&\quad = o_P\left(\frac{1}{n}\right),
\end{aligned}$$

where last equality follows from (2.4).

3. Let us show that $\int \frac{A'(y)^2}{B'(y)}\frac{B(y)-B'(y)}{f(y,\hat{\theta}_n)}dy = o_P(\frac{1}{n})$.
There exist $\theta_n^{(3)}$ and $\theta_n^{(4)}$ such that $|\theta_n^{(3)}-\hat{\theta}_n|<\delta$, $|\theta_n^{(4)}-\hat{\theta}_n|<\delta$ and

$$\begin{aligned}
\int \frac{A'(y)^2}{B'(y)}\frac{B'(y)-B(y)}{f(y,\hat{\theta}_n)}dy &= \int \frac{\left(\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} uf(y,\hat{\theta}_n+\frac{u}{\sqrt{n}})e^{C_n(u)}du\right)^2}{\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} f(y,\hat{\theta}_n+\frac{u}{\sqrt{n}})e^{C_n(u)}du}\times \\
&\quad \times \frac{\left(\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} f(y,\hat{\theta}_n+\frac{u}{\sqrt{n}})-f(y,\hat{\theta}_n)\right)e^{C_n(u)}du}{f(y,\hat{\theta}_n)}dy \\
&= \int \frac{\left(f(y,\hat{\theta}_n)\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} ue^{C_n(u)}du + \int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}\dot{f}(y,\theta_n^{(3)})\frac{u^2}{\sqrt{n}}e^{C_n(u)}du\right)^2}{\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} e^{C_n(u)}f(y,\hat{\theta}_n+\frac{u}{\sqrt{n}})du}\frac{\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}\dot{f}(y,\theta_n^{(4)})\frac{u}{\sqrt{n}}e^{C_n(u)}du}{f(y,\hat{\theta}_n)}dy \\
&\le 4\int \frac{f(y,\hat{\theta}_n)^2\left(\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} ue^{C_n(u)}du\right)^2 + \left(\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}\dot{f}(y,\theta_n^{(3)})\frac{u^2}{\sqrt{n}}e^{C_n(u)}du\right)^2}{\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} e^{C_n(u)}f(y,\hat{\theta}_n+\frac{u}{\sqrt{n}})du}\times \\
&\quad \times \frac{\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}\dot{f}(y,\theta_n^{(4)})\frac{u}{\sqrt{n}}e^{C_n(u)}du}{f(y,\hat{\theta}_n)}dy \qquad (2.23) \\
&\le 4\left(\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} ue^{C_n(u)}du\right)^2 \int \frac{\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}\dot{f}(y,\theta_n^{(4)})\frac{u}{\sqrt{n}}e^{C_n(u)}du}{\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} e^{C_n(u)}f(y,\hat{\theta}_n+\frac{u}{\sqrt{n}})du}f(y,\hat{\theta}_n)dy+
\end{aligned}$$

$$+4\int\frac{\left(\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}\dot{f}(y,\theta_n^{(3)})\frac{u^2}{\sqrt{n}}e^{C_n(u)}du\right)^2\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}\dot{f}(y,\theta_n^{(4)})\frac{u}{\sqrt{n}}e^{C_n(u)}du}{f(y,\hat{\theta}_n)\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}e^{C_n(u)}f(y,\hat{\theta}_n+\frac{u}{\sqrt{n}})du}dy$$

$$\leq 4\frac{1}{\sqrt{n}}\frac{\left(\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}ue^{C_n(u)}du\right)^3}{\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}e^{C_n(u)}du}\int\sup_{|\theta_1-\hat{\theta}_n|<\delta,|\theta_2-\hat{\theta}_n|<\delta}\frac{|\dot{f}(y,\theta_1)|}{f(y,\theta_2)}f(y,\hat{\theta}_n)dy+$$

$$+4\frac{1}{n\sqrt{n}}\frac{\left(\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}u^2e^{C_n(u)}du\right)^2\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}ue^{C_n(u)}du}{\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}e^{C_n(u)}du}\int\sup_{|\theta_1-\hat{\theta}_n|<\delta,|\theta_2-\hat{\theta}_n|<\delta,|\theta_3-\hat{\theta}_n|<\delta}\frac{\dot{f}(y,\theta_1)^2|\dot{f}(y,\theta_2)|}{f(y,\theta_3)f(y,\hat{\theta}_n)}dy$$

$$=\frac{1}{n^2}O_P(1)\left(\int\sup_{|\theta_1-\hat{\theta}_n|<\delta,|\theta_2-\hat{\theta}_n|<\delta}\frac{|\dot{f}(y,\theta_1)|}{f(y,\theta_2)}f(y,\hat{\theta}_n)dy+\right.$$

$$\left.+\int\sup_{|\theta_1-\hat{\theta}_n|<\delta,|\theta_2-\hat{\theta}_n|<\delta,|\theta_3-\hat{\theta}_n|<\delta}\frac{\dot{f}(y,\theta_1)^2|\dot{f}(y,\theta_2)|}{f(y,\theta_3)f(y,\hat{\theta}_n)}dy\right) \tag{2.24}$$

$$=o_P(\frac{1}{n}), \tag{2.25}$$

where in (2.23) we have used $(a+b)^2\leq 4(a^2+b^2)$ and in (2.24) we have invoked (2.13) and (2.21). Equation (2.25) follows from (2.5) and (2.6).

4. Let us show that $\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}e^{C_n(u)}du\to(2\pi)^{1/2}I_{\theta_0}^{-1/2}$.
We have, for $\mid\theta_n^*-\hat{\theta}_n\mid<\delta$,

$$\begin{aligned}\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}e^{C_n(u)}du&=\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}e^{a_{2,n}(\hat{\theta}_n)u^2/2+a_{3,n}(\theta_n^*)u^3/(6\sqrt{n})}du\\&=\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}e^{a_{2,n}(\hat{\theta}_n)}du+\tilde{R}_n\end{aligned}$$

with

$$\begin{aligned}\mid\tilde{R}_n\mid&\leq\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}e^{a_{2,n}(\hat{\theta}_n)}\left(e^{a_{3,n}(\theta_n^*)u^3/(6\sqrt{n})}-1\right)du\\&\leq\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}e^{a_{2,n}(\hat{\theta}_n)}a_{3,n}(\theta_n^*)\frac{u^3}{6\sqrt{n}}e^{a_{3,n}(\theta_n^*)u^3/(6\sqrt{n})}du\\&\leq\frac{1}{\sqrt{n}}\mid\frac{1}{n}\sum_{i=1}^{n}G_3(Y_i)\mid\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta}u^3e^{C_n(u)}du\\&=o_P(1).\end{aligned}$$

Since

$$e^{a_{2,n}(\hat{\theta}_n)u^2/2} \to e^{-I_{\theta_0}u^2/2} \quad \text{a.s.}$$

then

$$\int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} e^{C_n(u)}du = (2\pi)^{1/2}I_{\theta_0}^{-1/2} + o_P(1).$$

STEP 3: Asymptotic behavior of $\Delta_n - \tilde{\Delta}_n$

Let us show that $\Delta_n - \tilde{\Delta}_n = o_P(\frac{1}{n^2})$. It holds that

$$\begin{aligned}
\Delta_n - \tilde{\Delta}_n = {} & \frac{1}{\int \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi}\left[\int \frac{\left(\int \phi f(y,\hat{\theta}_n+\phi)\prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi\right)^2}{\int f(y,\hat{\theta}_n+\phi)\prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi}dy - \right. \\
& \left. - \frac{\left(\int \phi \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi\right)^2}{\int \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi}\right] - \\
& - \frac{1}{\int_{-\delta}^{\delta} \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi}\left[\int \frac{\left(\int_{-\delta}^{\delta} \phi f(y,\hat{\theta}_n+\phi)\prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi\right)^2}{\int_{-\delta}^{\delta} f(y,\hat{\theta}_n+\phi)\prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi}dy - \right. \\
& \left. - \frac{\left(\int_{-\delta}^{\delta} \phi \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi\right)^2}{\int_{-\delta}^{\delta} \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi}\right] \\
\leq {} & \frac{\int_{[-\delta,\delta]^c} \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi}{\int \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi}|\tilde{\Delta}_n| + \frac{1}{\int \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi} \times \\
& \times \left[\left|\int \frac{\left(\int \phi f(y,\hat{\theta}_n+\phi)\prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi\right)^2}{\int f(y,\hat{\theta}_n+\phi)\prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi}dy - \right.\right. \\
& \left. - \int \frac{\left(\int_{-\delta}^{\delta} \phi f(y,\hat{\theta}_n+\phi)\prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi\right)^2}{\int_{-\delta}^{\delta} f(y,\hat{\theta}_n+\phi)\prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi}dy\right| + \\
& \left. + \left|\frac{\left(\int \phi \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi\right)^2}{\int \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi} - \frac{\left(\int_{-\delta}^{\delta} \phi \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi\right)^2}{\int_{-\delta}^{\delta} \prod_{i=1}^n \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)}d\phi}\right|\right].
\end{aligned}$$

By STEP 2

$$\int_{[-\delta,\delta]} \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi = \frac{1}{\sqrt{n}} \int_{-\sqrt{n}\delta}^{\sqrt{n}\delta} e^{C_n(u)} du = \frac{1}{\sqrt{n}} (2\pi)^{1/2} I_{\theta_0}^{-1/2} + o_P(\frac{1}{\sqrt{n}}).$$

On the other hand, by (2.10),

$$\int_{[-\delta,\delta]^c} \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi \leq C' e^{-n\epsilon}.$$

Thus,

$$\int \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi = C \frac{1}{\sqrt{n}} + o_P(\frac{1}{\sqrt{n}})$$

and

$$\frac{\int_{[-\delta,\delta]^c} \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi}{\int \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi} |\tilde{\Delta}_n| = o_P(\frac{1}{n^2}).$$

Moreover,

$$\begin{aligned}
&\left| \int \frac{\left(\int \phi f(y, \hat{\theta}_n + \phi) \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi \right)^2}{\int f(y, \hat{\theta}_n + \phi) \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi} dy - \int \frac{\left(\int_{-\delta}^{\delta} \phi f(y, \hat{\theta}_n + \phi) \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi \right)^2}{\int_{-\delta}^{\delta} f(y, \hat{\theta}_n + \phi) \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi} dy \right| \\
&\leq \left| \int \frac{\left(\int \phi f(y, \hat{\theta}_n + \phi) \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi \right)^2 - \left(\int_{-\delta}^{\delta} \phi f(y, \hat{\theta}_n + \phi) \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi \right)^2}{\int f(y, \hat{\theta}_n + \phi) \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi} dy \right| + \\
&\quad + \int \left(\frac{\int_{-\delta}^{\delta} \phi f(y, \hat{\theta}_n + \phi) \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi}{\int_{-\delta}^{\delta} f(y, \hat{\theta}_n + \phi) \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi} \right)^2 \int_{[-\delta,\delta]^c} f(y, \hat{\theta}_n + \phi) \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi dy \\
&\leq 2 \int \frac{\int |\phi| f(y, \hat{\theta}_n + \phi) \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi}{\int f(y, \hat{\theta}_n + \phi) \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi} \int_{[-\delta,\delta]^c} \phi f(y, \hat{\theta}_n + \phi) \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi dy + \\
&\quad + \int \left(\frac{\int_{-\delta}^{\delta} \phi f(y, \hat{\theta}_n + \phi) \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi}{\int_{-\delta}^{\delta} f(y, \hat{\theta}_n + \phi) \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi} \right)^2 \int_{[-\delta,\delta]^c} f(y, \hat{\theta}_n + \phi) \prod_{i=1}^{n} \frac{f(Y_i, \hat{\theta}_n + \phi)}{f(Y_i, \hat{\theta}_n)} d\phi dy \\
&\leq C'' e^{-n\epsilon},
\end{aligned}$$

where last inequality comes from (2.10).

Analogously,

$$
\begin{aligned}
&\left| \frac{\left(\int \phi \prod_{i=1}^{n} \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi\right)^2}{\int \prod_{i=1}^{n} \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi} - \frac{\left(\int_{-\delta}^{\delta} \phi \prod_{i=1}^{n} \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi\right)^2}{\int_{-\delta}^{\delta} \prod_{i=1}^{n} \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi} \right| \\
&\leq \left| \frac{\left(\int \phi \prod_{i=1}^{n} \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi\right)^2 - \left(\int_{-\delta}^{\delta} \phi \prod_{i=1}^{n} \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi\right)^2}{\int \prod_{i=1}^{n} \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi} \right| + \\
&\quad + \left(\frac{\int_{-\delta}^{\delta} \phi \prod_{i=1}^{n} \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi}{\int_{-\delta}^{\delta} \prod_{i=1}^{n} \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi} \right)^2 \int_{[-\delta,\delta]^c} \prod_{i=1}^{n} \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi \\
&\leq 2 \frac{\int |\phi| \prod_{i=1}^{n} \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi}{\int \prod_{i=1}^{n} \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi} \int_{[-\delta,\delta]^c} \phi \prod_{i=1}^{n} \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi + \\
&\quad + \int \left(\frac{\int_{-\delta}^{\delta} \phi \prod_{i=1}^{n} \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi}{\int_{-\delta}^{\delta} \prod_{i=1}^{n} \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi} \right)^2 \int_{[-\delta,\delta]^c} \prod_{i=1}^{n} \frac{f(Y_i,\hat{\theta}_n+\phi)}{f(Y_i,\hat{\theta}_n)} d\phi \\
&\leq C''' e^{-n\epsilon}.
\end{aligned}
$$

This concludes the proof of STEP 3 and, thus, of Lemma 4. □

We are now in a position to prove Lemma 3.

Proof. (Lemma 3) Assumptions of Lemma 3 imply regularity conditions (a)-(e) given above. The result follows from Lemma 4. □

Reasoning as in the proof of Proposition 1, we can provide the following result, representing its improvement and generalization.

Proposition 3. *Under the assumptions of Lemma 3, it holds that, as $t \to \infty$, for $a \in \{0,1\}$*

$$
\hat{p}_{t,a} \longrightarrow \rho_a := \frac{I_{\theta_{0,a}}^{-\frac{h}{2h+1}}}{I_{\theta_{0,0}}^{-\frac{h}{2h+1}} + I_{\theta_{0,1}}^{-\frac{h}{2h+1}}} \ a.s. \ \ as \ t \to \infty. \tag{2.26}
$$

and

$$
p_{t,a} \longrightarrow \rho_a \ a.s. \ \ as \ t \to \infty. \tag{2.27}
$$

2.1.1 Application

To illustrate the result of Proposition 3, we consider a truncated Weibull model for $y \in (0, t_0)$

$$f_{\theta_a}(y) = \frac{e^{-(yr)^{\theta_a}}(ry)^{\theta_a - 1} r\theta_a}{1 - e^{-(t_0 r)^{\theta_a}}}$$

with unknown shape parameter θ_a and known rate r parameter. Panels A and B of Figure 2.1, show, similar to Figure 1, a trajectory of $p_{t,1}, t = 1, \cdots, 6000$ (Panel A) and $\hat{p}_{t,1}, t = 1, \cdots, 6000$ (Panel B) for a single simulated two-arm BUD trial with $r = 1, \theta_0 = 1, \theta_1 = 1.5$ (black curve). The shaded area shows (point-wise at each t) upper and lower 2.5% quantiles of the distribution of $p_{t,1}$ and $\hat{p}_{t,1}$ across 1,000 simulations.

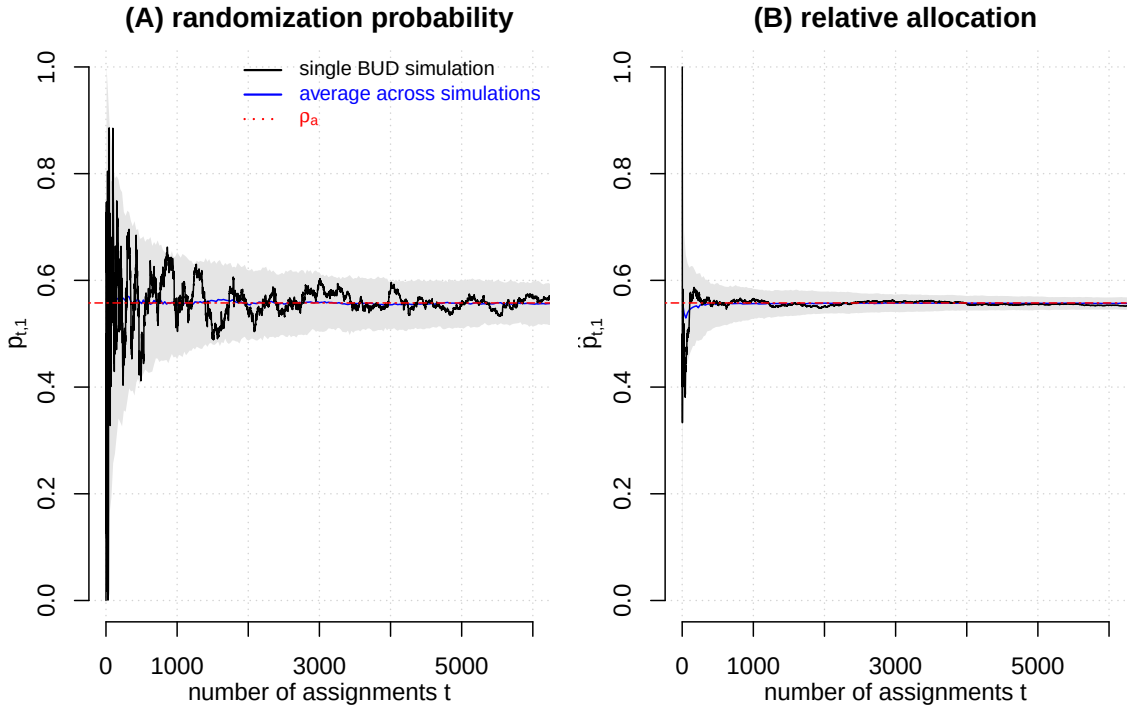

Figure 2.1: Allocation proportions and randomization probabilities of a two-arm BUDs. The primary outcomes are modeled with a truncated Weibull distribution and the information metric is the sum of the (negative) variance of the posterior distribution of the shape parameter of the outcomes in the different arms. The average allocation proportion and randomization probability across 1000 simulations (blue lines) are close to their limit ($t \to \infty$, red lines).

2.2 Convergence of allocations proportions: other utilities than variance

In this section we compute the limit of the allocation proportions (ρ_0, ρ_1) related to a two-arm BUD based on information metric

$$u(\Sigma_t) = -\sum_{a\in\{0,1\}} H(\pi(\theta_a \mid \Sigma_t)) = \sum_{a\in\{0,1\}} E(\log(\pi(\theta_a \mid \Sigma_t)) \mid \Sigma_t), \tag{2.28}$$

where H indicates the entropy and $\pi(\theta_a \mid \Sigma_t)$ denotes the posterior probability of the parameter θ_a given previous history Σ_t. For clarity of notation, we denote a random variable distributed as the posterior probability of θ_a given previous history of outcomes for $a \in \{0,1\}$ by $\tilde{\theta}_a$. We use properites of Gâteaux differentiable functions, defined in the Appendix. To anticipate the main heuristic result, confirmed by simulations, about the asymptotic behavior of $p_{t,a}$, in Lemma 5 we rewrite the information increment $\Delta_t(a)$ (defined in equation (1.1)) relative to utility (2.28) and we provide an analogous of the Taylor's formula for $H(f_{\tilde{\theta}_a}(y))$.

Lemma 5. *For a two-arm BUD whose information measure is specified in terms of the entropy of the posterior distribution of θ_a, for arm $a \in \{0,1\}$, we have*

$$\begin{aligned}\Delta_t(a) &:= H(\pi(\theta_a \mid \Sigma_t)) - E(H(\pi(\theta_a \mid \Sigma_{t+1})) \mid \Sigma_t, A_{t+1} = a) \\ &= E(H(E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a)) - H(f_{\tilde{\theta}_a}(y)) \mid \Sigma_t, A_{t+1} = a)\end{aligned} \tag{2.29}$$

and

$$\begin{aligned}&H(f_{\tilde{\theta}_a}(y)) = H(E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a)) + \\ &+ H'(E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a))(f_{\tilde{\theta}_a}(y) - E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a)) + \\ &+ \frac{1}{2}H''(E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a))(f_{\tilde{\theta}_a}(y) - E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a)) + \\ &+ \frac{1}{2}R_3,\end{aligned} \tag{2.30}$$

where H', H'', H''' are the 1^{st}, 2^{nd} and 3^{rd} order Gâteaux derivatives of H at $E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a)$ in the direction $f_{\tilde{\theta}_a}(y) - E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a)$ and R_3 equals

$H'''(E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1}=a)+\epsilon^*(f_{\tilde{\theta}_a}(y)-E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1}=a)))(f_{\tilde{\theta}_a}(y)-E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1}=a)),$

for some $\epsilon^* \in (0,1)$.

Proof. (Lemma 5)
It holds

$$E(H(\pi(\tilde{\theta}_a \mid \Sigma_{t+1})) \mid \Sigma_t, A_{t+1}=a) = E(E(-\log \pi(\tilde{\theta}_a|\Sigma_{t+1}) \mid \Sigma_{t+1}) \mid \Sigma_t, A_{t+1}=a) \tag{2.31}$$

$$= E(E(-\log\left(\frac{\pi(\tilde{\theta}_a \mid \Sigma_t) f_{\tilde{\theta}_a}(Y_{t+1})}{\int \pi(\theta_a \mid \Sigma_t) f_{\theta_a}(Y_{t+1}) d\theta_a}\right) \mid \Sigma_{t+1}) \mid \Sigma_t, A_{t+1}=a) \tag{2.32}$$

$$= E(E(-\log \pi(\tilde{\theta}_a \mid \Sigma_t) - \log f_{\tilde{\theta}_a}(Y_{t+1}) \mid \Sigma_{t+1}) \mid \Sigma_t, A_{t+1}=a) +$$

$$+ E(E(\log(\int \pi(\theta_a \mid \Sigma_t) f_{\theta_a}(y) d\theta_a) \mid \Sigma_{t+1}) \mid \Sigma_t, A_{t+1}=a) \tag{2.33}$$

$$= -E(\log \pi(\tilde{\theta}_a \mid \Sigma_t) \mid \Sigma_t, A_{t+1}=a) - E(E(\log f_{\tilde{\theta}_a}(Y_{t+1}) \mid \tilde{\theta}_a, \Sigma_t) \mid \Sigma_t, A_{t+1}=a)) +$$

$$+ E(\log \pi(y \mid \Sigma_t, A_{t+1}=a) \mid \Sigma_t, A_{t+1}=a) \tag{2.34}$$

$$= H(\pi(\tilde{\theta}_a \mid \Sigma_t)) + E(H(f_{\tilde{\theta}_a}(y)) \mid \Sigma_t, A_{t+1}=a) - H(\pi(y \mid \Sigma_t, A_{t+1}=a)) \tag{2.35}$$

$$= H(\pi(\tilde{\theta}_a \mid \Sigma_t)) + E(H(f_{\tilde{\theta}_a}(y)) \mid \Sigma_t, A_{t+1}=a) - H(E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1}=a)). \tag{2.36}$$

Equations (2.31) and (2.32) are a consequence of the definition of the entropy and of the properties of posterior analysis. (2.33) is obtained by applying properties of the logarithm, while (2.34) is derived from the Σ_{t+1}-measurability of the arguments of the inner expectation in (2.33) and law of total expectation. Equations (2.35) and (2.36) follow from the definition of the entropy and from rewriting $H(\pi(y \mid \Sigma_t, A_{t+1}=a))$ as $H(E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1}=a))$ due to properties of posterior analysis.
By definition of $\Delta_t(a)$ and due to (2.36), we get

$$\begin{aligned}\Delta_t(a) &= H(\pi(\tilde{\theta}_a \mid \Sigma_t)) - E(H(\pi(\tilde{\theta}_a \mid \Sigma_{t+1})) \mid \Sigma_t, A_{t+1}=a) \\ &= H(E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1}=a)) - E(H(f_{\tilde{\theta}_a}(y)) \mid \Sigma_t, A_{t+1}=a) \\ &= E(H(E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1}=a)) - H(f_{\tilde{\theta}_a}(y)) \mid \Sigma_t, A_{t+1}=a),\end{aligned} \tag{2.37}$$

where (2.37) follows from the Σ_t-measurability of $H(E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1}=a))$.

By Taylor's formula for Gâteaux differentiable functions

$$\begin{aligned}
&H(f_{\tilde{\theta}_a}(y)) = H(E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a))+ \\
&+ H'(E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a))(f_{\tilde{\theta}_a}(y) - E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a))+ \\
&+ \frac{1}{2}H''(E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a))(f_{\tilde{\theta}_a}(y) - E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a))+ \\
&+ \frac{1}{2}R_3,
\end{aligned}$$

where H', H'', H''' are the 1^{st}, 2^{nd} and 3^{rd} order Gâteaux derivatives of H at $E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a)$ in the direction $f_{\tilde{\theta}_a}(y) - E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a)$ and R_3 equals

$$H'''(E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a)+\epsilon^*(f_{\tilde{\theta}_a}(y)-E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a)))(f_{\tilde{\theta}_a}(y)-E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a)),$$

for some $\epsilon^* \in (0, 1)$. In the Appendix we recall the definition of Gâteaux derivative and Taylor's formula for Gâteaux differentiable functions. In particular, we recall that the 2^{nd} order Gâteaux derivative of the entropy at $E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a))$ in the direction $f_{\tilde{\theta}_a}(y) - E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a)$ is given by

$$-\int [f_{\tilde{\theta}_a}(y) - E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a)]^2 [E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a)]^{-1} dy,$$

the 3^{rd} order Gâteaux derivative of H at $E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a) + \epsilon(f_{\tilde{\theta}_a}(y) - E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a))$ in the direction $f_{\tilde{\theta}_a}(y) - E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a)$ equals

$$\begin{aligned}
\int [f_{\tilde{\theta}_a}(y) - E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a)]^3 [E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a) + \epsilon(f_{\tilde{\theta}_a}(y) - \\
- E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a))]^{-2} dy.
\end{aligned}$$

□

The results of Lemma 5 allow us to state the conjecture that in the limit, as $t \to \infty$, the allocation of patients to the two treatments in a two-arm BUD is equal. This is formally stated below and seems confirmed by simulation studies.

Conjecture 1. *Let us consider a two-arm BUD with information measure specified in terms of the entropy of the posterior distribution of the mean θ_a and let the outcomes distribution be in*

the NEF. Then, for $a \in \{0, 1\}$,

$$\hat{p}_{t,a} \longrightarrow \rho_a := \frac{1}{2} \ a.s. \ \ as \ t \to \infty. \tag{2.38}$$

The heuristics is as follows.

(Heuristic proof) Conjecture 1

Let us take conditional expectation of (2.30): the first order term of the expansion cancels out since

$$E(f_{\tilde{\theta}_a}(y) - E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a) \mid \Sigma_t, A_{t+1} = a) = 0.$$

Indeed, if $E(R_3 \mid \Sigma_t, A_{t+1} = a)$ is a negligible term with respect to the term $E(H''(E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a))(f_{\tilde{\theta}_a}(y) - E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a)) \mid \Sigma_t, A_{t+1} = a)$, then (2.29) turns into

$$\begin{aligned} &E(H(E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a)) - H(f_{\tilde{\theta}_a}(y)) \mid \Sigma_t, A_{t+1} = a) \\ &\qquad \approx \frac{1}{2} E\left(\int \frac{(f_{\tilde{\theta}_a}(y) - E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a))^2}{E(f_{\tilde{\theta}_a}(y) \mid \Sigma_t, A_{t+1} = a)} dy \mid \Sigma_t, A_{t+1} = a \right) \\ &\qquad \approx \frac{1}{2} \left(\int \frac{\int f_{\theta_a}(y)^2 \pi(\theta_a \mid \Sigma_t) d\theta_a}{\int f_{\theta_a}(y) \pi(\theta_a \mid \Sigma_t) d\theta_a} dy - 1 \right). \end{aligned} \tag{2.39}$$

Also,

$$\begin{aligned} \int f_{\theta_a}(y) \pi(\theta_a \mid \Sigma_t) d\theta_a &\approx \int \left[f_{E(\tilde{\theta}_a \mid \Sigma_t)}(y) + f'_{E(\tilde{\theta}_a \mid \Sigma_t)}(y)(\theta_a - E(\tilde{\theta}_a \mid \Sigma_t)) \right] \pi(\theta_a \mid \Sigma_t) d\theta_a + \\ &\quad + \frac{1}{2} \int f''_{E(\tilde{\theta}_a \mid \Sigma_t)}(y)(\theta_a - E(\tilde{\theta}_a \mid \Sigma_t))^2 \pi(\theta_a \mid \Sigma_t) d\theta_a \\ &\approx f_{E(\tilde{\theta}_a \mid \Sigma_t)}(y) + \frac{1}{2} f''_{E(\tilde{\theta}_a \mid \Sigma_t)}(y) \mathrm{Var}(\tilde{\theta}_a \mid \Sigma_t). \end{aligned} \tag{2.40}$$

Similarly,

$$\begin{aligned} \int f_{\theta_a}(y)^2 \pi(\theta_a \mid \Sigma_t) d\theta_a &\approx f_{E(\tilde{\theta}_a \mid \Sigma_t)}(y)^2 + f'_{E(\tilde{\theta}_a \mid \Sigma_t)}(y)^2 \mathrm{Var}(\tilde{\theta}_a \mid \Sigma_t) + \\ &\quad + f_{E(\tilde{\theta}_a \mid \Sigma_t)}(y) f''_{E(\tilde{\theta}_a \mid \Sigma_t)}(y) \mathrm{Var}(\tilde{\theta}_a \mid \Sigma_t). \end{aligned} \tag{2.41}$$

Thus, invoking (2.29) and plugging (2.40) and (2.41) into (2.39), we get

$$
\begin{aligned}
\Delta_t(a) &= E(H(E(f_{\theta_a}(y) \mid \Sigma_t, A_{t+1} = a)) - H(f_{\theta_a}(y)) \mid \Sigma_t, A_{t+1} = a) \\
&\approx \frac{1}{2}\left[\int \frac{f_{E(\tilde{\theta}_a|\Sigma_t)}(y)^2 + \left(f'_{E(\tilde{\theta}_a|\Sigma_t)}(y)^2 + f_{E(\tilde{\theta}_a|\Sigma_t)}(y) f''_{E(\tilde{\theta}_a|\Sigma_t)}(y)\right)\mathrm{Var}(\tilde{\theta}_a|\Sigma_t)}{f_{E(\tilde{\theta}_a|\Sigma_t)}(y) + \frac{1}{2} f''_{E(\tilde{\theta}_a|\Sigma_t)}(y)\mathrm{Var}(\tilde{\theta}_a|\Sigma_t)} dy - 1\right] \\
&\approx \frac{1}{2}\left[\int \frac{f_{E(\tilde{\theta}_a|\Sigma_t)}(y)^2 + \left(f'_{E(\tilde{\theta}_a|\Sigma_t)}(y)^2 + f_{E(\tilde{\theta}_a|\Sigma_t)}(y) f''_{E(\tilde{\theta}_a|\Sigma_t)}(y)\right)\mathrm{Var}(\tilde{\theta}_a|\Sigma_t)}{f_{E(\tilde{\theta}_a|\Sigma_t)}(y) + \frac{1}{2} f''_{E(\tilde{\theta}_a|\Sigma_t)}(y)\mathrm{Var}(\tilde{\theta}_a|\Sigma_t)} dy\right] - \\
&- \frac{1}{2}\int f_{E(\tilde{\theta}_a|\Sigma_t)}(y) dy \qquad (2.42) \\
&\approx \frac{1}{2}\left[\int \frac{\left(f'_{E(\tilde{\theta}_a|\Sigma_t)}(y)^2 + \frac{1}{2} f_{E(\tilde{\theta}_a|\Sigma_t)}(y) f''_{E(\tilde{\theta}_a|\Sigma_t)}(y)\right)\mathrm{Var}(\tilde{\theta}_a|\Sigma_t)}{f_{E(\tilde{\theta}_a|\Sigma_t)}(y)} dy\right] \qquad (2.43) \\
&\approx \frac{1}{2}\mathrm{Var}(\tilde{\theta}_a|\Sigma_t)\left[\int \left(\frac{d \log f_{\theta_a}(y)}{d\theta_a}|_{\theta_a = E(\tilde{\theta}_a|\Sigma_t)}\right)^2 f_{E(\tilde{\theta}_a|\Sigma_t)}(y) dy + \int f''_{E(\tilde{\theta}_a|\Sigma_t)}(y) dy\right] \qquad (2.44) \\
&\approx \frac{1}{2}\mathrm{Var}(\tilde{\theta}_a \mid \Sigma_t)\int \left(\frac{d \log f_{\theta_a}(y)}{d\theta_a}|_{\theta_a = E(\tilde{\theta}_a|\Sigma_t)}\right)^2 f_{E(\tilde{\theta}_a|\Sigma_t)}(y) dy \qquad (2.45) \\
&\approx \frac{1}{2}\mathrm{Var}(\tilde{\theta}_a \mid \Sigma_t) I_{E(\tilde{\theta}_a|\Sigma_t)}. \qquad (2.46)
\end{aligned}
$$

To obtain (2.42) we have used the fact that a probability density function integrates to 1. In (2.43) we have computed the common denominator.
Simplifying equation (2.43) and noting that

$$
\frac{f'_{E(\tilde{\theta}_a|\Sigma_t)}(y)^2}{f_{E(\tilde{\theta}_a|\Sigma_t)}(y)^2} = \left(\frac{d \log f_{\theta_a}(y)}{d\theta_a}|_{\theta_a = E(\tilde{\theta}_a|\Sigma_t)}\right)^2
$$

we have assessed (2.44). Equation (2.45) follows from the fact that $\int f''_{E(\tilde{\theta}_a|\Sigma_t)}(y) dy = 0$ and it is equal to (2.46) due to the definition of Fisher information. Now, Bernstein-Von Mises Theorem (Theorem 10.1 of [85]) and Delta method imply that for arm $a \in \{0, 1\}$

$$
\begin{aligned}
\mathrm{Var}(\theta_a \mid \Sigma_t) &= \mathrm{Var}(b'(\psi_a) \mid \Sigma_t) \\
&\approx b''(\psi_{0,a})^2 \mathrm{Var}(\psi_a \mid \Sigma_t) \\
&\approx b''(\psi_{0,a})^2 (t\hat{p}_{t,a} I_{\psi_{0,a}})^{-1} \qquad (2.47)
\end{aligned}
$$

and

$$\begin{aligned} I_{E(\theta_a|\Sigma_t)} &\approx I_{\theta_{0,a}} \\ &= I_{b'(\psi_{0,a})} \\ &= I_{\psi_{0,a}} b''(\psi_{0,a})^{-2}, \end{aligned} \tag{2.48}$$

where $\psi_{0,a}, \theta_{0,a}$ denote the fixed true values of the natural parameter and of the mean of the outcomes, respectively.

Thus, the approximate information gain $\Delta_t(a)$ -computed in (2.46)- becomes $(2t\hat{p}_{t,a})^{-1}$ and an approximate one-step-ahead randomization probability is $\tilde{p}_{t,a} := \dfrac{(2t\hat{p}_{t,a})^{-h}}{(2t\hat{p}_{t,1})^{-h} + (2t\hat{p}_{t,0})^{-h}}$.

Now, we use a fast algorithm to determine the limit of the allocation proportion.

The starting point is Proposition 1, suggesting that the convergence point is a fixed point where arm-specific proportions and expected randomization probabilities coincide.

So, the limit ρ_a is the solution of $\tilde{p}_{t,a}|_{\hat{p}_{t,a}=\rho_a} = \rho_a$.

By requiring that

$$\frac{\rho_1^{-h}}{\rho_1^{-h} + (1-\rho_1)^{-h}} = \rho_1, \tag{2.49}$$

it follows $\rho_1 = \frac{1}{2}$.

If conjecture 1 is true, then the entropy 2.28 is not a good metric since the allocation proportions converge to 0.5.

2.2.1 Simulation study

We investigate with simulations the asymptotic behavior of the allocation proportion of BUDs characterized by utility (2.28).

We consider Bernoulli model $f_{\psi_a}(1) = 1 - f_{\psi_a}(0) = \theta_a$, $\theta_a = 1/(1+e^{-\psi_a})$, with conjugated beta prior $\theta_a \sim \text{Beta}(\alpha_{0,a}, \beta_{0,a})$. Figure 2.2 illustrates the distribution of $\hat{p}_{t,1}$ across simulations, when $t = 100, 1000$ and 10000. The response probabilities (θ_0, θ_1) are set equal to 0.2 and 0.4 and a beta prior with parameters $\alpha_a = 1.5$ and $\beta_a = 3.5$ is used. The randomization parameter h is fixed to 3. The panel compares the empirical distribution of $t^{1/2}(\hat{p}_{t,1} - \frac{1}{2})$ with a normal density with mean 0 and empirical variance.

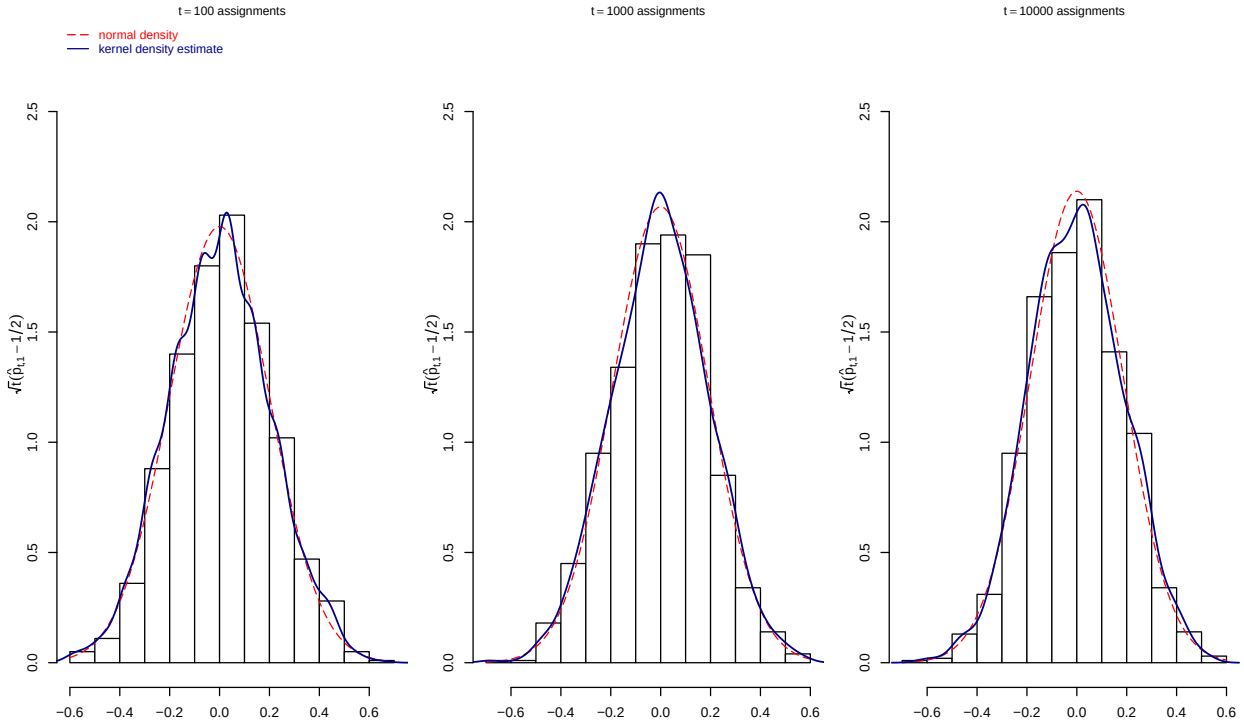

Figure 2.2: Comparison of gaussian density and empirical distributions of allocation proportions. We provide an example (binary) of the two-arm BUD trial with information metric the entropy of the posterior distribution of the mean of the outcomes.

Reference Bonsaglio, M., Fortini, S., Ventz, S., Trippa, L. (2021+), *Approximating the Operating Characteristics of Bayesian Uncertainty Directed Trial Designs*, http://arxiv.org/abs/2105.11177

Appendix B

Supplement to Chapter 2

B.1 Functional derivative

In this section we briefly discuss the concept of differentiation in function spaces. More precisely, we introduce the notions of Gâteaux and Fréchet derivatives and their analogues of Taylor's formulae, that we have used in the proof of Lemma 5. For a thorough account of the properties of these derivatives see Chapter 5.2 of [79].

Gâteaux derivative
Let X_1 and X_2 denote Banach spaces over $\mathbb{R}$, and let F denotes an operator on X_1 into X_2. Let f and h be given elements of X_1 and

$$\lim_{\epsilon \to 0} \left\| \frac{F(f + \epsilon h) - F(f)}{\epsilon} - F'(f)h \right\| = 0. \tag{B.1}$$

for every $h \in X_1$, where $\epsilon \to 0$ in $\mathbb{R}$. $F'(f)h \in X_2$ is called the value of the Gâteaux derivative of F at f in the direction h, and F is said to be Gâteaux differentiable at f in the direction h. Thus, the Gâteaux derivative of an operator F is itself an operator denoted by $F'(f)$.

The Gâteaux derivative of an operator F satisfies the following properties:

- ▷ It is unique provided it exists.
- ▷ If F is a linear operator, then $F'(f)h = F(h)$ for all $f \in X_1$.

▷ If F is a real-valued functional on X_1 and F is Gâteaux differentiable at some $f \in X_1$, then

$$F'(f)h = \frac{d}{d\epsilon}F(f + \epsilon h)|_{\epsilon=0},$$

and for each fixed $f \in X_1$, $F'(f)h$ is a linear functional of $h \in X_1$.

▷ The n^{th} order Gâteaux derivative of F at$f$ in the direction h is

$$F^n(f)h = \frac{d^n}{d\epsilon^n}F(f + \epsilon h)\bigg|_{\epsilon=0}. \tag{B.2}$$

Rather than a multilinear function, this is a homogeneous function of degree n in h.

▷ If F is $\mathcal{C}^k$, $f_1, f_2 \in U \subset X_1$ and $[f_1, f_1 + f_2]$ is a closed segment in U, the analogous of the Taylor's formula with remainder is

$$F(f_1 + f_2) = F(f) + F'(f)f_2 + \frac{1}{2!}F''(f_1)f_2 + \cdots + \frac{1}{(k-1)!}F^{k-1}(f_1)f_2 + R_k \tag{B.3}$$

with $R_k = \dfrac{1}{(k-1)!}F^k(f_1 + \epsilon^* f_2)f_2$ for some $\epsilon^* \in (0, 1)$.

Fréchet derivative

Let X_1 and X_2 denote Banach spaces over $\mathbb{R}$. A continuous linear operator $S : X_1 \to X_2$ is called the Fréchet derivative of the operator $F : X_1 \to X_2$ at $f \in X_1$ if

$$\lim_{\|h\|\to 0} \frac{\|F(f + h) - F(f) - S(h)\|}{\|h\|} = 0. \tag{B.4}$$

The Fréchet derivative of F at f is denoted by $F'(f)$. F is called Fréchet differentiable on its domain if $F'(f)$ exists at every point of the domain.
The Fréchet derivative of an operator F satisfies the following properties:

▷ In finite-dimensional spaces it is the usual derivative. In elementary calculus, the derivative at a point is a local linear approximation of the given function in the neighborhood of the point. Similarly, the Fréchet derivative can be interpreted as the best local linear approximation.

▷ If F is linear, then $F'(f) = F(f)$, that is, if F is a linear operator, then the Fréchet derivative of F is F itself.

▷ Every Fréchet differentiable operator is continuous and linear.

▷ If F is Fréchet differentiable, then it is also Gâteaux differentiable, and its Fréchet and Gâteaux derivatives agree. The converse is not true, since the Gâteaux derivative may fail to be linear or continuous. In fact, it is even possible for the Gâteaux derivative to be linear and continuous but for the Fréchet derivative to fail to exist.
Therefore, Fréchet derivative is unique.

▷ The n^{th} order Fréchet derivative of F of f in the direction h is obtained by iteration of the first order derivative.

▷ If F is k-times-differentiable, $f_1, f_2 \in U \subset X_1$ and $[f_1, f_1 + f_2]$ is a closed segment in U, the analogous of the Taylor's formula is

$$F(f_1 + f_2) = F(f_1) + F'(f_1)f_2 + \frac{1}{2!}F''(f_1)f_2 + \cdots + \frac{1}{k!}F^k(f_1)f_2 + \|f_2\|^k\epsilon(f_2) \qquad \text{(B.5)}$$

with $\lim_{f_2 \to 0} \epsilon(f_2) = 0$.

B.2 Applicability of BUDs to actual clinical trials

As shown in Chapters 1 and 2, BUDs can accomodate different information measures u tailored to different aims of a trial. The unifying element of these measures is the use of functionals of the posterior distribution of a parameter of interest to quantify information.
Here we provide some examples of utilities that enable the application of BUDs to biomarker-stratified clinical trials, trials with co-primary endpoints, dose-finding trials and trials with delayed responses.

Biomarker-Stratified clinical trials
In modern clinical trials information on a large number of covariates is often collected in addition to information on the primary outcome. For instance, genetic profiles of patients are sometimes available when running a novel trial. As a consequence, the interest in the development of treatments that target specific genetic alterations is increasing. Biomarker-stratified clinical trials enroll patients with multiple genomic abnormalities in single multi-arm trials, and identify subgroups of patients that respond to experimental treatments.
The goal is testing K treatments for patients with and without a genomic alteration.
Indeed, it is possible to define BUDs with the primary aim to test the presence of effects within subgroups and in the overall population. For each patient t, we use $X_t \in \{0, 1\}$ to denote the patients biomarker profile. We assume that the trial measures binary outcomes with parameters $\theta_{x,a}$ for subgroups $x = 0, 1$ and treatments $a = 0, \dots, K-1$. We test the presence of effects within subgroups $E_{x,a} = 1(\theta_a > \theta_0)$ and in the overall population $E_a = 1(\theta_a > \theta_0)$. We define $\theta_a = \beta\theta_{1,a} + (1-\beta)\theta_{0,a}$ and we denote the prevalence of the biomarker by $\beta \in [0, 1]$.
After specifying a Bayesian model, we can use a summary metric that weights convex functionals of interpretable posterior probabilities of $E_a, E_{1,a}, E_{0,a}$, given previous history Σ_t, as utility function u of the BUD. Then, allocation probabilities could be calculated on the basis of previous responses and the current and past values of certain known covariates of the patients. In fact, it may be not acceptable to base the allocation probabilities only on responses of previous patients if those patients have different characteristics. This is particularly true when ethical demands are cogent and the patients have different profiles that induce heterogeneity in the outcomes. Starting from the pioneering work of Rosenberger et al. [71], there has been a growing statistical interest in designs that change at each step the probabilities of allocating treatments by taking into account all the available information, namely previous responses, assignments and covariates, as well as the covariate profile of the current subject, with the aim of skewing the allocations

towards the superior treatment or, in general, of converging to a desired target allocation depending on the covariates. Therefore, BUD assigns a patient with biomarker profile x to treatment a, for $a = 0, \ldots, K-1$, at time $(t+1)$ with probability

$$p(A_{t+1} = a \mid X_{t+1} = x, \Sigma_t) \propto [E(u(\Sigma_{t+1} \mid X_{t+1} = x, A_t = a, \Sigma_t) - u(\Sigma_t)]^h.$$

Trials with co-primary endpoints

In several contexts, such as Alzheimers disease, a single endpoint has been shown to be insufficient to capture patients' response to treatments adequately. Several authors recommend to evaluate new treatments using multiple clinical endpoints [32].

It is possible to adapt the formulation of BUDs to the design of multi-arm trials with several co-primary endpoints.

As an example, we consider a controlled multi-arm trial that evaluates K experimental treatments using two binary endpoints $Y_t = (Y_{t,1}, Y_{t,2})$. For each treatment a, we set $p(Y_t = y|A_t = a) = \theta_{y,a} \geq 0$, with $y \in \{0,1\}^2$, and $\sum_{y\in\{0,1\}^2} \theta_{y,a} = 1$. We assume independent Dirichlet prior distributions for the arm-specific parameters $\theta_a = (\theta_{(1,1),a}, \theta_{(1,0),a}, \theta_{(0,1),a}, \theta_{(0,0),a})$, where the parameters θ_a specify the marginal probabilities $(\mu_{1,a}, \mu_{2,a})$ of the two endpoints.

We indicate with $\gamma_{l,a} = \mu_{l,a} - \mu_{l,0}, = 1, 2$ the treatment effects for both endpoints.

In this setting, the utility function characterizing the BUD is specified by

$$u(\Sigma_t) = -\sum_{a=1}^{K-1} \{Var(\gamma_a \mid \Sigma_t) + \omega[Var(\gamma_{1,a} \mid \Sigma_t) + Var(\gamma_{2,a} \mid \Sigma_t)]\} \quad \text{with } \omega \geq 0,$$

where γ_a is the difference between arm $a > 0$ and the control arm in the probability of an individual positive response on both endpoints.

Dose-finding trials

In a dose-finding clinical trial different doses of a drug are tested against each other to establish which dose works best and/or is least harmful.

More formally, the aim is to select one of K candidate dose levels $a \in \{0, \ldots, K-1\}$ using binary efficacy and toxicity outcomes. We let $\theta_{E,a}$ and $\theta_{T,a}$ denote the probabilities of response and toxicity at dose level a. For each dose level a, a score weights efficacy $\theta_{E,a}$ and toxicity $\theta_{T,a}$, say $S_a(\theta) = \omega\theta_{E,a} + (1-\omega)(1-\theta_{T,a})$ with $0 \leq \omega \leq 1$ and dose level $A^* = \text{argmax}_a S_a(\theta)$ has the

highest score. In Bayesian modeling $(\theta_{E,a}, \theta_{T,a})_a$, as well as $S_a(\theta)$ and A^*, are random variables. The posterior distribution $p(A^* = a \mid \Sigma_t) = p(\bigcap_{a'}\{S_a(\theta) \geq S_{a'}(\theta)\} \mid \Sigma_t), a = 0, \ldots, K-1$, changes over time as more information becomes available. The utility function of the BUD can be defined as

$$u(\Sigma_t) = -\sum_{a=0}^{K-1} F(p(A^* \mid \Sigma_t),$$

for a convex functionals F.

Trials with delayed responses

Treatment outcomes are not always complete and available immediately: clinical trials often involve delayed responses, i.e., outcomes that are observed with a substantial time delay after assigning a treatment or enrolling a patient. Such lagged responses create challenges for clinical trial designs when a treatment allocation requires outcomes from earlier enrolled patients. For BUDs and for general Bayesian designs, dependence on earlier outcomes is formalized by basing current decisions on the posterior distribution conditional on all previous outcomes. The principled nature of Bayesian inference offers an easy solution to the problem of delayed responses. The relevant posterior distribution could simply include the responses from already enrolled patients and/or partial responses from already enrolled patients with missing final response.

Chapter 3

Incorporating external data in the design of novel trials

3.1 Introduction

Randomization has been employed for decades in clinical trials to limit selection bias and confounding. These are the main potential drawbacks of the use in clinical practice of single-arm trials, where there is no control group receiving the standard treatment and the treatment is compared to historic benchmarks. Generally, single-arm trials require smaller sample sizes to achieve targeted power and they have more attraction for patients compared to randomized clinical trials. Clinical researchers have discussed the relative merits of single-arm versus randomized trial design extensively. In [35, 38, 65, 72, 74, 82, 97] the authors argue and explore the performance of single-arm trials versus randomized clinical trials: the scientific debate is still controversial and both single-arm and randomized trials are advised in some scenarios.
Often recommendations for randomization have been proposed based on qualitative arguments, ending up with a set of generic guidelines to aid in the choice of clinical trial designs [35, 77]. Also, comparisons between the characteristics of different designs are derived through simulations for specific scenarios and under some particular assumptions so that they may not hold in situations outside the range considered. Better choices may be made by adopting a quantitative approach, which translates into informed decisions in the design of future trials. Providing quantitative evidence of the role of randomization in modern clinical trial designs and incorporating information from external data sources in the design of novel trials are some of the main challenges currently faced by researchers.

Several methods for historical borrowing of existing information about the control treatment from an external study into a novel study have been proposed in literature [40, 60, 64, 93]. Most of these works adopt a Bayesian perspective. Bayesian paradigm offers a formal statistical framework for incorporating all sources of knowledge; in particular external information can be incorporated into the design and analysis of a novel randomized clinical trial through prior distributions for the parameters of interest, such as the control response rate.

Recently, the idea of taking advantage of real-world data and data from completed clinical trials to replace or complement data from current clinical trials is emerging [78] and the availability of data collected from electronic health records, patient registries and other clinical trials at scale has increased the interest in using existing data on the control treatment as an external control [1, 24, 50]. Meanwhile, data from previous clinical trials can be integrated in the design and analysis of single-arm trials rather than using a single published estimate of the standard of care primary outcome distribution to specify a benchmark.

The potential benefits of externally-controlled clinical trials designs are advocated by many researchers: in [86] the authors emphasize the need of a quantitative and theoretical evaluation of procedures to use external control data in the analysis of randomized clinical trials, in any disease indications, and they suppose that externally controlled single-arm studies may provide robust inference on treatment effects as randomized designs. In [89] the authors compare the performance of externally-controlled designs to randomized and single-arm designs using as criterium the sample size to achieve a targeted power for fixed type I error rate. Using a collection of clinical studies in glioblastoma and adopting a model-free approach, they show that externally-controlled clinical trials can increase power compared to randomized clinical trials by leveraging additional information from outside the trial than committing resources to an internal control.

We address the same research problems of the above works in an attempt to give a precise quantification of the value of randomization in standard and externally-controlled randomized clinical trials and to give an objective procedure to design a trial that is optimal, in the way it maximizes power among a set of candidate designs. In this context, the concept of power refers to the probability of detecting a statistically significant positive treatment effect of the experimental therapy compared to the control therapy when the experimental therapy is really superior to the control one. We hold the overall sample size fixed to reflect the following decision problem: "in testing the null hypothesis of no treatment effect against the one-sided alternative of positive treatment effect, once the type I error is fixed at a certain nominal level, what is the most powerful option between designs of trials characterized by different randomization ratios with enrollment up to

a fixed number of patients and that could include external information?" Therefore, our goal is to recommend how to design a forthcoming study, given external data on the control therapy: should the trial be run close to a single arm trial or to a randomized clinical trial? Is it worth using external sources of information?
Under the assumption of known within-study and between-studies variabilities, when responses are Gaussian, we provide closed-form expression of power of the hypothesis test for the treatment effect related to different designs and we give a way to identify the optimal randomization ratio. We show that randomized externally-controlled clinical trials with optimal randomization ratio are superior to standard randomized clinical trials. Then we relax the assumptions that the two sources of variability are known but we require that the number of available external studies is quite large: in this case in order to estimate power it is sufficient to plug-in the estimates of the within-study error variance and between-studies variance, which are obtained from one-way random-effect anova theory or random-effect meta-analysis, into the expressions of power obtained theoretically under the assumption of known sources of variability.
We verify through simulations the correctness of our findings, when the within-study and the between-studies variabilities are unknown, but estimated with external data, and the size of the internal study is large. Also, simulation studies show that the design guidelines that one should consider when clinical trials endpoint follows a Bernoulli distribution are similar to those provided in the Gaussian case.
Finally, we propose an overall procedure based on bootstrap algorithm to estimate power of the test of the treatment effects in general outcomes model associated to the design of externally-controlled randomized clinical trials when the sources of variability are unknown without any requirements on the number of external studies, controlling type I error at desired level. An application of this algorithm to Gaussian and time-to-event data is provided, which suggests that also in the case of small number of available external studies, the use of existing data to design clinical studies could have the potential to accelerate drug development process, provided that the between-studies variability is small compared to some magnitude dependent on the actual scenario.

3.2 Statement of the problem

We assume that n patients are enrolled in a clinical trial, aimed at comparing the effect of a novel treatment with a standard control treatment. We denote by $0 < \rho \leq 1$ the randomization ratio that characterizes the design of the trial, so that the participants will be splitted into

an experimental group and a control group of expected size $n_e = \text{round}(\rho n)$ and $n_c = n - n_e$, respectively. Also, we assume that data from K previous studies addressing the same research question on the control treatment are available when designing the forthcoming trial. We suppose initially that the evaluation of treatment for a patient can be summarized by a single quantitative measurement, which can be thought of as an observation from a Gaussian random variable.
If we design the forthcoming study as a standard randomized clinical trial, regardless of the information provided by external studies about the control treatment, we assume that the response of the j-th patient follows

$$y_j = \beta_0 + \beta_1 T_j + \epsilon_j \quad \text{for } j = 1, \ldots, n \tag{3.1}$$

or, if we also take into account the effect of an additional covariate on the response,

$$y_j = \beta_0 + \beta_1 T_j + \beta_2 x_j + \epsilon_j \quad \text{for } j = 1, \ldots, n \tag{3.2}$$

where in (3.1) and (3.2)

$$\epsilon_j \overset{\text{i.i.d.}}{\sim} N(0, \sigma_1^2).$$

In models (3.1) and (3.2), β_0 is the average effect of the control therapy, β_1 is the treatment effect, β_2 is the effect of the additional covariate, T_j denotes a binary random variable which takes value 1 if the patient is assigned to the experimental group and 0 if the patient is assigned to the control group, x_j has general continuous or discrete distribution. We have that $T_j = 0$ for $j = 1, \ldots, n_c$ and $T_j = 1$ for $j = n_c + 1, \ldots, n$.
On the other hand, if we design the forthcoming study as a randomized or single-arm clinical trials aided by external controls, we assume a linear mixed model for the response of the j-th patient in the i-th study in the form

$$y_{ij} = \beta_0 + \beta_1 T_{ij} + b_i + \epsilon_{ij} \quad \text{for } i = 1, \ldots, K+1, j = 1, \ldots, n_i \tag{3.3}$$

or, if we add the effect of an additional covariate on the response,

$$y_{ij} = \beta_0 + \beta_1 T_{ij} + \beta_2 x_{ij} + b_i + \epsilon_{ij} \quad \text{for } i = 1, \ldots, K+1, j = 1, \ldots, n_i \tag{3.4}$$

where in (3.3) and (3.4)

$$\epsilon_{ij} \overset{\text{i.i.d.}}{\sim} N(0, \sigma_1^2) \tag{3.5}$$

$$b_i \overset{\text{i.i.d.}}{\sim} N(0, \sigma_2^2). \tag{3.6}$$

In models (3.3) and (3.4), β_0 is the average effect of control therapy across studies, β_1 is the treatment effect, b_i is the random effect of the i-th study, T_{ij} denotes a binary random variable which takes value 1 if the patient is assigned to the experimental group and 0 otherwise, x_{ij} has general continuous or discrete distribution. We have that in external studies $T_{ij} = 0$ ($\forall i = 1, \dots, K, \forall j = 1, \dots, n_i$); instead, in the internal study $T_{K+1j} = 0$ if $j = 1, \dots, n_c$ and $T_{K+1j} = 1$ if $j = n_c + 1, \dots, n_{K+1}$. We assume that the values of the covariates x_{ij} are known for every $i = 1, \dots, K$ and for every $j = 1, \dots, n_i$, and we denote $s_i = \sum_{j=1}^{n_i} x_{ij}$, $s_{K+1} = \sum_{j=1}^{n_{K+1}} x_{K+1j}$ and $s^e_{K+1} = \sum_{j=n_c+1}^{n_{K+1}} x_{K+1j}$.

Random-effects models (3.3) and (3.4) are suitable choices for modeling externally-controlled clinical trials, since we have a representation of what the random effects are. In fact, it is true that a degree of variability in study estimates is present because of within-study sampling error, but additional variability might occur for many reasons such as differences in the way studies are conducted and how the treatment effects are measured. This additional variability is modelled using the between-studies variance parameter σ_2^2.

For convenience and simplicity, throughout the Chapter we assume that all the external studies have the same size (i.e. $n_i = n_{\text{ext}} \forall i = 1, \dots, K$) and that the internal study has size n (i.e. $n_{K+1} = n$). Also, due to randomization, we can assume that the additional covariate introduced in models (3.2) and (3.4) is equally distributed in the control and experimental group of the forthcoming study.

With models (3.1)-(3.4) we refer to different ways of designing novel clinical trials, when data from previous trials, where the control therapy have been administered to a group of patients, are at our disposal. In fact, there is a continuum way of using existing information on the control therapy in forthcoming trial: the spectrum ranges from single-arm trial aided by external controls (model (3.3) or model (3.4), $\rho = 1$), where all the future patients are assigned the experimental group, to hybrid trial (model (3.3) or model (3.4), $\rho < 1$), where we combine two sources of control data (randomized and external control data), towards standard randomized clinical trial with randomization ratio ρ (model (3.1) or model (3.2)), which doesn't encompass the external control data. The aim of our work is to determine what is the choice among the above designs

maximizing power of the study and to identify optimal randomization ratio in any scenario.
In particular, the null hypothesis that we test is that the treatment effect in models (3.1) - (3.4) is zero against the alternative hypothesis that it is positive. In other words, the statistical hypotheses tested are

$$H_0 : \beta_1 = 0 \text{ vs } H_1 : \beta_1 > 0, \tag{3.7}$$

where β_1 is
· the coefficient defined in model (3.1) [Hp RCT]
· the coefficient defined in model (3.2) [Hp RCT-COV]
· the fixed coefficient defined in model (3.3) [Hp ECT]
· the fixed coefficient defined in model (3.4) [Hp ECT-COV]
In all cases, we set $\beta_1 = \Delta > 0$ as the minimum desired response for the experimental treatment to constitute a clinically relevant benefit.
Finally, we will denote by ρ^{RCT} and ρ^{ECT} the values of the randomization ratio ρ that maximize power of the tests of statistical hypotheses [Hp RCT] and [Hp ECT], respectively.

3.3 Methods

3.3.1 Analytic results

We suppose initially that we know the two sources of variability in models (3.1)-(3.4), i.e. the within-study variance σ_1^2 and the between-studies variance σ_2^2. Under this assumption, in Propositions 4 and 2 we provide closed-form expression of power of the test of hypothesis (3.7) based on standard Least Squares estimators of the treatment effects of these models. In particular, we denote the statistical test of [Hp RCT] ([Hp RCT-COV]) based on Ordinary Least Squares estimator of the treatment effect in the linear model (3.1) ((3.2)) by [Test RCT] ([Test RCT-COV]). Similarly, we indicate the statistical test of [Hp ECT] ([Hp ECT-COV]) based on Generalized Least Squares estimator of the treatment effect in the linear mixed model (3.3) ((3.4)) by [Test ECT] ([Test ECT-COV]). As we show in the proofs of Propositions 4 and 5 in the Appendix, estimates of power of the above tests are affected by the inverse of the variances of the Least Squares estimators whose closed-form expressions involve the following quantities:

$$d_1 = \frac{n_e n_c}{n\sigma_1^2}, \tag{3.8}$$

$$d_2 = \frac{n_c n_e \sum_{j=1}^{n} x_{1j}^2 - n\left(\sum_{j=n_c+1}^{n} x_{1j}\right)^2 + n_e\left[2\left(\sum_{j=n_c+1}^{n} x_{1j}\right)\left(\sum_{j=1}^{n} x_{1j}\right) - \left(\sum_{j=1}^{n} x_{1j}\right)^2\right]}{\sigma_1^2\left[n\sum_{j=1}^{n} x_{1j}^2 - \left(\sum_{j=1}^{n} x_{1j}\right)^2\right]}, \tag{3.9}$$

$$d_3 = \frac{n_{ext}Kn_e(\sigma_1^2+n_c\sigma_2^2)(\sigma_1^2+n\sigma_2^2)+n_e(n\sigma_1^2+n_cn\sigma_2^2-n_e\sigma_1^2)(\sigma_1^2+n_{ext}\sigma_2^2)}{\sigma_1^2\left[n_{ext}K(\sigma_1^2+n\sigma_2^2)^2+n(\sigma_1^2+n_{ext}\sigma_2^2)(\sigma_1^2+n\sigma_2^2)\right]} \tag{3.10}$$

and

$$d_4 = \frac{c_1-c_2+c_3}{\sigma_1^2 c_0}, \tag{3.11}$$

where

$$c_0 = \left(\frac{n_{ext}K\sigma_1^2}{\sigma_1^2+n_{ext}\sigma_2^2}+\frac{n\sigma_1^2}{\sigma_1^2+n\sigma_2^2}\right)\left[\sum_{i=1}^{K+1}\frac{(\sigma_1^2+n_i\sigma_2^2)s_i-\sigma_2^2s_i^2}{\sigma_1^2+n_i\sigma_2^2}\right]-\left(\sum_{i=1}^{K+1}\frac{s_i\sigma_1^2}{\sigma_1^2+n_i\sigma_2^2}\right)^2, \tag{3.12}$$

$$\begin{aligned} c_1 = {} & \left(\frac{n_{ext}K\sigma_1^2}{\sigma_1^2+n_{ext}\sigma_2^2}+\frac{n\sigma_1^2}{\sigma_1^2+n\sigma_2^2}\right)\left\{\left(\frac{n_e\sigma_1^2+n_en_c\sigma_2^2}{\sigma_1^2+n\sigma_2^2}\right)\left[\sum_{i=1}^{K+1}\frac{(\sigma_1^2+n_i\sigma_2^2)s_i-\sigma_2^2s_i^2}{\sigma_1^2+n_i\sigma_2^2}\right]-\right. \\ & \left.-\left[\frac{(\sigma_1^2+n\sigma_2^2)s_{K+1}^e-\sigma_2^2n_es_{K+1}}{\sigma_1^2+n\sigma_2^2}\right]^2\right\}, \end{aligned} \tag{3.13}$$

$$\begin{aligned} c_2 = {} & \frac{n_e\sigma_1^2}{\sigma_1^2+n\sigma_2^2}\left\{\frac{n_e\sigma_1^2}{\sigma_1^2+n\sigma_2^2}\left[\sum_{i=1}^{K+1}\frac{(\sigma_1^2+n_i\sigma_2^2)s_i-\sigma_2^2s_i^2}{\sigma_1^2+n_i\sigma_2^2}\right]-\right. \\ & \left.-\left(\frac{(\sigma_1^2+n\sigma_2^2)s_{K+1}^e-\sigma_2^2n_es_{K+1}}{\sigma_1^2+n\sigma_2^2}\right)\left(\sum_{i=1}^{K+1}\frac{s_i\sigma_1^2}{\sigma_1^2+n_i\sigma_2^2}\right)\right\} \end{aligned} \tag{3.14}$$

$$\begin{aligned} c_3 = {} & \left(\sum_{i=1}^{K+1}\frac{s_i\sigma_1^2}{\sigma_1^2+n_i\sigma_2^2}\right)\left\{\frac{n_e\sigma_1^2}{\sigma_1^2+n\sigma_2^2}\left[\frac{(\sigma_1^2+n\sigma_2^2)s_{K+1}^e-\sigma_2^2n_es_{K+1}}{\sigma_1^2+n\sigma_2^2}\right]-\right. \\ & \left.-\left(\frac{n_e\sigma_1^2+n_en_c\sigma_2^2}{\sigma_1^2+n\sigma_2^2}\right)\left(\sum_{i=1}^{K+1}\frac{s_i\sigma_1^2}{\sigma_1^2+n_i\sigma_2^2}\right)\right\}. \end{aligned} \tag{3.15}$$

We also denote the cumulative distribution function of a standard normal distribution and the $(1-\alpha)$ quantile of a standard normal distribution by Φ and z_α, respectively.

Proposition 4. *Assume that models (3.1) and (3.2) are selected to design a randomized clinical trial. Assume that σ_1^2 is known. Then, controlling type I error at level α in testing [Test RCT], power equals*

$$1-\Phi\left(z_\alpha-\Delta\sqrt{d_1}\right) \tag{3.16}$$

and, controlling type I error at level α in testing [Test RCT-COV], power can be computed as

$$1-\Phi\left(z_\alpha-\Delta\sqrt{d_2}\right), \tag{3.17}$$

where d_1 and d_2 are defined in (3.8) and (3.9).

Proposition 5. *Assume that models (3.3) and (3.4) are selected to design an externally-controlled randomized clinical trial. Assume that σ_1^2 and σ_2^2 are known. Then, controlling type I error at level α in testing [Test ECT], power equals*

$$1 - \Phi\left(z_\alpha - \Delta\sqrt{d_3}\right), \tag{3.18}$$

and, controlling type I error at level α in testing [Test ECT-COV], power can be computed as

$$1 - \Phi\left(z_\alpha - \Delta\sqrt{d_4}\right), \tag{3.19}$$

where d_3 and d_4 are defined in (3.10) and (3.11).

Optimal randomization ratios ρ^{RCT} and ρ^{ECT} are the values of ρ that maximize (3.16) and (3.18), respectively, when variables $\sigma_1^2, \sigma_2^2, K, n_{ext}, n$ are assigned some specific values. In particular, ρ^{RCT} is 0.5, whatever scenario is considered. Instead, the values assumed by ρ^{ECT} depend on the scenario under examination; by way of illustration, refer to Table 3.1.
By comparing expressions (3.16)-(3.19), we can determine the characteristics of the design maximizing power of test of hypothesis (3.7) in any fixed scenarios.

Based on the findings from this research, the following recommendations are considered to be appropriate:

- For all values of σ_2^2, running an externally-controlled randomized clinical trial with optimal randomization ratio ρ^{ECT} is the optimal choice between all types of designs considered in this chapter.
- For small values of σ_2^2, if the number of external studies is quite large and the size of the internal study is small (for example $\sigma_2^2 \leq 0.01$ when $\sigma_1^2 = 1, K > 5$ and $n \leq 50$), the optimal randomization ratio ρ^{ECT} is approximately 1 (Table 3.1, Supplementary Figure C.4). In this scenario, externally-controlled single-arm trial is preferable to standard randomized clinical trial with balanced randomization; the situation reverses for larger values of variability between external studies and larger sizes of the internal study (Fig. 3.1).
- As the value of σ_2^2 increases, ρ^{ECT} gets closer to 0.5, faster if the size of the internal study is larger or the number of external studies is smaller (Table 3.1). Meanwhile, estimates of power of the test [Test ECT] related to an externally-controlled randomized clinical trial with optimal randomization ratio ρ^{ECT} becomes closer to that one of power of the test [Test

RCT] related to a standard randomized clinical trial with balanced randomization (Figure 3.1, Supplementary Figures C.4/C.6). Therefore, for large values of σ_2^2, it is not convenient to use external data anymore.

- ▷ When the number of available external studies is small and the variability between studies is quite small (for example $K \leq 5$ and $\sigma_2^2 = 0.01$ when $n = 100$ and $\sigma_1^2 = 1$), estimates of power of the test [Test ECT] related to externally-controlled randomized clinical trials characterized by different randomization ratios in the interval $(0.5, 1)$ are very close to each other (Supplementary Figure C.5). Any randomization ratio in this range would guarantee approximately optimal characteristics of the study.

- ▷ If $n_e = n_c = \frac{n}{2}$, then (3.18) is approximated by (3.16) in the limit as n and n_{ext} tend to ∞. Also, if $n_e = n$, then (3.18) is approximated by $1 - \Phi\left(z_\alpha - \Delta\sqrt{\frac{K}{(K+1)\sigma_2^2}}\right)$ in the limit as n and n_{ext} tend to ∞ (Supplementary Figure C.7).

- ▷ If the additional covariate in model (3.2) ((3.4)) is binary or it has general continuous or discrete distribution such that the sum of the covariate values in the internal study are of the same order of magnitude of the sum of the covariate values in the external studies, then the set of recommendations given above doesn't change (Figure 3.1).

So far, we have assumed that the error term variance σ_1^2 and the between-studies variance σ_2^2 are known: this assumption have allowed us to derive theoretically the expressions of power given in Propositions 4 and 5. Nevertheless, σ_1^2 and σ_2^2 could be unknown to researchers and in this case these parameters could be estimated through external data.
Since model (3.3) for $i = 1, \ldots, K$ is an example of one-way random effect ANOVA model, then, calling upon theory in [76], we can estimate the between-studies and within-study variances based on external data as

$$\hat{\sigma}_{1,A}^2 = \frac{\sum_{i=1}^{K}\sum_{j=1}^{n.ext}(y_{ij} - \bar{y}_i)^2}{K(n_{ext} - 1)} \tag{3.20}$$

and

$$\hat{\sigma}_{2,A}^2 = \frac{\sum_{i=1}^{K}(\bar{y}_i - \bar{y})^2}{K - 1} - \frac{\hat{\sigma_1^2}}{n_{ext}}, \tag{3.21}$$

where

$$\bar{y}_i = \frac{\sum_{j=1}^{n_{ext}} y_{ij}}{n_{ext}} \quad \text{and} \quad \bar{y} = \frac{\sum_{i=1}^{K}\sum_{j=1}^{n.ext} y_{ij}}{K n_{ext}}. \tag{3.22}$$

$n_{\text{ext}} = 30, K = 5$

	$n = 30$	$n = 100$
$\sigma_2^2 = 0.01$	1	0.767
$\sigma_2^2 = 0.05$	0.750	0.575
$\sigma_2^2 = 0.3$	0.545	0.514

$n_{\text{ext}} = 30, K = 30$

	$n = 30$	$n = 100$
$\sigma_2^2 = 0.01$	1	0.936
$\sigma_2^2 = 0.05$	0.815	0.594
$\sigma_2^2 = 0.3$	0.554	0.516

$n_{\text{ext}} = 30, K = 50$

	$n = 30$	$n = 100$
$\sigma_2^2 = 0.01$	1	0.960
$\sigma_2^2 = 0.05$	0.822	0.596
$\sigma_2^2 = 0.3$	0.554	0.516

$n_{\text{ext}} = 100, K = 50$

	$n = 30$	$n = 100$
$\sigma_2^2 = 0.01$	1	0.980
$\sigma_2^2 = 0.05$	0.825	0.597
$\sigma_2^2 = 0.3$	0.554	0.516

Table 3.1: The table shows the values of the optimal randomization ratio ρ^{ECT} for running externally-controlled randomized clinical trials. The parameters σ_2^2, n, n_{ext} and K of model (3.3) are considered in different scenarios and σ_1^2 equals 1. The sample size of the internal study listed in the table, $n = 30$ and $n = 100$, are selected in order that power of a standard randomized clinical trial is expected to be 0.707 and 0.990 when $\Delta = 0.6$.

The estimators (3.20) and (3.21) are minimum variance unbiased [76]. Alternatively, different methods, both iterative and non-interative, have been proposed to estimate the sources of variability through a random-effect meta-analysis. Among the meta-analysis methods used for estimating the between-studies variance and its uncertainty described in [91], REstricted Maximum Likelihood (REML) method is recommended as the best approach in terms of bias and efficiency [83] [92]. Also, REML estimates of variance components in mixed model ANOVA are consistent [27]. In the following, we denote REML estimate of σ_2^2 by $\hat{\sigma}^2_{2,REML}$. Unfortunately, a quite big number of observations is needed to have some reasonably accuracy in estimating the variances σ_1^2 and σ_2^2 even by using the above estimators. Typically, the number of observations in the external studies n_{ext} is sufficiently large to obtain an accurate estimate of σ_1^2 by $\hat{\sigma}^2_{1,A}$ defined in (3.21), even when we have few external studies at our disposal. Therefore, we could treat the estimates $\hat{\sigma}^2_{1,A}$ as the true σ_1^2 value and ignore any associated sampling error: we estimate power of the test [Test RCT] by formula (3.16) evaluated at $\hat{\sigma}^2_{1,A}$. Instead, a large number of studies is required to obtain an accurate estimate of the variance σ_2^2 by $\hat{\sigma}^2_{2,A}$ (or $\hat{\sigma}^2_{2,REML}$). For instance, when the number of eternal studies is small, $\hat{\sigma}^2_{2,A}$ can assume negative values and $\hat{\sigma}^2_{2,REML}$ can be skewed towards zero. In order to correct for this, we can consider a biased estimator of σ_2^2, such as $\hat{\sigma}^2_{2,B} = \dfrac{\sum_{i=1}^{K}(\bar{y}_i - \bar{y})^2}{K-1}$, which indeed is positive (Supplementary Figure C.8).

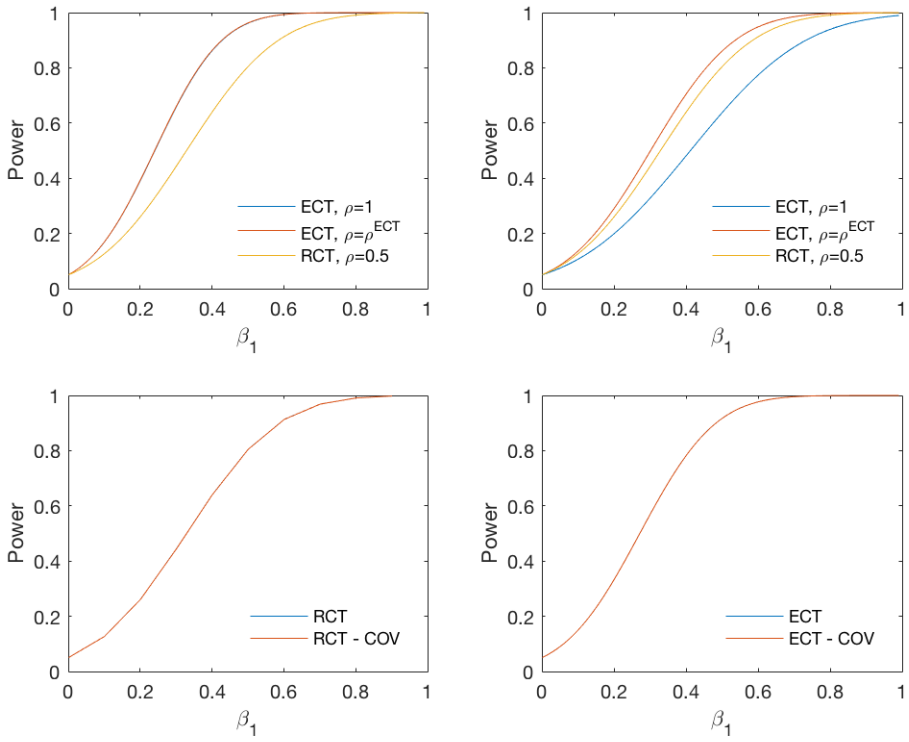

Figure 3.1: First row: Comparison of estimates of the power related to externally-controlled single-arm trials ([Test ECT], $\rho = 1$), externally-controlled randomized clinical trials with optimal randomization ratio ([Test ECT], $\rho = \rho^{ECT}$) and standard randomized clinical trials with balanced randomization ([Test RCT], $\rho = 0.5$). The parameter values are $n = 100, n_{ext} = 30, K = 30, \alpha = 0.05, \sigma_1^2 = 1$ and $\sigma_2^2 = 0.01, 0.05$. Second row, first column: Comparison of estimates of power of [Test RCT] vs [Test RCT-COV], assuming $x_j \sim Be(p) \forall j = 1, \ldots, n$ with $0 < p < 1$ in model (3.2). Second row, second column: Comparison of estimates of power of [Test ECT] vs [Test ECT-COV], assuming $x_{ij} \sim Be(p_i)$ for $0 < p_i < 1 \ \forall j = 1, \ldots, n_i, i = 1, \ldots, K$ and $x_{K+1j} \sim Be(p) \forall j = 1, \ldots, n_{K+1}$ for $0 < p < 1$ in model (3.4). The parameter values are $n = 100, n_{ext} = 30, K = 30, \alpha = 0.05, \sigma_1^2 = 1, \rho = 0.5$ and $\sigma_2^2 = 0.05$.

However, when K is large (e.g. $K \geq 30$), we can consider the estimate $\hat{\sigma}_2^2$ (or $\hat{\sigma}_{2,REML}^2$) as the true σ_2^2 value: by plugging this estimate and $\hat{\sigma}_{1,A}^2$ into formula (3.18) we estimate power of the test [Test ECT]. We will show through Monte Carlo simulations that if σ_1^2 and σ_2^2 are unknown, the sample size of the internal study is large ($n \geq 30$) and the number of external studies is large ($K \geq 30$), then estimates of power of the Wald tests of hypotheses [Hp RCT] and [Hp ECT] agree with expressions (3.16) and (3.18), respectively, both when these expressions

are evaluated at the true values of the variances and when they are evaluated at $\hat{\sigma}^2_{1,A}$ and $\hat{\sigma}^2_{2,REML}$.

3.3.2 Bootstrap algorithm

When the number of available external studies is small and the sources of varibility are unknown, it's not possible to obtain an accurate estimate of σ_2^2. Additionally, as in the case where the sample size of the forthcoming trial is small (e.g. $n < 30$) and the between-studies variability is unknown, exact distributional results for Maximum Likelihood estimator of β_1 in model (3.3) are unavailable and inference of this parameter can't be based on the asymptotic normal approximation of the distribution of this estimator. In these situations where the approach of previous section would fail, we propose a bootstrap algorithm to test hypothesis [Hp ECT]. We denote by [Test ECT-BOOT] the test performed by this algorithm. The algorithm is a variation of the bootstrap schemes proposed by Efron [33] and by Rosenberger [69] as a nonparametric tool for estimating standard errors and biases and as a parameteric tool for computing confidence intervals for the probability of success on a treatment in adaptive clinical trial designs, respectively.
We summarize the method below in Algorithm 1. The procedure takes as input data from internal and external studies. First, model (3.3) is fitted to these data by Maximum Likelihood and the estimators of the parameters $\beta_0, \beta_1, \sigma_1^2, \sigma_2^2$ are jointly determined; in particular Maximum Likelihood estimator $\hat{\beta}_1$ is computed. Next, replicates of data of internal and external studies are generated by sampling from model (3.3), where parameters β_0, σ_1^2 and σ_2^2 are evaluated at $\bar{y}$, $\hat{\sigma}^2_{1,A}$ and $\hat{\sigma}^2_{2,REML}$ (or $\hat{\sigma}^2_{2,B}$ if $K < 30$) based on external data and $\beta_1 = 0$. For each replicated dataset b, model (3.3) is fitted to data by Maximum likelihood and the estimators of the parameters $\beta_0, \beta_1, \sigma_1^2, \sigma_2^2$ are jointly determined, in particular Maximum Likelihood estimator $\hat{\beta}_1^{(b)}$ is computed. Then, estimates $\hat{\beta}_1^{(b)}$ for $b = 1, \ldots, B$ are compared to $\hat{\beta}_1$: an empirical p-value is given by the proportion of bootstrap estimates which are greater than the actual estimate of β_1. Last, the null hypothesis is rejected if this p-value is less than or equal to targeted α level.
Therefore, we could estimate power of the test [Test ECT-BOOT] as the proportion of rejections accrued by bootstrap algorithm when it is applied to different sets of input datasets, which can be simulated from model (3.3), once $\beta_0, \beta_1, \sigma_1^2$ and σ_2^2 are set to some values of interest.

Remark: extension to other outcomes models
Algorithm 1 can be easily generalized to different outcomes model, where exact distributional results for any estimators of fixed effect coefficients in mixed models are not available. For

example, if we assume outcomes distribution in the natural exponential family and a generalized linear model where the inverse of the link function of the mean of the outcomes distribution depends on a linear predictor of form $\beta_0 + \beta_1 T_{ij} + b_i$ for $i = 1, \dots, K+1$, $j = 1, \dots, n_i$ where $\beta_0, \beta_1, T_{ij}, b_i$ are defined as in (3.3), then the distribution of the Maximum Likelihood estimator of the treatment effect β_1 can not be approximated by a Gaussian distribution when the size of the trial is small or the number of available external studies is small (e.g. $n < 30$ or $K < 30$) and the variability between studies σ_2^2 is unknown.
The same holds for the distribution of penalized Maximum Likelihood estimator of the fixed effect coefficient β_1 of a mixed effects Cox model with hazard function of form $\lambda_0(t)e^{\beta_1 T_{ij}+b_i}$ for $i = 1, \dots, K+1$, $j = 1, \dots, n_i$ where β_1 and T_{ij}, b_i are defined as in (3.3) and $\lambda_0(t)$ is a baseline hazard function [66]. However, it is straightforward to adjust Algorithm 1 to test hypothesis $H_0 : \beta_1 = 0$ vs $H_1 : \beta_1 > 0$, where β_1 is the treatment effect of one of the mixed-effects models above. By way of example, we will also assume these models to design externally-controlled randomized clinical trials and we will provide estimates of power of the test of the treatment effects based on bootstrap procedure or Wald-type testing and Monte Carlo simulations.

Remark: extension to model (3.4)
When the variability between studies is unknown but we suspect that there is substantial unaccounted heterogeneity in the outcome of interest across studies assuming model (3.3), i.e. in cases where the meta-analytic estimate $\hat{\sigma}^2_{2,REML}$ of parameter σ_2^2 in (3.3) is large, it may be relevant to continue investigating whether such heterogeneity may be further explained by differences in characteristics of the studies (methodological diversity) or study populations (clinical diversity). For instance, we could suspect that one variable is related with the outcomes and, indeed, explains a lot of responses variability. In this case, we could decide to include a covariate in model (3.3), leading to model (3.4): there are several inherited methods from meta-analysis that we could apply to estimate unknown parameters in model (3.4) using external data, see [62]. Then, if the number of available external studies is large, estimates of power of test [Test ECT-COV] are given by (3.19) evaluated at the estimates of parameters σ_1^2, σ_2^2 obtained with the just mentioned methods. Instead, when the number of available external studies is small, a bootstrap algorithm similar to Algorithm 1 can be used to test hypothesys [Hp ECT-COV]. In particular, bootstrap data could be sampled from model (3.4) where β_0, β_2 and σ_1^2 are evaluated at the estimates obtained by fitting this mixed-effects model (excluding parameter β_1) on external data, β_1 takes zero value and σ_2^2 equals the variance of the estimates of fixed-effect coefficients

obtained by fitting a fixed-effect version of model (3.4) on external data.

Algorithm 1: A bootstrap algorithm for testing treatment efficacy (Plug-in estimates, test based on p-value), Gaussian outcomes, model (3.3)

Input: Data from experimental study of size n and data from K external studies of size n_{ext} (covariates and realizations of model (3.3))

Output: Test hypothesis [Hp ECT] on the treatment effect parameter β_1 of (3.3)

Fit model (3.3) to the input dataset by Maximum Likelihood;

Estimate the treatment effect by $\hat{\beta}_1$;

Estimate the variance of $\hat{\beta}_1$ by $\text{Var}(\hat{\beta}_1)$;

Determine estimators $\hat{\beta}_0 = \bar{y}$, $\hat{\sigma}_1^2 = \hat{\sigma}_{1,A}^2$ of β_0, σ_1^2 based on external data;

if $K < 30$ **then**

  Estimate σ_2^2 by $\hat{\sigma}_2^2 = \hat{\sigma}_{2,B}^2$ based on external data;

else

  Estimate σ_2^2 by $\hat{\sigma}_2^2 = \hat{\sigma}_{2,REML}^2$ based on external data;

end

for $i \in 1$ ***to*** B **do**

  Generate a new dataset of total size $n + n_{ext}K$ from model (3.3) where parameters $\beta_0, \sigma_2^2, \sigma_1^2$ are evaluated at $\hat{\beta}_0, \hat{\sigma}_1^2, \hat{\sigma}_2^2$ and $\beta_1 = 0$;

  Fit model (3.3) to bootstrap dataset by Maximum Likelihood ;

  Estimate the treatment effect by $\hat{\beta}_1^{(b)}$;

  Estimate the variance of $\hat{\beta}_1^{(b)}$ by $\text{Var}(\hat{\beta}_1^{(b)})$;

end

Compute $\hat{p} = \frac{1}{B}\sum_{b=1}^{B} 1\left(\frac{\hat{\beta}_1^{(b)}}{\sqrt{\text{Var}(\hat{\beta}_1^{(b)})}} > \frac{\hat{\beta}_1}{\sqrt{\text{Var}(\hat{\beta}_1)}}\right)$;

Reject H_0 at level α if $\hat{p} \leq \alpha$;

3.4 Simulations

In all the numerical examples that we provide, we set $\alpha = 0.05$.

Gaussian outcomes

First, we verify the analytic results of the previous section using Monte Carlo simulations: we simulate data from model (3.1) ((3.3)) under the alternative hypothesis given in [Hp RCT] ([Hp ECT]), we perform Wald test for the coefficient β_1 and we estimate power of this test as the proportion of statistically significant p-values across simulations.

In the first subplot of Figure 3.2 we compare the estimates of power of Wald test of [Hp RCT] based on 1000 simulations and expression (3.16). The sample size n is set equal to 100 and we use $\sigma_1^2 = 1$ and $\rho = 0.5$. Similarly, in the second subplot of Figure 3.2 we point out that the graphic of power of Wald test of [Hp ECT] based on 1000 simulations overlaps with the graphic of formula (3.18) evaluated at the true value of σ_1^2 and σ_2^2 (known variances) and with the graphic of formula (3.18) evaluated at the average of estimators $\hat{\sigma}_{1,A}^2$ and $\hat{\sigma}_{2,REML}^2$ based on external data across iterations. This is due to the fact that asymptotically Maximum Likelihood estimator of treatment effect parameter in model (3.3) computed when the sources of variability are unknown coincide with Generalized Least square estimator of the same parameter computed under the assumption that the sources of variability σ_1^2 and σ_2^2 are known and they are equal to the true parameter values or to the consistent and unbiased estimators $\hat{\sigma}_{1,A}^2$ and $\hat{\sigma}_{2,REML}^2$ based on external data. In this example, $n = 100, n_{ext} = 30, K = 30, \sigma_1^2 = 1, \rho = 0.5$ and $\sigma_2^2 = 0.05$.
Then, we validate the bootstrap Algorithm 1 proposed as a way to estimate power of the test [Test ECT-BOOT] whatever number of external studies K are available. The second row of Figure 3.2 compares estimates of power based on bootstrap Algorithm 1 to expression (3.18) evaluated at the true value of σ_1^2 and σ_2^2 (known variances). In this case $n = 100, n_{ext} = 30, \sigma_1^2 = 1, \rho = 0.5, \sigma_2^2 = 0.05$ and $K = 30, 5$. We notice that estimates of power of test [Test ECT-BOOT] (based on 600 iterations of bootstrap algorithm with $B = 600$ bootstrap datasets) are in accordance with expression (3.18), also when the number of external studies is small ($K = 5$). However, for randomization ratios different than 0.5, when we have few external studies at our disposal, estimates of power of test [Test ECT-BOOT] are in general smaller or equal to that ones of test [Test ECT]. Both tests are testing hypothesys [Hp ECT], but the former is not assuming that the between-studies and within-study variances are known.
Bootstrap estimates of the probability of type I error are coherent with the aim of controlling the probability of type I error at level α, but when $\Delta \neq 0$ we encounter a loss of power in testing [Test ECT-BOOT] compared to testing [Test ECT]. This phenomenon is more pronounced for values of ρ close to 1. This is due to the fact that we are not able to estimate accurately the between-studies variance σ_2^2 when we have few external studies at our disposal and in Algorithm 1 we generate bootstrap data by sampling from model (3.3) evaluated at a positive but biased estimate of σ_2^2, that is $\hat{\sigma}_{2,B}^2$. Also, we are not able to identify precisely the contributions of the random effect and of the treatment effect in the internal study when the randomization ratio is close to 1.

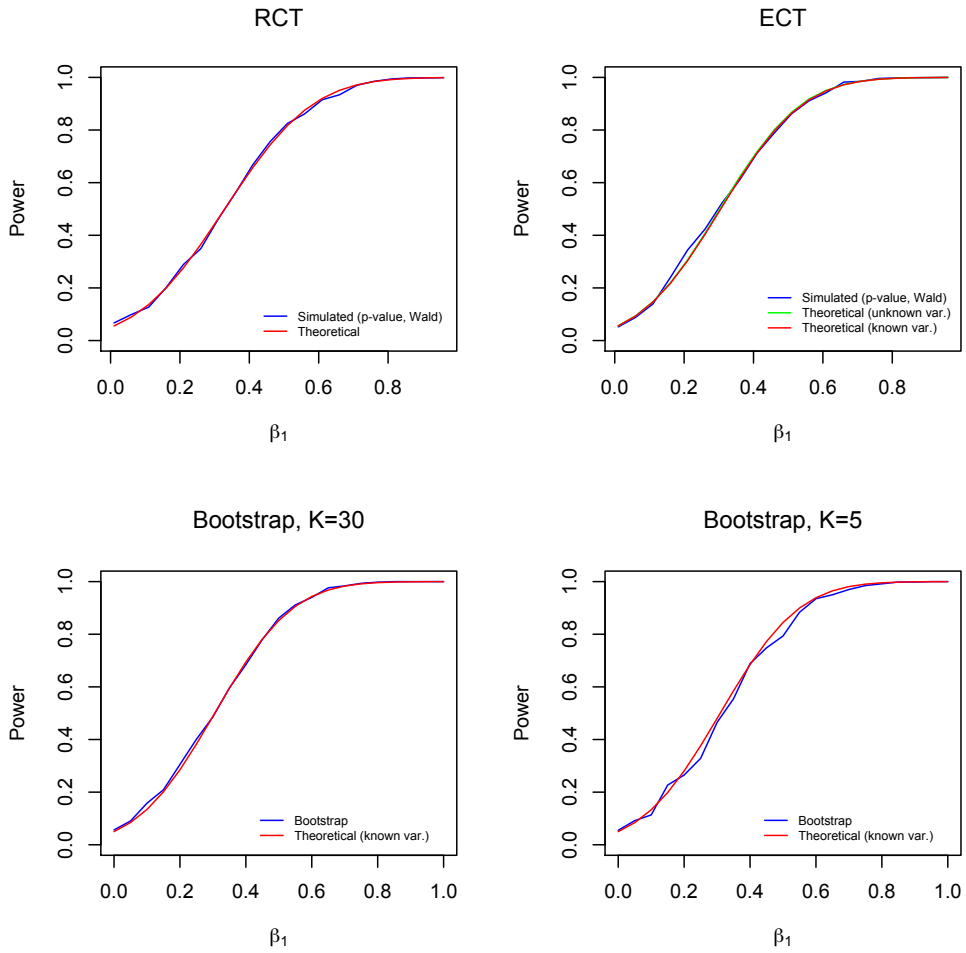

Figure 3.2: First row, first column: Comparison of theoretical expressions of power (3.16) and estimates of power of Wald tests for hypotheses [Hp RCT] based on Monte Carlo simulations. First row, second column: Comparison of theoretical expressions of power (3.18) and estimates of power of Wald tests for hypotheses [Hp ECT] based on Monte Carlo simulations.
Second row: Comparison of estimate of power of test of hypothesis [Hp ECT] (formula (3.18) evaluated at the true value of σ_1^2 and σ_2^2) and estimates of power of test [Test ECT-BOOT] when $\rho = 0.5$.

By comparing the estimates of power of test [Test ECT-BOOT] to the estimates of power of test [Test RCT] related to a randomized clinical trials with balanced randomization (Appendix), we can conclude as follows: when we have few external studies at our disposal and the between-study variability is unknown but low (for example $\sigma_2^2 \leq 0.05$ when $n = 100$ and $K = 5$) running an externally controlled randomized clinical trial with randomization ratio close to 0.5 would still

guarantee higher power than running a standard randomized clinical trial with balanced randomization: this gain in power is not present anymore when considering larger values of variability between studies.

Bernoulli outcomes, large number of external studies

In many trials it is impossible to obtain a single quantitative measure of response to treatment for a patient. Instead, a set of rules may be defined to determine if each patient achieved a response or not and this can be thought as the mean of a binary variable scoring 1 for response and 0 for no response. When outcomes of the patients enrolled in the forthcoming clinical trial and the responses collected in K external studies of size n_{ext} about the control treatment are Bernoulli random variables, we assume logistic regression models and logistic regression models with random intercepts, with same covariates and random effects as in models (3.1)-(3.4), in order to design randomized clinical trials and externally-controlled randomized clinical trials, respectively (see Appendix for further details).

Figure 3.3 compares the estimates of power of Wald test for the null hypothesis of no treatment effect versus the alternative hypothesis of positive treatment effect in these models based on Monte Carlo simulations (1000 simulated trials), when K and n are sufficiently large to consider Gaussian approximation of Wald test statistics. If the optimality goal is to maximize the power of the study, then the evidence-based recommendations about the design characteristics of the forthcoming clinical trial with binary endpoints are similar to those stated in Section 3.3.1 in the case of Gaussian endpoints, at least when a large number of external studies is available. For small values of between-studies variability, the best choice is to design a single-arm trial supported by external controls; instead for larger values of between-studies variability the optimal design is an externally-controlled randomized clinical trial with balanced randomization even if for very large values of between-studies variability it is not convenient to use external data anymore. Also, the set of guidelines remains the same if we add in the models additional binary covariates. In fact, if it is true that the additional covariate could explain variation in the outcomes and therefore reduce the estimate of the between-studies or within-study variance parameters, but it is also true that under the above assumptions on the distribution of the additional covariate, estimates of power of the test related to the models without covariates coincide with estimates of power of the test related to the models with additional covariate, as long as the parameters shared by these models assume the same value.

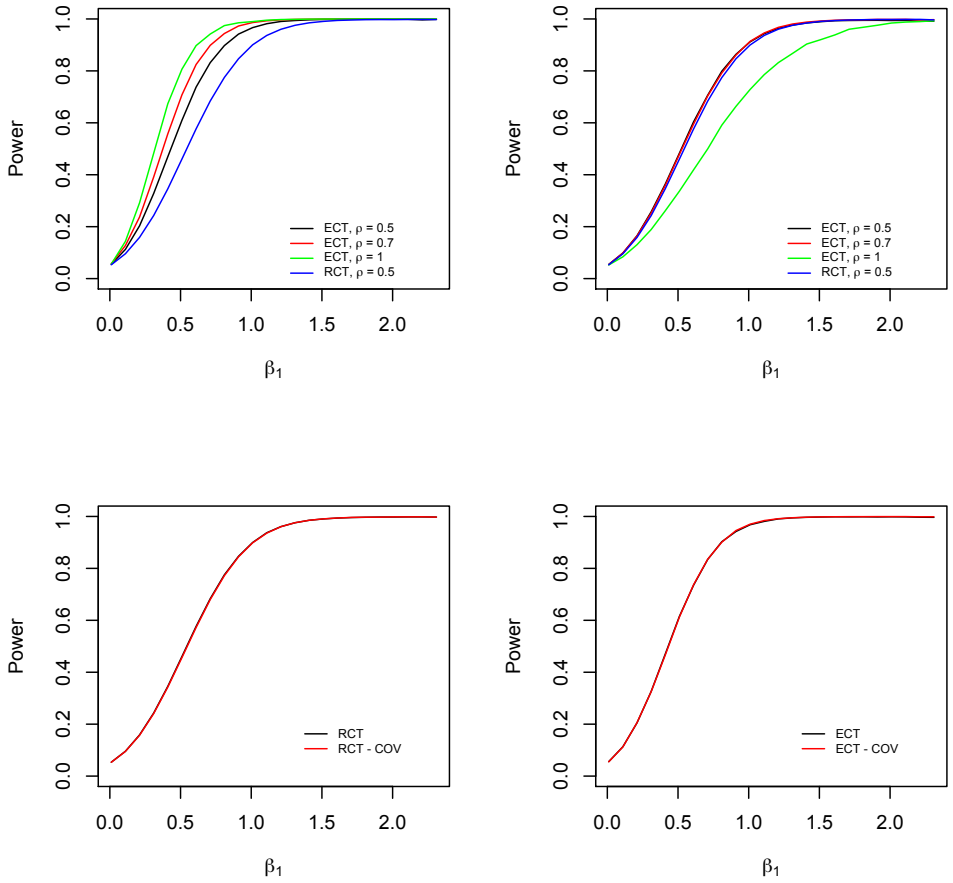

Figure 3.3: First row: Comparison of power of Wald test for the null hypothesis of no treatment effect versus the alternative hypothesis of positive treatment effect related to design of RCT with randomization ratio $\rho = 0.5$ and of ECT with randomization ratio $\rho = 0.5, 0.7, 1$ with binary endpoints. We set the parameters values $n = 150, n_{ext} = 30, K = 30$ and $\sigma_2^2 = 0.01, 0.2$. Second row: Comparison of power of Wald test for the null hypothesis of no treatment effect versus the alternative hypothesis of positive treatment effects related to design of RCT (first column) and ECT (second column) assuming models without an additional binary covariate (RCT and ECT) and with an additional binary covariate (RCT-COV and ECT-COV) for fixed values of between-studies and within-study variances. The parameters values are $n = 150, n_{ext} = 30, K = 30, \rho = 0.5, \sigma_2^2 = 0.01$ and p, p_i's are random numbers in the interval (0,1).

Time-to-event outcomes, small number of external studies

We assume that the outcomes of the patients enrolled in the forthcoming clinical trial and the re-

sponses collected in K external studies of size n_{ext} about the control treatment are time-to-event. We consider Cox model and mixed effects Cox model with hazard function denoted by $\lambda_0(t)$ to design randomized clinical trial and externally-controlled randomized clinical trials, with same covariates and random effects as in models (3.1) and (3.3), but excluding the intercept term β_0. If we design the trial as a randomized clinical trial and our goal is to test the null hypothesis of no treatment effect against the one-sided alternative of positive treatment effect, which is represented by the coefficient of a standard Cox model, then we use the log-rank test, which is the most powerful testing method, when the proportional hazards assumption holds, to quantify or measure the relative difference between the survival curves of different arms [45]. As we can see from Table 3.2, the optimal randomization ratio for randomized clinical trials is 0.5.
On the other hand, if we design the trial as an externally-controlled randomized clinical trial and our goal is to test the null hypothesis of no treatment effect against the one-sided alternative of positive treatment effect, which is represented by one fixed-effect coefficient of a mixed-effect Cox model, we apply a bootstrap algorithm similar to Algorithm 1, see Appendix. Table 3.2 shows estimates of power in some fixed scenarios, where the bootstrap procedure is iterated for 1000 times and the number of bootstrap samples is 600. Bootstrap estimates of type I error are coherent with the aim of controlling type I error at level 0.05.

ECT	$\sigma_2^2 = 0.01$	$\sigma_2^2 = 0.05$	$\sigma_2^2 = 0.1$
$\rho = 0.5$	0.917	0.870	0.852
$\rho = 0.7$	0.908	0.830	0.790
$\rho = 1$	0.744	0.503	0.364

RCT	
$\rho = 0.5$	0.900
$\rho = 0.7$	0.827
$\rho = 0.3$	0.838

Table 3.2: Power estimates of test of the treatment effect related to ECTs and RCTs with time-to-event endpoints. The sample size of the internal study is 100, the number of external studies is 5 and their size is 30. Also, the minimum desired response for the experimental treatment to constitute a clinically relevant benefit is $\Delta = 0.6$.

Nevertheless, when we have few external studies at our disposal and the between-study variability is unknown but low (for example $\sigma_2^2 \leq 0.01$ when $n = 100$ and $K = 5$) running an externally controlled randomized clinical trial with randomization ratio close to 0.5 would still guarantee higher power than running a standard randomized clinical trial with balanced randomization: this gain in power is not present anymore when considering larger values of between-studies variability. As we have noticed previously, similar considerations applied also in the case of Gaussian outcomes.

Remark: model misspecification

The testing procedures that we have introduced in Sections 3.3.1 and 3.3.2 above to evaluate the treatment effect in externally-controlled randomized clinical trials with Gaussian endpoints are based on model assumptions (3.3). A priori, these methods could fail if the model is misspecified: model misspecification refers to all of the ways that the model might fail to represent the real situation. For instance, the random effect distribution might be non-normal, or the error terms might be heteroscedastic/non-normal.

In particular, our testing procedures rely on the classical likelihood theory statement that, when the assumed model is correct (linear mixed model), the Maximum Likelihood estimators for fixed effects and variance components are consistent and asymptotically normally distributed with the inverse Fisher information matrix as asymptotic covariance matrix. Indeed, it has been been shown that these estimators are consistent and asymptotically normally distributed, even when the random-effects distribution is non-normal and general regularity conditions hold [48], but a sandwich-type correction to the inverse Fisher information matrix is then needed in order to get the correct asymptotic covariance matrix [90].

Nevertheless, research carried out in recent years illustrates that similar results do not hold when responses are non-normal and we consider generalized linear mixed models [61, 53]. In particular, when the random effect distributions are misspecified, the Maximum Likelihood estimators are inconsistent and the type I error rate and the power of Wald test for treatment effect can be also severely affected, depending on the shape and the variance of the random-effects distribution. As a consequence, the testing procedure and power estimates that we have considered in Section 3.4 when endpoints are Bernoulli or time-to-event is strictly connected to the assumptions of the model. Therefore, our approach should be incorporated into a more general sensitivity analysis framework, where different random-effects distributions are considered and the inferences obtained are compared. If the inferential procedures are similar, irrespective of the random effects distribution used to obtain them (normal / non-normal), one could feel relatively confident about the results. On the other hand, if the results vary considerably, caution is required.

3.5 Discussion

In Chapter 3, we provide a quantitative framework to support the choice of using existing data about the control treatment in the design of novel clinical trials. We use power as a metric to compare standard randomized clinical trials and externally-controlled randomized clinical trials designs.

When outcomes are Gaussian and the between-studies and within-study variances are known, we provide closed-form expression of power of the test of the null hypothesis of no treatment effect against the alternative hypothesis of positive treatment effect related to different designs and we propose a way to determine the type of design of the forthcoming clinical trial and the associated randomization ratio that are optimal. We show that if the between-studies and within-study variances are unknown, but a large number of external studies is available, then the theory developed under the assumption that the variances are known still holds: it is sufficient to replace in computation the two unknown variances by their estimates based on external data obtained using one-way random-effect anova theory and random-effect meta-analysis. Simulation studies are provided to confirm our findings, when the size of internal study is large.

Also, we propose a bootstrap algorithm that allows us to estimate power of the test of the treatment effect related to externally-controlled randomized clinical trial designs when the between-studies and within-study variances are unknown and a small number of external studies is available or a small number of patients are enrolled in the forthcoming study. We emphasize that one can apply a similar bootstrap procedure to estimate power of the test of the treatment effects (fixed-effects coefficients) when outcomes have a distribution in the natural exponential family and we consider a generalized linear mixed model where the inverse of the link function of the mean of the outcomes distribution depends on a linear predictor similar to that one in (3.3) and we don't put any requirements on the number of external studies and size of the forthcoming trial. This is true also when outcomes are time-to-event and we employ mixed-effect Cox proportional hazard model.

According to our analysis, if the sources of variability are known or they are unknown but a large number of external studies is available, then externally-controlled randomized clinical trials with optimal randomization ratio ρ^{ECT} are superior to standard randomized clinical trials with optimal randomization ratio ρ^{RCT}. We show that the variability between studies plays a crucial role in determining the choice of running a standard randomized clinical trial or an externally-controlled single-arm trial. This comes as no surprise: it is intuitive that if the sources of variability are known, or a large number of external studies is available, and both the heterogeneity between

studies and the size of the forthcoming study are not very large, then it is preferable to design a single-arm trial employing external controls instead of a standard randomized clinical trial with equal randomization ratio. Instead, as the heterogeneity between studies increases, two-arm studies should be preferred over externally-controlled single-arm studies, since in this case we need additional and more precise information on the control treatment additional to that one provided by external studies. Even if the sources of variability are unknown and the number of external studies is small, then the magnitude of the between-studies variability is a key factor in the decision of running a standard balanced randomized clinical trial or an externally-controlled clinical trial with balanced randomization.

We consider power related to externally-controlled randomized clinical trials as the probability of avoiding a type II error in testing the null hypothesis of no treatment effect versus the alternative hypothesis of positive treatment effect. Similarly, the testing procedure presented here allows us to control the probability of type I error at a targeted level. On the other hand, one could consider the conditional probability of avoiding type II error and the conditional probability of type I error of our testing procedure, given external data. In other words, we adopt a marginal perspective, where we integrate out a level of variability given by external data in estimating power and the probability of type I error. In particular, the choice of the optimal randomization ratio is affected by the estimates of the parameters of mixed-effects models explaining the data generating mechanism based on external data. Indeed, one could look at operating characteristics marginally (before looking at external data, considering external data as random) or conditionally (given external data). The estimate of the probability of type I error conditioned on external data depends upon the specific collection of external data under examination: the variability of the conditional probability distribution of type I error given external data decreases as the sample size of the internal study, the number of external studies or the variance of the random effects gets larger (Appendix, Figure C.3). Nevertheless, the conditional probability of type I error does not generally differ much from targeted α level, except where the variance of the random effects is very small. Similarly, when the incorporation of external information in a novel trial is performed through historical borrowing mechanisms adopting a Bayesian perspective, this could have harmful consequences on the trials' frequentist (conditional) operating characteristics in case of inconsistency between prior information and data collected in the novel trials [22, 93]. Indeed, to remedy this, one could point to a priori reduced fixed (nominal) significance level.

Of course, it is also possible to consider a Bayesian version of the models that we have considered. For instance, we could choose a hierarchical modeling by assuming prior distributions for

the parameters $\beta_0, \beta_1, \beta_2, \sigma_1^2$ and σ_2^2 in (3.4).
In that case, the prior distribution for parameter β_1 would have a large impact on inference and this could be potentially harmful when few external studies are available.
To sum up, our recommendations can be applied to any disease and to general clinical trials intended to demonstrate the efficacy of an experimental treatment: incorporating existing information on the control treatment in the design of a novel clinical trial could lead to a more efficient allocation of patients in the execution of clinical trials and accelerate the drug development process.
Augmenting clinical trials with external data and borrowing strength from external control information is particularly valuable in rare disease settings or in situations where there isn't enough time to conduct the study. The enhanced availability of external data sources have promise to improve the execution of traditional clinical trials and strengthen the current ecosystem of data supporting healthcare decisions.

Reference Bonsaglio, M., Fortini, S., Ventz, S., Trippa, L. (2021+), *Incorporating external data in the design of novel trials*

Appendix C

Supplement to Chapter 3

C.1 Proofs of analytic results

Proof of Proposition 4

Formula (3.16)*: randomized clinical trial in standard formulation, [Test RCT]*
We can rewrite model (3.1) in form

$$\boldsymbol{y} \sim N(\boldsymbol{X}\boldsymbol{\beta}, \sigma_1^2 \boldsymbol{I}), \tag{C.1}$$

where $\boldsymbol{X}$ is an $n \times 2$ design matrix of full rank with the j-th row $(1, T_j)$; $\boldsymbol{y}$ is a $n \times 1$ vector of responses of the patients, $\boldsymbol{\beta} = (\beta_0, \beta_1)'$ is the vector of the parameters; $\boldsymbol{I}$ is the identity matrix of dimension $n \times n$. We test hypothesis [Hp RCT] under the assumptions of Proposition 4.
We denote with $\hat{\boldsymbol{\beta}}$ the Ordinary Least Squares estimator of $\boldsymbol{\beta}$. It has bivariate normal distribution with mean $\boldsymbol{\beta}$ and covariance matrix

$$\mathrm{Var}(\hat{\boldsymbol{\beta}}) = \sigma_1^2(\boldsymbol{X}'\boldsymbol{X})^{-1} = \frac{\sigma_1^2}{n_c n_e}\begin{bmatrix} n_e & -n_e \\ -n_e & n \end{bmatrix}. \tag{C.2}$$

The variance of $\hat{\beta}_1$ equals the entry (2,2) of (C.2). The test statistic is $Z := \dfrac{\hat{\beta}_1\sqrt{n_e n_c}}{\sqrt{n}\sigma_1} \sim N(0,1)$ under H_0 and $Z \sim N\left(\dfrac{\Delta\sqrt{n_e n_c}}{\sqrt{n}\sigma_1}, 1\right)$ under H_1. We reject H_0 if $Z > z_\alpha$, where z_α is the threshold to control targeted type I error rate at level α: $P(Z > z_\alpha \mid H_0 \text{ True}) = \alpha$. Therefore, power of the test [Test RCT] equals (3.16).

Formula (3.17)*: randomized clinical trial in standard formulation, [Test RCT-COV]*
We can rewrite model (3.1) in form

$$\boldsymbol{y} \sim N(\boldsymbol{X}\boldsymbol{\beta}, \sigma_1^2 \boldsymbol{I}), \tag{C.3}$$

where $\boldsymbol{X}$ is an $n \times 3$ design matrix of full rank with the j-th row $(1, T_j, x_j)$; $\boldsymbol{y}$ is a $n \times 1$ vector of responses of the patients, $\boldsymbol{\beta} = (\beta_0, \beta_1, \beta_2)'$ is the vector of the parameters; $\boldsymbol{I}$ is the identity matrix of dimension $n \times n$.
We test [Hp RCT-COV] assuming that σ_1^2 is known. We denote with $\hat{\boldsymbol{\beta}}$ the Ordinary Least Squares estimator of $\boldsymbol{\beta}$. It has bivariate normal distribution with mean $\boldsymbol{\beta}$ and covariance matrix

$$\mathrm{Var}(\hat{\boldsymbol{\beta}}) = \sigma_1^2(\boldsymbol{X}'\boldsymbol{X})^{-1} = \sigma_1^2 \begin{bmatrix} n & n_e & \sum_{j=1}^{n} x_j \\ n_e & n_e & \sum_{j=n_c+1}^{n} x_j \\ \sum_{j=1}^{n} x_j & \sum_{j=n_c+1}^{n} x_j & \sum_{j=1}^{n} x_j^2 \end{bmatrix}^{-1} \tag{C.4}$$

The variance of $\hat{\beta}_1$, denoted by $\mathrm{Var}(\hat{\beta}_1)$, equals the entry (2,2) of (C.4), that is

$$\frac{\sigma_1^2 \left[n \sum_{j=1}^{n} x_j^2 - \left(\sum_{j=1}^{n} x_j \right)^2 \right]}{n \left[n_e \sum_{j=1}^{n} x_j^2 - \left(\sum_{j=n_c+1}^{n} x_j \right)^2 \right] + n_e \left[-n_e \sum_{j=1}^{n} x_j^2 + 2 \left(\sum_{j=n_c+1}^{n} x_j \right) \left(\sum_{j=1}^{n} x_j \right) - \left(\sum_{j=1}^{n} x_j \right)^2 \right]}. \tag{C.5}$$

Controlling targeted type I error rate at level α, power of the test [Test RCT-COV] equals $1 - \Phi\left(z_\alpha - \frac{\Delta}{\sqrt{\mathrm{Var}(\hat{\beta}_1)}} \right)$, where $\mathrm{Var}(\hat{\beta}_1)$ is given in (C.5). This gives (3.17).

Proof of Proposition 5

Formula (3.18)*: externally-controlled randomized clinical trials, [Test ECT]*
We can rewrite model (3.3) in form

$$\boldsymbol{y}_i \sim N(\boldsymbol{X}_i\boldsymbol{\beta}, \sigma_1^2 \boldsymbol{I} + \sigma_2^2 \mathbf{1}_i \mathbf{1}_i'), \tag{C.6}$$

where $\boldsymbol{X}_i$ is an $n_i \times 2$ design matrix of full rank with the i-th row $(1, T_{ij})$; $\boldsymbol{y}_i$ is a $n_i \times 1$ vector of responses of the patients in the i-th study, $\boldsymbol{\beta} = (\beta_0, \beta_1)'$ is the vector of the fixed effects; $\mathbf{1}_i$ is a $n_i \times 1$ unit vector; $\boldsymbol{I}$ is the identity matrix of dimension $n_i \times n_i$. The model is identifiable, see

Chapter 3 in [28]. We test hypothesis [Hp ECT] under the assumptions of Proposition (1) and we define

$$\bar{\boldsymbol{x}}_i = n_i^{-1}\boldsymbol{X}_i'\mathbf{1}_i, \quad \bar{y}_i = n_i^{-1}\boldsymbol{y}_i'\mathbf{1}_i.$$

The Generalized Least Squares estimator of β is

$$\hat{\boldsymbol{\beta}} = \left[\sum_{i=1}^{K+1}\left(\boldsymbol{X}_i'\boldsymbol{X}_i - \frac{n_i^2\sigma_2^2}{\sigma_1^2+n_i\sigma_2^2}\bar{\boldsymbol{x}}_i\bar{\boldsymbol{x}}_i'\right)\right]^{-1}\left[\sum_i\left(\boldsymbol{X}_i'\boldsymbol{y}_i - \frac{n_i^2\sigma_2^2}{\sigma_1^2+n_i\sigma_2^2}\bar{\boldsymbol{x}}_i\bar{y}_i\right)\right]. \tag{C.7}$$

It is unbiased and normal with covariance matrix

$$\begin{aligned}\mathrm{Var}(\hat{\boldsymbol{\beta}}) = \sigma_1^2\left[\sum_{i=1}^{K+1}\left(\boldsymbol{X}_i'\boldsymbol{X}_i - \frac{n_i^2\sigma_2^2}{\sigma_1^2+n_i\sigma_2^2}\bar{\boldsymbol{x}}_i\bar{\boldsymbol{x}}_i'\right)\right]^{-1} \\ \begin{bmatrix}\frac{n_{\text{ext}}K\sigma_1^2}{\sigma_1^2+n_{\text{ext}}\sigma_2^2}+\frac{n\sigma_1^2}{\sigma_1^2+n\sigma_2^2} & \frac{n_e\sigma_1^2}{\sigma_1^2+n\sigma_2^2} \\ \frac{n_e\sigma_1^2}{\sigma_1^2+n\sigma_2^2} & \frac{n_e(\sigma_1^2+n_c\sigma_2^2)}{\sigma_1^2+n\sigma_2^2}\end{bmatrix}^{-1}.\end{aligned} \tag{C.8}$$

Refer to [28] Chapter 2 for the statistical properties of estimator (C.7).
In particular, the variance of $\hat{\beta}_1$ (i.e. $\mathrm{Var}(\hat{\beta}_1)$) equals the entry (2,2) of (C.8), that is

$$\mathrm{Var}(\hat{\beta}_1) = \frac{n_{\text{ext}}K\sigma_1^2(\sigma_1^2+n\sigma_2^2)^2 + n\sigma_1^2(\sigma_1^2+n_{\text{ext}}\sigma_2^2)(\sigma_1^2+n\sigma_2^2)}{n_{\text{ext}}Kn_e(\sigma_1^2+n_c\sigma_2^2)(\sigma_1^2+n\sigma_2^2) + n_e(n\sigma_1^2+n_cn\sigma_2^2-n_e\sigma_1^2)(\sigma_1^2+n_{\text{ext}}\sigma_2^2)}. \tag{C.9}$$

Now, $Z := \frac{\hat{\beta}_1}{\sqrt{\mathrm{Var}(\hat{\beta}_1)}} \sim N(0,1)$ under H_0 and $Z \sim N\left(\frac{\Delta}{\sqrt{\mathrm{Var}(\hat{\beta}_1)}}, 1\right)$ under H_1. Controlling type I error at level α, power of the test [Test ECT] can be computed as $1-\Phi\left(z_\alpha - \frac{\Delta}{\sqrt{\mathrm{Var}(\hat{\beta}_1)}}\right)$, where $\mathrm{Var}(\hat{\beta}_1)$ equals (C.9). This proves (3.18).

Formula (3.19): externally-controlled randomized clinical trials, [Test ECT-COV]
We can rewrite model (3.4) in form

$$\boldsymbol{y}_i \sim N(\boldsymbol{X}_i\boldsymbol{\beta}, \sigma_1^2\boldsymbol{I} + \sigma_2^2\mathbf{1}_i\mathbf{1}_i'), \tag{C.10}$$

where $\boldsymbol{X}_i$ is an $n_i \times 3$ design matrix of full rank with the i-th row $(1, T_{ij}, x_{ij})$; $\boldsymbol{y}_i$ is a $n_i \times 1$ vector of responses of the patients in the i-th study, $\boldsymbol{\beta} = (\beta_0, \beta_1, \beta_2)'$ is the vector of the fixed effects; $\mathbf{1}_i$

is a $n_i \times 1$ unit vector; $\boldsymbol{I}$ is the identity matrix of dimension $n_i \times n_i$.
We test hypothesis [Hp ECT-COV] and we denote with $\hat{\boldsymbol{\beta}}$ the Generalized Least Squares estimator of $\boldsymbol{\beta}$. Also, we define

$$\bar{\boldsymbol{x}}_i = n_i^{-1}\boldsymbol{X}_i'\mathbf{1}_i, \quad \bar{y}_i = n_i^{-1}\boldsymbol{y}_i'\mathbf{1}_i.$$

Then,

$$\hat{\boldsymbol{\beta}} = \left[\sum_i \left(\boldsymbol{X}_i'\boldsymbol{X}_i - \frac{n_i^2\sigma_2^2}{\sigma_1^2 + n_i\sigma_2^2}\bar{\boldsymbol{x}}_i\bar{\boldsymbol{x}}_i'\right)\right]^{-1}\left[\sum_i \left(\boldsymbol{X}_i'\boldsymbol{y}_i - \frac{n_i^2\sigma_2^2}{\sigma_1^2 + n_i\sigma_2^2}\bar{\boldsymbol{x}}_i\bar{y}_i\right)\right] \tag{C.11}$$

is unbiased and normal with covariance matrix

$$\begin{aligned}\mathrm{Var}(\hat{\boldsymbol{\beta}}) &= \sigma_1^2\left[\sum_i \left(\boldsymbol{X}_i'\boldsymbol{X}_i - \frac{n_i^2\sigma_2^2}{\sigma_1^2 + n_i\sigma_2^2}\bar{\boldsymbol{x}}_i\bar{\boldsymbol{x}}_i'\right)\right]^{-1} \\ &= \sigma_1^2\begin{bmatrix} \frac{n_{\text{ext}}K\sigma_1^2}{\sigma_1^2 + n_{\text{ext}}\sigma_2^2} + \frac{n_{K+1}\sigma_1^2}{\sigma_1^2 + n_{K+1}\sigma_2^2} & \frac{n_e\sigma_1^2}{\sigma_1^2 + n_{K+1}\sigma_2^2} & \sum_{i=1}^{K+1}\frac{s_i\sigma_1^2}{\sigma_1^2 + n_i\sigma_2^2} \\ \frac{n_e\sigma_1^2}{\sigma_1^2 + n_{K+1}\sigma_2^2} & \frac{n_e\sigma_1^2 + n_e n_c\sigma_2^2}{\sigma_1^2 + n_{K+1}\sigma_2^2} & \frac{(\sigma_1^2 + n_{K+1}\sigma_2^2)s^e_{K+1} - \sigma_2^2 n_e s_{K+1}}{\sigma_1^2 + n_{K+1}\sigma_2^2} \\ \sum_{i=1}^{K+1}\frac{s_i\sigma_1^2}{\sigma_1^2 + n_i\sigma_2^2} & \frac{(\sigma_1^2 + n_{K+1}\sigma_2^2)s^e_{K+1} - \sigma_2^2 n_e s_{K+1}}{\sigma_1^2 + n_{K+1}\sigma_2^2} & \sum_{i=1}^{K+1}\frac{(\sigma_1^2 + n_i\sigma_2^2)s_i - \sigma_2^2 s_i^2}{\sigma_1^2 + n_i\sigma_2^2} \end{bmatrix}^{-1}.\end{aligned}$$

The variance of $\hat{\beta}_1$ equals the entry (2,2) of $\mathrm{Var}(\hat{\boldsymbol{\beta}})$, that can be computed as $\mathrm{Var}(\hat{\beta}_1) = d_4^{-1}$ with d_4 given in (3.11). Controlling targeted type I error rate at level α, power of the test [Test ECT-COV] equals (3.19).

C.2 Bernoulli outcomes: models and inference

In Section 3.4 we consider the design of a novel trial with binary endpoints. In particular, when we run it as a standard randomized clinical trial, regardless of external information, we assume that the response of the j-th patient in the forthcoming study follows

$$P(y_j = 1 \mid T_j) = \pi_j$$

with

$$\left(\frac{\pi_j}{1 - \pi_j}\right) = \beta_0 + \beta_1 T_j, \tag{C.12}$$

or, if we take into account the effect of an additional covariate (binary) on the response in (C.12),

$$P(y_j = 1 \mid T_j, x_j) = \pi_j$$

with

$$\left(\frac{\pi_j}{1-\pi_j}\right) = \beta_0 + \beta_1 T_j + \beta_2 x_j. \tag{C.13}$$

In the above models β_0 is the effect of the control therapy, β_1 is the treatment effect, β_2 is the effect of the additional covariate, T_j denotes a binary random variable which takes value 1 if the patient is assigned to the experimental group and 0 if the patient is assigned to the control group, $x_j \sim Be(p)$ for some $0 < p < 1$. We assume that $T_j = 0$ for $j = 1, \ldots, n_c$ and $T_j = 1$ for $j = n_c + 1, \ldots, n$.

Instead, if we use external information provided by K external studies with binary endpoints and we design the novel study as an externally-controlled randomized clinical trial, then we assume a logistic regression model with random intercept for the response of the j-th patient in the i-th study in the form

$$P(y_{ij} = 1 \mid T_{ij}, b_i) = \pi_{ij}$$

and

$$\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right) = \beta_0 + \beta_1 T_{ij} + b_i \quad \text{for } i = 1, \ldots, K+1,\ j = 1, \ldots, n_i \tag{C.14}$$

or, if we add the effect of an additional covariate on the response,

$$P(y_{ij} = 1 \mid T_{ij}, x_{ij}, b_i) = \pi_{ij}$$

and

$$\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right) = \beta_0 + \beta_1 T_{ij} + \beta_2 x_{ij} + b_i. \tag{C.15}$$

In models (C.14) and (C.15)

$$b_i \overset{\text{i.i.d.}}{\sim} N(0, \sigma_2^2),$$

β_0 is the population-average intercept, β_1 is the treatment effect, b_i is the random effect of the i-th study, T_{ij} denotes a binary random variable which takes value 1 if the patient is assigned to the experimental group and 0 otherwise, $x_{ij} \sim Be(p_i)$ for some $0 < p_i < 1$. In the external studies we have $T_{ij} = 0$ $(\forall i = 1, \ldots, K, \forall j = 1, \ldots, n_i)$; instead, in the internal study we have

$T_{K+1j} = 0$ if $j = 1, \ldots, n_c$ and $T_{K+1j} = 1$ if $j = n_c + 1, \ldots, n_{K+1}$.

We assume that all the external studies have the same size ($n_i = n_{\text{ext}} \forall i = 1, \ldots, K$) and that the internal study has size n ($n_{K+1} = n$).
We test statistical hypotheses $H_0 : \beta_1 = 0$ vs $H_1 : \beta_1 > 0$ where β_1 is
· the coefficient defined in model (C.12) [Hp RCT-BE]
· the coefficient defined in model (C.13) [Hp RCT-COV-BE]
· the fixed coefficient defined in model (C.14) [Hp ECT-BE]
· the fixed coefficient defined in model (C.15) [Hp ECT-COV-BE]
In all cases, we set $\beta_1 = \Delta$ as the minimal effect of the experimental arm compared to standard of care that we wish to detect.

Estimating treatment effect in randomized clinical trial
If our goal is to test hypothesis [Hp RCT-BE] on the coefficient β_1 of model (C.12) under the assumption that n is large (e.g. $n \geq 30$), then we consider Wald-type test ([Test RCT-BE]). The large sample distribution of the Maximum Likelihood estimator $\hat{\beta}_1$ of β_1 is normal with mean β_1 and variance $\text{Var}(\hat{\beta}_1)$ which equals the entry (2,2) of the inverse of the Fisher information of $\boldsymbol{\beta} = (\beta_0, \beta_1)$. This variance has a closed form expression, since the model is in the class of Generalized Linear Models, see Chapter 7 of [28].
Simple computation shows that the information matrix equals

$$\sum_{j=1}^{n} \frac{e^{\beta_0+\beta_1 x_j}}{(1+e^{\beta_0+\beta_1 x_j})^2} \begin{bmatrix} 1 & x_j \\ x_j & x_j^2 \end{bmatrix},$$

so that $\text{Var}(\hat{\beta}_1) = \left(\sum_{j=1}^{n} \frac{e^{\beta_0+\beta_1 x_j}}{(1+e^{\beta_0+\beta_1 x_j})^2} \right)^{-1}$. Therefore, the Wald test statistic is $Z := \frac{\hat{\beta}_1}{\sqrt{\text{Var}(\hat{\beta}_1)}} \sim N(0,1)$ under H_0 and $Z \sim N\left(\frac{\Delta}{\sqrt{\text{Var}(\hat{\beta}_1)}}, 1 \right)$ under H_1.
Controlling targeted type I error rate at level α, power of the test [Test RCT-BE] can be computed as $1 - \Phi\left(z_\alpha - \frac{\Delta}{\sqrt{\text{Var}(\hat{\beta}_1)}} \right)$. In simulations, we generate data following model (C.12), we fit the model on simulated data by Maximum Likelihood estimation and we use Wald-like testing procedure to estimate power as explained above. A similar approach would allow us to estimate power of the Wald test for the hypothesis [Hp RCT-COV-BE] related to model (C.13).

Estimating treatment effect in externally-controlled randomized clinical trials

If our goal is to test hypothesis [Hp ECT-BE] on the coefficient β_1 of model (C.14) under the assumption that K and n are large (e.g. $n, K \geq 30$) and that σ_2^2 is unknown, then we consider Wald-type test ([Test ECT-BE]). We can assume that log-likelihood of $(\boldsymbol{\beta}, \sigma_2^2)$, given observations from model (C.14), takes the form

$$l(\boldsymbol{\beta}, \sigma_2^2) = -\frac{K+1}{2}\log(2\pi\sigma_2^2) + \boldsymbol{\beta}' \sum_{i=1}^{K+1}\sum_{j=1}^{n_i} y_{ij}\boldsymbol{x}_{ij} + \sum_{i=1}^{K+1}\log\int_{-\infty}^{+\infty} e^{h_i(\boldsymbol{\beta};u)}du, \tag{C.16}$$

where $\boldsymbol{\beta} = (\beta_0, \beta_1)'$, $\boldsymbol{x}_{ij} = (1, T_{ij})'$ and $h_i(\boldsymbol{\beta}; u) = \sum_{j=1}^{n_i} y_{ij}u - \frac{u^2}{2\sigma_2^2} - \sum_{j=1}^{n_i}\log(1 + e^{\boldsymbol{\beta}'\boldsymbol{x}_{ij}+u})$. In order to determine the Maximum Likelihood estimators of $\boldsymbol{\beta}$ and σ_2^2, we are concerned with the maximization of (C.16) over $\boldsymbol{\beta}$ and σ_2^2. One could consider two different approaches to estimation. Iterative methods, such as Empirical Fisher scoring algorithm, maximize (C.16) and involve several one-dimensional integration for each study. Likelihood approximation, such as quadratic or Laplace, avoid integration. When the number of studies and the size of the studies are large, the Maximum Likelihood estimator $\hat{\beta}_1$ of β_1 is asymptotically unbiased and consistent, asymptotically normal and efficient (see Chapter 7 of [28]). Therefore, in simulation studies, we generate observations of internal and external studies from model (C.14) in fixed scenario and in order to estimate power of the test of treatment effect β_1 we use Wald testing, where the variance of $\hat{\beta}_1$ can be estimated as in [28]. A similar approach would allow us to estimate power of the Wald-test for the hypothesis [Hp ECT-COV-BE] related to model (C.15).

Guidelines

The evidence-based recommendations about the design characteristics of the forthcoming clinical trial with binary endpoints are similar to those stated in Section 3.3.1 for Gaussian endpoints:

- ▷ For a small value of σ_2^2, it is preferable to design a single-arm trial supported by external controls than a randomized clinical trial with randomization ratio 0.5; the situation reverses for a larger value of between-studies variability.
- ▷ As the value of σ_2^2 increases, estimates of power of test [Test ECT-BE] related to externally-controlled randomized clinical trials with balanced randomization get closer to estimates of power of test [Test RCT-BE] related to randomized clinical trials with balanced randomization. Therefore, for large values of σ_2^2 it is not convenient to use external data anymore.
- ▷ If our aim is to test the treatment effect of the experimental therapy and we consider a

logistic regression model to design a randomized clinical trials, then estimates of power of the Wald-tests for the hypotheses [Hp RCT-BE] and [Hp RCT-COV-BE], computed under the same parameter values, are equal. Instead, if our aim is to test the treatment effect of the experimental therapy and we consider a logistic regression model with random intercept to design an externally-controlled randomized clinical trial, then power is not affected by adding in the model an additional binary covariate as long as the value of the between-studies variance σ_2^2 remains the same: estimates of power of the Wald-tests for hypotheses [Hp ECT-BE] and [Hp ECT-COV-BE] coincide (Fig. 3.3).

Closed-form expression for power related to externally-controlled randomized clinical trials with binary endpoints and known between-studies variability

We provide a way to compute closed-form expression for power of the test of the null hypothesis of no treatment effect versus the alternative of positive treatment effect in externally-controlled randomized clinical trials with binary endpoints, assuming the mixed effect logistic regression model (C.14). We suppose that the between-studies variance σ_2^2 is known and the size of the internal study is large (e.g. $n \geq 30$) and we consider Wald test for hypothesis [Hp ECT-BE] about the fixed-effect coefficient β_1.

First, we use external data, which are collected in studies $i = 1, \ldots, K$, to estimate the intercept β_0. The likelihood of β_0 is

$$L(\beta_0) = \prod_{i=1}^{K} \int_{-\infty}^{\infty} \prod_{j=1}^{n_i} \frac{e^{(\beta_0+b_i)y_{ij}}}{(1+e^{\beta_0+b_i})^2} \frac{e^{-\frac{b_i^2}{2\sigma_2^2}}}{\sqrt{2\pi\sigma_2^2}} db_i$$

and the log-likelihood takes form

$$l(\beta_0) = -\frac{K}{2}\log(2\pi\sigma_2^2) + \beta_0 \sum_{i=1}^{K}\sum_{j=1}^{n_i} y_{ij} + \sum_{i=1}^{K} \log \int_{-\infty}^{\infty} e^{h_i(\beta_0,b_i)} db_i \tag{C.17}$$

with

$$h_i(\beta_0, b_i) = \sum_{j=1}^{n_i} y_{ij} - \frac{b_i^2}{2\sigma_2^2} - \sum_{j=1}^{n_i} \log(1+e^{\beta_0+b_i}).$$

The Maximum Likelihood estimator $\hat{\beta}_0$ of β_0 solves the score equation and maximizes the log-likelihood function. This maximization can be done numerically using Empirical Fisher Scoring

algorithm, as explained in [28] (Chapter 7). The generic form of the iterative algorithm is

$$\hat{\beta}_{0,s+1} = \hat{\beta}_{0,s} + \lambda_s H^{-1} \left(\frac{dl}{d\beta_0} |_{\beta_0 = \beta_{0,s}} \right),$$

where $0 < \lambda_s \leq 1$ is a step length to provide a decrease of the log-likelihood and H is the expected negative second-order derivatives (Fisher information). Indeed, H can be estimated as the sum of product of the derivative

$$d_i = \sum_{j=1}^{n_i} y_{ij} - \frac{\int_{-\infty}^{\infty} \left[\sum_{j=1}^{n_i} \frac{e^{\beta_0 + b_i}}{1+e^{\beta_0+b_i}} e^{h_i(\beta_0, b_i)} \right] db_i}{\int_{-\infty}^{\infty} e^{h_i(\beta_0, b_i)} db_i}.$$

Then iterations

$$\hat{\beta}_{0,s+1} = \hat{\beta}_{0,s} + \lambda_s (\sum_{i=1}^{K} d_i^2)(\sum_{i=1}^{K} d_i)$$

approximate β_0. In practice, $\lambda_s = 1$ usually leads to an increase in l from iteration to iteration, but sometimes it is necessary to decrease the step length to avoid divergence.

Next, we consider model (C.14) for $i = K + 1$ (internal study) and we assign the value $\hat{\beta}_0$ calculated above to the parameter β_0. We have

$$P(y_{K+1j} = 1 \mid x_{K+1j}) = \pi_{x_{K+1j}}$$

and

$$\left(\frac{\pi_{x_{K+1j}}}{1 - \pi_{x_{K+1j}}} \right) = \hat{\beta}_0 + \beta_1 x_{K+1j} + b_{K+1} \quad \text{for } j = 1, \ldots, n_{K+1} \tag{C.18}$$

with

$$b_{K+1} \overset{\text{i.i.d.}}{\sim} N(0, \sigma_2^2).$$

We denote with $l(\beta_1)$ the log-likelihood of a sample from model (C.18) for a fixed value of b_{K+1}, viewed as a function of β_1 given b_{K+1}. Conditioning on b_{K+1}, model (C.18) is a logistic regression model with intercept at $\hat{\beta}_0 + b_{K+1}$. The Maximum Likelihood estimator of β_1 has approximately a normal distribution with mean equal to the true parameter value ($\beta_1 = 0$ under H_0 and $\beta_1 = \Delta$ under H_1) and variance given by the inverse of the Fisher information (denoted by $H^{(H_0)}$ or $H^{(H_1)}$ if it is computed under H_0 or H_1, respectively).

By law of total expectation, the Fisher information equals

$$-E\left(E\left(\frac{d^2l}{d\beta_1^2} \mid b_{K+1}\right)\right)$$

where, by properties of Generalized Linear Models,

$$E\left(\frac{d^2l}{d\beta_1^2} \mid b_{K+1}\right) = \sum_{j=1}^{n_{K+1}} \frac{e^{\hat{\beta}_0+\beta_1 x_{K+1j}+b_{K+1}}}{(1+e^{\hat{\beta}_0+\beta_1 x_{K+1j}+b_{K+1}})^2} x_{K+1j}^2.$$

Therefore, Wald test statistic is $Z := \frac{\hat{\beta}_1}{\sqrt{H^{(H_0)^{-1}}}} \sim N(0,1)$ under H_0 and $Z \sim N\left(\frac{\Delta}{\sqrt{H^{(H_1)^{-1}}}}, 1\right)$ under H_1. Power can be estimated based on the asymptotic distributions of this test statistic.

C.3 Time-to-event outcomes: models and inference

In Section 3.4 we consider the design of a novel trial with time-to-event endpoints. In particular, when we design the study as a randomized clinical trial in standard formulation, we assume Cox proportional hazards model, so that the hazard function of the j-th patient in the forthcoming study follows

$$\lambda(t \mid T_j) = \lambda_0(t)e^{\beta_1 T_j} \quad \text{for } j = 1, \dots, n \tag{C.19}$$

where $\lambda_0(t)$ is the baseline hazard function, describing how the risk of event per time unit changes over time at baseline level of the covariate, β_1 is the treatment effect, T_j denotes a binary random variable which takes value 1 if the patient is assigned to the experimental group and 0 if the patient is assigned to the control group. We assume that $T_j = 0$ for $j = 1, \dots, n_c$ and $T_j = 1$ for $j = n_c + 1, \dots, n$.

Instead, when we design an externally-controlled randomized clinical trial, we assume a mixed-effect Cox model, so that, for the response of the j-th patient in the i-th study, the hazard function equals

$$\lambda(t \mid T_{ij}, b_i) = \lambda_0(t)e^{\beta_1 T_{ij}+b_i} \quad \text{for } i = 1, \dots, K+1,\ j = 1, \dots, n_i \tag{C.20}$$

where

$$b_i \overset{\text{i.i.d.}}{\sim} N(0, \sigma_2^2),$$

$\lambda_0(t)$ is the baseline hazard function, β_1 is the treatment effect, b_i is the random effect of the i-th study, T_{ij} denotes a binary random variable which takes value 1 if the patient is assigned

to the experimental group and 0 otherwise. We set $T_{ij} = 0 \forall i = 1, \ldots, K, \forall j = 1, \ldots, n_i$; instead, $T_{K+1j} = 0$ if $j = 1, \ldots, n_c$ and $T_{K+1j} = 1$ if $j = n_c + 1, \ldots, n_{K+1}$. Again, $n_i = n_{\text{ext}}$ for $i = 1, \ldots, K$ and $n_{K+1} = n$.

Model (C.20) can be seen as a proportional hazard shared frailty model with log-normal frailty (see [7]), where units (patients) are clustered in a way that introduces association of survival probabilities within a group (study). The within-cluster homogeneity may be induced by unmeasured cluster characteristics that affect the outcome or by unmeasured covariates at the subject level that take a similar value for all subjects within the cluster. The event times are assumed to be independent conditional on unobserved frailty terms and conditional unit-specific hazards are proportional over time. The random effects in model (C.20) modify the baseline hazard function and describe the excess risk or frailty for the patients in distinct studies: the idea is that in the studies characterized by higher frailty the patients experiment the event (such as death) earlier than the patients in other studies.

We test hypothesis $H_0 : \beta_1 = 0$ vs $H_1 : \beta_1 > 0$ where β_1 is

· the coefficient defined in model (C.19) [Hp RCT-TE]

· the coefficient defined in model (C.20) [Hp ECT-TE]

In both cases, we set $\beta_1 = \Delta > 0$ as the minimal effect of the experimental arm compared to standard of care that we wish to detect. The goal is to determine statistical testing procedure to test [Hp RCT-TE] and [Hp ECT-TE] in fixed scenarios and determine the type of design (standard randomized or externally-controlled clinical trial design) and its associated randomization ratio, among a set of candidates, that maximize power of these tests.

Testing treatment effects

Cox proportional-hazards models are generally fitted by maximisation of the partial likelihood [26] and the log-rank test is the most powerful testing method, when the proportional hazards assumption holds, to quantify or measure the relative difference between the survival curves of different arms in randomized clinical trials [45]. Therefore, we indicate the statistical test of [Hp RCT-TE] based on log-rank test by [Test ECT]. In order to estimate power of this test, we simulate data of internal trial from model (C.19) for fixed $\lambda_0(t)$, we compute log-rank test statistic and reject the null hypothesis if the p-value of the one-sided test (under normal distribution) is less than α. The proportion of rejections across iterations is an estimate of power.

On the other hand, mixed effects Cox models are generally fitted by maximisation of a penalized partial log-likelihood [66]. In order to test [Hp ECT-TE], we develop a bootstrap algorithm

(Algorithm 2), which is the analogous of Algorithm 1 for time-to-event outcomes and rely on penalized Maximum Likelihood estimation of the treatment effect in model (C.20). We denote this test by [Test ECT-TE]. In order to estimate power of this test, we simulate internal and external data from model (C.20) in fixed scenario, we apply bootstrap Algorithm 2 on these data and we estimate power as the proportion of rejections accrued across iterations by bootstrap procedure. We summarize below Algorithm 2.

Algorithm 2: A bootstrap algorithm for testing treatment efficacy (Plug-in estimates, test based on empirical p-value), Time-to-event endpoints, model (C.20)

Input: Data from experimental study of size n and data from K external studies of size n_{ext} (covariates T_{ij} and realizations y_{ij} of model (C.20), for $i = 1, \dots, K+1$, $j = 1, \dots, n_i$)

Output: Test hypothesis [Hp ECT-TE] on the treatment effect parameter β_1 of (C.20)

Fit model (C.20) to the input dataset by penalized Maximum Likelihood ;

Estimate the treatment effect by $\hat{\beta}_1$;

Estimate the variance of $\hat{\beta}_1$ by by $\text{Var}(\hat{\beta}_1)$;

Determine Breslow estimator $\hat{\lambda}_0(t)$ of $\lambda_0(t)$ based on external data;

if $K < 30$ **then**

  Estimate σ_2^2 by $\hat{\sigma}_2^2$ defined as the value of variance of the estimates of $(b_1, \dots, b_K)$ obtained by fitting a fixed-effect Cox model with covariates $(b_1, \dots, b_K)$ to external data ;

else

  Determine estimator $\hat{\sigma}_2^2$ of σ_2^2 obtained by fitting model (C.20) to external data;

end

for $i \in 1$ ***to*** B **do**

  Generate a new dataset of total size $n + n_{\text{ext}}K$ from model (C.20) where λ_0, σ_2^2 are evaluated at $\hat{\lambda}_0(t), \hat{\sigma}_2^2$ and $\beta_1 = 0$;

  Fit model (3.3) to bootstrap dataset by penalized Maximum Likelihood ;

  Estimate the treatment effect by $\hat{\beta}_1^{(b)}$;

  Estimate the variance of $\hat{\beta}_1^{(b)}$ by by $\text{Var}(\hat{\beta}_1^{(b)})$;

end

Compute $\hat{p} = \frac{1}{B} \sum_{b=1}^{B} 1 \left(\frac{\hat{\beta}_1^{(b)}}{\sqrt{\text{Var}(\hat{\beta}_1^{(b)})}} > \frac{\hat{\beta}_1}{\sqrt{\text{Var}(\hat{\beta}_1)}} \right)$;

Reject H_0 at level α if $\hat{p} \leq \alpha$;

In practice, in order to perform Algorithm 2 it is required that we are able to compute the variance of the Penalized Maximum Likelihood estimator of fixed effect coefficient β_1 and this can be done following the approach described in Ripatti and Palmgren [66].

C.4 Bootstrap algorithms for testing [Hp ECT]

In Section 3.3.2, we propose and validate bootstrap Algorithm 1 as an instrument to test hypothesis of no treatment effect versus positive treatment effect in externally-controlled randomized clinical trials with Gaussian endpoints. This method can be defined as parametric, since bootstrap data are generated from a well-defined statistical model (model (3.3)). On the other hand, bootstrap data could be sampled with replacement from the input dataset, collecting data from external and internal studies. In this case, the algorithm would be defined as non-parametric. Also, the key step in testing [Hp ECT] in Algorithm 1 is to determine an empirical p-value based on the comparison between the value of the Maximum Likelihood estimator of the treatment effect in model (3.3) based on input data and the value that it would take if the null hypothesis was true. Instead, the testing procedure could be also centred around approximate confidence intervals for the treatment effect formed by sorted Maximum Likelihood estimators of the treatment effect (fixed-effect coefficient in linear mixed model) based on bootstrap datasets.
Here we propose one non-parametric bootstrap algorithm (Algorithm 3) and one additional parametric bootstrap algorithm (Algorithm 4) to test [Hp ECT]. In both algorithms, quantiles of appropriate order of a sorted sample of fixed-effect estimates based on bootstrap dataset are chosen to form the approximate confidence interval for the treatment effect and the null hypothesis is rejected if this doesn't contain the value of the parameter defined in the null hypothesis.

Algorithm 3: A bootstrap algorithm for testing treatment efficacy (Plug-in estimates, test based on confidence interval), Gaussian outcomes, model (3.3)

Input: Data from experimental study of size n and data from K external studies of size n_{ext}
Output: Test [Hp ECT] on the treatment effect parameter β_1 of (3.3)
Fit model (3.3) to the input dataset by Maximum Likelihood;
Determine estimators $\hat{\beta}_0, \hat{\beta}_1, \hat{\sigma}_1^2, \hat{\sigma}_2^2$ of $\beta_0, \beta_1 \sigma_1^2, \sigma_2^2$;
for $i \in 1$ ***to*** B **do**
  Generate a new dataset of total size $n + n_{\text{ext}}K$ from model (3.3) where parameters $\beta_0, \beta_1\sigma_2^2, \sigma_1^2$ are evaluated at $\hat{\beta}_0, \hat{\beta}_1, \hat{\sigma}_1^2, \hat{\sigma}_2^2$;
  Fit model (3.3) to bootstrap dataset by Maximum Likelihood ;
  Estimate the treatment effect by $\hat{\beta}_1^{(b)}$;
end
Identify the α quantile $\hat{\beta}_1^*$ of the ordered estimates $\hat{\beta}_1^{(b)}$ for $b = 1, \ldots, B$;
Reject H_0 at level α if $\hat{\beta}_1^* > 0$;

Algorithm 4: A bootstrap algorithm for testing treatment efficacy (Resampling, test based on confidence interval) , Gaussian outcomes, model (3.3)

Input: Data from experimental study of size n and data from K external studies of size n_{ext}
Output: Test [Hp ECT] on the treatment effect parameter β_1 of (3.3)
for $i \in 1$ ***to*** B **do**
  Generate a new dataset of total size $n + n_{\text{ext}}K$ by resampling with replacement data from the input dataset (collecting internal and external data) ;
  Fit model (3.3) to bootstrap dataset by Maximum Likelihood ;
  Estimate the treatment effect by $\hat{\beta}_1^{(b)}$;
end
Identify the α quantile $\hat{\beta}_1^*$ of the sorted estimates $\hat{\beta}_1^{(b)}$ for $b = 1, \ldots, B$;
Reject H_0 at level α if $\hat{\beta}_1^* > 0$;

In order to estimate power of the tests based on Algorithms 3 and 4, we generate iteratively simulated data of external and internal studies from model (3.3) where parameters $\beta_0, \sigma_1^2, \sigma_2^2$ and β_1 are set to some value of interest. Then, we apply these bootstrap algorithms on each simulated complete dataset (internal and external data) and we estimate power as the proportion of rejections accrued across bootstrap iterations. Algorithms 3 and 4 work well only when n_c is quite large (e.g. $n_c \geq 30$), since in this scenario it is possible to identify the contribution of the treatment effect and of the random effect to the responses of the patients enrolled in the internal study. Otherwise, in the limit, when $n_c = 0$, fixed effects are confounded with random effects in model (3.3) and Maximum Likelihood estimation could fail. Also, when we have few external studies Maximum Likelihood estimate of σ_2^2 can take zero value: in this case, Algorithm 3 should be modified such that bootstrap data are generated from model (3.3) where the parameter σ_2^2 is not evaluated at Maximum Likelihood estimator $\hat{\sigma}_2^2$ but at the biased positive ANOVA estimator $\hat{\sigma}_{2,B}^2$.
Figure C.1 compares estimates of power ot tests based on Algorithm 1, Algorithm 3 and Algorithm 4, expression (3.18) evaluated at the true value of σ_1^2 and σ_2^2 (known variances) and expression (3.18) evaluated at the average of estimates $\sigma_{1,A}^2$ and $\sigma_{2,REML}^2$ across simulations (unknown variances).

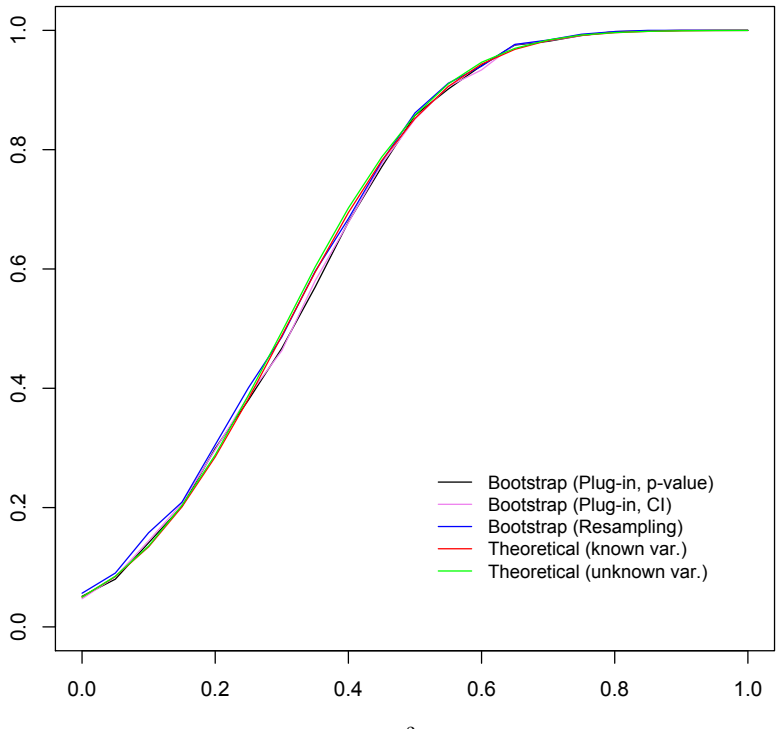

Figure C.1: Comparison of theoretical expression of power (3.18) evaluated at the true value of σ_1^2 and σ_2^2 (known variance), theoretical expression of power (3.18) evaluated at the average of $\hat{\sigma}_{1A,}^2$ and $\hat{\sigma}_{2,REML}^2$ across simulations based on external data (unknown variance) and estimates of power of the test of hypothesis [Hp ECT] based on bootstrap algorithms. The parameters value are $n = 100, n_{\text{ext}} = 30, \sigma_1^2 = 1, \rho = 0.5, \sigma_2^2 = 0.05$ and $K = 30$.

C.5 Conditional probability of avoiding type II error and conditional probability of type I error given external data and random effect of the internal study in testing [Hp-ECT]

In Chapter 3, we have considered power related to externally-controlled randomized clinical trials with Gaussian endpoints as the probability of avoiding a type II error in testing hypothesis [Hp ECT]. Under this assumption, we have derived closed form expression of power when the between-studies and within-study variabilities are known, we have proposed a strategy to estimate power when the sources of variability are unknown and we have performed simulations to confirm our results, mainly using Wald testing in large sample scenarios. On the other hand, one could consider power as the conditional probability of avoiding a type II error in testing hypothesis [Hp ECT], given external data and eventually also the random effect of the internal study. We distinguish between the two above interpretations of power, by referring to marginal power and conditional power given external data and eventually also the random effect of the internal study. Similarly, one could be interested in the conditional probability of type I error in testing hypothesis [Hp ECT], given external data and eventually the random effect of the internal study, instead of the marginal probability obtained integrating out these two levels of variability. Indeed, the conditional probability of avoiding type II error (probability of type I error) in Wald testing of hypothesis [Hp ECT] can be estimated as the proportion of significant p-values across Monte Carlo simulations, where internal data are generated under the alternative (null) hypothesis from model (3.3), external data are generated from model (3.3), external data and eventually the random effect of the internal study ($b_{K+1} \sim N(0, \sigma_2^2)$) don't vary between iterations of the simulation procedure.

The first subplot in Figure C.2 shows the power curve for Wald testing of hypothesis [Hp ECT] as a function of the values of alternative hypothesis β_1, obtained keeping fixed both external data and the random effect of the internal study across 1000 simulations: each of the ten blue lines refers to one particular combination of external data and random effect of the internal study. The red line corresponds to the estimates of power given by (3.18) (marginal estimates) and the green line is obtained by averaging the blue lines values. Instead, each point in the second subplot in Figure C.2 represents the estimate of the conditional probability of type I error in Wald testing, given one particular combination of external data and random effect of the internal study (b_{K+1}), obtained keeping fixed both external data and the random effect of the internal study across 1000 simulations. The red line corresponds to the value of targeted α level of the testing procedure

(marginal) and the green line is the average value of the points. As the random effects increases, the conditional probability of type I error increases.

We notice that the estimates provided in the subplots in the first row of Figure C.2 (blue lines and black points) overestimate or underestimate the marginal probability of avoiding a type II error and the marginal probability of type I error (red lines), but the averages of these estimates (green lines) equal the marginal estimates. This is a consequence of the law of total probability. As we can see from the second row of Figure C.2, the variability of the conditional probability of type I error given random external data and random effect of the internal study decreases as the between-studies variability gets larger or the size of the internal study increases. Also, as the number of available external studies increases, the standard deviation and interquantile range of this distribution reduce.

One could be also interested in the distribution of the conditional probability of avoiding type II error and conditional probability of type I error in Wald testing of hypothesis [Hp ECT], fixing the external dataset, conditioning on it and on the random effect of the internal study, where both probabilities are seen as functions of the random effect of the internal study and a fixed external dataset. The first row in Figure C.3 shows estimates of the conditional probability of avoiding type II error (value of the alternative hypothesis $\beta_1 = \Delta \neq 0$) and conditional probability of type I error ($\beta_1 = 0$), given one specific fixed external dataset: each of the ten blue lines refer to one particular random effect of the internal study, kept fixed within 1000 simulations. The average of these estimates (green line) can't be approximated well by the marginal estimate (3.18) (red line) and, in particular, the average conditional probability of type I error is not close to α. In general, if the interest relies in the distribution of this average, seen as functions of external data, then this is equivalent to consider the distribution of the probability of avoiding type II error and probability of type I error conditionally only on external data (one level of variability).

The second row in Figure C.3 shows the conditional probability distribution of type I error given external data, based on a sample of size 100, in different scenarios. The variability of the distribution gets smaller as the sample size of the internal study, the variance of the random effects or the number of external studies increases. Nevertheless, the conditional probability of type I error does not generally differ much from targeted α level, except where the variance of the random effects is very small. In this case we could point to a priori fixed (nominal) significance level lower than α to have a guarantee of controlling the conditional probability of type I error at targeted level. Although the actual estimate of the probability of type I error conditioned on external data and random effect of the internal study depends upon the specific collection of

external data and the random effect of the internal study, but the latter is unknown to researchers. However, if several trials are run as externally-controlled randomized clinical trials in different experimental conditions (e.g. hospitals) and they are based on different collections of external studies, then on average the conditional probability of avoid type II error (probability of type I error) in Wald testing for hypothesis [Hp ECT] equals the marginal probability of avoiding type II error (probability of type I error) and this average can be approximated by (3.18) (α).

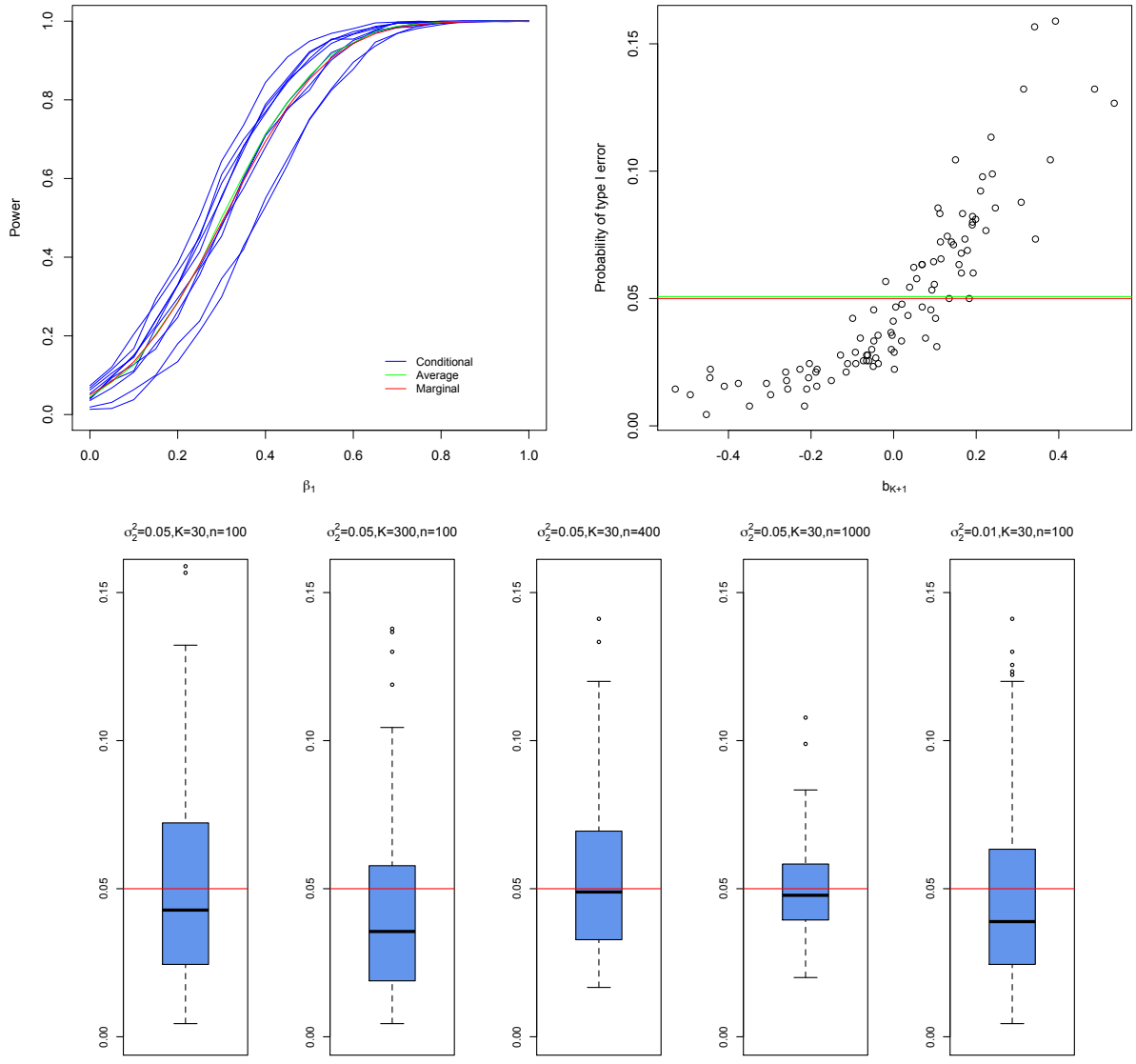

Figure C.2: First row, first subplot: Comparison of the estimates of the conditional probability of avoiding type II error (value of the alternative hypothesis $\beta_1 \neq 0$) and of the conditional probability of type I error ($\beta_1 = 0$) in Wald testing of [Hp ECT], given random external datasets and random effect of the internal study, based on Monte Carlo simulations, and estimates of the marginal probability given by (3.18). First row, second subplot: Comparison of the estimate of the conditional probability of type I error in Wald testing of [Hp ECT] based on Monte Carlo simulations and targeted α level. The value of the parameters are $\rho = 0.5, n_{\text{ext}} = 30, K = 30, n = 100, \sigma_1^2 = 1$ and $\sigma_2^2 = 0.05$. Second row: Conditional probability distribution of type I error in Wald testing of [Hp ECT], given random external data and random effect of the internal study. The value of the parameters are $\rho = 0.5, n_{\text{ext}} = 30$ and $\sigma_1^2 = 1$.

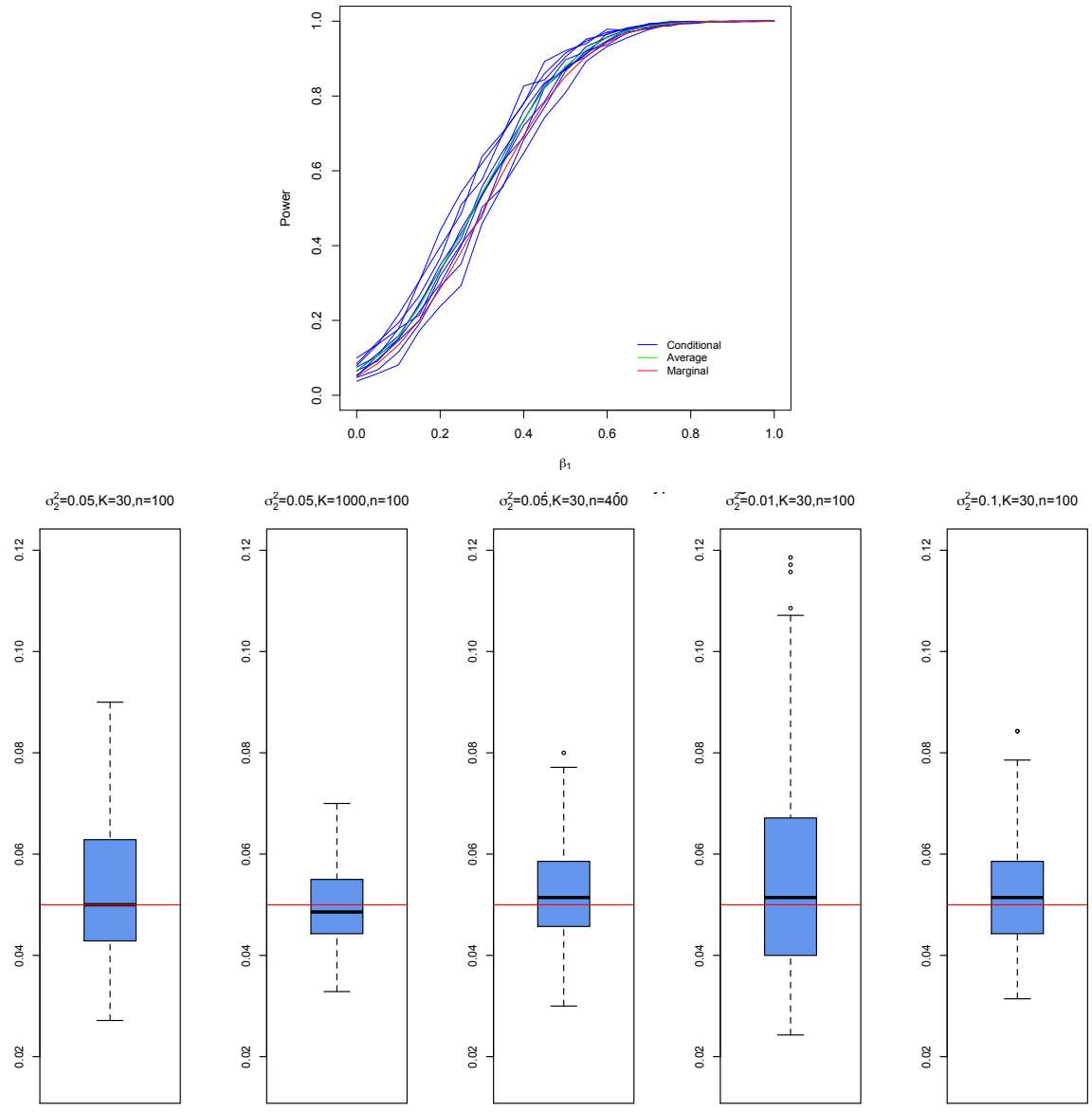

Figure C.3: First row: Estimates of the conditional probability of avoiding type II error (value of the alternative hypothesis $\beta_1 \neq 0$) and of the conditional probability of type I error ($\beta_1 = 0$) in Wald testing of [Hp ECT] given a fixed external dataset and random effect of the internal study, based on Monte Carlo simulations, are compared to the estimates of the marginal probabilities given by (3.18). Each blue line refers to one particular random effect of the internal study and to a common collection of external data. The value of the parameters are $\rho = 0.5, n_{\text{ext}} = 30, K = 30, n = 100, \sigma_1^2 = 1$ and $\sigma_2^2 = 0.05$. Second row: Conditional probability distribution of type I error in Wald testing of [Hp ECT], given external data. The values of the parameters are $\rho = 0.5, n_{\text{ext}} = 30$ and $\sigma_1^2 = 1$.

C.6 Supplementary Figures

Figure C.4 shows that if the number of external studies is quite large ($K = 30$) and outcomes are Gaussian, then the optimal randomization ratio ρ^{ECT} for running an externally-controlled randomized clinical trial equals 1 when the between-studies variability is small and the size of the internal study is not large. For instance, in the first and second subplots we consider the scenario where the parameters in model (3.3) are $\sigma_2^2 \leq 0.01$, $n \leq 50$ and $\sigma_1^2 = 1$. Instead, as we can notice in third and fourth subplots, ρ^{ECT} decreases up to 0.5 when σ_2^2 gets larger.

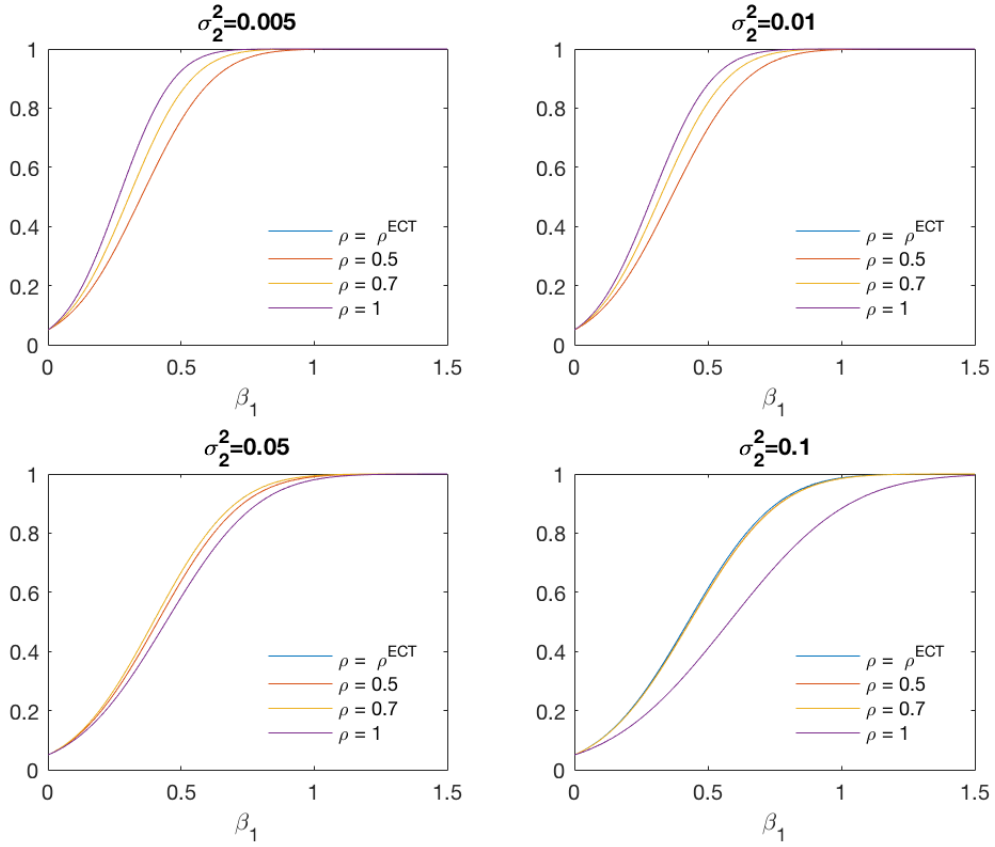

Figure C.4: Comparison of power of the test of treatment effects related to externally-controlled single-arm trials ([Test ECT]) with Gaussian endpoints for different randomization ratios ($\rho = \rho^{ECT}, 0.5, 0.7, 1$) and variances of the random effects ($\sigma_2^2 = 0.005, 0.01, 0.05, 0.1$). The parameters are $n = 50, n_{\text{ext}} = 30, K = 30, \sigma_1^2 = 1$.

In Figure C.5 we consider Gaussian outcomes and we show that if the sources of between-studies and within-study variabilities are known and the number of external studies is small ($K = 5$), then there's almost no convenience in designing an externally-controlled single-arm trial than an externally-controlled randomized clinical trials with randomization ratio in the range $0.5 - 0.99$, when the variance of the random effects is small. For instance, the first and second subplots refer to the scenario where $\sigma_2^2 \leq 0.01$, $n = 100$ and $\sigma_1^2 = 1$, assuming model (3.3). Also, as we can notice in third and fourth subplots, for larger values of σ_2^2, externally-controlled single-arm clinical trials should be avoided.

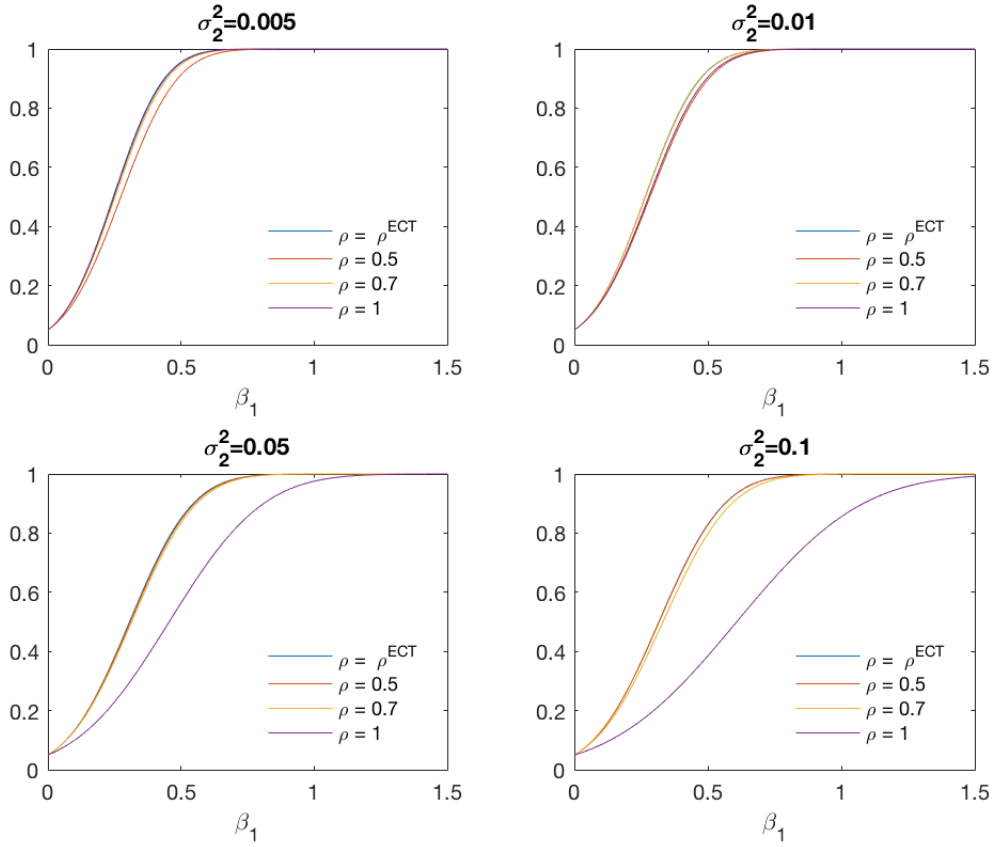

Figure C.5: Comparison of power of the test of treatment effects related to externally-controlled single-arm trials ([Test ECT]) with Gaussian endpoints for different randomization ratios $\rho = 0.5, 0.7, 1, \rho^{ECT}$. The parameters are $n = 100, n_{\text{ext}} = 30, K = 5, \sigma_1^2 = 1$ and $\sigma_2^2 = 0.005, 0.01, 0.05, 0.1$.

In Figure C.6 we consider Gaussian outcomes and we show that if the sources of between-studies and within-study variabilities are known and the between-studies variance (σ_2^2) and size of the internal study (n) are small, then externally-controlled single-arm trial is preferable to standard randomized clinical trial with randomization ratio 0.5 (first subplot). The situation reverses for larger values of σ_2^2 and n (other subplots). Moreover, as the value of σ_2^2 increases, the power of the test [Test ECT] related to an externally-controlled randomized clinical trial with optimal randomization ratio ρ^{ECT} gets closer to that one of the test [Test RCT] related to a standard randomized clinical trial with balanced randomization (it is not convenient to use external data anymore).

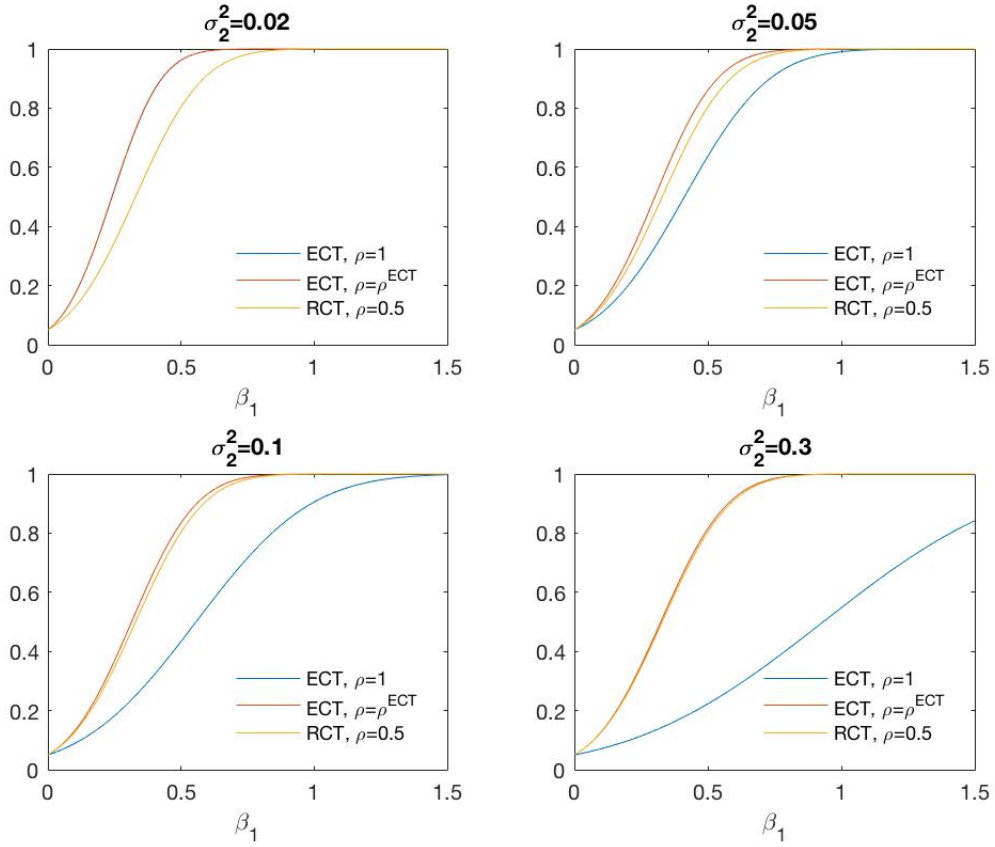

Figure C.6: Comparison of power of the test of treatment effects related to externally-controlled single-arm trials ([Test ECT], $\rho = 1$), externally-controlled randomized clinical trials with optimal randomization ratio ([Test ECT], $\rho = \rho^{ECT}$) and standard randomized clinical trials with balanced randomization ([Test RCT], $\rho = 0.5$). The parameters are $n = 100$, $n_{\text{ext}} = 30$, $K = 30$, $\sigma_1^2 = 1$ and $\sigma_2^2 = 0.01, 0.05, 0.1, 0.3$.

Figure C.7 shows that asymptotically, if n and n_{ext} tend to infinity, outcomes are Gaussian and $\rho = 0.5$, then power of test [Test ECT] coincide with power of test [Test RCT]. Instead, if n and n_{ext} tend to infinity, outcomes are Gaussian and $\rho = 1$, then power of test [Test ECT] can be approximated by $1 - \Phi\left(z_\alpha - \frac{\beta_1\sqrt{K}}{\sqrt{(K+1)\sigma_2^2}}\right)$.

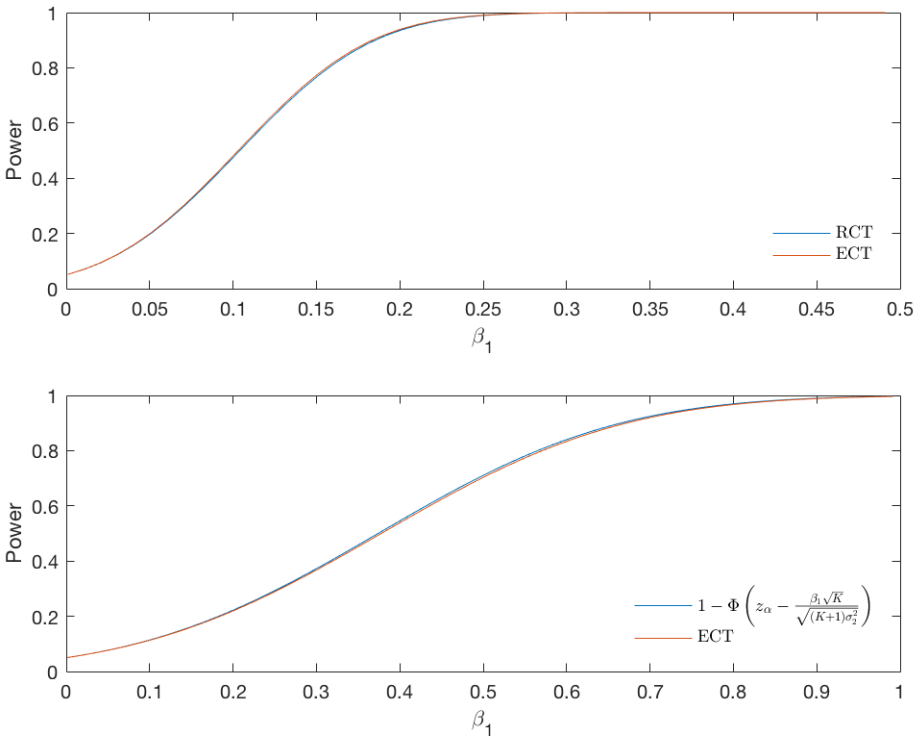

Figure C.7: First row: Comparison of estimates of power of tests [Test ECT] and [Test RCT] when $\rho = 0.5$ and n and n_{ext} tend to infinity. Second row: Comparison of estimates of power of test [Test ECT] and expression $1 - \Phi\left(z_\alpha - \frac{\beta_1\sqrt{K}}{\sqrt{(K+1)\sigma_2^2}}\right)$ when $\rho = 1$ and n and n_{ext} tend to infinity. In both subplots the parameters are $n = 1000, n_{\text{ext}} = 1000, K = 30, \sigma_1^2 = 1$ and $\sigma_2^2 = 0.05$.

Figure C.8 shows that when the size and number of external studies are small, the ANOVA estimators $\hat{\sigma}^2_{2,A}$ (unbiased) and $\hat{\sigma}^2_{2,B}$ (biased) and the REML estimator $\hat{\sigma}^2_{2,REML}$ of the between-studies variance parameter σ_2^2 in model (3.3) have large variability (first subplot). The variability of the above estimators significantly reduces when the size of the external studies is large (second subplot) or a quite large number of external studies is available (third subplot). Also, when the number of external studies is small, $\hat{\sigma}^2_{2,A}$ and $\hat{\sigma}^2_{2,REML}$ can take non-positive values (first and second subplots).

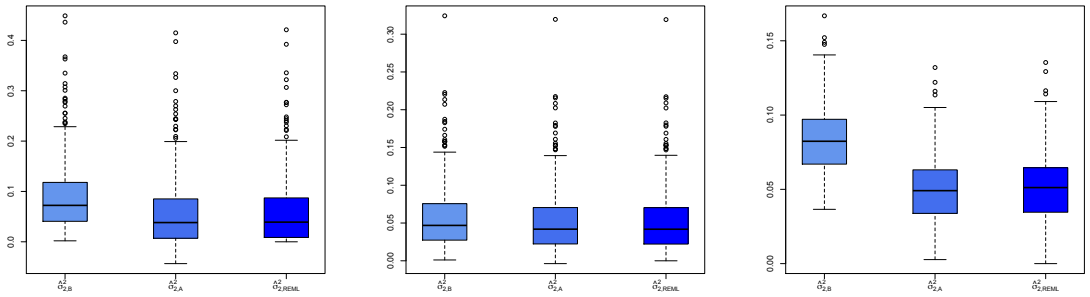

Figure C.8: Distribution of ANOVA estimator $\hat{\sigma}^2_{1,A}$ of σ_1^2, ANOVA estimators $\hat{\sigma}^2_{2,B}$ (biased) and $\hat{\sigma}^2_{2,A}$ (unbiased) of σ_2^2 and REML estimator $\hat{\sigma}^2_{2,REML}$ of σ_2^2 based on external data. The parameters in model (3.3) are $\sigma_1^2 = 1, \sigma_2^2 = 0.05$. In first subplot $n_{\text{ext}} = 30, K = 5$; in the second subplot $n_{\text{ext}} = 200, K = 5$ and in the third subplot $n_{\text{ext}} = 30, K = 30$.

Chapter 4

Conclusions and discussion

4.1 Summary of research findings

The broad goal of this PhD thesis has been to thoughtfully tackle some fundamental statistical issues in the design of clinical trials. The main objectives have been to investigate the asymptotic properties of response-adaptive procedures and to assess the value of randomization in the design of clinical trials using quantitative arguments.

The research questions that we have addressed arise from clinical practice, where it is essential that the statistical properties of the designs of clinical trials are evaluated before the designs are implemented. This is even more so for adaptive clinical trials, whose key trial characteristics (e.g., randomization probabilities, sample size, treatment arms, eligibility criteria) evolve according to prespecified rules during the trial, in response to information accruing within the trial itself. For simple adaptive designs, the statistical properties are well understood and can be determined analytically; instead newer complex adaptive designs require Monte Carlo simulations to fully understand the operating characteristics.

We showed that asymptotic analyses of adaptive procedures simplify the design of clinical trials and reduce the need for time-consuming simulations to evaluate operating characteristics across potential trial scenarios. In particular, we studied the asymptotic characteristics of BUDs. BUDs seek to maximize the acquisition of information on the effectiveness of new experimental treatments. These designs are an example of adaptive clinical trial designs using a Bayesian methodology. These designs can be very flexible and the Bayesian approach naturally fits the

adaptive paradigm. On the other hand, they are typically complex adaptive designs. The computing time to simulate a BUD trial increases linearly with respect to the sample size and with respect to the number of possible actions (see [88]).
In Chapters 1 and 2 we derived asymptotic results for the randomization probabilities and allocation proportions of BUDs without the need of simulations by using stochastic approximation techniques. BUD's randomization procedure was expressed as a sequence of recursive equations which allowed the application of techniques from classical stochastic approximation theory (see Appendix A).

Potential applications of stochastic approximation theory in the analysis of clinical trial designs have been previously discussed by [52]. The fact that stochastic approximation techniques have seldom been used in actual clinical studies stands in stark contrast with their constant application in engineering and finance. In this thesis, we showed that they allow to evaluate major operating characteristics of BUDs. We considered for example the variability of the allocation proportions during the trials and the power of the BUD with a fixed sample size under a parameter of interest.

Besides adopting a novel methodology to study asymptotic characteristics of response-adaptive randomized clinical trials designs, the key contibution of this thesis has been to provide statistical evidence to support the use of externally-controlled randomized clinical trials designs in clinical practice. The interest in augmenting or replacing the concurrent control in a novel clinical trial, using existing information on a control treatment as an external control, has increased exponentially in last years, due to the growing availability of data collected from already completed clinical trials and real-world data. However, there's an almost total lack of discussion about the statistical properties of externally-controlled randomized clinical trials designs in literature. When considering evaluation of externally-controlled randomized clinical trials, this research has provided some valuable insights, allowing key recommendations to be made.

In Chapter 3, we considered that it would be naive to use external control data from individual patients directly as if these were from a concurrent control group. In fact, differences between source and target with respect to patient populations or external factors are usually present: variability between the source and the target data might occur for many reasons such as differences in the way studies are conducted and how the treatment effects are measured. Thus, we incorporated the statistical heterogeneity into mixed effects models and we estimated power of

the test of the null hypothesis of no treatment effect versus the alternative of positive treatment effect assuming these models.

When outcomes are Gaussian we provided a closed form expression for power under the assumption that the sources of variability are unknown or that a large number of external studies is available. On the other hand, we showed the difficulties to assess a closed form expression for power when outcomes are binary or time-to-event. In this case, we proposed an overall procedure based on Monte Carlo simulations and bootstrap algorithm to test treatment effects and estimate power of the study. Then, we compared estimates of power related to externally-controlled randomized clinical trials with that one that we could obtain by running a randomized clinical trial in standard formulation. Finally, we gave a set of recommendations to determine the characteristics of the design of forthcoming trials that maximize power of the study in fixed scenarios.

According to our analysis, borrowing strength using relevant individual patient data on control treatment from external trials may allow to reduce (externally-controlled randomized clinical trials), or even eliminate (single-arm trial supported by external controls), the concurrent control group. In particular, we exhibited that, under general conditions, externally-controlled randomized clinical trials with optimal randomization ratio are superior to standard randomized clinical trials. This finding is particularly relevant, since it proves that the use of existing data to design clinical studies could have the potential to enhance the assignment of patients in clinical trials. However, when the heterogeneity between studies is large, it is not convenient to use external data anymore and this is even more so if the number of external studies is small.

To sum up, the research presented in this thesis provides a number of contributions to the development of statistical methodology in the context of clinical research and it enriches the literature about response-adaptive and externally-controlled randomized clinical trials designs. The theoretical approach used to evaluate asymptotic properties and operating characteristics of modern designs of clinical trials gives a reliable mean, confirmed by simulation studies, that can further benefit to clinical and statistical researchers attempting to improve and accelerate drug development process.

4.2 Further work

While this research leads to original findings in the evaluation of the statistical properties of response-adaptive and externally-controlled randomized clinical trials designs, there are a number of potential areas for further research.

Most notably, the investigations within this research are limited to the goal of estimating or testing treatment effects in clinical trials. On the other hand, the formulation of BUDs allows the selection of information metrics that represent different primary aims of clinical studies: selecting therapies with positive effects, identifying relevant treatment effects on multiple endpoints, choosing subgroups of patients that respond to experimental treatments, determining the right dose of drugs (Appendix B).

Moreover, the asymptotic results given in Chapter 1 and Chapter 2 hold under some restrictive assumptions:

- ▷ The information metric is (minus) the variance or the entropy of the posterior distribution of the parameter of interest of the outcomes of the different arms. Extending asymptotic results to other metrics is an open problem.
- ▷ Two-arm trials are considered. The results about the asymptotic normality of randomization probabilities and allocation proportions can't be generalized to multi-arm trials by using similar methods of proof.
- ▷ The model is a single parameter model. In applications, besides the parameter we are interested in, there can be some nuisance parameters which are also unknown. For example, in the normal response model, both the mean and variance are usual unknown.
- ▷ Conjugate priors are used. Based on the conjugate prior and the independence assumption, most of the variances of the mean estimates in the exponential family have closed-form and it is possible to derive an approximated sample size formula. However, this result is not straightforward in the not-conjugate setting.
- ▷ The randomization probability is updated with the enrollment of each new patient. However, real trials don't use a continuous update of the randomization probability. The limiting behaviors need to be generalized to a context where decisions are made cohort-wise.

The major avenue for future research that has been opened by this work is the way it is possible to provide power estimates or sample size formulas for BUDs when the assumptions listed above are relaxed or removed. We think that the stochastic approximation framework developed as part of this research enables useful approximations of the operating characteristics of BUDs, but may also offer advantages in the asymptotic analysis of other response-adaptive randomized designs. The general strategy for the assessment of asymptotic properties of a generic response-adaptive randomized clinical trials design would consist of writing the randomization probabilities or allocation proportions as a stochastic approximation process of form (A.10) (Appendix A). Then, the arguments used to prove Theorem 1 can be adapted to establish the asymptotic normality of the just mentioned random variables; instead the procedure used in Section 1.3.2 can be adjusted to approximate the operating characteristics, whereas any adequate characterization of the operating characteristics may need extensive simulations.
Also, even if our work complement from the informative point of view the majority of recent Bayesian literature, which is focused on utility functions which combines inferential and ethical concerns, for example related to the maximization of total expected outcomes in a bandit perspective [94], a comparison between the two approaches would be useful to understand the potentiality of BUDs.

In this thesis we highlight the fact that availability of appropriate statistical methodology for evaluating novel randomized clinical trials designs is generally a key contributing factor to their eventual use. For example, understanding the possible context-specific benefit from the use of external data in the design of novel trials is important for therapeutic development. However, the existing literature discusses the advantages of incorporating external information in novel randomized clinical trials by using mainly qualitative arguments.

In Chapter 3 we provide a quantitative and statistical framework to support the choice of using existing data on the control treatment in the design of novel clinical trials, by using power as a metric to compare standard randomized clinical trials and externally-controlled randomized clinical trials designs. Our results indicate that externally-controlled randomized clinical trials designs constitute a useful alternative to standard single-arms trials and randomized clinical trials designs. In particular, in clinical settings and scenarios where randomization may be difficult or not feasible (e.g. rare disease, small patient population, loss of equipoise), the use of external controls represents an opportunity to potentially reduce the number of patients in the control

arm and enhance data obtained from clinical trials.

The results of our work confirm the worthiness of additional research to extend our findings to other clinical outcomes and to evaluate different study designs for using external controls.
In this thesis, consideration is given to the common setting in which randomized clinical trials with normal, binary and time-to-event endpoints are analysed using simple linear model, generalized linear model and proportional hazard Cox model, respectively. On the other hand, externally-controlled clinical trials with normal, binary and time-to-event endpoints are analysed using linear mixed model, generalized linear mixed model and mixed effect Cox model, respectively, where the random effects variance represents the between-studies variability that is additional to within-study sampling error and that might occur for many reasons such as differences in the way studies are conducted and how the treatment effects are measured. In general, random effects meta-analytic approaches take account of between-trial heterogeneity among the external trials as well as between the external and the internal trials. The main strengths of these models are their ability to account for unexplained between-studies heterogeneity, their flexibility to adapt to different types of source data, and the possibility to integrate both individual patient data and aggregate data from publications.

Whilst the use of these mixed effects models was used herein, it would be beneficial for further work to be undertaken to determine whether considering extensions or alternatives to these models would lead to similar conclusions and design guidelines. For instance, models that can handle interval censoring or non proportional hazards may be of interest, since in some clinical trials, the treatment effect may not manifest itself right after patients receive the treatment. We think as a general rule, it would be needed to investigate the robustness of sensitivities of the underlying statistical methods for including external controls in novel trial designs.

Also, it is important to deepen the limitations associated with the various sources of external data when designing and analyzing externally-controlled randomized clinical trials: robust external controls should be selected to control for potential biases that can be encountered, such as selection bias and allocation bias (confounding). Such biases should be mitigated where possible. In particular, in the design phase, key baseline prognostics and confounding factors should be identified and accordingly key inclusion/exclusion criteria for external cohort selection should be pre-specified. Despite careful selection of the external cohort in alignment with the trial eligibility

criteria, imbalances in key confounding factors may still exists that need to be further mitigated through pre-specification of statistical methods, such as propensity score methods.
Even though a Bayesian perspective is used to combine external controls with concurrent controls, using hierarchical modeling to borrow strength from previous studies, it is important to assess whether the external studies are sufficiently similar to the current study to be considered exchangeable. Exchangeability of trials is important in the development of realistic models for combining trial data with prior information. To achieve study-level exchangeability, statistical adjustments for certain differences in covariates may be necessary. However, to this point, the selection and use of covariates in the borrowing of external data has seemingly limited investigation in the literature, revealing a potential research gap.

Finally, we recognize that the use of external control information from an historical trial in the design of novel trials brings its own unique challenges with regards to generalisability of results, interpretation and associated statistical methodology. Nevertheless, it is likely that there will be an increasing number of clinical trials that use external information. In fact, regulatory authorities have begun to endorse the use of external controls in certain circumstances, with some positive outcomes for new drug approvals.

It is the sincere hope of us that this thesis will stimulate interest in further development of statistical methodology to improve the design of clinical trials and will promote the use of stochastic approximation techniques in clinical setting. Also, we wish that our work will provide the incentive for future research about the value of asymptotic analysis of randomized clinical trials designs and also will give the impetus for the use of external controls in future clinical trials.

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